Journal of Gastrointestinal Surgery (2019) 23:1973–1983
https://doi.org/10.1007/s11605-018-3952-1

ORIGINAL ARTICLE

The Relationship Between Postoperative Chemotherapy and Remnant Liver Regeneration and Outcomes After Hepatectomy for Colorectal Liver Metastasis

Yoshihiro Inoue[1] · Kensuke Fujii[1] · Masatsugu Ishii[1] · Syuji Kagota[1] · Hiroki Hamamoto[1] · Wataru Osumi[1] · Tetsuji Terasawa[2] · Yusuke Tsuchimoto[2] · Shinsuke Masubuchi[1] · Masashi Yamamoto[1] · Akira Asai[2] · Koji Komeda[1] · Shinya Fukunishi[2] · Fumitoshi Hirokawa[1] · Masahiro Goto[2] · Yoshihumi Narumi[3] · Kazuhide Higuchi[2] · Kazuhisa Uchiyama[1]

Received: 13 June 2018 / Accepted: 23 August 2018 / Published online: 5 September 2018

Abstract

Background Postoperative chemotherapy for treating colorectal liver metastasis (CLM) has been introduced with the aim of improving therapeutic outcomes. However, there is no consensus on the utility of multidisciplinary treatments with postoperative chemotherapy. Therefore, we evaluated surgical outcomes in patients with CLMs who underwent hepatectomy, while focusing on the effects of post-hepatectomy chemotherapy on remnant liver regeneration.

Methods Two hundred ninety patients who underwent hepatectomy were retrospectively analyzed using propensity score matching. Postoperative outcomes were evaluated with a focus on the effects of post-hepatectomy chemotherapy on regeneration of the remnant liver in patients with CLM. The remnant liver volumes (RLVs) were measured postoperatively using multi-detector computed tomography on day 7 and months 1, 2, 5, and 12 after the operation.

Results RLV regeneration and postoperative blood laboratory data did not differ significantly between patients who received postoperative chemotherapy and those who did not receive postoperative chemotherapy immediately after surgery or at any time point from postoperative day 7 to postoperative month 12. The recurrence rates, including same and other segmental intrahepatic recurrences, as well as the resection frequency of the remnant liver were not significantly different between the two groups.

Conclusion Postoperative chemotherapy may be of small significance for patients with CLM in terms of the remnant liver volume regeneration and functional recovery.

Keywords Postoperative chemotherapy · Hepatectomy · Liver regeneration · Surgical outcome

Introduction

Colorectal cancer (CRC) is often accompanied by distant metastases and recurrences affecting the liver. Curative resection is not indicated for liver metastases resulting from many other types of primary carcinomas. In the case of CRC, however, curative resection can be often performed even when it is accompanied by liver metastases, and therapeutic strategies for these liver metastases largely determine the outcome of CRC.

Therapeutic options for colorectal liver metastasis (CLM) include hepatectomy, chemotherapy, hepatic artery embolization, and thermal ablations including microwave coagulation therapy (MCT) and radiofrequency ablation (RFA). Among these options, hepatectomy is recommended because it is currently the most reliable therapy. However, recurrences have been reported to occur in 57 to 78% of patients who underwent hepatectomy. The remnant liver is the most frequent location for recurrences, occurring in about half of these patients.[1–5]

✉ Yoshihiro Inoue
sur129@osaka-med.ac.jp

[1] Department of General and Gastroenterological Surgery, Osaka Medical College Hospital, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan

[2] The Second Department of Internal Medicine, Osaka Medical College Hospital, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan

[3] Department of Radiology, Osaka Medical College Hospital, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan

Consequently, various postoperative chemotherapy regimens that include molecular-targeted drugs have been introduced with the aim of improving therapeutic outcomes. An increasing number of studies have reported that these adjuvant chemotherapy regimens substantially improved survival prognosis.[6,7] However, few studies have investigated in detail the impact of these postoperative chemotherapy regimens on remnant liver regeneration and any other relevant factors. In this study, we evaluated surgical outcomes in patients with CLMs who underwent hepatectomy, while focusing on the effects of post-hepatectomy chemotherapy on remnant liver regeneration.

Materials and Methods

Patient Population and Selection

Between January 23, 2009 and May 31, 2017, 290 consecutive patients underwent hepatic resection for CLM at Osaka Medical College Hospital in Takatsuki City, Japan. The medical records of these patients were retrospectively analyzed. Patients with an associated biliary-enteric anastomosis and gastrointestinal procedures were excluded from the study.

The preoperative workup consisted of a specified protocol including blood tests, abdominal ultrasound, multi-detector computed tomography (MDCT) scanning, magnetic resonance imaging (MRI), and fluorodeoxyglucose-positron emission tomography (FDG-PET). Hepatic function was evaluated using the Child-Pugh classification[8] of liver dysfunction. Unenhanced computed tomography (CT) images were used as inputs into the Volume Analyzer SYNAPSE VINCENT image analysis system (Fujifilm Medical, Tokyo, Japan) to quantify the body composition index. The total psoas major muscle volume (cm^3/m^2) and the area of the psoas major muscle at L3 (cm^2/m^2) were obtained for analysis. Liver volumetry was estimated using Synapse Vincent (Fujifilm, Tokyo, Japan) and MDCT.

Patients who underwent additional therapy, such as repeat hepatic resection or radiofrequency ablation during the six postoperative months were also excluded. Ultimately, 290 patients who underwent hepatic resection and liver volumetry at four time points were included in our study.

Postoperative Chemotherapy

The postoperative chemotherapy regimens were determined at the time of surgery by the oncologists belonging to the Internal Medicine Department, based on the clinical guidelines.[6,9] The postoperative chemotherapy regimens were oxaliplatin-based in 45 subjects, 5-FU-based in 40 subjects, capecitabin in 4 subjects, and others in 2 subjects. The median number of treatment cycles was 6 (range 4–18). The standard period between the completion of chemotherapy and surgery was set at 4–6 weeks.[10]

Liver Volume Measurements

Three hepatobiliary surgeons with expertise in performing abdominal CT (YI, KF, and KU) traced the contours of the total liver. The Volume Analyzer SYNAPSE VINCENT image analysis system automatically calculated an approximate total liver volume (TLV) from preoperative CT scans. The remnant liver volumes (RLV) were postoperatively measured using MDCT at day 7 and months 1, 2, 5, and 12 after the operation. We calculated the following values: (a) the RLV at day 0 after operation, calculated as (TLV + tumor volume) − resected liver volume, and (b) the regeneration rate, calculated as (RLV at day 7 and at 1, 2, 5, and 12 months / TLV) × 100.[11]

Surgical Procedure

Details of the surgical technique routinely used in our department have been described previously.[12–14] Briefly, a standard diagnostic and staging laparotomy was conducted. The liver was mobilized, and intraoperative ultrasonography was routinely performed. Parenchymal transection was achieved using the Sonop 5000 ultrasonic dissector (Hitachi Aloka Medical, Ltd., Tokyo, Japan). Small vessels were ligated or coagulated using a soft-coagulation system or bipolar electrocautery. Intraparenchymal control of major vessels was accomplished using non-absorbable sutures, whereas biliary and vascular vessels were ligated with stapling devices or non-absorbable sutures. The hepatic pedicle was always isolated to enable performance of the Pringle maneuver when required. Intermittent clamping was applied using 15-min clamping and 5-min release periods. The surgical margin was confirmed using intraoperative ultrasonography to obtain a surgical margin of 2–10 mm when possible.

Definitions

Operative procedures were classified according to conventional terminology derived from the eight segments of the liver per the Couinaud classification.[15] Anatomical resection was defined as resection of the neoplasm with the portal vein related to the neoplasm and the surrounding hepatic territory. Non-anatomical resection was defined as the resection of a lesion without regard to segmental, sectional, or lobar anatomy. Major hepatectomy was defined as resection of three or more liver segments according to the Brisbane 2000 system.[16]

Complications were stratified according to the Clavien-Dindo classification of surgical complications.[17,18] Postoperative bile leakage and post-hepatectomy liver failure were defined based on the criteria of the International Study Group of Liver Surgery.[19,20] We defined massive ascites as ascites that could not be mobilized, or as that which could not be satisfactorily prevented with medical therapy.[21] The R classification denoted the absence or presence of residual tumor after surgery.[22]

Patient Follow-up

Patients were closely followed until November 1, 2017. They were examined for CLM recurrence using ultrasonography and contrast-enhanced CT on postoperative day 7; months 1, 2, 5, and 12; and every 6–12 months thereafter. Blood tests including carcinoembryonic antigen and carbohydrate antigen 19–9 were performed at 1–2 months after discharge and every 2–3 months thereafter. When recurrence was suspected, contrast-enhanced CT and/or MRI were performed to assess the occurrence of new lesions in the remnant liver. Systemic recurrence was evaluated by chest and pelvic CT, FDG-PET, or gallium scintigraphy. Recurrence was defined as intra- and/or extrahepatic recurrence of colorectal cancer and was diagnosed when at least two imaging studies confirmed new lesions showing typical features of colorectal cancer/CLM. Recurrence-free survival (RFS) was defined as the interval between hepatectomy and the first occurrence of recurrent lesion(s).

Statistical Analysis

To minimize the influence of potential confounders on selection bias, propensity scores were generated using binary logistic regression which included the following variables: age, sex, body mass index (BMI), diabetes mellitus, hepatitis viral infection, largest tumor size, tumor number, bilobar distribution, albumin, total bilirubin, prothrombin time or platelet count, and preoperative chemotherapy. The choice of these variables was based on the univariate analysis results and/or the known influence of specific factors on the selection of the intervention type. Independent variables entered into the propensity model included the patients' preoperative information. One-to-one matching between groups was accomplished using the nearest-neighbor matching method, which was performed without replacement and using a caliper width of 0.2 standard deviations of the logit of the estimated propensity score. After propensity score matching (PSM), the two matched groups were handled as unpaired independent groups. Continuous variables were expressed as medians ± standard deviation. Univariate analysis results were compared using the Student's t and χ^2 tests, Mann-Whitney U test, Wilcoxon signed-rank test, or Fisher's exact test, as appropriate. Factors that were found to be significant in the univariate analysis were subjected to multivariate logistic regression analysis to determine the adjusted odds ratios. Actuarial overall survival (OS) rates and RFS rates were calculated using the Kaplan-Meier method, and were compared using the log-rank test (univariate analysis) or Cox proportional hazards regression (multivariate analysis). Values of $p < 0.05$ were considered significant. All statistical analyses were performed using JMP version 12 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient Demographics

A group of patients who received postoperative chemotherapy ($n = 91$) was compared to a group of patients who did not receive postoperative chemotherapy ($n = 199$). The patient demographics for each group are shown in Table 1. The median follow-up period was 27 months. PSM was used to reduce the bias in the distribution of demographic factors. After PSM, 80 patients each in the 2 groups were detected. After PSM, no statistical differences were found between the two groups with regard to patient demographic factors and postoperative course (Table 2).

Changes in Liver Volume

Perioperative changes in hepatic volume are as shown in Table 3. The postoperative chemotherapy group did not differ significantly from the group that did not receive postoperative chemotherapy with respect to RLV determined immediately after surgery (postoperative day 0). Similar results were noted at all time points during the period from postoperative day 7 to postoperative month 12. The groups did not differ significantly from each other in post-PSM changes in hepatic volume, as seen in the liver regeneration rates.

The median liver regeneration rates in the oxaliplatin-based chemotherapy group were 91.6, 100.9, 85.9, 99.2, 95.7, and 98.0% at day 0, 7 and months 1, 2, 5, and 12 after the operation. These liver regeneration rates in the 5-FU-based chemotherapy group were 84.7, 83.2, 87.2, 94.7, 93.0, and 98.1%. There were no significant difference between the two different chemotherapy groups ($p = 0.613$, 0.741, 0.632, 0.867, 0.592, and 0.778, respectively).

Postoperative Changes of Laboratory Data

Postoperative blood chemistry tests revealed no significant differences between the two groups in changes over time in total bilirubin, albumin, prothrombin time, or platelet count on

Table 1 Preoperative clinical and laboratory patient data

	Postoperative chemotherapy group	Non-postoperative chemotherapy group	*p* value
Before PSM	*N* = 91	*N* = 199	
Age (years)	63 (28–79)	68 (33–89)	< 0.001*
Sex (M / F)	52 / 39	114 / 85	1.000
BMI, kg/m^2	22.3 (16.1–31.5)	22.5 (15.4–32.1)	0.432
Size of largest tumors, cm	2.5 (0.7–14.8)	2.5 (0.5–16.7)	0.776
Number of lesion	1 (1–24)	1 (1–18)	0.506
Bilobar distribution	31 (34.1%[a])	47 (23.6% [a])	0.066
Synchronous metastasis	50 (55.0% [a])	96 (48.5% [a])	0.314
Serum albumin, g/dL	4.2 (2.9–4.9)	4.0 (2.5–5.0)	0.003*
Serum total bilirubin, mg/dL	0.6 (0.2–1.3)	0.5 (0.2–2.2)	0.025*
Prothrombin time, %	110 (52–148)	107 (26–150)	0.344
Platelet count, ×10^4/μL	22.8 (10.4–52.5)	21.0 (8.7–49.1)	0.084
Child-Pugh classification, A	91 (100.0%[a])	198 (99.5%[a])	1.000
PNI	50.0 (38.4–53.1)	46.3 (32.3–61.0)	0.664
Hepatitis viral infection, %	9 (9.9%[a])	38 (19.1%[a])	0.059
Psoas major muscle volume, cm^3/m^2	319.0 (133.8–400.6)	232.5 (122.9–579.7)	0.829
Psoas major muscle area at L3, cm^2/m^2	20.8 (9.6–25.7)	14.9 (8.6–35.0)	0.534
Total liver volume, cm^3	1139 (750–1735)	1126 (630–2143)	0.499
Preoperative chemotherapy	32 (35.2%[a])	55 (27.6%[a])	0.215
After PSM	*N* = 80	*N* = 80	
Age (years)	64 (28–79)	64 (33–87)	0.893
Sex (M / F)	45 / 35	42 / 38	0.634
BMI, kg/m^2	22.3 (16.1–31.5)	21.9 (15.4–30.5)	0.839
Size of largest tumors, cm	2.5 (0.7–14.8)	2.5 (0.5–16.7)	0.680
Number of lesion	1 (1–24)	1 (1–12)	0.424
Bilobar distribution	25 (31.3%[a])	17 (21.3%[a])	0.208
Synchronous metastasis	43 (53.8%[a])	41 (51.9%[a])	0.874
Serum albumin, g/dL	4.2 (2.9–4.9)	4.1 (3.2–5.0)	0.480
Serum total bilirubin, mg/dL	0.6 (0.2–1.3)	0.5 (0.2–2.2)	0.861
Prothrombin time, %	110 (52–148)	107 (54–150)	0.989
Platelet count, ×10^4/μL	21.8 (10.4–52.5)	22.3 (8.9–37.0)	0.738
Child-Pugh classification, A	80 (100.0%[a])	80 (100.0%[a])	1.000
PNI	50.0 (38.4–53.1)	47.9 (41.9–61.0)	0.451
Hepatitis viral infection, %	9 (11.3%[a])	9 (11.3%[a])	1.000
Psoas major muscle volume, cm^3/m^2	319.0 (133.8–400.6)	231.8 (122.9–579.7)	0.724
Psoas major muscle area at L3, cm^2/m^2	20.8 (9.6–25.7)	16.9 (8.8–35.0)	0.915
Total liver volume, cm^3	1145 (750–1657)	1079 (630–2143)	0.432
Preoperative chemotherapy	30 (37.5%[a])	27 (33.8%[a])	0.741

Data was presented as median (range)

PSM propensity scores matching, *BMI* body mass index, *PNI* prognostic nutritional index, *ICGR-15* indocyanine green retention rate at 15 min

*$p < 0.05$

[a] Percentage (%) of the group

postoperative days 1, 2, 4, 7, 14, and months 1, 2, 5, and 12. Post-PSM changes also showed no differences (Fig. 1). One month after surgery, all laboratory data returned to nearly normal values.

Prognosis for 1-, 2-, 3-, and 5-Year OS and RFS

The 1-, 2-, 3-, and 5-year OS rates for all patients were 94.5, 87.2, 81.0, and 73.7%, respectively, with a median survival

Table 2 Outcomes of hepatic resection surgery

	Postoperative chemotherapy group	Non-postoperative chemotherapy group	*p* value
Before PSM	*N* = 91	*N* = 199	
Hepatic resection			0.818
Parenchymal-sparing	59 (64.8%)	136 (68.3%)	
Sectionectomy	17 (18.7%)	35 (17.6%)	
Lobectomy	15 (16.5%[a])	28 (14.1%)	
Operative time (min)	230 (85–520)	223 (43–765)	0.692
Resected liver volume (g)	100 (3–900)	125 (2–1380)	0.438
Remnant liver volume (%)	91.8 (40.1–99.7)	87.8 (27.3–99.8)	0.285
Blood loss (mL)	200 (0–3460)	210 (0–5040)	0.805
Blood transfusion, %	18 (19.8%[a])	38 (19.1%[a])	0.874
Surgical margin, (mm)	7 (0–30)	4 (0–29)	0.541
Curative resection, R0 (%)	81 (89.0%[a])	160 (80.4%[a])	0.060
Complication			
Superficial incisional SSI	7 (7.7%[a])	5 (2.5%[a])	0.055
Deep incisional SSI	4 (4.4%[a])	2 (1.0%[a])	0.080
Organ/Space SSI	9 (9.9%[a])	25 (12.6%[a])	0.562
Bile leakage	3 (3.3%[a])	12 (6.0%[a])	0.404
PHLF	0 (0%[a])	2 (1.0%[a])	1.000
Ascites	4 (4.4%[a])	16 (8.0%[a])	0.324
Clavien-Dindo classification > IIIa	19 (20.9%[a])	41 (20.6%[a])	1.000
Mortality	0 (0%[a])	2 (1.0%[a])	1.000
Postoperative hospital stay (days)	11 (4–89)	12 (5–173)	0.148
Recurrence	58 (63.7%)	116 (58.3%)	0.243
Liver	38 (75.0%)	82 (69.8%)	0.487
Same segment recurrence	6 (15.8%)	12 (14.5%)	0.849
Other segments	32 (84.2%)	71 (85.5%)	
Lung	26 (44.8%)	36 (31.0%)	0.075
Only other sites	16 (27.6%)	30 (25.9%)	0.808
Multiple organ	18 (31.0%)	28 (24.1%)	0.331
Recurrence within 1 year	40 (69.0%)	86 (74.1%)	0.795
Recurrence within 2 years	50 (86.2%)	109 (94.0%)	0.796
Recurrence within 3 years	53 (91.4%)	114 (98.3%)	0.687
Repeat hepatectomy	22 (57.9%)	46 (56.1%)	0.682
After PSM	*N* = 80	*N* = 80	
Hepatic resection			0.806
Parenchymal-sparing	54 (67.5% [a])	52 (65.0% [a])	
Sectionectomy	15 (18.8% [a])	14 (17.5% [a])	
Lobectomy	11 (13.8% [a])	14 (17.5% [a])	
Operative time (min)	224 (60–515)	231 (74–601)	0.306
Resected liver volume (g)	100 (3–900)	110 (2–1380)	0.508
Remnant liver volume (%)	89.9 (40.1–99.7)	89.4 (42.3–99.5)	0.679
Blood loss (mL)	200 (0–3460)	208 (0–1770)	0.852
Blood transfusion, %	15 (18.8%[a])	7 (8.8%[a])	0.107
Surgical margin, (mm)	7 (0–30)	5 (0–20)	0.126
Curative resection, R0 (%)	81 (89.0%[a])	81 (89.0%[a])	1.000
Complication			
Superficial incisional SSI	5 (6.3%[a])	2 (2.5%[a])	0.443
Deep incisional SSI	3 (3.8%[a])	1 (1.3%[a])	0.620
Organ/Space SSI	8 (10.0%[a])	9 (11.3%[a])	1.000

Table 2 (continued)

	Postoperative chemotherapy group	Non-postoperative chemotherapy group	*p* value
Bile leakage	2 (2.5%[a])	5 (6.3%[a])	0.443
PHLF	0 (0%[a])	0 (0%[a])	–
Ascites	3 (3.8%[a])	8 (90.0%[a])	0.210
Clavien-Dindo classification > IIIa	16 (20.0%[a])	19 (23.8%[a])	0.703
Mortality	0 (0%[a])	0 (0%[a])	–
Postoperative hospital stay (days)	11 (4–89)	11 (5–57)	0.748
Recurrence	51 (63.8%)	50 (62.5%)	0.618
Liver	34 (66.7%)	34 (68.0%)	0.886
Same segment recurrence	5 (14.7%)	7 (20.6%)	0.525
Other segments	29 (85.3%)	27 (79.4%)	
Lung	24 (47.1%)	17 (34.0%)	0.182
Only other sites	14 (27.5%)	14 (27.5%)	0.951
Multiple organ	17 (33.3%)	12 (24.0%)	0.300
Recurrence within 1 year	35 (68.6%)	31 (62.0%)	0.391
Recurrence within 2 years	44 (86.3%)	47 (94.0%)	0.840
Recurrence within 3 years	46 (90.2%)	49 (98.0%)	0.848
Repeat hepatectomy	16 (47.1%)	21 (61.8%)	0.293

Data was presented as median (range)

PSM propensity scores matching, *SSI* surgical site infection, *PHLF* post-hepatectomy liver failure

*$p < 0.05$

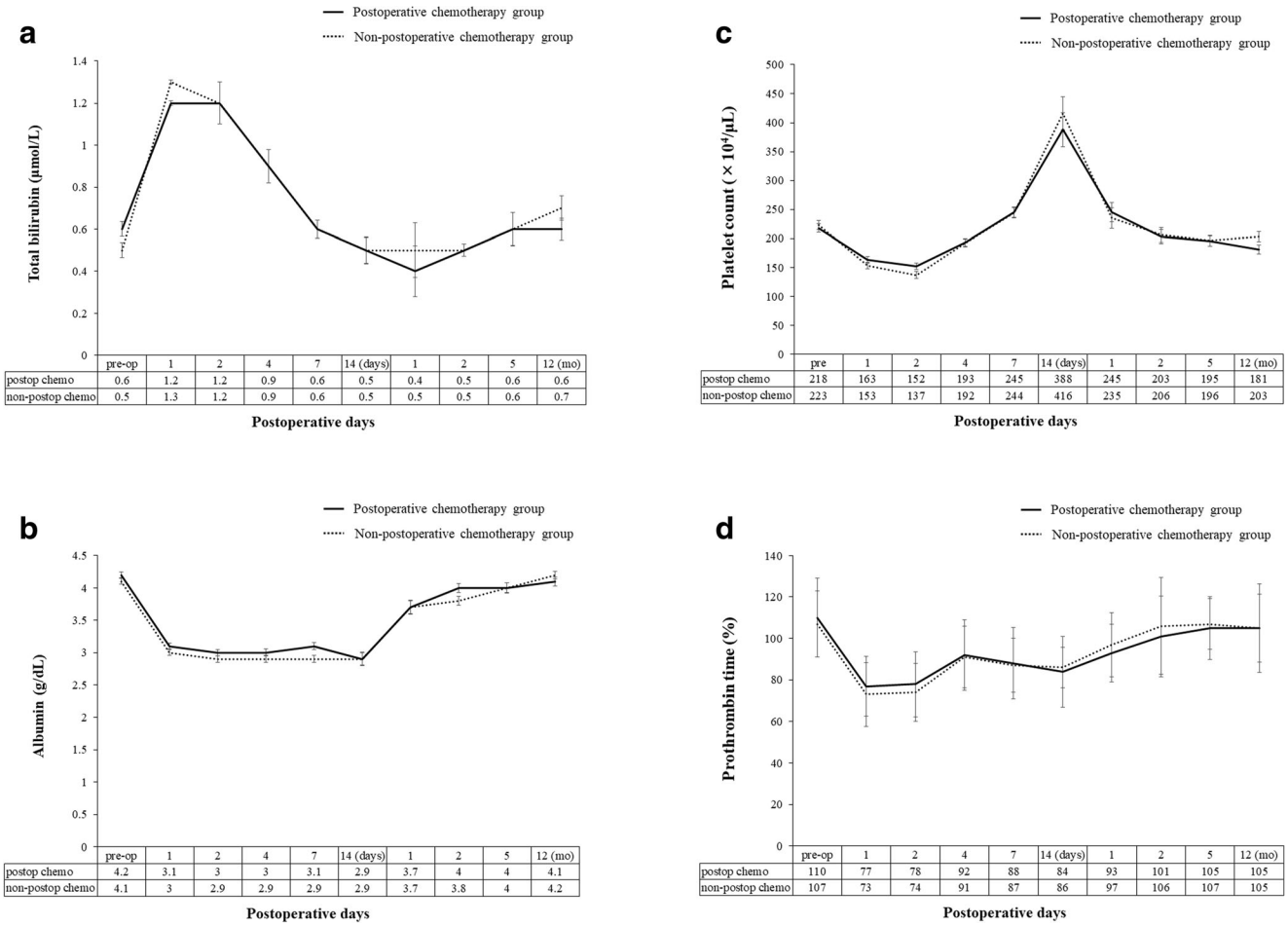
[a] Percentage (%) of the group

Table 3 Assessment of remnant liver volume rate

	Postoperative chemotherapy group	Non-postoperative chemotherapy group	*p* value
Before PSM	$N = 91$	$N = 199$	
TLV before operation, cm^3	1139 (750–1735)	1126 (630–2143)	0.499
At day 0 after operation, %	91.8 (40.1–99.7)	87.8 (27.3–99.8)	0.285
At day 7, %	100.0 (45.5–120.8)	95.1 (45.6–168.0)	0.887
At month 1, %	86.5 (71.4–112.3)	89.6 (58.1–120.1)	0.966
At month 2, %	96.7 (76.7–133.7)	93.9 (52.6–133.4)	0.308
At month 5, %	93.7 (73.4–122.0)	96.2 (61.7–128.0)	0.925
At month 12, %	97.9 (71.4–143.6)	96.0 (64.7–145.5)	0.784
After PSM	$N = 80$	$N = 80$	
TLV before operation, cm^3	1145 (750–1657)	1079 (630–2143)	0.432
At day 0 after operation, %	89.9 (40.1–99.7)	89.4 (42.3–99.5)	0.679
At day 7, %	92.6 (45.5–119.9)	96.0 (45.6–168.0)	0.437
At month 1, %	86.5 (71.4–112.3)	86.8 (73.4–107.7)	0.959
At month 2, %	96.7 (76.7–133.7)	91.8 (52.6–133.4)	0.571
At month 5, %	93.7 (73.4–122.0)	94.0 (61.7–114.8)	0.336
At month 12, %	96.8 (75.5–143.6)	94.6 (64.7–145.5)	0.850

Data was presented as median (range)

TLV total liver volume, *PSM* propensity score matching



a	pre-op	1	2	4	7	14 (days)	1	2	5	12 (mo)
postop chemo	0.6	1.2	1.2	0.9	0.6	0.5	0.4	0.5	0.6	0.6
non-postop chemo	0.5	1.3	1.2	0.9	0.6	0.5	0.5	0.5	0.6	0.7

b	pre-op	1	2	4	7	14 (days)	1	2	5	12 (mo)
postop chemo	4.2	3.1	3	3	3.1	2.9	3.7	4	4	4.1
non-postop chemo	4.1	3	2.9	2.9	2.9	2.9	3.7	3.8	4	4.2

c	pre	1	2	4	7	14 (days)	1	2	5	12 (mo)
postop chemo	218	163	152	193	245	388	245	203	195	181
non-postop chemo	223	153	137	192	244	416	235	206	196	203

d	pre-op	1	2	4	7	14 (days)	1	2	5	12 (mo)
postop chemo	110	77	78	92	88	84	93	101	105	105
non-postop chemo	107	73	74	91	87	86	97	106	107	105

Fig. 1 Postoperative changes in laboratory data. Postoperative total bilirubin (**a**), serum albumin (**b**), platelet count (**c**), and prothrombin time (**d**) in patients after hepatectomy (the postoperative chemotherapy group and the group that did not receive postoperative chemotherapy)

time (MST) of 27 months. The 1-, 2-, 3-, and 5-year RFS rates for all patients were 49.9, 37.9, 33.1, and 27.0%, respectively. There was no significant difference between the postoperative chemotherapy group and the group that did not receive postoperative chemotherapy in OS or RFS rates after hepatic resection ($p = 0.770$ and 0.903) (Fig. 2).

Comparisons between initial hepatectomy and repeat hepatectomy for recurrent carcinomas in the liver also revealed no differences between the two groups in 1-, 2-, 3-, and 5-year OS and RFS rates ($p = 0.613$ and 0.498) (Fig. 3).

Recurrences After Hepatectomy

Within 1, 2, and 3 years of hepatectomy, recurrences occurred in 72.4, 91.4, and 96.0% of all patients with recurrences, respectively. The recurrence rates did not significantly differ between the postoperative chemotherapy group and the group that did not receive postoperative chemotherapy (Table 2). The frequencies of remnant liver hepatectomy for cases of recurrence in these periods did not significantly differ between the groups ($p = 0.293$).

Discussion

Many clinical studies have been conducted to evaluate the various postoperative adjuvant chemotherapy regimens in patients with CRC.[23,24] Randomized studies performed in European and North American countries investigated the additive effects of oxaliplatin (OX) (FOLFOX or CapeOX) combined with 5-FU + LV in the inhibition of recurrence and improving OS. These findings in these studies indicated that postoperative adjuvant chemotherapy is useful in stage III CRC.[25,26] However, the pros and cons of postoperative adjuvant chemotherapy in stage IV CRC, which is more advanced and associated with higher risks of recurrence, are still controversial.

Several clinical studies have been carried out to investigate the effects of perioperative chemotherapy regimens in the inhibition recurrence in patients with stage IV CRC. Some of them compared hepatectomy alone to hepatectomy in combination with postoperative 5-FU/LV therapy,[6] and one of them was a pooled analysis including the ENG Study.[7] These studies demonstrated that in postoperative chemotherapy arms,

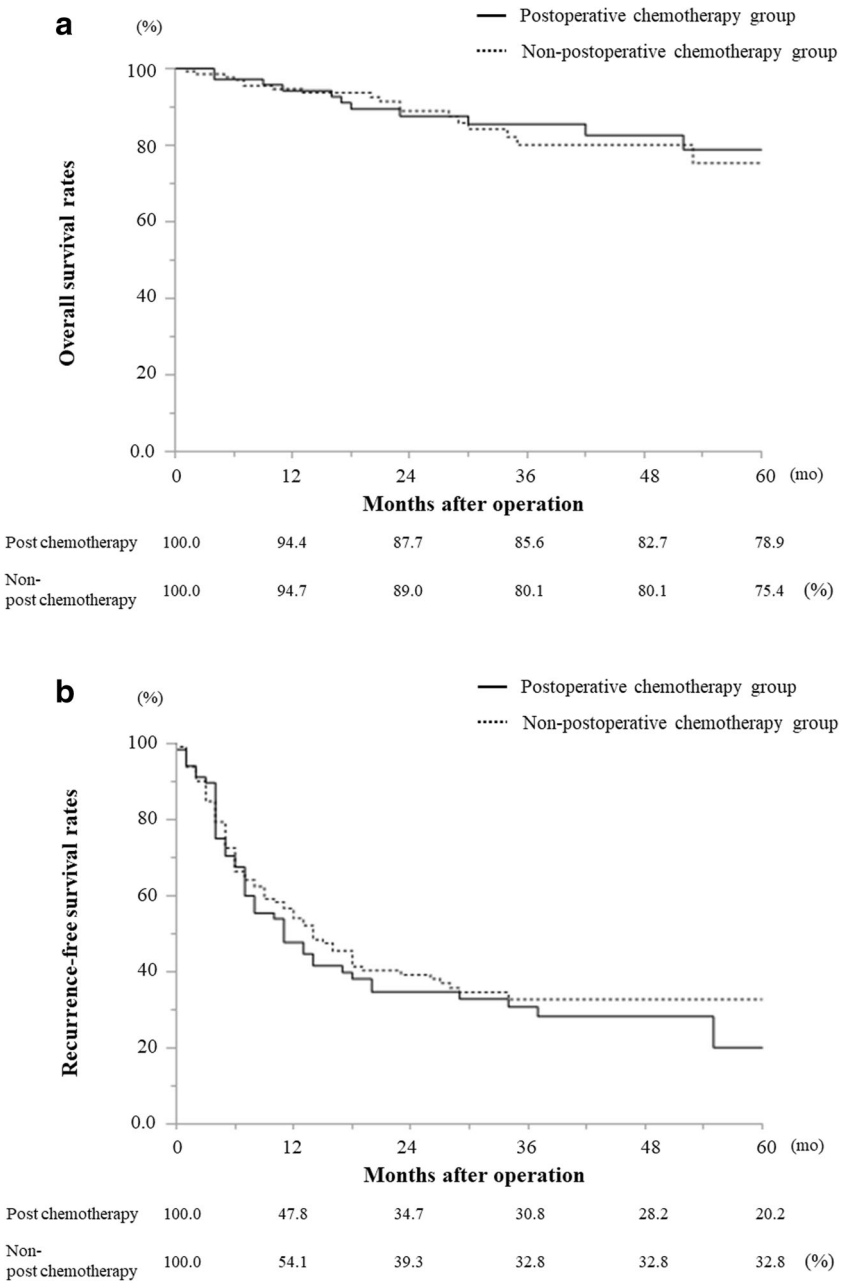


Fig. 2 Surgical outcomes **a** OS, **b** RFS. There was no significant difference between the postoperative chemotherapy group and the group that did not receive postoperative chemotherapy in OS or RFS rates after hepatic resection ($p = 0.770$ and 0.903). *OS* overall survival, *RFS* recurrence-free survival

RFS was prolonged but OS did not change. The reports published so far are concerned with comparisons of outcomes indicated by OS or RFS, whereas the effects of postoperative chemotherapy on the body, including those on remnant liver generation, have rarely been investigated. Under the circumstances in which postoperative chemotherapy is not proven to be beneficial, it is questionable whether it should really be recommended.

Due to recent technical advancements in MDCT, preoperative simulations using 3D-CT have been rapidly spreading in the area of hepatectomy. In the case of major hepatectomy in particular, it is extremely important to accurately predict the postoperative RLV for the purposes of preventing serious complications such as post-hepatectomy liver failure. In this study, the authors used three-dimensional image processing technology to determine the RLV and remnant liver function over time. This is the basis on which we primarily evaluated the effects of postoperative chemotherapy on remnant liver in CLM. Our study results indicated that at all time points during the postoperative follow-up period, irrespective of whether or not postoperative chemotherapy was administered, no differences were noted in recovery rates of RLV or postoperative blood laboratory data. Adequate remnant

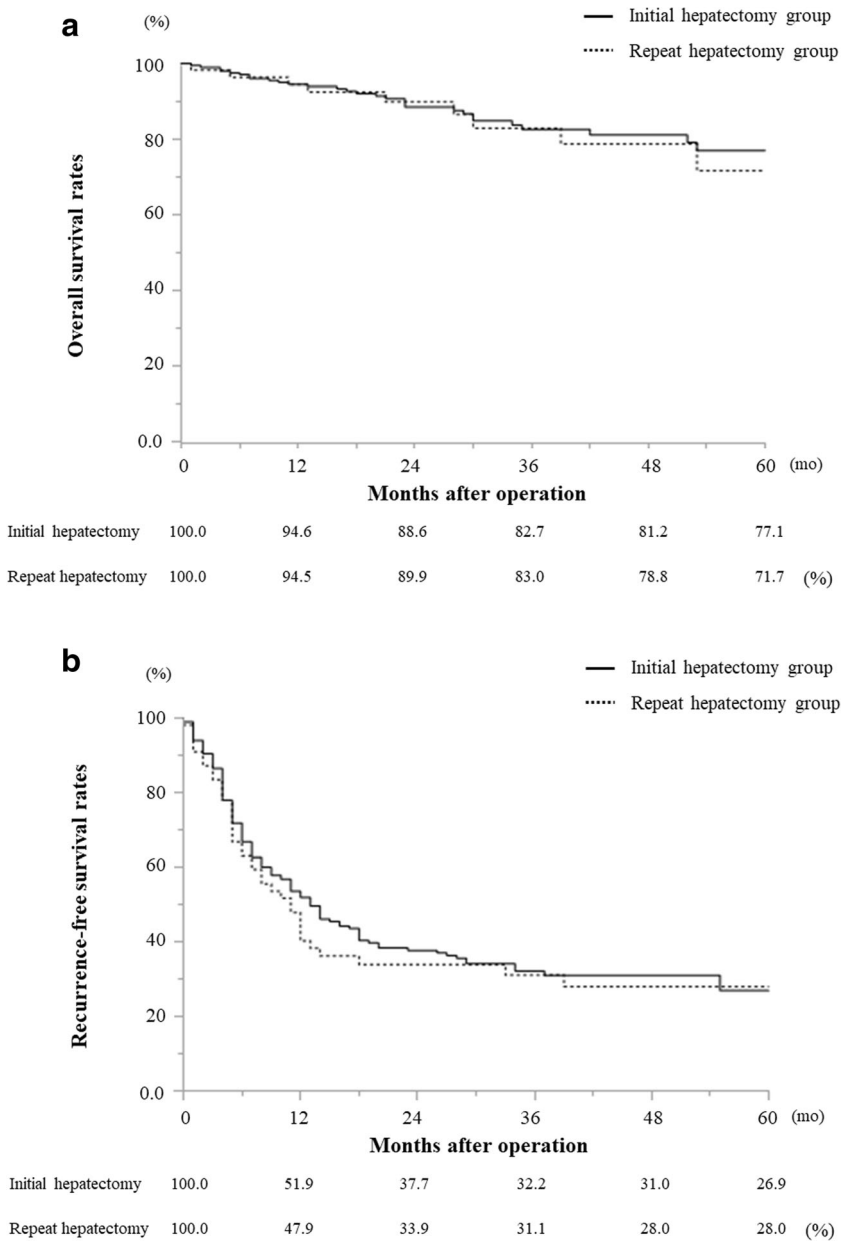


Fig. 3 Surgical outcomes **a** OS, **b** RFS after initial and repeat hepatectomy. There was no significant difference between initial hepatectomy and repeat hepatectomy as to recurrences in the remnant liver in OS or RFS rates after hepatic resection (p = 0.613 and 0.498). *OS* overall survival, *RFS* recurrence-free survival

liver regeneration was achieved. None of the patients in our study gave credence to the idea that postoperative chemotherapy would inhibit the progress of remnant liver regeneration, leading to insufficient RLV the impracticability of conducting repeat hepatectomy for intrahepatic recurrence. The RLV and remnant liver function in our patients were sufficient for conducting second-line therapies including repeat hepatectomy and chemotherapy. These findings are extremely important. In this study, 120 (41.4%) of the 290 patients were recurrent in remnant liver. Sixty-eight (56.7%) patients of intrahepatic recurrences underwent repeat hepatectomy, and the rates of repeat hepatectomy were similar irrespective of whether postoperative chemotherapy was performed. The effects of hepatic resection are similar between patients undergoing repeat hepatectomy and initial hepatectomy. Therefore, repeat hepatectomy is highly likely to be necessary for CLM causing frequent recurrences in remnant liver. Considering the future repeat hepatectomies, it is extremely important to develop a long-term treatment strategy focused on recurrence and adequately preserving the regenerated remnant liver.

The authors previously reported that preoperative chemotherapy also had limitations in its effectiveness.[27] In light of these results, pre- and postoperative chemotherapy may not have an effect on remnant liver regeneration.

This study has the following limitations among others: our postoperative chemotherapy regimens were not standardized; the number of patients included was small; the study population was heterogenous; and the length of the follow-up period was short. We cannot say that the level of evidence obtained from this study is high. Further investigation with accumulated cases, including randomized controlled trials and meta-analyses, will be required.

In conclusion, postoperative chemotherapy for CLM was not inferior with respect to liver volume regeneration and functional recovery. These findings may indicate that conducting postoperative chemotherapy may be of small significance for remnant liver regeneration.

Author Contributions YI conceived the study concept and design, was involved with patient care, and drafted the manuscript. KF, MI, SK, HH, WO, TT, YT, SM, MY, AA, KK, SF, FH, MG, YN, KH, and KU were involved with creation of the study concept and design, patient care, and drafting of the manuscript. All authors have read and approved the final version of the manuscript.

Funding This work was supported by the Mitsui Life Social Welfare Foundation.

Compliance with Ethical Standards

All patients were fully informed of the study design according to the Ethics Committee on Clinical Investigation of Osaka Medical College Hospital (No. 2001 and 2059) and provided their written informed consent to participate.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Suzuki S, Sakaguchi T, Yokoi Y, Kurachi K, Okamoto K, Okumura T, et al. Impact of repeat hepatectomy on recurrent colorectal liver metastases. Surgery 2001;129:421–428.
2. Nakamura S, Suzuki S, Konno H. Resection of hepatic metastases of colorectal carcinoma: 20 years' experience. J Hep Bil Pancr Surg 1999;1:16–22.
3. Pawlik TM, Schlick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. Oncologist 2008;13:51–64.
4. Assumpcao L, Choti MA, Gleisner AL, Schulick RD, Swartz M, Herman J, et al. Patterns of recurrence following liver resection for colorectal metastases. Arch Surg 2008;143:743–749.
5. Malafosse R, Penna Ch, Cunha AS, Nordlinger B. Surgical management of hepatic metastases from colorectal malignancies. Ann Oncol 2001;12:887–894.
6. Portier G, Elias D, Bouche O, Rougier P, Bosset JF, Saric J, et al. Multicentric randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. J Clin Oncol 2006;24(31):4976–4982.
7. Mitry E, Fields AL, Bleiberg H, Labianca R, Portier G, Tu D, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol 2008;26:4906–4911.
8. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–649.
9. Kanemitsu Y, Kato T, Shimizu Y, Inaba Y, Shimada Y, Nakamura K, et al; Colorectal Cancer Study Group (CCSG) of Japan Clinical Oncology Group. A randomized phase II/III trial comparing hepatectomy followed by mFOLFOX6 with hepatectomy alone as treatment for liver metastasis from colorectal cancer: Japan Clinical Oncology Group Study JCOG0603. Jpn J Clin Oncol. 2009 Jun;39(6):406–409.
10. Welsh FK, Tilney HS, Tekkis PP, John TG, Rees M. Safe liver resection following chemotherapy for colorectal metastases is a matter of timing. Br J Cancer 2007;96:1037–1042.
11. Inoue Y, Suzuki Y, Ota M, Fujii K, Kawaguchi N, Shimizu T, et al. Comparison of regeneration of remnant liver after hemihepatectomy with or without the middle hepatic vein. World J Surg 2018;42:1100–1010.
12. Inoue Y, Hayashi M, Komeda K, Masubuchi S, Yamamoto M, Yamana H, et al. Resection margin with anatomic or nonanatomic hepatectomy for liver metastasis from colorectal cancer. J Gastrointest Surg 2012;16:1171–1180.
13. Inoue Y, Imai Y, Osumi W, Shimizu T, Asakuma M, Hirokawa F, et al. What is the optimal timing for liver surgery of resectable synchronous liver metastases from colorectal cancer? Am Surg 2017;83: 45–53.
14. Inoue Y, Imai Y, Fujii K, Hirokawa F, Hayashi M, Uchiyama K. The utility of 5-aminolevulinic acid-mediated photodynamic diagnosis in the detection of intraoperative bile leakage. Am J Surg 2017;213:1077–1082.
15. Couinaud C. Surgical anatomy of the liver. Several new aspects [Article in French]. Chirurgie 1986;112:337–342.
16. Strasberg SM. Nomenclature of hepatic anatomy and resection: a review of the Brisbane 2000 system. J Hepatobiliary Pancreat Surg 2005;12:351–355.
17. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213.
18. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187–196.
19. Koch M, Garden J, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery 2011;149:680–688.
20. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713–724.
21. Arroyo V, Gines P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology 1996;23:164–176.
22. Sobin LH, Gospodarowitz MK, Wittekind C. TNM classification of malignant tumours. 7th ed. New York (NY): Wiley-Blackwell; 2009.
23. Laurie JA, Moertel CG, Fleming TR, Wieand HS, Leigh JE, Rubin J, et al. Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and

fluorouracil. The North Central Cancer Treatment Group and the Mayo Clinic. J Clin Oncol. 1989;7:1447–1456.
24. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990;322:352–358.
25. André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27:3109–3116. https://doi.org/10.1200/JCO.2008.20.6771. Epub 2009 May 18.
26. Schmoll HJ, Cartwright T, Tabernero J, Nowacki MP, Figer A, Maroun J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. J Clin Oncol 2007;25:102–109.
27. Inoue Y, Fujii K, Tashiro T, Ishii M, Masubuchi S, Yamamoto M, et al. Preoperative chemotherapy may not influence the remnant liver regenerations and outcomes after hepatectomy for colorectal liver metastasis. World J Surg 2018 (in press).