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The predictors and oncological outcomes of repeat surgery for recurrence after hepatectomy for colorectal liver metastases

Katsunori Imai[1] · Yo-ichi Yamashita[1] · Yuji Miyamoto[1] · Shigeki Nakagawa[1] · Hirohisa Okabe[1] · Daisuke Hashimoto[1] · Akira Chikamoto[1] · Hideo Baba[1]

Abstract

Purpose Although recurrence after hepatectomy for colorectal liver metastases (CRLM) is common, the optimal treatment strategy remains unclear. The aims of this study were to clarify the impact of repeat surgery and identify the predictive factors for repeat surgery.

Methods Among the 170 patients who underwent potentially curative surgery for CRLM, 113 developed recurrence. The predictive factors for the performance of repeat surgery were identified and a predictive model was constructed.

Results The patterns of recurrence were as follows; single site [$n = 100$ (liver, $n = 61$; lung, $n = 22$; other, $n = 17$)], multiple site ($n = 13$). Repeat surgery was performed in 54 patients (47.8%) including re-hepatectomy ($n = 25$), radiofrequency ablation ($n = 12$), and resection of the extrahepatic recurrent disease ($n = 17$), and their overall survival (OS) was significantly better than that of those who could not (5-year OS 60.7 vs 19.5%, $P < 0.0001$). A multivariate analysis revealed that a primary N-negative status [relative risk (RR) 2.93, $P = 0.017$], indocyanine retention rate at 15 min ≤ 10% before hepatectomy (RR 2.49, $P = 0.04$), and carcinoembryonic antigen ≤ 5 ng/mL before hepatectomy (RR 2.96, $P = 0.017$) independently predicted the performance of repeat surgery. For patients who did not present any factors, the probability of repeat surgery was 19.6%. The addition of each subsequent factor increased the probability to 41.9, 67.8, and 84.0% (for 1, 2, and 3 factors, respectively).

Conclusions Repeat surgery for not only intrahepatic but also extrahepatic recurrence is crucial for prolonging the survival of CRLM patients. The proposed model may help to predict the possibility of repeat surgery and provide optimal individualized treatment.

Keywords Colorectal liver metastases · Hepatectomy · Repeat surgery · Predictive model

Introduction

Colorectal cancer is the third most common form of malignancy in the world [1]. The liver is the most common site of metastasis and approximately 50% of patients with colorectal cancer develop liver metastasis at some point during their disease course [2–4]. Surgical resection in combination with systemic chemotherapy is currently the treatment of

✉ Katsunori Imai
katsuimai@hotmail.com

1 Department of Gastroenterological Surgery, Graduate School of Life Sciences, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan

choice and can offer the possibility of long-term survival or a cure. However, more than half of the patients with colorectal liver metastases metastasis (CRLM) develop recurrence after hepatectomy—in the majority of such cases, recurrence takes place within 2 years [5–7].

Repeat surgery for recurrence after hepatectomy has been shown to carry a survival benefit [8–13], even in patients with early recurrence [14]. However, recent advances in oncosurgical approaches, consisting of aggressive surgery for intrahepatic, extrahepatic, and recurrent disease, perioperative chemotherapy and the advent of specific treatment techniques such as radiofrequency ablation (RFA), portal vein embolization, and two-stage hepatectomy—which may facilitate curative treatment in specific settings—have dramatically changed the treatment strategy for patients with recurrence after hepatectomy for CRLM. Thus, the indications and the outcomes of resection in patients with recurrent

disease remain uncertain and the patients who are very probable to be able to receive repeat surgery for recurrent disease have not yet been identified.

The aim of the present study was to clarify the oncological benefit of repeat surgery for recurrence after hepatectomy for CRLM. We also identified the predictive factors and developed a predictive model for the performance of repeat surgery.

Patients and methods

Patients who underwent curative-intent hepatectomy for CRLM between September 2000 and April 2016 at Kumamoto University Hospital, Kumamoto, Japan, were retrospectively identified from a prospectively maintained database. Patients who underwent repeat surgery for CRLM were excluded. Additional information was supplemented from a review of the medical records of each patient. This study was approved by the Human Ethics Review Committee of the Graduate School of Life Sciences, Kumamoto University, Kumamoto, Japan. Written informed consent was obtained from all the patients prior to treatment.

The preoperative workup

Before hepatectomy, all patients underwent routine laboratory tests, including the measurement of the serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 levels, and liver function tests, including the indocyanine retention rate at 15 min (ICG-R15) and ^{99m}Tc-galactosyl human serum albumin (GSA) scintigraphy. Routine imaging modalities, including ultrasonography (US), enhanced computed tomography (CT), and magnetic resonance imaging (MRI), were performed to determine the disease stage. Preoperative chemotherapy was administered to patients with initially unresectable or marginally resectable disease, including those with concomitant extrahepatic disease in a conversion setting, or to patients with disease that was thought to be highly malignant (including those who were diagnosed synchronously, patients with a greater number of tumors, and patients with higher of tumor marker levels) in a neoadjuvant setting [15]. The response to chemotherapy was evaluated by CT, according to the Response Evaluation Criteria in Solid Tumors (RECIST) [16, 17].

Surgery

The objective of surgery was to remove all detectable lesions with a tumor-free margin. The type of hepatectomy was based on the preoperative imaging findings, intraoperative US, and the liver functional reserve [15]. In principal, non-anatomical partial hepatectomy was selected if the tumor

location allowed. Portal vein embolization was performed if the future remnant liver was too small. RFA during hepatectomy was performed to treat unresectable or tumors that were located deep within the remnant liver to spare the liver parenchyma (in principle for metastatic tumors of ≤ 2 cm in size) [18]. In case with concomitant extrahepatic disease, sequential resection was considered when both sites were deemed to be resectable.

The postoperative workup

After treatment, all patients underwent regular follow-up examinations with imaging and their tumor marker levels were estimated. Postoperative chemotherapy was usually recommended.

The treatment strategy for recurrence after hepatectomy was basically same with the first hepatectomy; that is, recurrent disease was treated surgically only when the overall strategy was considered to be potentially curative, often in combination with chemotherapy. For intrahepatic recurrence, as with the first hepatectomy, hepatectomy with a tumor-free margin was indicated as a first-line choice. RFA was used for the treatment of unresectable or deeply located tumors which required extended resection. For extrahepatic recurrence, surgical resection was considered when the tumors were deemed to be resectable and controllable under chemotherapy.

Statistical analysis

Continuous variables were expressed as the median (range) and were compared using the Mann–Whitney U test. Categorical variables were compared using the χ^2 test. Survival analyses were performed using the Kaplan–Meier method and the results were compared using the log-rank test. Overall survival (OS) was calculated from the date of initial hepatectomy until death or last follow-up. Disease-free survival (DFS) was calculated from the date of initial hepatectomy or the last potentially curative surgery for concomitant extrahepatic disease (if present) until the date of recurrence or death. For the univariate analysis of the factors that predicted repeat surgery, the optimal cutoff values of the continuous variables for differentiation between the groups were determined based on a receiver operating characteristics (ROC) analysis. For CEA, CA19-9, and ICG-R15, the upper limit of the normal range (CEA 5 ng/mL, CA19-9 37 U/mL, ICG-R15 10%) was used as a cutoff value because the cutoff values that were determined by the ROC analysis were lower than their upper limit of the normal range. Variables for which the P value in the univariate analysis was < 0.10 were included in a subsequent multivariate logistic regression analysis using a stepwise backward elimination procedure. A predictive

model was then created based on the results of the multivariate logistic analysis. To identify independent prognostic factors, multivariate cox regression analysis was performed using a stepwise backward elimination procedure. All the statistical analyses were performed using the JMP (SAS institute, Cary, NC, USA) and R (version 3.1.1; http://www.r-project.org) software programs. *P* values of < 0.05 were considered to indicate statistical significance.

Results

Among the 193 patients who underwent hepatectomy for CRLM during the study period, 179 patients underwent initial hepatectomy and were eligible for inclusion in the present study (whole cohort). The demographic and clinical characteristics of study patients are summarized in Table 1. There were 117 male patients and 62 female patients; the median age of the patients was 64 (range 25–94) years. The

Table 1 Demographic and clinical characteristics of study patients

	No. of patients ($n = 179$)
Age	63.1 ± 11.0
Gender (male/female)	117/62
Primary location (colon/rectum)	108/71
Primary T (1–2/3–4)	17/155
Primary N (0/1–2)	67/105
Timing of liver diagnosis (synchronous/metachronous)	105/74
Bilobar distribution	70 (39.3%)
Major hepatectomy (≥ 3 segments)	46 (25.7%)
Simultaneous colorectal resection	43 (24.0%)
Portal vein embolization	13 (7.3%)
Laparoscopic hepatectomy	31 (17.4%)
Concomitant use of RFA	26 (14.5%)
Blood loss (mL)	380 (0–4500)
Operating time (min)	426 (90–1222)
Red blood cell transfusion	15 (8.3%)
Major complication (Clavien ≥ III)	40 (22.3%)
Tumor size (mm)	28 (3–160)
Tumor number	2 (1–19)
ICG-R15 (%)	9.5 (0–36.5)
^{99m}Tc-GSA LHL15	0.94 (0.77–0.98)
CEA (ng/mL)	7.1 (0.5–2061.1)
CA19-9 (U/mL)	19.2 (0.1–1756)
KRAS mutation[a]	29 (31.9%)
Preoperative chemotherapy	96 (53.6%)
Chemotherapy cycle	6 (2–38)
Chemotherapy line	1 (1–3)
Chemotherapy regimens	
1st-line (oxaliplatin/irinotecan/both/FU-LV/others)	86/3/1/5/1
2nd-line (oxaliplatin/irinotecan/both/FU-LV/others)	3/17/0/1/2
Use of biologic agents	58 (60.4%)
Initially unresectable disease	41 (23.0%)
Concomitant extrahepatic disease	14 (7.8%)
Adjuvant chemotherapy	86 (48.0%)
Globally curative surgery	170 (95.0%)
Recurrence	113 (66.5%)

[a]Available in 91 patients

RFA radiofrequency ablation, *ICG-R15* indocyanine retention rate at 15 min, *GSA* galactosyl human serum albumin, *LHL15* uptake ratio of the liver to the liver plus heart at 15 min, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9

primary tumor was located in the colon in 108 patients and in the rectum in 71 patients. Liver metastases were diagnosed synchronously (before, during or within 6 months after colorectal resection) in 105 (58.7%) patients and bilobar distribution was observed in 70 (39.3%) patients. The median number of tumors was 2 (1–19) and the median tumor size was 28 (3–160) mm. Concomitant extrahepatic disease was present in 14 (7.8%) patients; the locations included the lung ($n = 9$), lymph nodes ($n = 3$), colorectal local ($n = 1$), and lung + bone ($n = 1$). Preoperative chemotherapy was administered to 96 patients (53.6%), with a median number of 1 line (range 1–3) and 6 cycles (range 2–38). Oxaliplatin-based chemotherapy was administered in most of the patients who received preoperative chemotherapy (89.6%). Biologic agents were used for 58 patients (60.4%).

The median length of follow-up was 43.0 (3–147) months after the diagnosis of CRLM and 36.5 (0.4–146) months after hepatectomy. Nine patients could not undergo curative surgery because their concomitant extrahepatic disease was not resected. The cumulative OS at 1, 3, and 5 years was 94.7, 69.1 and 51.9%, respectively, while the cumulative DFS was 45.0, 30.3 and 21.4% (Fig. 1).

Repeat surgery for recurrence

Of the 179 patients who underwent first hepatectomy for CRLM, 170 patients underwent potentially curative surgery. Among them, 113 patients (66.5%) developed recurrence after hepatectomy during the study period. Even in patients with recurrence, the 5-year OS rate after hepatectomy was 38.4%. The sites of the first recurrence are summarized in Table 2. One hundred patients (88.5%) developed single site recurrence [liver ($n = 61$), lung ($n = 22$), lymph node ($n = 9$), and other ($n = 8$)], while 13 patients developed multiple site recurrence. Numbers of recurrent tumor in total, liver, and lung were 2 (1–37), 2 (1–24), and 2 (1–37), and sizes of recurrent tumor in total, liver, and lung were 17 mm (3–130), 18 mm (5–65), and 7 mm (3–40), respectively. CEA and
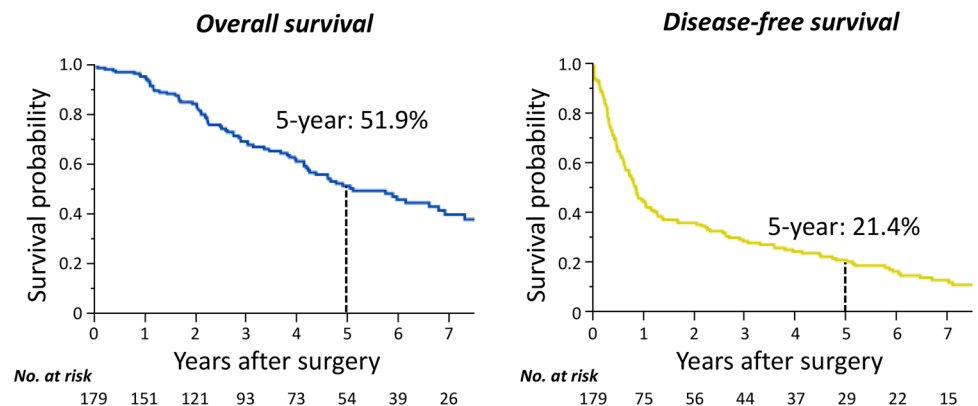
Table 2 Features of first recurrence tumor after hepatectomy

Number of recurrence site	
Single site ($n = 100$)	
Liver	61
Lung	22
Lymph node	9
Pelvis	2
Peritoneum	1
Colorectal local	1
Adrenal gland	1
Abdominal wall	1
Bone	1
Bile duct	1
Multiple sites ($n = 13$)	
Liver + lung	5
Liver + peritoneum	2
Liver + bone	1
Liver + adrenal gland	1
Peritoneum + lymph node	1
Peritoneum + ovary	1
Liver + lung + peritoneum	2
Number of recurrent tumor	
Total ($n = 113$)	2 (1–37)
Liver ($n = 72$)	2 (1–24)
Lung ($n = 29$)	2 (1–37)
Size of recurrent tumor	
Total ($n = 113$)	17 (3–130)
Liver ($n = 72$)	18 (5–65)
Lung ($n = 29$)	7 (3–40)
Tumor markers at recurrence	
CEA (ng/mL)	5.3 (0.5–490)
CA19-9 (U/mL)	17.6 (0.1–1200)

CEA carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9

CA19-9 levels at recurrence were 5.3 ng/mL (0.5–490) and 17.6 U/mL (0.1–1200), respectively. For the first recurrence, potentially curative repeat surgery could be performed in

Fig. 1 Overall and disease-free survival after initial hepatectomy in the whole cohort ($n = 179$). **a** Overall survival, **b** disease-free survival

Overall survival

Survival probability — 5-year: 51.9%
Years after surgery

No. at risk
179 151 121 93 73 54 39 26

Disease-free survival

Survival probability — 5-year: 21.4%
Years after surgery

No. at risk
179 75 56 44 37 29 22 15

54 patients (47.8%). The detailed information regarding the procedures of repeat surgery is summarized in Table 3. Among the patients who underwent repeat surgery for recurrence, 38 patients (70.4%) received perioperative chemotherapy, including before (28 patients, 51.9%) and/or after (20 patients, 37.0%) repeat surgery. The OS in patients who underwent repeat surgery was significantly better than that in those who did not (5-year OS rate 60.7 vs. 19.5%; $P < 0.0001$, Fig. 2). Multivariate cox regression analyses identified repeat surgery for recurrence as one of the independent prognostic factors for OS in patients who developed recurrence (hazard ratio: 0.17, 95% confidence interval 3.41–10.96, $P < 0.0001$) (Supplementary Table 1).
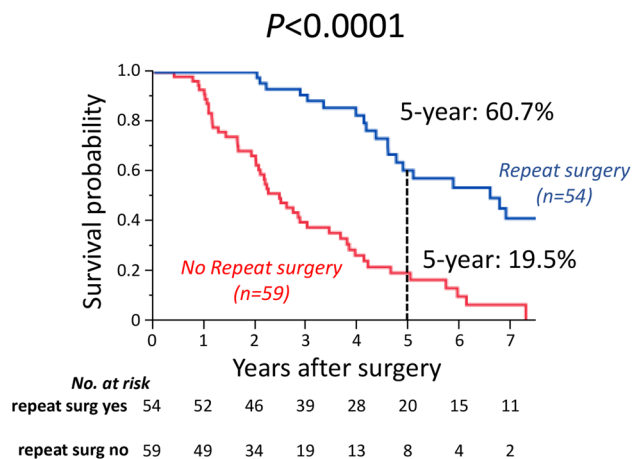

Fig. 2 Overall survival after initial hepatectomy in patients who underwent repeat surgery ($n = 54$) vs. those who did not ($n = 59$)

Table 3 Procedures of repeat surgery and perioperative chemotherapy for first recurrence

Procedure of repeat surgery	
Liver	
Hepatectomy	21
Hepatectomy + RFA	3
Hepatectomy + resection of peritoneal metastasis	1
RFA for liver metastasis	8
RFA for liver + lung metastasis	1
Lung	
Resection of lung metastasis	10
RFA for lung metastasis	2
Others	
Resection of lymph node metastasis	2
Resection of adrenal gland metastasis	1
Resection of pelvic metastasis	1
Resection of abdominal wall metastasis	1
Resection of bile duct metastasis	1
Resection of peritoneum + ovarian metastasis	1
RFA for bone metastasis	1
Perioperative chemotherapy	38 (70.4%)
Preoperative chemotherapy	28 (51.9%)
Oxaliplatin-based chemotherapy	4
Oxaliplatin-based chemotherapy + biologic agents	5
Irinotecan-based chemotherapy	2
Irinotecan-based chemotherapy + biologic agents	12
Oxaliplatin and irinotecan-based chemotherapy + biologic agents	1
Others	4
Postoperative chemotherapy	20 (37.0%)
Oxaliplatin-based chemotherapy	9
Oxaliplatin-based chemotherapy + biologic agents	1
Irinotecan-based chemotherapy	0
Irinotecan-based chemotherapy + biologic agents	1
Oxaliplatin and irinotecan-based chemotherapy + biologic agents	0
Others	9

RFA radiofrequency ablation

Predictive factors for repeat surgery

Table 4 shows the results of the univariate and multivariate analyses of the factors related to the performance of repeat surgery for recurrence. According to the univariate analysis, age ≤60 years, a primary N-negative status, CEA at hepatectomy ≤ 5 (ng/mL), CA19-9 at hepatectomy ≤ 37 (U/mL), ICG-R15 ≤ 10 (%), the uptake ratio of the liver to the liver plus heart at 15 min (LHL15; determined by ^{99m}Tc-GSA scintigraphy) > 0.92, non-early recurrence (> 8 months [14]), and single site recurrence were associated with the performance of repeat surgery ($P < 0.10$). The multivariate logistic regression analysis identified a primary N-negative status [relative risk (RR) 2.93, $P = 0.017$], ICG-R15 ≤ 10 (%) (RR 2.49, $P = 0.04$), and CEA ≤ 5 (ng/mL) at hepatectomy (RR 2.96, $P = 2.96$) as independent predictive factors for the performance of repeat surgery. These factors were available before hepatectomy for CRLM.

Table 4 Univariate and multivariate analyses of the factors related to performing a repeat surgery for recurrence

	Repeat surgery ($n = 54$)	No repeat surgery ($n = 59$)	P	RR	95% CI	P
Factors at first hepatectomy						
Age < 60	42 (71.2%)	30 (55.6%)	0.0838	NS		
Primary location (colon/rectum)	32/22	34/25	0.860			
Primary T (1–2/3–4)	5/48	4/52	0.664			
Primary N (0/1–2)	24/30	16/41	0.0718	2.93	1.21–7.38	0.0169
Timing of liver diagnosis (synchronous/ metachronous)	31/23	39/20	0.342			
Bilobar distribution	26 (49.1%)	23 (39.0%)	0.283			
Major hepatectomy (≥ 3 segments)	11 (20.4%)	16 (27.1%)	0.400			
Simultaneous colorectal resection	14 (25.9%)	14 (23.7%)	0.787			
Portal vein embolization	3 (5.6%)	5 (8.5%)	0.543			
Laparoscopic hepatectomy	10 (18.9%)	7 (11.9%)	0.302			
Concomitant use of RFA	8 (14.8%)	12 (20.3%)	0.441			
Blood loss ≤ 400 (mL)	26 (48.2%)	31 (52.5%)	0.641			
Operating time ≤430 (min)	29 (53.7%)	27 (45.8%)	0.399			
Red blood cell transfusion	4 (7.4%)	5 (8.5%)	0.834			
Major complication (Clavien ≥ III)	15 (27.8%)	15 (25.4%)	0.777			
Tumor size ≤ 30 (mm)	31 (57.4%)	31 (52.5%)	0.604			
Tumor number ≤ 3	36 (66.7%)	34 (42.4%)	0.322			
ICG-R15 ≤ 10 (%)	34 (70.8%)	26 (48.2%)	0.0193	2.49	1.04–6.20	0.0399
^{99m}Tc-GSA LHL15 ≥ 0.92	38 (77.6%)	32 (59.3%)	0.0452	NS		
CEA ≤ 5 (ng/mL)	25 (47.2%)	14 (23.7%)	0.009	2.96	1.21–7.58	0.0172
CA19-9 ≤ 37 (U/mL)	43 (79.6%)	35 (59.3%)	0.0185	NS		
Preoperative chemotherapy	28 (51.9%)	36 (61.0%)	0.326			
Initially unresectable disease	14 (25.9%)	14 (23.7%)	0.787			
Use of biologic agents	17 (60.7%)	21 (58.3%)	0.847			
Chemotherapy cycles ≤ 8	16 (57.1%)	22 (61.1%)	0.749			
Chemotherapy line ≤ 1	20 (71.4%)	28 (77.8%)	0.562			
1st-line response (CR or PR)	16 (57.1%)	21 (58.3%)	0.924			
Last-line response (CR or PR)	20 (71.4%)	23 (63.9%)	0.523			
Concomitant extrahepatic disease	3 (5.6%)	3 (5.1%)	0.911			
Adjuvant chemotherapy	30 (55.6%)	30 (50.9%)	0.616			
Factors at recurrence						
Early recurrence (< 8 months)	22 (40.7%)	39 (66.1%)	0.0066	NS		
Multiple site recurrence	3 (5.6%)	10 (17.0%)	0.0514	NS		
Liver-only recurrence	32 (59.3%)	29 (49.2%)	0.281			

RFA radiofrequency ablation, *ICG-R15* indocyanine retention rate at 15 min, *GSA* galactosyl human serum albumin, *LHL15* uptake ratio of the liver to the liver plus heart at 15 min, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *CR* complete response, *PR* partial response, *RR* relative risk, *CI* confidence interval, *NS* not significant

The predictive model for the performance of repeat surgery

We subsequently created a predictive model for predicting the performance of repeat surgery for recurrence based on the 3 independent predictive factors that were identified in the multivariate logistic regression analysis. For patients without any factors, the probability of performing repeat surgery was 19.6%. The addition of each predictive factor increased the probability to 41.9% for 1 factor, 67.8% for 2 factors, and 84.0% for 3 factors (Table 5). The c-index, a measure of model discrimination represented by the area under the ROC curve, was 0.72. According to the number of predictive factors present, the 5-year OS rates after hepatectomy were 71.1% for a score of 0, 37.3% for a score of 1, 48.0% for a score of 2, and 10.8% for a score of 3.

Discussion

In the current study, of the 179 patients who underwent initial hepatectomy for CRLM, 170 patients could undergo potentially curative surgery. Among them, 113 patients (66.5%) experienced recurrence. Among them, potentially curative repeat surgery could be performed in 54 patients (47.8%) and their OS was significantly better than that in the patients in whom repeat surgery could not be performed. A primary N-negative status, normal ICG-R15 and a CEA value within the normal range before hepatectomy were identified as independent predictive factors for the performance of repeat surgery.

Complete resection is obviously the treatment of choice for resectable CRLM. However, the majority of patients with CRLM will experience recurrence after hepatectomy, mainly in the liver and lung [6, 7, 19]. Repeat hepatectomy for recurrence has been reported to be associated with an equivalent long-term outcome to initial hepatectomy, with a similarly low surgical risk [9–11, 20–25]; thus, its role in the treatment of metastatic colorectal cancer has recently been established. Nevertheless, the analyses of these studies only included patients undergoing repeat hepatectomy for intrahepatic recurrence. Considering the fact that recurrence after hepatectomy for CRLM can develop outside of the remnant liver, repeat surgery for extrahepatic recurrence should also be taken into account when investigating the long-term outcomes after hepatectomy for CRLM.

Some previous studies have reported that repeat surgery for recurrence (including extrahepatic recurrences) after hepatectomy provides favorable long-term outcomes and identified it as a prognostic factor in patients with CRLM [12, 13, 26–28]. In their studies, the rates of repeat surgery for intra- and extrahepatic recurrence after initial hepatectomy were reported to be ranged from 27 to 67%, and the 5-year OS rate ranged from 45 to 70%. Similarly, in the present study, repeat surgery could be performed in approximately half of the patients with recurrence and their 5-year OS reached 60.7%—which was significantly better than that of those who did not undergo repeat surgery. In the present study, repeat surgery was performed for recurrence in the liver (59.3%), lung (22.2%), other sites (13.0%), and multiple sites (5.6%). Our first choice of treatment strategy for metastatic disease from colorectal cancer was to perform surgical resection in combination with perioperative chemotherapy. Indeed, 78.2% of the patients in the whole cohort received perioperative chemotherapy before and/or after hepatectomy, and 70.4% of the patients who developed recurrence after hepatectomy received repeat surgery with perioperative chemotherapy. Although the prognostic role of perioperative chemotherapy remains controversial, these findings suggest that an aggressive oncosurgical approach can achieve a high repeat surgery rate and prolonged long-term survival.

The current study identified three independent predictive factors for the performance of repeat surgery: a primary N-negative status, ICG-R15 ≤ 10 (%), and CEA ≤ 5 (ng/mL) at hepatectomy (Table 4). Interestingly, the factors related to recurrence such as early recurrence, liver-only recurrence, and the number of site of recurrence were not independent predictive factors. Likewise, the administration of adjuvant chemotherapy after hepatectomy did not significantly affect the performance of repeat surgery. All three of the factors identified in this study were available before hepatectomy and the predictive model revealed that the presence of these three factors was associated with an increasing probability of repeat surgery; repeat surgery was performed in 84% of the patients in whom all three factors were present (Table 5). In the modern era, in addition to the current disease state of patients with metastatic colorectal cancer, future disease should be anticipated and

Table 5 The predictive model estimating the probability of performing a repeat surgery

Factors	Primary N0	ICG-R15 < 10 (%)	CEA < 5 (ng/mL)	Probability (%)
0	−	−	−	19.6
1	+	−	−	41.6
	−	+	−	37.7
	−	−	+	41.9
2	+	+	−	63.9
	−	+	+	64.2
	+	−	+	67.8
3	+	+	+	84.0

ICG-R15 indocyanine retention rate at 15 min, *CEA* carcinoembryonic antigen

subsequent recurrence should be taken into account when determining the treatment strategy. Thus, the proposed predictive model may be useful for providing optimal individualized treatment for patients who are expected to be able to undergo repeat surgery. We should consider the further treatment for recurrent disease which is strongly expected after curative surgery throughout the course of this disease.

In the current study, in addition to the primary N stage and CEA, the ICG-R15 value was significantly associated with the performance of repeat surgery. Although it is difficult to describe clearly, one of the possible reasons for this is that an impaired liver function after major hepatectomy or prolonged chemotherapy might limit the ability to perform subsequent repeat surgery. Obviously, the main site of recurrence after hepatectomy is the liver. Indeed, in the present study, a total of 72 out of 113 patients (63.7%) had intrahepatic recurrence (Table 2). Mise et al. recently reported that parenchyma-sparing hepatectomy increased the likelihood of repeat hepatectomy for liver recurrence and improved survival in patients with CRLM [29]. Although the current study failed to demonstrate the association between the performance of major hepatectomy and repeat surgery, the effort to preserve liver parenchyma during hepatectomy may be crucial for enabling repeat surgery in patients with CRLM. Another consideration is that impaired liver function might be due to prolonged chemotherapy prior to hepatectomy. The patients who required prolonged chemotherapy would have more extensive and/or chemotherapy-resistant diseases. These might be associated with lower rate of repeat surgery.

The present study is associated with some limitations, namely the retrospective nature of the study, the small sample size and the fact that it was performed in a single institution. In addition, the follow-up period was relatively short. In the modern chemotherapy era, the survival of patients with metastatic colorectal cancer is gradually increasing; thus, patients with metastatic colorectal cancer now have a greater chance of undergoing repeat surgery during their disease course, even after previous repeat surgery or prolonged chemotherapy. A validation study using an external cohort will be necessary to confirm the usefulness of the proposed predictive model. Finally, a selection bias may exist due to its retrospective nature of this study. However, the policy for the treatment of metastatic disease from colorectal cancer has not significantly changed during the study period. At this time, it would be very difficult to establish the patient selection criteria for repeat surgery after hepatectomy for CRLM. Further prospective large-size studies would be required for the development of appropriate treatment strategy for recurrence after hepatectomy for CRLM.

Conclusion

Repeat surgery for not only intrahepatic recurrence but also extrahepatic recurrence is crucial for prolonging the survival of CRLM patients after initial hepatectomy. The proposed model may help to predict the possibility of repeat surgery and enable the provision of optimal individualized treatment.

Compliance with ethical standards

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