Survival benefit of repeat resection of successive recurrences after the initial hepatic resection for colorectal liver metastases

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Background. *Relapse is common after the resection of colorectal liver metastases (CLM); however, the optimal treatment for such recurrent disease remains uncertain. We investigated whether repeat resections for successive recurrences of CLM provide survival benefit on the postrecurrence survival.*
Methods. *We reviewed patients who underwent upfront, curative resection for CLM at our center during a 15-year period. Of these, 263 patients who had not received any other perioperative treatment for the metastases were eligible for our analysis. The recurrence-free survival (RFS_0) after the initial hepatic resection and after the first (n = 108), second (n = 43), and third (n = 15) repeat resections for recurrent disease were assessed ($RFS_{1–3}$). The overall survival after the initial hepatic resection and the postrecurrence survival (n = 198) also was assessed.*
Results. *The median RFS_0 was 0.8 years, and RFS_1, RFS_2, and RFS_3 were 1.3, 1.1, and 2.0 years, respectively. The hazard ratio for RFS for the first, second, and third resections versus the initial hepatic resection was 0.9 (95% confidence interval [95% CI] 0.7–1.1; P = .34), 1.00 (95% CI 0.7–1.4; P = .97), and 0.7 (95% CI 0.4–1.3; P = .29). The 5-year and 10-year OS rates were 54.6% and 42.2%, and the 5-year and 10-year postrecurrence survival was 34.3% and 28.6%, respectively.*
Conclusion. *Repeat resection in patients with recurrent disease after CLM resection is beneficial, offering the potential for cure in a small proportion of patients with recurrent disease. (Surgery 2016;159:632-40.)*

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Hepatic resection is the only treatment that offers the possibility of cure or long-term survival benefit; 5-year survival rates of more than 40% have been reported in patients with resectable colorectal liver metastases (CLMs), as demonstrated by recent larger series.[1-6] Nonetheless, more than 70% of patients with CLM who undergo curative resection develop recurrent disease, and the majority of these recurrences occur during the early postoperative phase, ie, within the first 2 years after the initial hepatic resection.[3,5-7] In the era of modern chemotherapy, the necessity of developing adjuvant therapies has been emphasized to improve the outcomes of patients with resectable CLM; however, lack of a significant impact on the overall survival (OS)[8-12] has made it difficult to select definitive strategies.

The long-term outcomes of patients with CLM seem to be composite, because the postrecurrence survival (PRS) is influenced strongly by the treatment modality adopted for the further recurrences involving operative or nonoperative therapy with chemotherapy, ablation therapy, hepatic arterial infusion therapy, etc.

With regard to operative management after recurrence relapse, for selected patients, repeated hepatic resections for successive hepatic recurrences after the initial liver resection for CLM

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are accepted as a feasible strategy that can prolong survival.[13-16] In the patients with relapse after the initial hepatic resection, the recurrences were distributed relatively equally among the liver, lung, and liver and lung concurrently,[3] and patients with pulmonary or pulmonary with hepatic recurrence had poorer prognoses than those with isolated intrahepatic recurrence, as reported previously by our colleagues.[7] It remains unclear whether sequential operative management for successive recurrences provides survival benefit after relapse. Furthermore, the actual benefit of repeated resections alone without chemotherapy for successive recurrences in colorectal cancer patients is still to be confirmed.

Therefore, we hypothesized that repeat resections for successive recurrences might be an optimal therapeutic strategy that could have positive prognostic impact on the PRS after an initial CLM resection. To minimize any selection bias, we compared the survival results in consecutive patients undergoing the first, second, and third repeat resections with those in patients undergoing optimal nonoperative treatment for unresectable recurrences in the same treatment-line, based on data accumulated through strict long-term follow-up during a 15-year period at a single specialized center of patients treated by resection for the initial CLM.

MATERIALS AND METHODS

Patients and treatment. The data collected during a 15-year period (January 1996–December 2010) of 336 patients who underwent upfront curative hepatic resection for CLM at the Hepato-Biliary-Pancreatic Surgery Division of the Tokyo University Hospital, Japan were reviewed. Of these, 33 patients who received postoperative adjuvant chemotherapy (which was not administered routinely during this study period, but rather selectively, at the doctors' discretion or the patient's request) and 40 patients who were enrolled in an ongoing, phase 3 trial to evaluate the efficacy of oral adjuvant chemotherapy with uracil-tegafur plus leucovorin after resection of CLM (UMIN Clinical Trials Registry: C000000013) were excluded from the current study.[17] The remaining 263 patients were eligible for the analysis (Fig 1).

Because sufficient evidence for the efficacy of standard adjuvant treatment during the study period was lacking at the time in Japan, adjuvant chemotherapy was not administered routinely between 1996 and 2010 until recruitment for the uracil-tegafur plus leucovorin trial was completed. The following data of these 263 patients were analyzed: sex, age, performance status, primary tumor site, histologic differentiation (grade), pathologic T and N stages according to the current TNM (ie, tumor, nodes, metastases) classification, characteristics of the initial liver metastases, type of hepatic resection, operative margin, date of development of recurrence, dates of the repeat resections, and the date of death or of the last visit.

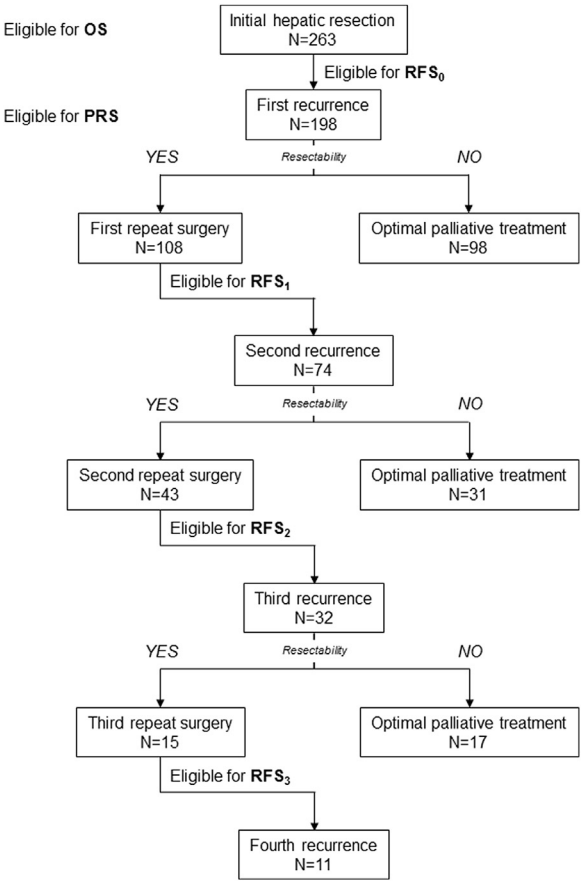

Fig 1. Study profile. *Yes*, recurrence, resectable; *No*, recurrence, unresectable.

Table I shows the profiles of the current study patients at the baseline. The resected liver metastases were diagnosed synchronously with the primary tumor in 142 patients (54%). Major hepatic resection was defined as the resection of 3 or more segments, as described by Couinaud. Of the 263 patients enrolled, 69 (26%) underwent major hepatic resection, and 194 (73%) underwent minor hepatic resection. All the patients were assessed preoperatively by contrast-enhanced computed tomography (CT), and the selection criteria for reoperation were as follows: (1) primary lesion resectable or curatively resected; (2) all the liver metastases were amenable to complete resection with a clear margin, allowing an acceptable remnant liver volume of at least 40% without

Table I. Patient and tumor characteristics at baseline

Variable	*Characteristic*	*Study patients* (n = *263*)
Sex, *n* (%)	Male/female	172 (65)/91 (35)
Age	Median (range)	62 (29–81)
ECOG PS, *n* (%)	0/1	253 (96)/10 (4)
Primary tumor, *n* (%)		
Location	Colon/rectum	147 (56)/116 (44)
Grade of differentiation	Grade 1/Grade 2/Grade 3–4	135 (51)/124 (47)/4 (2)
pT stage	T1–2/T3/T4	23 (9)/189 (72)/51 (19)
pN stage	N0/N1/N2	98 (37)/90 (34)/75 (29)
Initial liver metastases, *n* (%)		
Timing of diagnosis	Synchronous/metachronous	142 (54)/121 (46)
Tumor distribution	Unilobar/bilobar	156 (59)/107 (41)
Tumor number	1–4/5–8/≥9	194 (74)/40 (15)/29 (11)
Size of the largest tumor, cm	<2/2–5/≥5	50 (19)/129 (49)/84 (32)
Preoperative serum CEA, μg/L	<50/50–200/≥200	160 (61)/47 (18)/56 (21)
Type of hepatic resection, *n* (%)	Major/minor	69 (26)/194 (74)
	Preoperative PVE	16 (6)
Resectability, *n* (%)	R0/R1	231 (88)/32 (12)

CEA, Carcinoembryonic antigen; *ECOG PS*, Eastern Cooperative Oncology Group performance status; *Grade 1*, well differentiated adenocarcinoma; *Grade* 2, moderately differentiated adenocarcinoma; *Grade 3–4*, poorly differentiated adenocarcinoma; *pT and pN*, pathologic stage of the primary tumor (T) and regional lymph nodes (N) according to the current TNM classification (UICC 2010); *PVE*, portal vein embolization.

potentially ischemic or congested areas; and (3) no unresectable extrahepatic sites of disease.

During the period of this investigation, our medical center maintained the same policy toward hepatic resection for CLM, ie, upfront resection was performed, regardless of the number, distribution, or extent of the liver metastases. Intraoperative ultrasonography (US) was performed routinely to confirm the preoperative findings on imaging and diagnosis. Moreover, contrast-enhanced intraoperative US was introduced in 2007[18] and performed consecutively to obtain more accurate intraoperative diagnosis. The patients were followed by serial assays of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9, abdominal US, and by chest and abdominal CT every 3 months during the first 2 years. Thereafter, patients were followed by measurements of CEA and carbohydrate antigen 19-9 and abdominal US every 3 months, and by CT every 6 months.

We performed repeat hepatic resection immediately on detecting resectable recurrent disease without delaying the resection to select appropriate patients for repeat resection. In cases with recurrence in the remnant liver, repeat hepatic resection was performed according to the aforementioned criteria. In cases with recurrent pulmonary metastases, the following criteria were applied for resection of the recurrent pulmonary metastases, taking into account the volume of the lung parenchyma remaining after the resection: (1) number of metastatic tumors ≤3 regardless of whether unilateral or bilateral; and (2) no involvement of thoracic lymph node, as assessed by preoperative imaging.

Resectability was determined by an experienced thoracic surgeon who determined whether a metastasectomy could be performed safely. In cases with simultaneous intrahepatic plus pulmonary recurrence, the indication for operation was decided according to the aforementioned criteria for the respective metastases, and simultaneous or staged resection was performed. The presence of extrahepatic and nonpulmonary metastases, in principle, was treated as a contraindication for re-resection, except in cases with a solitary metastasis or metastasis limited to an organ such as the primary (colorectal) local site, local lymph node, celiac lymph node, para-aortic lymph node, adrenal gland, or peritoneum, with or without intrahepatic and/or pulmonary recurrence.

During the current study period, ablation therapy was not performed as a substitute for resection in patients with resectable recurrent disease, because its efficacy for CLM is inferior to resection, both in terms of the rates of local recurrence and the 5-year OS.[3,19] After repeat resection, all patients were followed in the same way as after the initial hepatic resection. Our historic strategy in our center for the treatment of recurrent disease from colorectal cancer has been to perform repeated resections alone for the management of intrahepatic and/or extrahepatic disease if resectable and to withhold chemotherapy until the

recurrent disease became unresectable during the study period.

Data and outcomes. OS was defined as the time from the date of initial hepatic resection to all-cause death or the date of the last follow-up used for censoring, and PRS was defined as the time from the date of the first relapse after the initial hepatic resection to all-cause death or the date of the last follow-up used for censoring. RFS_0 was defined as the time from the date of initial hepatic resection to recurrence from colorectal cancer or all-cause death, whichever occurred first. RFS_1, RFS_2, and RFS_3 were defined as the time from the date of the first, second, and third repeat surgery, respectively, to relapse from colorectal cancer or all-cause death, whichever occurred first. The median follow-up period was 7.4 years. Detailed information on the type of relapse was always available.

Standard criteria for the resectability of recurrent disease are difficult to specify, because they depend on technical aspects related to the skill level of the operating surgeon. The current study was undertaken at a single, specialized institute, where the staff adopted the same policy towards the potential window for cure, considering the possibility of repeat resections whenever possible as part of a multidisciplinary approach, and if repeat resection was not feasible or impossible, optimal nonoperative therapy for unresectable relapse was selected, eg, systemic chemotherapy or other palliative therapy.

Statistical methods. Continuous variables were compared with the Mann–Whitney *U* test, and categorical variables were compared using the χ^2 test or Fisher exact test where appropriate. Survival curves were generated by the Kaplan–Meier method, and the differences between curves were evaluated by the log-rank test. With regard to comparison of the RFS, patients who underwent initial hepatic resection, and first, second, and third repeat resections were defined as independent groups eligible for the analysis. To identify the prognostic factors for PRS, a multivariate regression analysis was performed using the Cox proportional hazards model with backward elimination for variables identified as significant with $P < .1$ in the univariate analysis. All statistical analyses were performed using JMP 11 (SAS Institute Inc, Cary, NC).

RESULTS

OS after the initial hepatic resection and the PRS. The median OS was 5 years (95% confidence interval [CI], 4.1–6.3 years) in the patients who had undergone the initial resection for CLM ($n = 263$). The 5-year and 10-year OS rates were 54% and 42%, respectively. Relapses occurred in 198 patients (75%) after the initial hepatic resection, and repeat resection(s) was performed in 108 patients (54%) (Table II). In regard to the results classified according to subgroups, the 5-year OS in the recurrence-free ($n = 63$) subgroup and subgroups with resectable recurrence ($n = 108$) and unresectable recurrence ($n = 90$) were 96%, 63%, and 13% and the 10-year OS rates were 84%, 51% and 0%, respectively (Fig 2). The median PRS was 2.8 years (95% CI, 2.5–3.3 years), and the 5-year and 10-year PRS rates were 34% and 28%, respectively (Fig 3). The sequential outcomes of the study patients are shown in Fig 1. Of the 108 patients undergoing the first repeat resection, 74 (68%) developed a second relapse; of these 74 patients, 43 (58%) underwent a second repeat resection. Of the 43 patients who underwent a second repeat resection, 32 (74%) developed a third relapse, of which 15 (47%) underwent a third repeat resection. Of the 15 patients who underwent a third repeat resection, 11 (73%) developed a fourth recurrence, of which 4 (36%) underwent a fourth repeat resection (Table II).

Efficacy and safety of the first, second, and third repeat resections. The median RFS_0 was 0.82 years (95% CI, 0.63–1.12), and the median RFS_1, RFS_2 and RFS_3 were 1.3 years (95% CI, 0.76–1.71), 1 years (95% CI; 0.61–1.69), and 2 years (95% CI, 0.27–NR), respectively. The 3-year RFS_0 rate was 27%, and the 3-year RFS_1, RFS_2, and RFS_3 rates were 35%, 29%, and 38%, respectively. The hazard ratio (HR) for the recurrence-free survival for the first repeat surgery was 0.88 (95% CI, 0.68–1.14; $P = .34$), that for the second repeat surgery vs the initial hepatic resection was 0.99 (95% CI, 0.67–1.42; $P = .97$), and that for the third repeat surgery vs the initial hepatic resection was 0.72 (95% CI, 0.36–1.29; $P = .29$) (Fig 4).

In regard to the postoperative complications classified according to the Clavien-Dindo classification,[20] severe complications (Grade III) occurred in 15 of 108 patients (14%) after the first repeat resection, 8 of 43 patients (19%) after the second repeat surgery, and 3 of 15 patients (20%) after the third repeat resection. There were no cases of life-threatening complications (Grade IV) or death (Grade V) at any repeat surgery (Table II).

Multivariate analysis. A multivariate analysis revealed that the nonresectability was the only independent prognostic factor for PRS ($P < .0001$; HR, 4.29; 95% CI, 2.47–7.84), and that a recurrence-free interval of <6 months, preoperative CEA values of >50 μg/L, presence of

Table II. Profiles of the repeat hepatic resections and safety

Variable	*First repeat resection* (n = *108*)	*Second repeat resection* (n = *43*)	*Third repeat resection* (n = *15*)	P *value*
Resection organ site, *n* (%)				.25
Liver only	61 (57)	21 (49)	8 (54)	
Lung only	29 (27)	14 (33)	5 (33)	
Liver plus lung	13 (12)	5 (12)	2 (13)	
Liver plus others	3 (2)	2 (4)	0 (0)	
Others only	2 (2)	1 (2)	0 (0)	
Resected tumor number (liver), *n*				<.0001
1	28	18	5	
2–4	30	8	4	
5 or more	19	2	1	
Resected tumor number (lung), *n*				.002
1	23	11	4	
2–3	15	7	3	
4 or more	4	1	0	
Type of hepatic resection, *n* (%)				
Partial resection	65 (85)	24 (86)	8 (80)	.99
Segmentectomy/Sectionectomy	8 (10)	2 (7)	1 (10)	
Hemihepatectomy	4 (5)	2 (7)	1 (10)	
Type of pulmonary resection, *n* (%)				
Wedge resection	34 (80)	16 (84)	7 (100)	.38
Segmentectomy	4 (10)	1 (5)	0 (0)	
Lobectomy	4 (10)	2 (11)	0 (0)	
Resectability				
R0/R1/R2	97/8/3	39/3/1	13/2/0	.91
Complications (Clavien-Dindo), *n*				
Grade I/II	26/18	13/9	4/4	.09
Grade IIIa/IIIb	12/3	6/2	2/1	.33
Grade IVa/IVb	0/0	0/0	0/0	—
Grade V	0	0	0	—
Overall recurrence rates, %	68.5	74.4	70.8	.91
Median recurrence-free survival, y (95% CI)	1.28 (0.76–1.71)	1.06 (0.61–1.69)	1.96 (0.27–NR)	—
Median overall survival, y (95% CI)	11.3 (4.92–14.21)	7.86 (3.51–NR)	NR (3.18–NR)	—

"Others" includes metastasis at the site of the primary tumor, or in the local lymph nodes, celiac lymph nodes, para-aortic lymph nodes, adrenal glands, or peritoneum.
CI, Confidence interval; *NR*, not reached.

multiple metastases, largest tumor size ≥5 cm, and an intrahepatic plus extrahepatic relapse pattern had no statistically significant influence.

DISCUSSION

The current study demonstrated the survival benefit of repeated resections for successive recurrences after CLM. The PRS was prolonged by this treatment modality, as shown by strict long-term follow-up, potentially offering the possibility of cure in some proportion of patients, notwithstanding the development of recurrent disease.

In this study, there were no significant differences in the RFS after the initial hepatic resection, or after the first, second, and third repeat resections. This observation suggests that the survival benefit of repeat resections of recurrent CLM was maintained consistently, regardless of the number of previous resections. Although the effectiveness of repeated resection for CLM has been suggested with the use of the results of surgery for the first recurrence, the current data including cases of resections for the second and third recurrence is new and clinically important. Thus, we suggest that sequential repeat resections may offer the possibility of cure in some patients, notwithstanding the development of recurrent disease. At each of the repeat resections with curative intent, approximately one-third of the patients remained recurrence-free, and two-thirds developed recurrence events; of the latter, one-half were found to be suitable candidates for further resection.

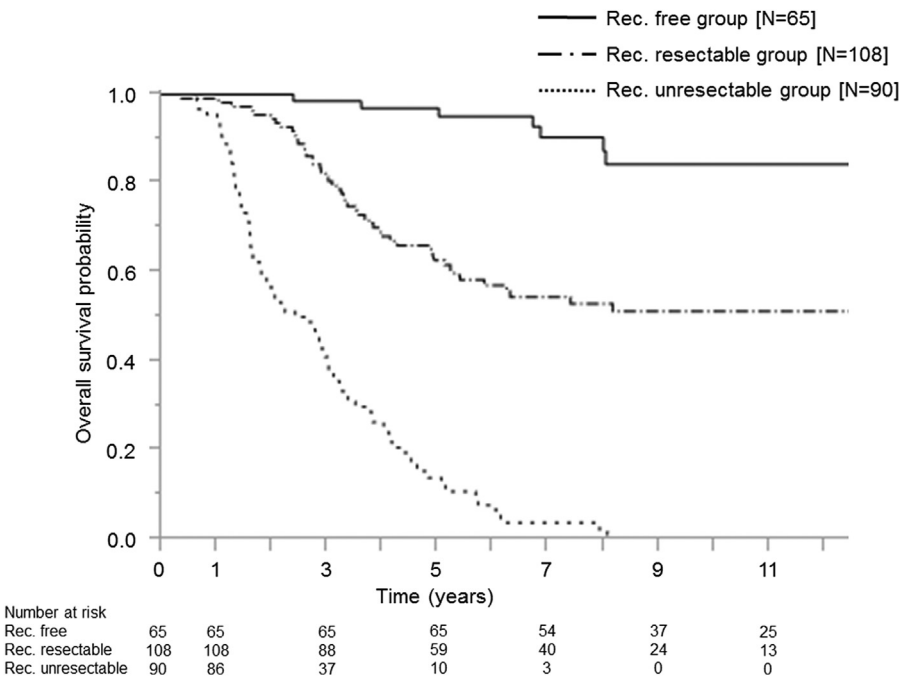

Fig 2. OS in the recurrence-free ($n = 65$) subgroup, subgroup with resectable recurrence ($n = 108$), and subgroup with unresectable recurrence ($n = 90$) of the 263 patients included in the current analysis after the initial hepatic resection for CLM. *Rec.*, Recurrence.

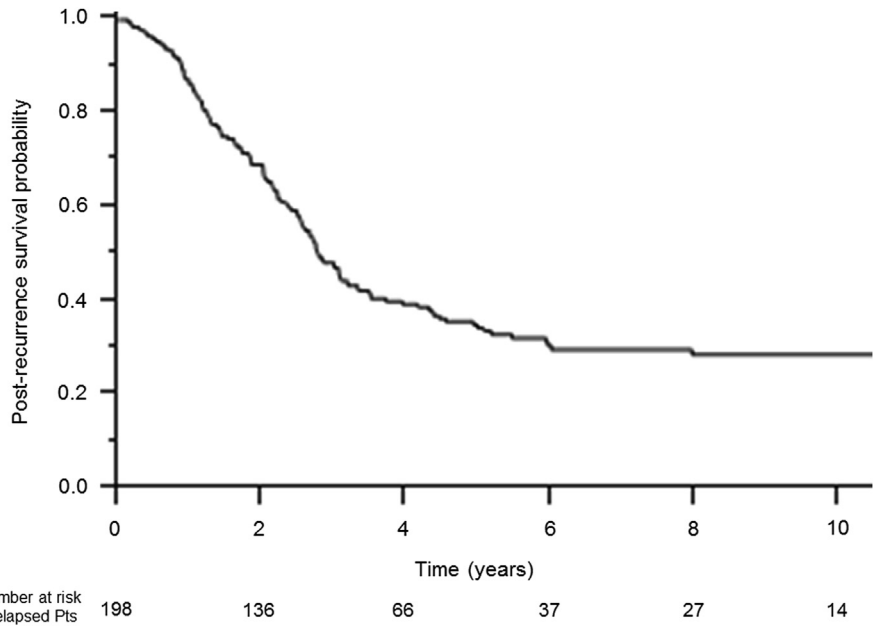

Fig 3. PRS in all 198 patients with relapse of the 263 patients included in the current analysis after the initial hepatic resection for CLM.

Compared with previous studies in which repeated resections were carried out for selected recurrences in the liver or lung (Supplementary Table I, online version only),[13-16,21] our results provide the following additional clinically beneficial information: (1) the outcomes of sequential resections for successive recurrences, namely, natural history in the patients who underwent upfront curative hepatic resection; (2) the actual benefit of the repeat resection itself without perioperative

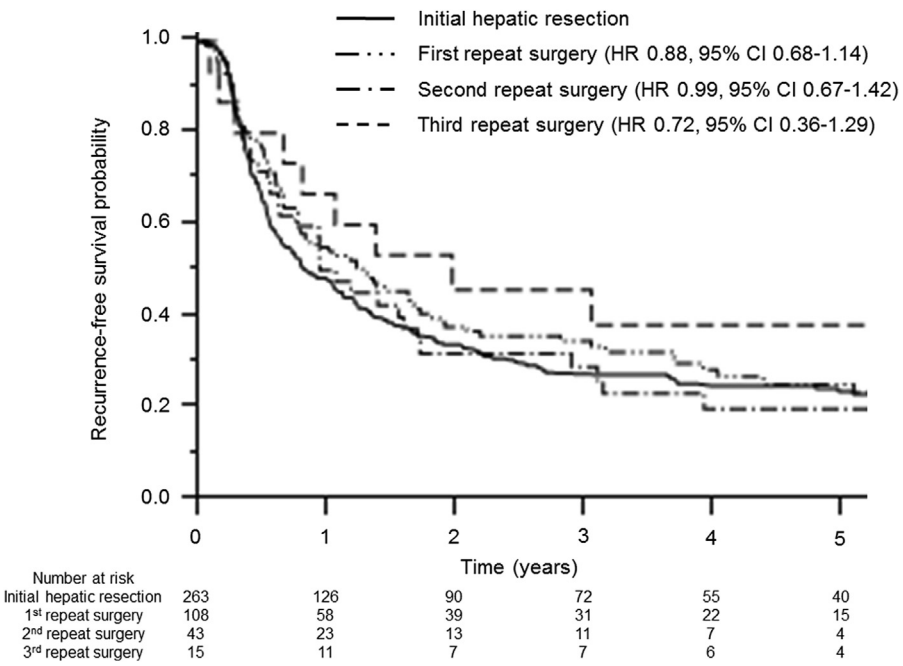

Fig 4. Comparison of the RFS after the initial hepatic resection ($n = 263$), and after the first ($n = 108$), second ($n = 43$), and third ($n = 15$) repeat resections.

intervention (ie, systemic chemotherapy, ablation therapy, or hepatic arterial infusion therapy) as the second, third, and fourth lines of treatment; and (3) data from a sufficient number of patients treated according to the same therapeutic policy for CLM and followed for a sufficient duration of time at a single specialized center. The recent report by Saiura et al[21] also lends support to the potentially curative role of repeat resection, especially for a first recurrence in the liver or lung alone after the initial liver resection for CLM.

Our experience demonstrated that the frequency of severe morbidity (grade III according to the Clavien-Dindo classification) after first, second, and third repeat resection was 14%, 19%, and 20%, respectively, which we consider to be acceptable. Therefore, repeat resection should be a part of multidisciplinary management in specialized centers, where the incidence of operative complications would be expected to be reasonable. Our findings suggest that the frequency (about 80%) of parenchyma-saving resections (ie, partial hepatic resection or pulmonary wedge resection) appears to increase the chance of a safe subsequent repeat resection in the event of another recurrence developing at the same site.

It remains uncertain whether re-resection, systemic chemotherapy, or both combined are the optimal treatment choice for recurrence after hepatic resection of CLM. Modern chemotherapy for unresectable metastatic colorectal disease evidently offers improved survival (median survival 20–30 months), even in the palliative setting, according to recent clinical trials.[22-25] The PRS in selected patients in our study, however, was still prolonged by our strategy of repeated resections for successive recurrences, with the possibility of cure, which cannot be achieved by modern chemotherapy alone. Thus, we suggest that the optimal treatment choice for recurrence is resection if the lesion is resectable, just as for the initial CLM. As we reported previously, the presence or absence of recurrence after CLM resection is not a reliable endpoint for determining the clinical outcome, and re-resection for successive recurrences appears to result in an improvement of the long-term survival.[26] This finding suggests the importance of reporting the characteristics of recurrent disease in detail and employing further treatment modalities including those with curative intent for CLM patients in clinical trials.

We are aware of the methodologic limitations of our study, which was based on the data from a selected cohort from a single institution over a long period, in which various kinds of chemotherapeutic regimens were available as palliative therapies. During the current study period, we had maintained a consistent therapeutic strategy, in which repeat resection was considered as the treatment of first choice for resectable recurrence,

without chemotherapy administered until a recurrence proved to be unresectable. Therefore, we believe that any potential bias on our results by the long study period of 15 years and the changes in the chemotherapy regimens would be minimal.

We should pay careful attention before applying our results in clinical practice, especially in western countries, because perioperative chemotherapies are generally used in these countries, quite different from the situation in Japan. In contrast, this study has clinical importance because our data showed the true survival impact of repeated resections, which cannot be evaluated in western countries. The next step should be to investigate how to improve prognosis of repeat resection with full use of modern and advanced chemotherapies.

We determined the OS after CLM resection composed in three subgroups of patients, ie, the recurrence-free subgroup, the subgroup with resectable recurrence, and the subgroup with unresectable recurrence. Currently, the ideal adjuvant strategy using systemic chemotherapy could potentially suppress the risk of recurrence or increase the possibility of re-resection, which could result in improved OS.

In summary, our study showed that the efficacy of repeated resections for successive recurrences (first, second, and third recurrence) after the initial hepatic resection was similar to that of the initial resection for CLM. Therefore, attempts at repeat resection should be considered as the optimal treatment strategy for each successive recurrence in patients with recurrent disease after CLM resection.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.surg.2015.09.003

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