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The Surgical Benefits of Repeat Hepatectomy for Colorectal Liver Metastasis

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Abstract: The most common site of distant metastasis from colorectal cancer is the liver, and hepatectomy presents the best curative treatment for recurrence of colorectal liver metastasis (CRLM). This study aimed to identify factors of prognostic value for repeat hepatectomy for CRLM and to determine whether a third such procedure could similarly produce favourable outcomes for CRLM. We analyzed data for 161 patients in our department with colorectal metastasis. Of these, 22 patients underwent repeat hepatectomy for recurrent metastasis, with 16 undergoing a second hepatectomy and 6 a third hepatectomy. We analyzed patient characteristics, tumor status, operation-related variables, and short- and long-term outcomes. Univariate analysis for repeat hepatectomy identified the following five prognostic risk factors: T factor (>SE) of the primary cancer, number of tumors involved in the initial hepatectomy (>5), interval from first to second hepatectomy (< 1 year), number of tumors involved in second hepatectomy (>3), and post-operation time (>30 days). By multivariate analysis, T factor (>SE) of the primary cancer, number of tumors in the initial hepatectomy (>5), and number of tumors in the second hepatectomy (>3) were independently associated with a worse survival after surgery for CRLM. Although surgical outcomes of the third hepatectomy were not compared with those of the first and second hepatectomy, there were no obvious differences, nor did the 1-, 3-, and 5-year survival rates differ significantly among the three groups. Repeat hepatectomy for CRLM could improve long-term survival. In addition, patients undergoing a third hepatectomy showed a similar survival benefit to those having one or two resections.

Key words: repeat hepatectomy, third hepatectomy, colorectal liver metastasis, CRLM, factors of prognostic value

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Introduction

The liver is the most common organ for metastasis from colorectal cancer, and despite colorectal liver metastasis (CRLM) being classified as distant, hepatectomy offers the best chance of cure with 5-year survival rates of 30–50%[1,2]. Unfortunately, 45–80% of patients who undergo hepatectomy for CRLM develop recurrence[3–6], although 30% of patients have recurrent spots only in the liver after hepatic resection[5] and are potentially candidates for further resection[7–9]. In addition, recent innovations in combination chemotherapy, such as FOLFOX or FORFIRI with targeted therapies, have also extended remarkable surgical opportunities to patients with unresectable metastasis[10–12]. Such advances in surgical techniques and perioperative management have enabled some centers to perform repeat hepatectomy in selected groups of patients[13–16], with 5-year survival rates currently at 21–41% for repeat hepatectomy[17–19]. Thus, repeat hepatic resections for CRLM are increasingly performed under appropriate conditions in selected patients.

Previous studies have evaluated factors associated with favorable outcome after a repeat hepatectomy, without clarity. In addition, a third hepatectomy for CRLM is considered more complex and associated with a higher incidence of complications[20–22], although few reports have documented the surgical outcomes based on individual factors[23–25].

This study thus aimed to identify factors associated with repeat hepatectomy that are of prognostic value for CRLM and to determine whether a third hepatectomy could be performed with similarly acceptable surgical outcomes.

Patients and methods

From January 1998 to October 2015, 161 patients underwent a liver resection for CRLM in our surgical department. These patients were divided into three groups: first resection only (n = 139), second resection (n = 16), and third resection (n = 6). No patient underwent more than three resections. We identified patients from prospective databases, and retrospectively reviewed office and hospital charts. The median follow-up time from primary colon surgery was 52.3 months.

The selection criteria for hepatectomy were the presence of technically resectable liver metastasis, the possibility of an oncological radical operation, and the absence of any unresectable extra-hepatic disease. Extra-hepatic disease was defined as infiltration of contiguous structures, presence of other distant metastasis, or local recurrence of the primary colorectal tumor. The indication for repeat hepatectomy was not limited by number of metastatic tumors, tumor size, or disease-free interval from initial hepatectomy. Following the primary colorectal tumor resection or after each hepatectomy, we performed a careful search for local recurrence, extrahepatic metastasis, and peritoneal dissemination. The patients were followed up every 3 months for the first postoperative year, then every 6 months during the subsequent 2 years, and then at 12-month intervals to postoperative year 5; the follow-up comprised liver function tests, serum carcinoembryonic antigen (CEA) testing, thoracic and abdominal computed tomography

(CT), and colonoscopy (CS).

Morbidity was defined by complications during hospitalization or within 30 days following the resection, based on abdominal wall morbidity (wound infections and wound dehiscence), intraperitoneal morbidity (bleeding, abscess, peritonitis, and biliary fistula, etc), and medical complications (septicemia from extra-abdominal causes; catheter, respiratory, and urinary infections; and, other systemic non-infectious complications). Mortality was defined as deaths occurring during hospitalization or within 30 days.

Statistical analysis was conducted using JMP software (version 13, Inc., SAS Institute). All means are expressed with standard deviation (SD). Survival probabilities were estimated using the Kaplan-Meier method, while univariate associations between potential risk factors and survival were assessed using the log-rank test with two-tailed hypothesis. Factors identified in univariate associations were assessed using the Cox multivariate regression test. The significance level of $P<0.05$ was used in all hypothesis testing.

The Showa University School of Medicine Ethics Committee approved the experimental protocols used in this study (#2924).

Results

1. Factors of prognostic value for repeat hepatectomy

We analyzed the data for 16 of the 161 study patients to investigate the prognostic value of repeat hepatectomy for CRLM (Table 1). The mean age of this subgroup was 65.6 years (range: 35-85) and the mean 5-year survival rate for repeat hepatectomy was 66.1%. The primary tumor was carcinoma of the colon in 8 patients and carcinoma of the rectum in 8 patients, while liver metastasis was synchronous in 9 patients (56.2%). The mean interval between colectomy and the first hepatectomy was 5.7 months, with 87.5% of the patients undergoing the hepatectomy within 1 year. In terms of patient characteristics, neither age nor gender predicted the long-term outcome, but primary tumor status and T factor (>SE) of the primary tumor were predictive factors ($P = 0.028$). Invaded depth, lymph node status, and CEA level (> 5 ng/ml) were also not predictive of the outcome. In terms of the initial liver metastatic status, number of tumors in the initial hepatectomy (> 5) predicted the outcome ($P = 0.021$), whereas tumor size (> 50 mm) and CEA level (> 5 ng/ml) were not predictive of the outcome. The interval from first to second hepatectomy (< 1 year) predicted the outcome ($P = 0.031$), as did tumor number in the second hepatectomy (> 3) ($P = 0.047$). Size of tumor (> 50 mm) and CEA level (> 5 ng/ml) were again not associated with outcome. In terms of operation-related variables, only postoperative hospital stay (> 30 days) was predictive of the outcome ($P = 0.019$), with blood loss (> 2,000 ml), operation time (> 500 min), and morbidity showing no predictive value (Table 2). Our multivariate analysis identified T factor (> SE) of the primary tumor ($P = 0.024$, risk ratio 1.93, 95%CI 1.50-1.61), tumor number at initial hepatectomy (> 5) ($P = 0.024$, risk ratio 2.35, 95%CI 1.13-1.65) and tumor number at second hepatectomy (> 3) ($P = 0.045$, risk ratio 2.83, 95%CI 1.07-1.10) were independently associated with a worse survival after surgery for CRLM (Table 3).

Table 1. Characteristics of repeat hepatectomy for CRLM

Characteristics	n = 16
Age	65.6 (35-85)
Gender (M/F)	12/4
Location of primary tumor	
colon (A/T/D/S)	8 (2/0/2/4)
rectum	8
Interval time from primary operation	
metachronous	9
synchronous	7 (43.8%)
First hepatectomy	
number of tumor	2.47 (1-6)
tumor size (mm)	32.8 (4-85)
operative methods (Hr 0/Hr S/Hr >1)	8/3/4
operative time (min)	293 (125-615)
blood loss (ml)	365 (5-1,240)
operative morbidity (>grade 3) (%)	8 (50.0%)/8 (50.0%)
post-operative chemotherapy (Y/N)	8.3
Interval time from first hepatectomy (days)	412 (46-1,060)
Second hepatectomy	
number of tumor	1.9 (1-7)
tumor size (mm)	31.9 (12-50)
operative methods (Hr 0/Hr S/Hr >1)	12/3/1
operative time (min)	265 (95-710)
blood loss (ml)	742 (5-3,435)
operative morbidity (>grade 3) (%)	0
operative mortality (%)	0
post-operative chemotherapy (Y/N)	6 (37.5%)/10 (62.5%)
Time until recurrence (days)	446 (75-1,574)
5-year survival rate after second hepatectomy (%)	66.1

2. Operative outcomes for third hepatectomy

The patients in this study were divided according to their number of resections, i.e., 3 resections (n = 6), 2 resections (n = 16), or a single resection (n = 139). The disease characteristics at hepatectomy for all patients are summarized in Table 4. The patient characteristics, tumor status, operation-related variables, and short- and long-term outcomes were analyzed including age, gender, pathology and depth of the primary tumor, lymph node metastasis from the primary tumor, lymphatic or vascular invasion of the primary tumor, CEA level of primary tumor and CRLM, blood platelet count (PLT), liver Child-Pugh classification, indocyanine green retention 15 (ICG R15), ^{99}mTc-galactosyl serum albumin (^{99}mTc-GSA), tumor number, and maximum tumor diameter.

The only significant difference among the three groups was in the H classification of the primary tumor ($P = 0.01$). All cases of third hepatectomy were synchronous, and although there was significantly less operation-associated blood loss with the third hepatectomy compared to that for the first and second hepatectomy ($P = 0.03$), operation time and blood loss were not significantly different across the groups. There was no intraoperative mortality. Complications included liver-related complications (perihepatic abscess: n = 9, bile fistula: n =

Table 2. Univariate predictors repeat hepatectomy for CRLM

	Number of patients	5-year survival rate (%)	P value
Age			
<70 years	9	50	0.50
>70 years	7	57	
Gender			
male	12	64	0.156
female	4	0	
Primary tumor			
CEA level			
< 5 ng/ml	3	50	0.493
> 5 ng/ml	8	54	
T factor			
<SE	11	63	0.028
>SE	2	0	
N factor			
<N1	6	53	0.340
>N1	7	46	
Interval time from primary operation			
metachronous	9	63	0.695
synchronous	6	33	
First hepatectomy			
number of tumor			
>5	13	65	0.021
<5	2	0	
size of tumor			
<50 mm	11	54	0.754
>50 mm	4	67	
CEA level			
< 5 ng/ml	4	100	0.220
> 5 ng/ml	11	43	
post-operative chemotherapy			
Yes	8	55	0.651
N o	7	42	
Interval time from first hepatectomy			
>1year	9	32	0.031
<1year	7	75	
Second hepatectomy			
number of tumor			
> 3	13	61	0.047
< 3	3	33	
size of tumor			
>50 mm	12	48	0.485
<50 mm	2	50	
CEA level			
< 5 ng/ml	5	67	0.319
> 5 ng/ml	9	35	
operative time			
<500 min	12	49	0.980
>500 min	2	50	
blood loss			
<2,000 ml	12	49	0.980
>2,000 ml	2	50	
post-operative hospital stay			
<30 days	12	56	0.019
>30 days	2	0	
post-operative chemotherapy			
Yes	6	33	0.228
N o	9	68	

Table 3. Multivariate predictors of repeat hepatectomy for CRLM

Factor	P-value	HR (95%CI)
T factor of primary tumor ＞SE	0.024	1.93 (1.50-1.61)
Number of nodules for first hepatectomy ＞5	0.024	2.35 (1.13-1.65)
Interval time from first hepatectomy ＜1 year	0.395	0.29 (0.01-7.33)
Number of nodules for Repeat hepatectomy ＞3	0.045	2.83 (1.07-1.10)
Post-operative hospital stay ＞30 days	0.621	0.45 (0.01-13.90)

Values in parentheses are 95% confidence intervals.

5, and post-operative liver failure: n = 1) and general complications (surgical site infection: n = 5, pneumonitis: n = 2, and other: n = 3). Ten cases showed complications of grade-IIIa and over (Clavien-Dindo classification), namely perihepatic abscess (n = 5) and bile fistula (n = 4) at first hepatectomy, and bile fistula (n = 1) at third hepatectomy. Post-operative hospital stay also did not differ among the three groups, nor did the 1-, 3-, and 5-year survival rates (100.0, 83.3, and 62.5% for the third hepatectomy group vs. 100.0, 79.3, and 66.1% for the second hepatectomy group vs. 87.5, 59.8, and 47.6% for the first hepatectomy group) (Fig. 1).

Discussion

For recurrence cases of CRLM, 20-41% of recurrence was localized at the liver and thus potentially amenable to further hepatic resection[17-19]. In addition, repeat hepatic resection for CRLM is an increasingly effective treatment when performed under appropriate conditions[20, 26-29].

This study aimed to detect criteria of prognostic value for repeat hepatectomy for CRLM. We identified five such factors by single-variable analysis, namely T factor of primary tumor (＞SE), tumor number at initial hepatectomy (＞5), interval from first to second hepatectomy (＜1 year), tumor number at second hepatectomy (＞3), and postoperative day (＞30 days). Subsequent multivariate analysis identified T factor (＞SE) of the primary cancer, tumor number at initial hepatectomy (＞5) and tumor number at second hepatectomy (＞3) as predictive of the outcome. A previous review reported six predictors for length of survival after repeat hepatectomy[30], being disease-free survival after first hepatectomy of ＞1 year, solitary CRLM, unilobar CRLM, maximal size of CRLM ＜5 cm, lack of extrahepatic metastases, and R0 resection at repeat hepatectomy. Number of liver metastasis for CRLM and interval from first to second hepatectomy (＜1 year) were also important prognostic factors in our study and in previous work. Although all studies including this one analyzed tumor location as a factor, no reports cited extrahepatic metastases and R0 resection as important. We also found no prognostic value associated with maximum tumor size of CRLM or postoperative chemotherapy.

Another aim of this study was to investigate the surgical benefits of a third hepatectomy for CRLM. Comparing the surgical outcomes of patients undergoing three hepatectomies with those undergoing one or two hepatectomies found no worsening of the following factors after the third operation: preoperative liver function, PLT, Child-Pugh classification, ICG R15, and ^{99}mTc-

Table 4. Characteristics of third hepatectomy for CRLM

Characteristics	Third hepatectomy (n = 6)	First hepatectomy (n = 139)	*P* value*	Second hepatectomy (n = 16)	*P* value**
Age	68.7 (58-78)	67.9 (37-89)	0.85	65.6 (35-85)	0.63
Gender (M/F)	4/2	72/51	0.90	12/4	0.70
Primary tumor factor					
Location (C/A/T/D/S/R)	0/0/1/1/2/2	6/21/4/8/25/51	–	0/2/0/2/3/8	–
CEA level (ng/ml)	56.2 (3.1-141)	60.8 (1.4-567)	0.91	36.4 (1.6-176)	0.53
Pathology (tub1/ tub2/other)	0/6/0	33/60/10	0.13	5/8/0	0.08
Depth (MP/SS/>SE)	0/5/1	6/68/34	0.62	3/8/2	0.43
Lymph node (N0/N1/N2/N3)	2/4/0/0	37/40/19/9	0.58	6/3/3/1	0.42
Lymphatic invasion (ly0/ly1/ly2/ly3)	2/4/0/0	19/53/24/5	0.50	1/6/3/2	0.24
Vascular invasion (v0/v1/v2/v3)	2/1/2/1	14/44/29/13	0.47	1/2/7/2	0.57
H classification (H0/H1/H2/H3)	0/5/1/0	51/21/12/7	0.01	7/5/1/0	0.08
Onset of liver metastasis (Synchro/Metachro)	0/6	51/40	0.01	7/6	0.08
M classification (M0/M1)	5/1	88/6	0.34	12/0	0.15
Liver metastasis factor					
Liver function PLT (10^4/μl)	25.5 (22.5-29.4)	24.4 (8.5-47.6)	0.78	22.4 (13.4-40.8)	0.48
Child-Pugh classification	5.0 (5-5)	5.11 (5-7)	0.49	5.14 (5-6)	0.40
ICG 15 (%)	9.8 (5-19)	10.1 (3-29)	0.90	18.6 (9-43)	0.17
LHL15 (GSA)	0.91 (0.85-0.94)	0.84 (0.63-0.96)	0.57	0.89 (0.82-0.96)	0.92
Location (S1/2/3/4/ 5/6/7/8)	0/0/1/0/ 0/3/1/1	6/13/10/14 24/24/19/14	–	0/1/1/1/ 5/3/3/1	–
CEA level (ng/ml)	31.8 (5.5-99.7)	80.5 (1.2-2313)	0.65	18.8 (1.4-56.5)	0.46
Number of tumor	1.7 (1-3)	2.4 (1-13)	0.44	1.9 (1-7)	0.71
Maximum Diameter (mm)	37.0 (15-50)	34.8 (1.0-160)	0.86	31.9 (12-50)	0.42
Operative factor					
Methods					
(Hr0/HrS/Hr1/>Hr2)	3/2/1/0	89/19/14/13	–	12/3/1/0	–
(Hr0/>HrS)	3/3	89/46	0.41	12/4	0.26
Time (min)	461 (275-470)	323 (47-815)	0.07	265 (95-710)	0.03
Blood loss (ml)	788 (425-997)	580 (5-3475)	0.07	742 (5-3435)	0.28
Morbidity (>Clavien IIIa)	1	9	0.01	0	0.20
Hospital stay (days)	16.5 (11-27)	22.2 (4-136)	0.57	17.5 (5-49)	0.87

*: Third hepatectomy vs First hepatectomy **: Third hepatectomy vs Second hepatectomy

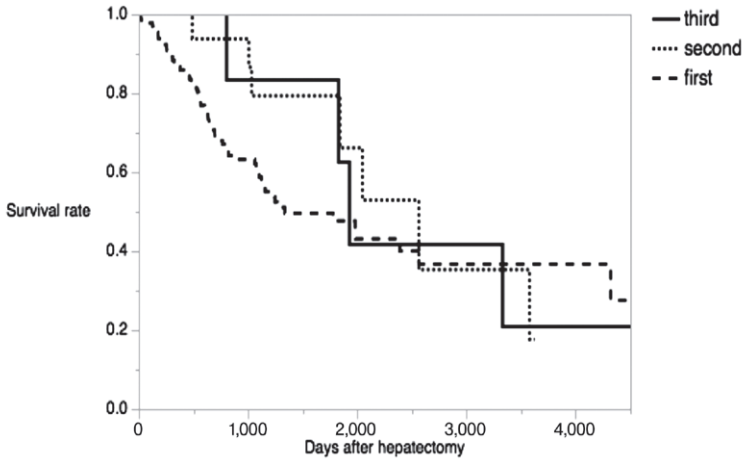

Fig. 1. Survival for third/second/first hepatectomy for CRLM

GSA. As severe adhesions are generally caused by repetitive tissue separations, we suspect that operative time and blood loss in the third hepatectomy cases were inferior to those during the first or second surgeries, although in our cases, only operative blood loss with the third hepatectomy vs second hepatectomy was inferior. Of note, almost all of the third hepatectomy cases analyzed herein were performed at the time prior to anti-adhesive material being used. In addition, the main operative technique of this study was laparoscopy and partial hepatectomy, providing a minimally invasive surgery compared to the open method, while partial hepatectomy involves only a small resection of parenchymal transection. Thus, it is not surprising that there were few complication risks with the analyzed patients. Cases receiving neoadjuvant chemotherapy were also scarce in this study, thus we could not include that factor in the analysis. Regardless, the present study revealed that a third hepatectomy was safe to perform and provided survival benefits and rates comparable to those of previous liver resections without increasing mortality or morbidity.

Conclusion

Repeat hepatectomy for CRLM can achieve long-term survival by selective classification of patients, with the number of liver metastases a particularly important factor of prognostic value. Additionally, a third hepatectomy had a similar survival benefit as first or second resections, and long-term survival was achieved in selected patients following careful classification.

Conflict of interest disclosure

The authors have no conflict (s) of interest to declare.

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