

Repeat reduction surgery after an initial hepatectomy for patients with colorectal cancer

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Abstract. A hepatectomy is the only treatment offering long-term survival in patients with colorectal liver metastases. However, 70-80% of the patients with a complete resection develop recurrent disease after an initial hepatectomy. Sixty-one patients who underwent metastases from colorectal carcinoma with a curative hepatectomy were entered into this study. Recurrence after hepatectomy was observed in 41 patients (67.2%). We reviewed the outcome of these 41 patients. Repeat reduction surgery was performed on 16 out of 41 patients (39.0%). According to a multivariate analysis, repeat reduction surgery and tumor size were found to be independent prognostic factors for the survival rate ($p=0.007$, $p=0.018$). Furthermore, in the group that underwent repeat reduction surgery, the rate of positive lymph nodes was significantly lower in the primary lesions, and the disease-free interval (DFI) was also significantly longer than in the group that did not undergo repeat reduction surgery ($p=0.023$, $p=0.045$), respectively. Repeat reduction surgery was found to be the most important prognostic factor. Patients with a longer DFI and with negative lymph node findings at the primary site may therefore be considered to be good candidates for repeat reduction surgery.

Introduction

A hepatic resection remains the most effective therapy for metastatic colorectal cancer. Unfortunately, 70-80% of patients suffer from recurrence after the initial hepatectomy (1). There have been numerous reports which have evaluated prognostic factors in the initial resection of colorectal liver metastases (1-6). On the other hand, there have been few

reports so far on the prognostic factors focusing on recurrent patients. It is very important to reveal which recurrent patients may have a poor prognosis. In this study, we first tried to identify the profile of patients with a long-term survival after recurrence and who had previously undergone an initial hepatectomy. There have been several reports describing the survival for repeat liver (7-13) and pulmonary (14-17) resection in patients with recurrence after a curative resection of colorectal metastases. On the other hand, there have also been few reports about such treatments for extra-hepatic and extra-pulmonary metastases after the initial hepatectomy (18,19). Although the significance of repeat reduction surgery has been reported, only a small number of patients with recurrence can undergo this procedure. Secondly, in this study we attempted to evaluate which patients are likely to benefit from repeat reduction surgery.

Materials and methods

Between January 1993 and December 2005, 61 patients with colorectal metastases who underwent a curative hepatectomy at Wakayama Medical University Hospital participated in this study. The median follow-up period in our study was 49 months. The criteria for the initial hepatectomy included that all liver tumors could be completely removed assuring the preservation of the liver function and that metastatic lesions were localized in the liver except for resectable extra-hepatic metastases. The criteria for a repeat hepatectomy were the same as those for the initial hepatectomy. Intraoperative ultrasonography was used routinely to rule out unexpected lesions. The criteria of a resection for extra-hepatic metastases included the complete removal of all detected tumors and an acceptable residual function of organs. After the initial hepatectomy, the patients were followed up closely on an outpatient basis in order to detect any recurrence. The patients routinely underwent abdominal computed tomography (CT) every 4 months, chest CT every 6 months, determination of the serum carcinoembryonic antigen (CEA) level every 3 months and colonoscopy annually. Adjuvant chemotherapy after the initial hepatectomy basically consisted of systemic l-leucovorin (LV)/5-FU (RPMI regimen) plus hepatic arterial infusion of 5-FU for 1 year after surgery. After recurrence, irinotecan (CPT-11)-based chemotherapy was performed since 2001. Oxaliplatin was not available in Japan until 2005, therefore we did not use it in this study.

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Table I. Univariate analysis of the prognostic factors influencing survival due to recurrence after an initial hepatectomy.

Category	No. of patients	Overall survival (%)		p-value
		3 years	5 years	
Gender				
Male	24	30.2	30.2	0.153
Female	17	14.9	7.5	
Age				
<70 years	30	26.7	21.4	0.685
≥70 years	11	15.9	15.9	
Primary location				
Colon	24	33.9	25.4	0.580
Rectum	17	15.8	15.8	
Synchronicity				
Synchronous	20	16.7	8.3	0.677
Metachronous	21	28.6	28.6	
Serum CEA level before the initial hepatectomy				
<200 ng/ml	34	29.6	24.7	0.020
≥200 ng/ml	4	0.0	0.0	
Number of hepatic metastases at the initial hepatectomy				
Single	20	30.4	20.3	0.202
≥2	21	18.9	18.9	
Maximum size of tumor at the initial hepatectomy				
<50 mm	31	35.3	29.4	0.012
≥50 mm	10	0.0	0.0	
Positive LNs at the primary site				
Yes	30	13.8	9.2	0.028
No	8	68.6	68.6	
Disease-free interval (DFI) after the initial hepatectomy				
≥12 months	14	31.3	31.3	0.053
<12 months	27	21.0	15.8	
Repeat reduction surgery				
Yes	16	44.6	44.6	<0.001
No	25	7.2	0.0	
Anatomical resection				
Yes	27	15.2	15.2	0.110
No	14	45.7	30.5	

LNs, lymph nodes.

Eleven characteristics were analyzed of the 41 recurrent patients at the initial hepatectomy: gender, age at the initial hepatectomy, location of the primary tumor, synchronicity, the serum CEA level before the initial hepatectomy, the number of hepatic metastases at the initial hepatectomy, the maximum size of the tumor at the initial hepatectomy, the lymph node status of the primary tumor, the disease-free interval (DFI) after the initial hepatectomy, the presence or absence of repeat reduction surgery and the type of initial hepatic resection.

A statistical analysis was performed using the StatView-J program ver. 5.0 with the Windows XP operating system. Survival was calculated by the Kaplan-Meier method and the findings were compared for significance by the log-rank test. The Cox proportional hazard regression model was used to assess the independent prognostic influence of various categories. The characteristics of clinical features in patients with or without repeat reduction surgery were determined by either the Chi-square test or Fisher's exact test. A value of $p < 0.05$ was considered to be significant.

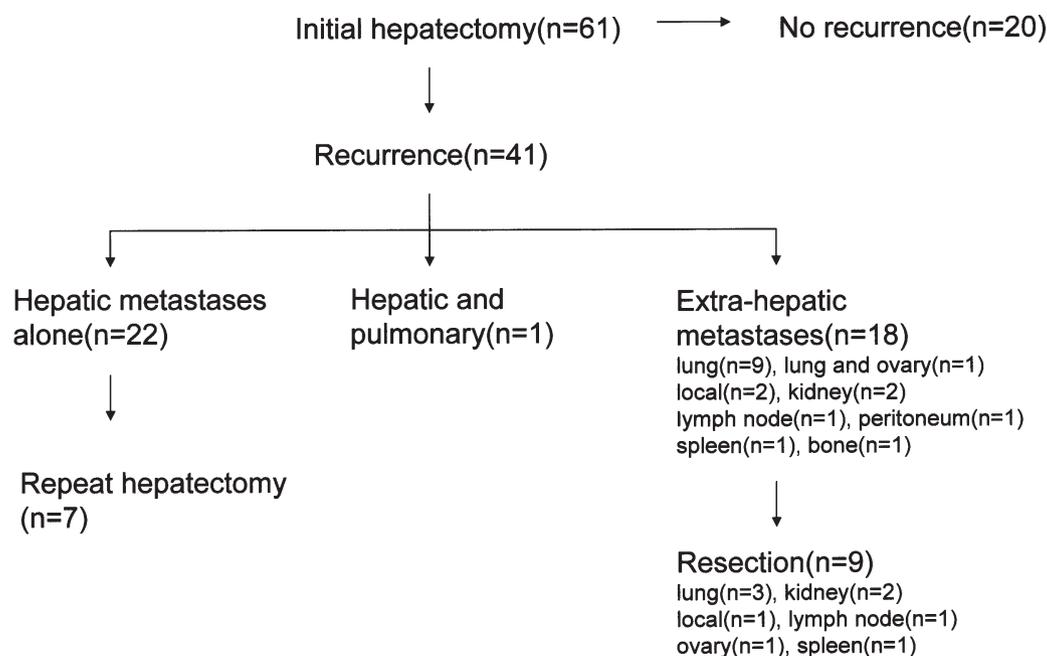


Figure 1. A schematic diagram of the 61 patients who underwent a hepatic resection. Sixteen patients had repeat reduction surgery. Of these patients, 7 had a repeat hepatectomy, while 9 had a resection of extra-hepatic metastases.

Table II. Multivariate analysis of prognostic factors at the initial hepatectomy.

Category	RR	95% confidence interval	p-value
Repeat reduction surgery			
Yes	1.00		0.007
No	4.37	1.50-12.68	
Serum CEA level before the initial hepatectomy (ng/ml)			
<200	1.00		0.583
≥200	1.45	0.39-5.42	
Positive LNs at the primary site			
No	1.00		0.427
Yes	1.88	0.40-8.91	
Maximum size of tumor at the initial hepatectomy			
<50 mm	1.00		0.018
≥50 mm	3.30	1.23-8.87	
Disease-free interval (DFI) after the initial hepatectomy			
≥12 months	1.00		0.252
<12 months	1.92	0.63-5.86	

RR, relative risk; LNs, lymph nodes.

Results

Lesions of recurrence and the resected sites. Fig. 1 shows the lesions of recurrence after an initial hepatectomy and the lesions that had undergone repeat reduction surgery. Twenty-

two patients had recurrences which were localized in the remnant liver. One patient had both hepatic and pulmonary recurrence. Eighteen patients had extra-hepatic recurrences including 9 pulmonary metastases. One had both pulmonary and ovary metastases, 2 had local recurrence, 2 had kidney

Table III. Characteristics of the clinical features in patients with or without repeat reduction surgery.

Category	Repeat reduction surgery		p-value
	Yes (n=16)	No (n=25)	
Gender (n)			
Male	11	13	0.300
Female	5	12	
Age (n)			
<70 years	12	18	0.838
≥70 years	4	7	
Primary location (n)			
Colon	10	14	0.689
Rectum	6	11	
Synchronicity (n)			
Synchronous	7	13	0.617
Metachronous	9	12	
Serum CEA level before the initial hepatectomy (ng/ml)	36.6±52.9	90.4±158.3	0.201
Number of hepatic metastases at the initial hepatectomy	1.75±0.9	1.96±1.0	0.524
Maximum size of tumor at the initial hepatectomy (mm)	30.1±15.6	46.2±29.7	0.055
Positive LNs at the primary site (n)	10	20	0.023
Disease-free interval (DFI) after the initial hepatectomy (n)			
<12 months	7	20	0.045
≥12 months	9	5	

LNs, lymph nodes. Data are expressed as the mean ± standard deviation.

metastases, one had lymph node involvement, one had peritoneal dissemination, one had spleen metastases and one patient had bone metastases. Seven of the 22 patients (32%) who had hepatic recurrence alone underwent a repeat hepatectomy. Nine of 18 patients (50%) who had extra-hepatic recurrences underwent repeat reduction surgery. The resected lesions included 3 lung, 2 kidney, one local, one lymph node, one ovary and one spleen. Eight patients who showed extra-hepatic recurrences underwent a potentially curative resection. One patient who had multiple pulmonary and ovary metastases underwent only an ovary resection to control massive ascites which had been produced by the ovary.

Prognostic factors of recurrent patients after the initial hepatectomy. The median survival after the initial hepatectomy of 61 patients was 38 months and the 5-year survival rate was 33.7% (Fig. 2). A univariate analysis using the log-rank test revealed that the serum CEA level (>200 ng/ml or less) before the initial hepatectomy, the maximum size of the tumor (>5 cm or smaller) at the initial hepatectomy, the presence or absence of positive lymph nodes at the primary tumor and the performance of repeat reduction surgery were significant prognostic factors ($p=0.020$, $p=0.012$, $p=0.028$ and $p<0.001$),

respectively (Table I). The median survival for 16 patients with repeat reduction surgery was 36 months, and the cumulative 5-year survival rate from the time of recurrence was 44.6%. On the other hand, for patients without repeat reduction surgery ($n=25$), the 5-year survival rate from the time of recurrence was 0% (Fig. 3). No postoperative mortality was observed in the group with repeat reduction surgery. Next, five characteristics with a p -value <0.1 based on a univariate analysis were entered into the multivariate analysis. In the multivariate analysis, the presence of repeat reduction surgery and the maximum tumor size (>5 cm or smaller) at the initial hepatectomy were found to be independent prognostic factors ($p=0.007$, $p=0.018$), respectively (Table II).

Characteristics of the clinical features in patients with or without repeat reduction surgery. Sixteen patients underwent repeat reduction surgery. Seven patients had repeat hepatectomies while 9 had a resection of extra-hepatic recurrences (Fig. 1). The rate of positive lymph nodes at the primary tumor and a DFI of 12 months or less after the initial hepatectomy were significantly higher in the patients without repeat reduction surgery ($p=0.023$, $p=0.045$), respectively (Table

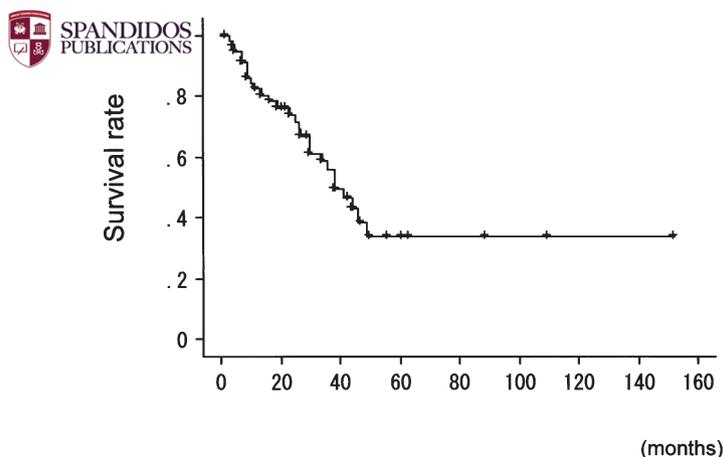


Figure 2. Cumulative survival curves measured from the time of the initial hepatectomy. The median survival after the initial hepatectomy of 61 patients was 38 months and the 5-year survival was 33.7%.

III). The maximum size of the tumor at the initial hepatectomy also tended to be larger in the groups without rather than with repeat reduction surgery ($p=0.055$).

Discussion

The 5-year survival rate has been reported to be 28-40% in patients with an initial hepatic resection for colorectal metastases (1-6). Unfortunately, 70-80% of these patients develop recurrent disease after the initial hepatectomy (1). Prognostic factors after the initial hepatectomy remain controversial in such recurrent patients (18-20) and identifying the prognostic factors may therefore help us to design more individualized treatments for these recurrent patients.

Although our study may be of small scale, there are few reports which have focused on the appropriate treatment for recurrent patients. In this study, we clarified that repeat reduction surgery and the tumor size at the initial hepatectomy (<5 cm) were independent favorable prognostic factors for patient survival. The 5-year survival rate of these 16 patients who underwent repeat reduction surgery was 44.6%. These results revealed a better survival rate, in comparison to patients without repeat tumor reduction surgery.

The DFI and positive lymph nodes at the primary site were found to be significantly different between the patients with and without repeat reduction surgery. In addition, several reports have also mentioned that DFI after the first hepatectomy is an important prognostic factor (9,10,12,19). Patients with a longer DFI after the initial hepatectomy and with negative lymph nodes at the primary site may be therefore good candidates for repeat reduction surgery.

Several patients in the group who underwent repeat reduction surgery continued to demonstrate a disease-free status during the 49-month follow-up period in our study. Although, the median survival time of patients with recurrent and unresectable colorectal cancer metastases has now reached over 20 months because of recent advances in chemotherapy (21-23), it is still very rare for such patients to demonstrate a disease-free status. We also have reported the poor prognosis of unresectable colorectal liver metastases

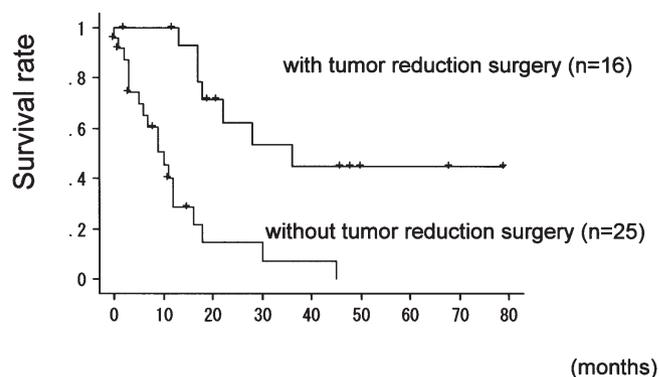


Figure 3. Cumulative survival curves measured from the time of recurrence in patients with or without repeat reduction surgery. The survival rate of patients with repeat reduction surgery was higher than that of patients without it ($p<0.001$).

(24). We therefore recommend repeat reduction surgery when the recurrent lesions are resectable.

Repeat reduction surgery may not be recommended if the patients have a short DFI. Presumably, one of the causes for early recurrence was the oversight of unsuspected metastases which could not be detected at the initial hepatectomy by various imaging modalities including CT and MRI. Recently, we used F18 fluorodeoxyglucose-positron emission tomography (FDG-PET) for preoperative screening at the initial hepatectomy. Several papers have reported that FDG-PET screening before a hepatectomy improves patient selection (25-27) while also increasing the survival rate (28). Therefore, if FDG-PET can be routinely performed, it may reduce the early recurrent cases, while also increasing the number of resectable recurrent cases.

We herein identified that repeat reduction surgery and the size of the tumor in the initial hepatectomy (<5 cm) were independent prognostic factors in the recurrent patients. Furthermore, we also recognized that the DFI and the lymph node status at the primary site might be prognostic of a longer survival. In well-selected patients, repeat reduction surgery should thus be considered for resectable recurrence after a potentially curative resection of colorectal hepatic metastases.

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