

# Repeat Hepatic Resections for Metastatic Colorectal Cancer

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## Objective

The authors weighed the risks and benefits of repeat liver resections for colorectal metastatic disease.

## Method

In the 6-year period between January 1985 and June 1991, 499 patients underwent liver resections for colorectal metastases at the Memorial Sloan-Kettering Cancer Center. Of these, 25 patients had repeat surgical resections for isolated recurrent disease to the liver. The clinical data for these patients were reviewed.

## Results

The median interval between the two resections was 11 months. There were no perioperative deaths, and the complication rate was 28%. Median follow-up after the second liver resection is 19 months, with median survival of 17 months for nonsurvivors. Although the median survival after the second resection is 30 months, 20 of the 25 patients have had recurrences with a median disease-free interval of only 9 months. No characteristic of primary or metastatic disease predicted outcome, including time between presentation of the primary and development of liver metastases, disease-free interval after the first liver resection, and bilobar liver involvement.

## Conclusions

Although repeat liver resections can be performed safely and improve survival, the likelihood of cure from such resection therapy is low. This likelihood of further recurrences encourage studies of adjuvant or alternative treatments of this population.

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Liver resection for metastatic disease from colorectal cancer has been practiced since the 1950s,<sup>1</sup> but only recently has such surgical therapy received general acceptance.<sup>2-5</sup> During the last decade, numerous reports have confirmed that patients treated by resections of liver colorectal metastases have a median survival of approximately 30 months and 5-year survivals from 25% to

40%.<sup>2,4-7</sup> This is a significant improvement over results of untreated colorectal liver metastases, for which median survival is between 5 to 14 months, and 5-year survivors are rare.<sup>8-10</sup> In the 5% of colorectal cancer patients who have isolated metastases to the liver, surgical resection currently is considered the treatment of choice.<sup>2,4,5</sup>

The role of repeat resection for a second liver metastasis is less secure. In patients who undergo a first liver resection for metastatic disease from colorectal cancer, between 17% to one third will have isolated recurrent liver metastases.<sup>11-13</sup> Of these, approximately one third will be candidates for further resection.<sup>11,12</sup> Although at least eight reports have been published that examine the re-

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**Table 1. RESULTS OF PAST STUDIES ON REPEAT HEPATIC RESECTIONS**

Author	Time (yr)	Year	All Liver Resections	Liver Only Recurrence	Resected	Mortality	Follow-Up			Survivors	
							NED	AWD	DOD	2-yr	5-yr
Vaillant	21	1993	189	60	16	1/16	26, 33, 38, 93	8, 9, 10	14, 14, 15, 24, 24, 32, 47, 61	9	2
Bozzetti	10	1992	120	34	10	1/11	17, 24, 42	6, 16	12, 15, 22, 25	3	0
Hohenberger	7	1990	105	12	6	0/6	—	—	—	1	0
Griffith	17	1990	106	—	9	1/9	9, 19, 21, * 25, * 31, 50, 67	16	1	3	1
Fortner	14	1988	380	8	3	0/3	5	39	16	1	0
Nordlinger	15	1987	80	21	6	0/6	2, 12	28, 14, 16	10	1	0
Butler	31	1986	62	10	2	0/2	6, 17	—	—	0	0
Lange	15	1989	82	—	9	0/9	1, 3, 23, 35	6	6, 15, 24, 41	3	0
Total			1124		61					21	3
Current series	6	1993	499	—	25	0/25	†	†	†	11	0

\* Rendered disease free by subsequent third liver resection.

† Rendered disease free by subsequent lung resection.

Time = length in years covered by study; mortality = perioperative mortality.

sults of hepatic surgery in this setting (Table 1) and generally advocate resection of such recurrent liver disease, none of these studies can be considered definitive.<sup>3,11,12,14-18</sup> All have a small number of patients (median = 6), and most span a long period in experience of the respective institutions (median = 15 years) (Table 1). The current study examined 25 patients who underwent repeat liver resections for colorectal metastases in the last 6 years in a single institution, to determine if outcome from such repeat resections justified the morbidity.

## MATERIALS AND METHODS

In the 6-year period between January 1985 and July 1991, patients were identified who had two liver resections for metastatic disease from a colorectal primary disease. During this study, 499 patients underwent liver resections for metastatic colorectal cancer at the Memorial Sloan-Kettering Cancer Center. Of these, 44 (9%) were re-explored subsequently for presumed resectable liver recurrence. Nineteen patients who underwent re-exploration were found to have unresectable disease, two of whom were found to have unresectable isolated liver metastases and were treated by hepatic artery infusion chemotherapy. Twenty-five patients with liver as the only site of recurrent metastatic disease received surgical resection as treatment. Data regarding these patients form the basis of the current report.

Data for these patients were extracted from the hospital and office charts and interviews with the patients. Data examined included 1) demographics (including age and sex); 2) clinical course of primary, recurrent, and

metastatic disease; 3) pathology of primary, recurrent, and metastatic disease; 4) surgical and adjuvant treatments of the primary disease or metastases; and 5) outcome. Follow-up was with the patient, patient's family, or attending physician.

Survival was calculated according to the methods of Kaplan and Meier.<sup>19</sup> The log-rank test was used to compare differences in survival distributions observed in subsets of patients.<sup>20</sup> Survival end points are based on survival after primary disease and after each of the liver resections for metastases.

## RESULTS

Eleven men and 14 women underwent repeat resections of hepatic colorectal metastases. The median age of the patients was 54 years (range = 33 to 75 years). Median follow-up from resection of the primary tumor was 37 months (mean = 42 months; range = 12 to 87 months). Median follow-up from the first liver resection was 35 months (mean = 36 months; range = 11 to 87 months). Median follow-up from the second resection was 19 months (mean = 22 months; range = 4 to 59 months). Median survival of nonsurvivors calculated from time of the second resection is 17 months.

### Pathology

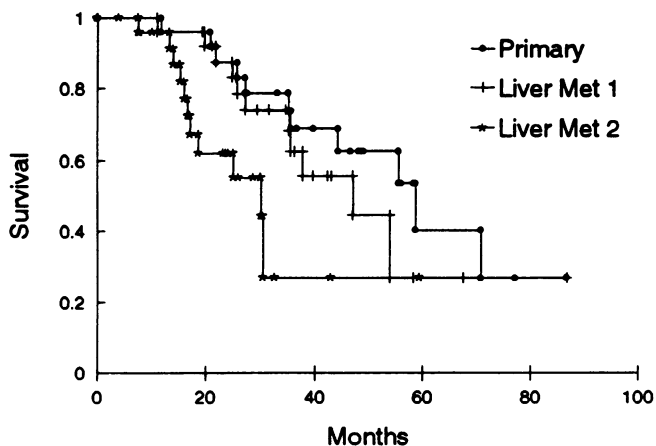
#### Primary

Six of the patients had metastatic disease from right colonic primary disease. One case was from the transverse colon, four were from the left colon, eight

**Table 2. CHARACTERISTICS OF PATIENTS UNDERGOING REPEAT LIVER RESECTION FOR COLORECTAL METASTASES**

Patient	Age/Sex	Primary Location/Stage	First Hepatic Resection			Second Hepatic Resection			Status Follow-Up (mo)		
			DFI (mo)	Operation	Nodules	DFI (mo)	Operation	Nodules		Adj	
1	62/F	Rectum/C	0	L lobe	1	R wedge	12	R wedge	1	CRYO	NED 8
2	65/F	Rectum/B	0	R wedge	1	R triseg	4	R triseg	1	SC	NED 10
3	52/M	Sigmoid/C	0	R wedge	1	R lobe, L wedge	60	R lobe, L wedge	3	IMM	NED 24
4	38/M	Rectum/C	0	R wedge	1	R lobe	12	R lobe	1	—	NED 26
5	56/F	Sigmoid/B	0	R wedge/L wedge	4	R triseg	6	R triseg	2	HAC/SC	NED 30
6	65/F	T colon/C	0	L lat seg	1	R seg	30	R seg	1	—	NED 29*
7	50/F	Sigmoid/C	9	R wedge	1	R wedge	9	R wedge	1	BT	NED 59†
8	66/F	Sigmoid/C	19	R wedge	2	R seg	32	R seg	1	HAC/SC	AWD 4
9	72/M	L colon/C	0	L lobe	2	R wedge	16	R wedge	1	—	AWD 15
10	49/F	L colon/B	0	L lat seg	1	R wedge	8	R wedge	1	—	AWD 16
11	54/M	R colon/C	5	R seg/L wedge	2	R lobe	18	R lobe	1	—	AWD 23
12	56/F	R colon/C	14	L lat seg/R wedge	2	R wedge	5	R wedge	1	—	AWD 24
13	39/M	R colon/B	0	L lobe	1	R seg	3	R seg	1	—	AWD 33
14	72/M	Rectum/C	0	L lat seg	2	R wedge	18	R wedge	1	—	AWD 42
15	65/M	R colon/C	0	R lobe	7	R wedge	3	R wedge	3	SC	DOD 8
16	33/F	Rectum/B	0	L wedge	1	L lobe	8	L lobe	3	—	DOD 13
17	59/F	Sigmoid/C	0	R wedge	1	R triseg	12	R triseg	1	—	DOD 14
18	36/F	R colon/C	0	R seg	1	R seg	26	R seg	1	SC	DOD 15
19	75/F	L colon/B	34	R lobe	1	L wedge	8	L wedge	1	SC	DOD 16
20	38/F	Sigmoid/C	0	R lobe	5	L wedge	3	L wedge	3	HAC/SC	DOD 16
21	36/M	Sigmoid/C	0	R wedge	2	R lobe	17	R lobe	1	—	DOD 17
22	58/M	Sigmoid/B	0	R wedge	1	R lobe	6	R lobe	1	—	DOD 19
23	55/F	Rectum/C	0	R triseg	7	L wedge	15	L wedge	1	—	DOD 25
24	71/M	R colon/C	0	R wedge/L wedge	2	L wedge	4	L wedge	2	—	DOD 30
25	47/F	L colon/C	0	R lobe/L wedge	4	L wedge	12	L wedge	1	—	DOD 31

Adj = adjuvant therapy after second liver resection; BT = brachytherapy; CRYO = cryotherapy; IMM = immunotherapy; HAC = hepatic artery chemotherapy; SC = systemic chemotherapy; DFI = disease-free interval; Follow-up = calculated from time of second liver resection; seg = segmental resection; stage = Dukes stage of primary; triseg = trisegmentectomy; wedge = wedge resection.  
 \* Rendered disease free by subsequent third liver resection.  
 † Rendered disease free by subsequent lung resection.



**Figure 1.** Results of repeat resections for liver metastases from colorectal cancer. Overall survival is shown as calculated from time of 1) resection of primary disease, 2) first liver resection, and 3) second liver resection.

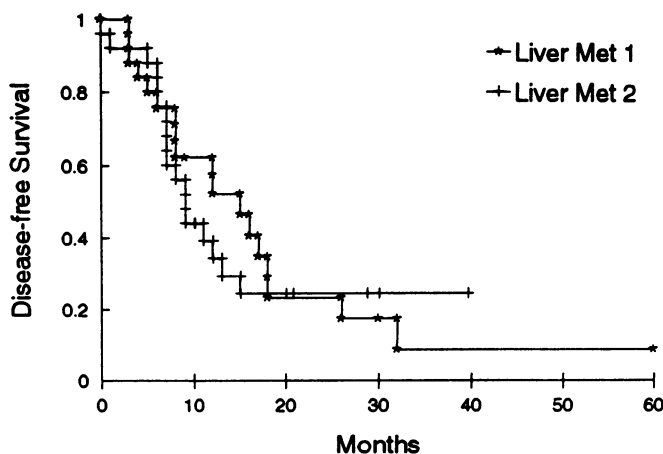
were from the sigmoid colon, and six were from the rectum (Table 2). The primary lesion could be classified as a Dukes' B lesion in 7 cases, and as a Dukes' C lesion in 18 cases.

**First Liver Metastases**

In 20 of these cases, the first liver metastatic disease was synchronous with the primary lesion (Table 2). Metastatic disease was in the left lobe in 7 cases, in the right lobe in 13 cases, and bilobar in 5 cases. The median number of lesions was two (range = 1 to 7). Five cases had lesions 5 cm or larger.

**Second Liver Metastases**

The median disease free interval before the second liver metastases was 12 months (Table 2). The metastatic disease recurred in the lobe opposite to the initial liver disease in 11 cases, for a total of 16 cases of bilobar dis-



**Figure 3.** Comparison of disease-free survival after the first liver resection with disease-free survival after the second liver resection.

ease. In six of the cases of second liver metastases, the lesions were larger than 5 cm.

**Therapy of Liver Metastases**

Surgical therapy for the first liver metastases consisted of 11 wedge resections, 4 left lateral segmentectomies, 2 anatomic segmentectomies, 7 lobectomies, and 1 trisegmentectomy. Nine patients received adjuvant chemotherapy for synchronous node-positive colorectal cancer. Although margins were grossly negative, there was enough concern to use brachytherapy in two cases and cryotherapy in one (Table 2).

Surgical therapy for the second liver metastases consisted of 12 wedge resections, 4 anatomic segmentectomies, 6 lobectomies, and 3 trisegmentectomies. Ten patients received adjuvant therapy, including chemotherapy in seven cases, brachytherapy in one case, cryotherapy in one case, and immunotherapy in one case (Table 2).

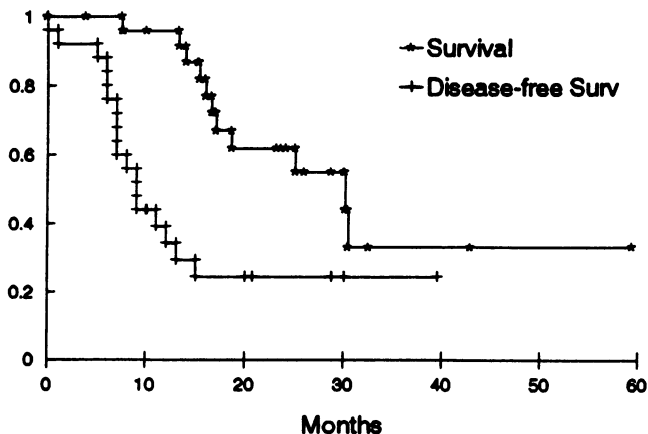
**Outcome**

**Perioperative Course**

For the repeat liver resection, there was no in-hospital or 30-day mortality. Seven perioperative complications occurred in these patients (28%). These included a wound infection, two cases of biloma, one intra-abdominal abscess, one significant pleural effusion, one case of congestive heart failure, and one case of bacteremia from an unidentified source. The median hospital stay for the repeat liver resections was 11 days (range = 7 to 20 days).

**Overall Survival**

At the time of this report, 11 patients have died from disease. Seven others are alive with disease. Seven currently are without evidence of disease, but two of these



**Figure 2.** Comparison of survival with disease-free survival after a second liver resection for metastases from colorectal cancer.

**Table 3. PREDICTORS OF OUTCOME IN PATIENTS UNDERGOING REPEAT LIVER RESECTIONS FOR COLORECTAL METASTASES**

Parameter	n	Overall Survival	Disease-Free Survival	
		p	p	
Demographics				
Age	≤50/>50 yr	14/11	0.8	1.0
Sex	M/F	11/14	0.6	0.4
Primary tumor				
Site	Rectal-sigmoid/colonic	14/11	0.9	0.4
Dukes stage	B/C	7/18	0.6	0.9
First liver metastases				
Size	<5 cm/≥5 cm	14/11	0.3	0.6
Size of resection	<Lobectomy/≥lobectomy	13/12	0.7	0.4
Timing with primary	Synchronous/metachronous	20/5	0.1	0.6
Other				
Site of liver metastases	Unilobar/bilobar	9/16	0.9	0.7
No. of metastases	<4/≥4	17/8	0.06	0.4
Disease-free interval	<12 mo/> 12 mo	9/16	0.1	0.9

patients are disease-free because of further surgical resection of recurrence (one liver, one lung). Therefore, there have been 20 recurrences after the second liver resections. These include ten liver, three lung, one lung and liver, five intra-abdominal, and one spine lesion as sites of further recurrence. There have been 11 2-year survivors after the second liver resection. No patient is as yet a 5-year survivor (Table 2).

Survival as calculated from time of surgical treatment for the primary disease, time of treatment for first liver resection, and time of treatment of second liver are shown in Figure 1. Mean actuarial survival was 58.7 months from the time of the primary disease, 47.0 months from the time of the first liver resection, and 30.2 months from the time of the second liver resection.

#### *Disease-Free Survival*

The median disease-free interval is 9 months after the second liver resection compared with 12 months after the first liver resection (Fig. 2). Comparison of disease-free survival with overall survival after the second liver resection is shown in Figure 3. The median disease-free survival is 9 months; the median survival is 30.2 months.

#### **Predictors of Outcome**

Parameters analyzed as potential predictors of outcome included demographics (age, sex), characteristics of the primary tumor (site, Dukes' stage), characteristics of the first liver metastases (size, size of resection, timing with primary disease), and combined characteristics of the liver metastases (unilobar vs. bilobar involvement, total number of metastases, disease-free interval). These

were analyzed by univariate analysis using log-rank test. None of these parameters predicted survival or disease-free survival (Table 3).

#### **DISCUSSION**

Reports of clinical experience in resecting recurrent liver metastases demonstrate that repeat hepatic resections can be performed safely.<sup>3,11,12,14-17</sup> There were no operative deaths in the current series. Further, there have been only two perioperative deaths in the previous 46 patients reported,<sup>12,15</sup> (Table 1) for a total mortality of approximately 3% (3/87). Two previous series had reported morbidity associated with a repeat hepatic resection. Lange et al. reported a complication rate of 15%,<sup>17</sup> whereas Bozetti reported a complication rate of 50%.<sup>12</sup> The complications reported by the previous studies included biliary fistula, hepatic duct stenosis, hemorrhage, hepatic failure, and subphrenic abscess. The complication rate in the current report is 28%. These mortality and morbidity figures compare well with those reported for first resections of liver metastases.<sup>2,4,5</sup> All studies of repeat liver resections reported to date, including the current one, are retrospective in nature and contain highly selected populations. The paucity of cardiopulmonary complications reported in previous studies and the current study attests to the selection against patients with significant cardiopulmonary risk. Nevertheless, these results are a testimony to the clinicians' ability to select patients who can safely undergo repeat liver surgery.

Although repeat liver resections can be performed safely, the benefits of such resections are less clear. A comparison of resection results to historic data on un-

treated colorectal metastases strongly suggests that survival is prolonged by surgical therapy. Median survival from untreated colorectal liver metastases ranges from 4.5 to 14.2 months.<sup>5,10,21,22</sup> Median survival of untreated cases of recurrence after liver resection is 4 months.<sup>16</sup> The current results also compare well with standard chemotherapeutic regimens. Most published results of chemotherapy for liver metastases report less than a 30% response, and a median response duration of less than 6 months.<sup>23</sup> The median survival in the current study is more than 30 months as calculated from the time of second liver resection and more than 47 months as calculated from the time of the first liver resection. However, it would not be possible to consider resection of second metastatic lesions to the liver curative therapy. In the current study, tumors have recurred in 20 patients in less than an 18-month mean follow-up period. It also is sobering to note that there are only three 5-year survivors reported in the literature (Tables 1 and 2). The multitude of adjuvant therapies attempted in this and other reports attests to the clinicians' frustration in dealing with the problem, as well as lack of proven efficacy of any particular regimen. It is unknown how other methods of ablating tumor, such as alcohol injection or cryosurgery, may compare to surgical excision in terms of effectiveness or toxicity.

Other studies had attempted to identify parameters that could distinguish subpopulations of patients with recurrent liver metastases who have particularly favorable prognoses after resections. Bozzetti contends that patients with a disease-free interval of greater than 1 year between the first and the second liver resections had a greater disease-free survival after the second resection.<sup>12</sup> This conclusion was based on a very small number of patients. The current study reports the largest single institution experience to date. No parameter can be identified that is related significantly to outcome. It is not surprising that once a second liver metastases has become apparent, the prognosis is poor and liver metastatic disease dominates the clinical course.

Resection therapy for liver metastases from colorectal primaries has only been widely accepted during the last decade. Resections of second liver metastases from colorectal cancer are rare events. Fewer than 5% of all patients undergoing first resections will have second resections. These factors explain the paucity of data regarding outcome from these second resections. However, certain conclusions are clear. Second resections can be performed safely. Such resections may provide prolonged survival. In the absence of other proven therapy, resection treatment of patients with no medical contraindications to major surgery still is the standard of care. However, the likelihood of further recurrences encourages the study of alternate or adjuvant therapy in the treatment of these patients.

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