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Repeat Hepatic Resection as Effective Treatment for Recurrent Colorectal Liver Metastases

Todd M. Tuttle, MD, Steven A. Curley, MD, and Mark S. Roh, MD

Background: Approximately 20–40% of patients who undergo liver resection for colorectal metastases develop recurrent disease confined to the liver. The goals of this study were to determine whether the survival benefit of repeat hepatic resection justified the potential morbidity and mortality.

Methods: A retrospective review was performed on all patients who underwent liver resection for colorectal cancer metastases between 1983 and 1995 (N = 202). Repeat liver resections were performed on 23 patients for recurrent metastases.

Results: There were no operative deaths in the 23 patients, and the postoperative morbidity rate was 22%. The 5-year actuarial survival rate after repeat resection was 32%, with a median length of survival of 39.9 months. There were three patients who survived for >5 years after repeat resection. Sixteen patients (70%) developed recurrent disease at a median interval of 11 months after the second resection; 10 of these 16 patients (62%) had new hepatic metastases. No clinical or pathological factors were significant in predicting long-term survival.

Conclusions: Repeat liver resection for recurrent colorectal metastases (a) can be performed safely with acceptable mortality and morbidity rates and (b) may result in long-term survival in some patients.

Key Words: Hepatic resection—Colorectal liver cancer—Liver metastases—Repeat hepatic resection.

Approximately 50% of patients with colorectal cancer develop hepatic metastases during the course of their disease (1,2). Untreated patients with colorectal liver metastases have a poor record of survival (median 6–13 months), with only a few 5-year survivors reported in the literature (1,3,4). Systemic chemotherapy has been associated with limited success, with antitumor response rates of ~30% and a median length of survival of 12–15 months (5–7). In contrast, hepatic resection of colorectal metastases has consistently resulted in 5-year survival rates of 25–35%, with a median length of survival of 25–35 months (8–10). With operative mortality rates of ≤5% at most major centers, liver resection is currently considered the treatment of choice for patients with colorectal metastases isolated to the liver (11,12).

After liver resection, nearly 75% of patients develop recurrent disease (13,14). The liver is the only site of recurrence for ~20–40% of patients after hepatic resection. Of patients with isolated hepatic recurrences, 25–30% may be candidates for repeat hepatic resection (15,16). However, the role of repeat resection for recurrent colorectal liver metastases is not well established. Although a number of series have been published, most involve fewer than 10 patients, and only four 5-year survivors have been reported to date (16–22). Moreover, other investigators have reported that repeat hepatic resection is more difficult and associated with a higher incidence of hemorrhagic complications (20).

The purpose of this study was to determine whether the long-term survival results of repeat hepatic resection for recurrent colorectal metastases would justify the potential morbidity. We also exam-

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From the Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA.
Address correspondence and reprint requests to Dr. Mark S. Roh, Division of Surgical Oncology, Allegheny General Hospital, 320 E. North Ave., CCC 5th floor, Pittsburgh, PA 15212, USA.
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ined various clinical and pathological parameters in an attempt to predict which patients might benefit from a second liver resection.

METHODS

A retrospective review was performed on all patients who underwent liver resection for colorectal cancer metastases at The University of Texas M.D. Anderson Cancer Center between 1983 and 1995. Patients with colorectal metastases to the liver were evaluated via history, physical examination, chest radiography, colonoscopy, and computed tomography (CT) of the abdomen and pelvis. Patients with metastatic disease confined to the liver based on the above evaluation and considered medically fit to tolerate a laparotomy were then evaluated by CT portography and angiography. The number of liver tumors and their relationship to the hepatic and portal veins were noted.

Patients with more than four lesions on preoperative diagnostic imaging studies were considered ineligible for resection. Evidence of tumor abutment to portal or hepatic veins responsible for the blood supply or drainage of the hepatic parenchyma not intended for resection excluded some patients from operation because a margin-negative resection would have been impossible. A standardized approach was used for intraoperative staging, which has been described in further detail elsewhere (23). Briefly, a thorough exploration of the peritoneal cavity is performed via a generous subcostal incision. The peritoneal surfaces are visualized and palpated, and any suspicious lesions are examined via biopsy. Likewise, the periportal lymph nodes are inspected, and any enlarged or hardened lymph nodes are also examined via biopsy. Intraoperative hepatic ultrasound was used to identify any additional lesions not palpated or visualized on preoperative imaging. Patients with more than four metastases or with positive periportal lymph nodes did not undergo resection.

During this time period, hepatic resection was performed on 202 patients with metastases from colorectal primary tumors. Repeat resections were performed on 23 patients for recurrent metastases. Noncurative resections and liver biopsies were excluded from review. The patient demographics and clinical information are listed in Table 1.

Statistical Analysis

Data were obtained for these patients retrospectively from patient histories, operative and pathology reports, outside records, and patient interview. Survival was calculated according to the Kaplan and Meier methodology (24). The log-rank test was used to compare differences in survival distributions between different variables (25). Survival and disease-free survival were calculated from the time of the repeat liver resection.

TABLE 1. *Clinical and pathologic data of 23 patients undergoing repeat hepatic resection*

Age (yr)
Median 60
Range 31–74
Sex
Male n = 16
Female n = 7
Primary Dukes' stage
B n = 2
C n = 7
D n = 14
Location primary
Rectal n = 6
Colon n = 17
DFI-1 (between primary and first liver metastases)
Median 0 mo
Range 0–51 mo
DFI-2 (between first liver resection and second liver metastases
Median 14 mo
Range 2–48 mo
Adjuvant chemotherapy
At time of primary n = 12
At time of first metastases n = 12
At time of recurrent metastases n = 9
Size of recurrent liver metastasis
Median 2.6 cm
Range 1–7.8 cm
No. of recurrent liver metastases
Median n = 1
Range 1–3

DFI, disease-free interval.

RESULTS

The distribution of types of resection for the first and second hepatic resections are shown in Table 2. There were no postoperative deaths in this series of 23 patients. The morbidity rate was 22% (pneumonia, n = 2; intraabdominal abscess, n = 2; fascial dehiscence, n = 1). The median blood loss from the repeat liver resection was 800 ml (range 100–5,000). The median red blood cell transfusion requirement was

TABLE 2. *Type of resections*

Procedure	First liver resection	Second liver resection
Lobectomy	7	7
Segmentectomy	5	12
Wedge	11	4

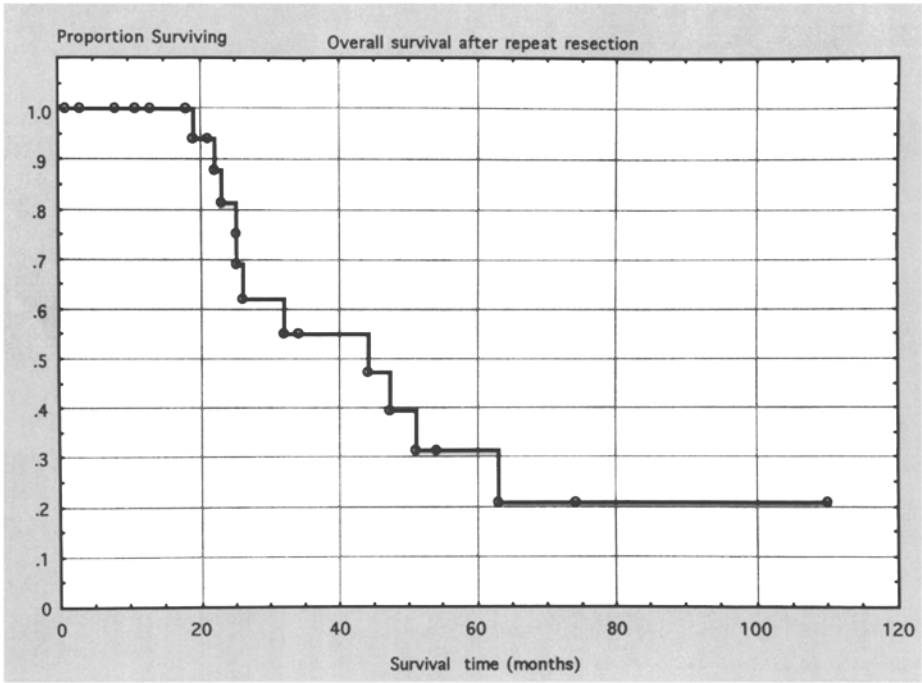

FIG. 1. Actuarial survival of patients undergoing repeat hepatic resection for recurrent colorectal metastases.

0 unit (range 0–8); 17 patients (74%) did not require perioperative blood transfusion.

The actuarial overall lengths of survival and disease-free survival after repeat resection are shown in Figs. 1 and 2, respectively. The 5-year overall and disease-free 5-year survival rates were 32% and 16%, respectively. The median length of survival and median disease-free length of survival were 39.9 and 12.7 months, respectively. Thirteen, seven, and three patients survived 2, 3, and 5 years, respectively, after

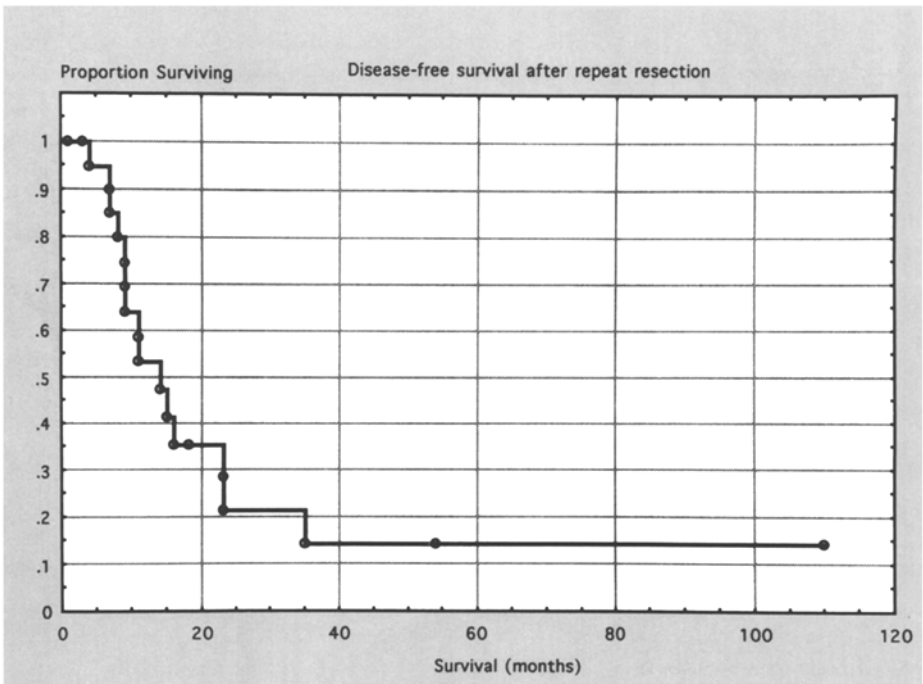

FIG. 2. Actuarial disease-free survival of patients undergoing repeat hepatic resection for recurrent colorectal metastases.

TABLE 3. *Prognostic factors and survival*

Factors	p	
	Overall survival	DFS
Synchronous/metastasis	0.42	0.59
DFI-1 (primary to first liver metastasis <12 mo/≥12 mo	0.95	0.68
DFI-2 (first liver resection to second liver metastasis) <12 mo/≥12 mo	0.87	0.98
Size of recurrent liver metastasis <4 cm/≥4 cm	0.17	0.27
No. of recurrent liver metastases 1/>1	0.66	0.98
EBL <1 L/≥1 L	0.86	0.31
PRBC transfusions, Yes/No	0.58	0.36
Type of procedure Lobectomy/segmental/wedge	0.36	0.66
Age <60/≥60 yr	0.94	0.34
CEA <10/≥10	0.94	0.92
Stage of primary LN+/LN−	0.80	0.49

EBL, estimated blood loss; PRBC, packed red blood cell; LN, mesenteric lymph node status.

the second resection. Two of the three 5-year survivors are presently free of disease.

Potential prognostic indicators listed in Table 3 were examined to predict outcome after repeat liver resection. Several of these factors have been shown to be significant predictors of survival after initial liver resection for colorectal metastases (10). However, none of these variables had prognostic significance in predicting either long-term or disease-free survival after repeat resection.

Sixteen patients (70%) developed recurrent disease after repeat hepatic resection. The median time to recurrence was 11 months, and the pattern of recurrence is shown in Table 4. Two patients with isolated hepatic recurrence underwent a third liver resection; one of these patients has subsequently developed pulmonary metastases, whereas the other has no evidence of disease 34 and 23 months after the second and third liver resections, respectively. Resection of pulmonary metastases was performed on three patients after repeat liver resection; two of these patients have died with recurrent disease, whereas the third has no evidence of disease 67 and 23 months after repeat liver and lung resection, respectively.

DISCUSSION

Approximately 20–40% of patients develop isolated liver recurrence after hepatic resection of colorectal metastases (13,14). The ideal treatment for patients with recurrent colorectal metastases is unclear. Hohenberger reported a 4-month median length of survival for all untreated patients (26). In contrast,

TABLE 4. *Patterns of recurrence after repeat hepatic resection*

Liver only	3 (19%)
Extrahepatic only	6 (37%)
Liver plus extrahepatic	7 (44%)
Total	16 (100%)

Recurrences after repeat resection, n = 16 (70%).

patients whose recurrent disease was resected had an improved length of survival. Although these two groups of patients are not comparable, this study does address the potential for improving survival in patients with recurrent colorectal metastases with repeat resection.

A concern regarding repeat liver resection is whether the procedure can be performed with acceptable rates of morbidity and mortality. Previous investigators have reported that hepatic resection for recurrent colorectal metastases is more difficult and is associated with a higher incidence of bleeding complications (20). However, review of the reported clinical experience of repeat hepatic resection indicates that the operative mortality rate is <5% (Table 5). Fong et al. reported a complication rate of 28%, which included wound infection, two cases of biloma, one intraabdominal abscess, one significant pleural effusion, one case of congestive heart failure, and one case of bacteremia from an unidentified source (22). In the present series, we report a 22% complication rate with no operative mortality. These morbidity and mortality figures are comparable with those reported for initial resection (10–12), including a report from our own institution involving the same group of surgeons (23).

Although there is no prospective trial comparing hepatic resection versus nonresection, these data combined with other series indicate that long-term survival is possible after repeat resection for recur-

TABLE 5. *Repeat hepatic resection for recurrent colorectal liver metastases*

Study	No. of patients	Mortality	Median survival	5-year survivors
Griffith et al. (17)	9	1/9	23.0	1
Stone et al. (18)	10	0/10	25.0	0
Bozzetti et al. (16)	10	1/11	23.0	0
Vaillant et al. (19)	16	1/16	33.0	2
Elias et al. (20)	28	1/28	30.0	—
Que and Nagorney (21)	21	1/21	40.8	1
Fong et al. (22)	25	0/25	30.2	0
Current	23	0/23	39.9	3

rent colorectal liver metastases. The Repeat Hepatic Metastases Registry recently reported a 32% 5-year actuarial survival rate after repeat resection of 170 patients from 20 institutions around the world (27). However, to date, only four actual 5-year survivors have been reported (Table 5). The median length of survival in the present study was 39.9 months, with a 5-year actuarial survival rate of 32% as calculated from the time of the second resection. We also report three patients who have survived 5 years after repeat hepatic resection; two remain free of disease. These results are similar to the survival data obtained after first hepatic resection by the same group of surgeons during the same time period (23) and parallel the long-term survival data of initial liver resection reported in other series (8–10).

Several published reports have identified specific determinants of survival for patients undergoing initial hepatic resection for colorectal metastases. Although agreement is not complete for every parameter, the importance of margins of resection, disease-free interval, stage of primary, and the number of metastases is well documented (10,12,28). However, the identification of such prognostic indicators for repeat liver resection is not established. One investigator reported that patients with a disease-free interval of >1 year between the first and the second liver resections had a greater disease-free survival rate after the second resection (16). However, a 5-year survivor was identified in this series whose disease-free interval between liver resections was <1 year. Others have suggested that repeat resection should only be offered to patients with a single recurrent metastasis (18). Nevertheless, two of the three 5-year survivors in the present study had more than one recurrent metastasis at the time of repeat resection. Neither the data in this report nor those from the Repeat Hepatic Metastases Registry (27) identified any significant prognostic indicators in patients who underwent complete resections.

Only a minority of patients (19% in the present study) have recurrences isolated to the liver after repeat hepatic resection of colorectal metastases. In the literature, few series involve any patients undergoing a third liver resection (20,22). Here we report two patients who underwent a third liver resection for recurrent disease. One of these two patients is free of disease 34 and 23 months after the second and third liver resections, respectively. Whether the highly selected patient with an isolated hepatic recurrence after repeat liver resection will benefit from a third liver resection is unknown.

Repeat hepatic resection appears to be a safe and potentially effective treatment for recurrent colorectal metastases. The morbidity, mortality, and survival data after repeat resection are comparable with the results after first hepatic resection. Surgery remains the treatment of choice for colorectal liver metastases because no other treatment modality has been proven to be more effective. Because nearly all patients in this series received chemotherapy at some point in the course of their disease, no definite conclusions can be made regarding the role of adjuvant chemotherapy in the management of patients with recurrent colorectal liver metastases. The data from this and other series suggest that patient selection criteria for repeat hepatic resection should be the same as for the initial resection: satisfactory medical condition, technical ability to obtain negative margins, and the absence of extrahepatic disease. Intraoperative staging including intraoperative hepatic ultrasound should be performed in all cases to exclude those patients unlikely to benefit from resection (i.e., extrahepatic disease or inability to obtain negative margins). Finally, encouraging results with hepatic cryosurgery suggest that this technology may play a future role in the management of patients with recurrent colorectal metastases.

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