Repeat Hepatic Surgery for Colorectal Cancer Metastasis to the Liver

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Objective

The authors addressed whether a repeat hepatic operation is warranted in patients with recurrent isolated hepatic metastases. Are the results as good after second operation as after first hepatic operation?

Summary Background Data

Five-year survival after initial hepatic operation for colorectal metastases is approximately 33%. Because available alternative methods of treatment provide inferior results, hepatic resection for isolated colorectal metastasis currently is well accepted as the best treatment option. However, the main cause of death after liver resection for colorectal metastasis is tumor recurrence.

Methods

Records of 95 patients undergoing initial hepatic operation and 10 patients undergoing repeat operation for isolated hepatic metastases were reviewed for operative morbidity and mortality, survival, disease-free survival, and pattern of failure. The literature on repeat hepatic resection for colorectal metastases was reviewed.

Results

The mean interval between the initial colon operation and first hepatic resection was 14 months. The mean interval between the first and second hepatic operation was 17 months. Operative mortality was 0%. At a mean follow-up of 33 ± 27 months, survival in these ten patients was 100% at 1 year and 88% ± 12% at 2 years. Disease-free survival at 1 and 3 years was 60% ± 16% and 45% ± 17%, respectively. After second hepatic operation, recurrence has been identified in 60% of patients at a mean of 24 ± 30 months (median 9 months). Two of these ten patients had a third hepatic resection. Survival and disease-free survival for the 10 patients compared favorably with the 95 patients who underwent initial hepatic resection.

Conclusions

Repeat hepatic operation for recurrent colorectal metastasis to the liver yields comparable results to first hepatic operations in terms of operative mortality and morbidity, survival, disease-free survival, and pattern of recurrence. This work helps to establish that repeat hepatic operation is the most successful form of treatment for isolated recurrent colorectal metastases.

The incidence of hepatic surgery for colorectal metastasis has increased in the last decade,[1-3] with reported 5-year survival figures of approximately 33%, ranging from 16% to 45%.[2,4,5] Improvements in anesthesia, postoperative care, and better understanding of hepatic anatomy have contributed to low operative mortality rates of 0% to 5%[2,6,7] and a morbidity rate of 25%, ranging from 10% to 60%.[2,8] Furthermore, the available alternative methods of treatment provide inferior results, with most chemotherapeutic regimens yielding less than a 30% response over less than 6 months.[9] Supportive care alone in matched unresected patients yields significantly poorer median survival of 3 to 24 months.[5,10,11] Thus, hepatic resection for isolated colorectal metastasis currently is well accepted as the most successful treatment and the only potentially curative form of treatment.[12,13]

However, the main cause of death after liver resection for colorectal metastasis is tumor recurrence. Between 55% and 80% of patients will develop recurrence,[1,3,7,12,14-16] which involves the liver in 35% to 50% of patients.[1,6,7,8,12,15-19] Isolated hepatic recurrence initially occurs in approximately 30% of patients, with authors reporting between 17% and 55%.[1,3,4,6,7,12,14-16,18-21]

The question we addressed is whether a repeat hepatic operation is warranted in this group of patients with recurrent isolated hepatic metastasis. It would appear that 10% to 40% of such patients are candidates for further surgery.[6,12,14,16,19,21] We have reviewed our institutional experience and the literature to determine if survival *versus* operative morbidity and mortality supports an aggressive surgical approach.

PATIENTS AND METHODS

From January 1984 to November 1995, a consecutive sample of 95 patients underwent hepatic surgery with curative intent for colorectal metastasis at Vanderbilt University Medical Center and the Nashville Veterans Affairs Medical Center. Of these, six patients were identified who underwent a second hepatic operation. Another four patients underwent initial hepatic surgery elsewhere, but repeat hepatic procedures were performed at this institution. The ten repeat operations took place between August 1987 and March 1995. These patients underwent preoperative extensive tumor staging with carcinoembryonic antigen level, computed tomography

(CT) of the abdomen, pelvis, and thorax, CT portography of the liver, and/or whole-body positron emission tomography (PET).[22]

Patients underwent thorough exploratory laparotomy and since 1990, intraoperative ultrasound evaluation. The liver was fully mobilized[23] and examined by bimanual palpation. Ultrasound was performed to assess the extent and number of hepatic tumors and their relationship to intrahepatic vasculobiliary structures. Cholangiogram usually was obtained as well.

In some hepatic operations, cryosurgery was used in combination with standard surgical techniques to ablate all lesions. Ultrasound was used to monitor cryosurgery probe placement and extent of the freeze process. We attempted to obtain a freeze zone larger than 1 cm around tumors. Two freeze and spontaneous thaw cycles were used.

In patients in whom the tumor was adjacent to major vascular structures, occlusion of inflow by placing a vascular clamp across the hepatoduodenal ligament or total hepatic vascular isolation consisting of occlusion of the portal inflow, occlusion of the inferior vena cava above and below the liver and right adrenal vein was used. Otherwise, standard techniques for hepatic resection were used.

Patients were followed at 3- to 6-month intervals with carcinoembryonic antigen levels, abdominal CT scans, and/or PET scans. Tumor recurrence was identified by increasing carcinoembryonic antigen levels or increasing findings on serial radiographic studies.

Data from the ten patients who underwent one or more repeat hepatic operations were collected from office and hospital charts and direct contact with patients. This included demographics, clinical course, pathology (primary site and stage, number, size, and location of lesions), surgical treatment, and outcome in terms of tumor recurrence and survival. Patient survival and recurrence data were compared with that of patients who underwent initial hepatic operations. The literature on repeat hepatic resections for colorectal metastasis was reviewed. When individual patient data were available, they were recorded and summarized with similar primary data from other reports and also used for comparison.

Data are reported as mean ± standard deviation. Survival and disease-free survival were calculated by the Kaplan-Meier product limit estimate of the survivor function (NCSS, Kaysville, UT). Survival curves were compared by Peto and Peto's log-rank testing, and differences were accepted if the probability was < 0.05.

RESULTS

Ninety-five patients underwent initial hepatic surgery for colorectal carcinoma metastasis. In 18 of these pa-

Figure 1. Survival curves for 95 patients who underwent an initial hepatic operation and 10 patients who underwent a second hepatic operation for colorectal carcinoma metastasis to the liver. Standard error of the cumulative proportion surviving is between 4% and 7% for initial hepatic operations and is 12% for second hepatic operations. The number of patients with available follow-up at each time point is shown in the parentheses.
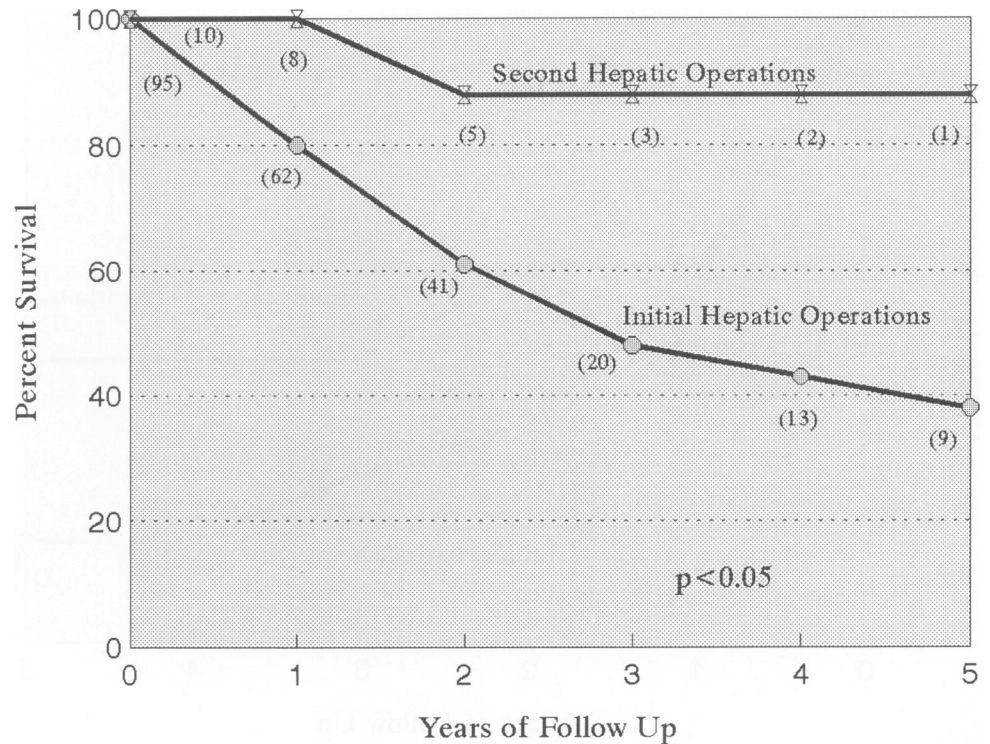
tients, cryosurgical techniques were used in conjunction with standard hepatic resection techniques. There were four operative deaths (4%). Follow-up was available in 100% and current (within 1 month) in 99%. Follow-up averaged 27 ± 28 months, with a median of 21 months and a total of 212 years. Figure 1 shows the 1- to 5-year actuarial survival estimates to be 80% ± 4%, 61% ± 6%, 48% ± 6%, 43% ± 6%, and 38% ± 7%, respectively. Actual 5-year survival was 9 of 28 (32%) patients.

Figure 2 demonstrates the 1- to 5-year actuarial disease-free survival as 57% ± 5%, 35% ± 5%, 27% ± 5%, 16% ± 5%, and 16% ± 5%, respectively. Recurrent colorectal carcinoma metastasis has been found at a mean of 13 ± 11 months and a median of 8 months in 67 of these 95 (71%) patients. This involved the liver in a total of 52 patients (55%) and was confined to the liver in 31 patients (33%).

Of the 31 patients with recurrence confined initially to the liver, 6 (19%) underwent a second hepatic operation. This represents 6% of the 95 patients undergoing initial surgery. Four other patients underwent initial resection at another institution.

The ten patients (6 women, 4 men) who underwent repeat hepatic operations for colorectal carcinoma metastasis were at the time of their initial colon resections 53 ± 10 years of age (median 56 years). The location for the primary resected colon lesion was in the rectum in three patients, in the sigmoid colon in four patients, in the left colon in one

patient, in the transverse colon in one patient, and in the right colon in one patient. The primary stage was B in two patients, C in three patients, and D in 5 patients. Eight of these patients received adjuvant 5-fluorouracil-based chemotherapy, and two also received radiation therapy. All ten patients had isolated hepatic metastasis treated by hepatic surgery either synchronously or up to 39 months later. This interval averaged 14 ± 13 months, with a median of 15 months (Table 1).

The first hepatic operation in these ten patients involved resection of one to three lesions by lobectomy in one patient, left lateral segmentectomy in two patients, and wedge resections in seven patients. Margins were negative in all cases. Total hepatic isolation was used in four patients. Transfusions were required in four of these ten operations, totalling 21 units of packed erythrocytes. There were no operative deaths, but two patients had complications, one a pulmonary embolus, and one a subphrenic abscess. Half of the patients (patients 2, 3, 6, 7, and 9) received postoperative 5-fluorouracil-based chemotherapy.

The findings leading to the diagnosis of recurrent tumor thereafter included an increase in the carcinoembryonic antigen level in most patients (Table 2). The remaining patients had enlarging hypodense lesions on serial CT scans. This prompted complete staging, concluding in the finding of isolated hepatic recurrence.

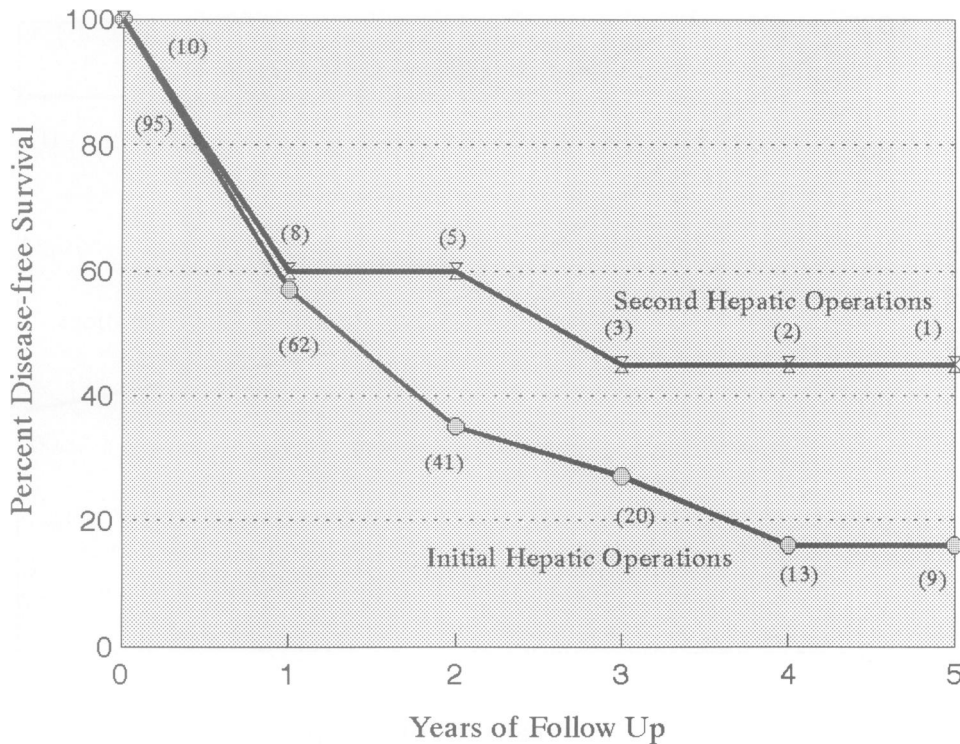The interval between the first and second hepatic op-

Figure 2. Disease-free survival curves for 95 patients who underwent an initial hepatic operation and 10 patients who underwent a second hepatic operation for colorectal carcinoma metastasis to the liver. Standard error of the cumulative proportion surviving is 5% for initial hepatic operations and 16% to 17% for second hepatic operations for each time point shown. The number of patients with available follow-up at each time point is shown in parentheses.

erations was 17 ± 11 months (median 14 months). At this time, the mean age of the patients was 56 ± 10 years of age (median 57 years). The second hepatic operation addressed one to three lesions in eight patients but addressed five and eight lesions, respectively, in two patients. The operation consisted of a right lobectomy in one patient, segmentectomy in one patient, and wedge resections in seven patients, with cryosurgery used in four patients. Margins were negative in all cases. One patient (patient 2) also underwent a simultaneous abdominal aortic aneurysm repair. Total vascular isolation was used in two patients, and the Pringle maneuver was used in one. Transfusions were used in six patients, totalling 32 units of packed erythrocytes, 12 units of fresh frozen plasma, and 6 units of platelets. There were no operative deaths, but six patients had complications consisting of transient bile leaks in three, bile duct stenosis in one, subphrenic abscess in one, and transient hepatic failure in one. Intensive care unit stay was 2 ± 0.8 days, with mean hospital stay of 11 ± 6 days. At the second hepatic operation, hepatic artery catheters were placed in five patients (patients 2, 3, 4, 6, and 7) who received postoperative fluorodeoxyuridine. One other patient (patient 9) received fluorouracil systemically.

Follow-up in these ten patients was current in 100%. The mean follow-up was 33 ± 27 months (median 25 months) and a total of 27 years. Survival in these ten patients was 100% at 1 year and 88% ± 12% at 2 years

and thereafter (Fig. 1). Disease-free survival at 1 and 3 years was 60% ± 16% and 45% ± 17%, respectively (Fig. 2). With these limited data and follow-up, there was a significant difference in the survival curves comparing our 95 first-time hepatic operation patients with our 10 second hepatic operation patients (p < 0.05, Fig. 1). However, there was no difference between the disease-free survival curves for these two groups (Fig. 2).

After the second hepatic operation, recurrence has been identified in six (60%) patients at a mean of 24 ± 30 months (median 9 months). This was isolated hepatic disease in one patient, hepatic plus extrahepatic disease in four patients, and pulmonary recurrence in one patient.

In the patient with isolated hepatic disease and one patient with hepatic and limited abdominal recurrence, a third hepatic operation was performed. The interval from the second to the third hepatic operation was 32 months and 90 months, respectively, in these two patients. One patient had three lesions and underwent three wedge resections with negative margins. The second patient had one hepatic lesion excised with the use of cryosurgical assistance, and an abdominal recurrence also was excised with negative margins. Both patients were discharged 6 days postoperatively. Follow-up in these two patients identified tumor recurrence in both after this third liver resection. The first patient recurred at 15 months and the second at 6 months, both in the liver, lung, and abdomen.

Table 1.   DATA ON PATIENTS UNDERGOING SECOND HEPATIC OPERATION

Pt. #	Sex	Age	Duke's stage	Operation (Primary Colon Surgery)	Interval (mo)	# Lesions	Size (cm)	Operation (First Hepatic Surgery)	Margin (cm)	Interval (mo.)	# Lesions	Size (cm)	Operation (Second Hepatic Surgery)	Margin (cm)	DFI	Site (Recurrence)	Time	Status (Survival)
1	F	65	C2	Transverse colectomy	12.6	1	2	R wedge	<1 cm	12.6	1	4.5	R wedge	1.5			33.9	ADF
2	F	61	B1	Low anterior resection	23.5	2	1, 2	R and L wedge	1, 1	5.2	2	2.7, 1.0	R & L wedge, triple A	1.2, 1	30.0	liver	48.3	AWD
3	F	55	D	Sigmoid colectomy	1.4	1	8.5	R lobectomy	1	5.6	2	2.5, 1	L wedge	1.5, 1.5			29.0	ADF
4	F	62	C2	Left colectomy	38.8	1	3.5	L wedge	1	12.2	1	3	L wedge, cryo	>1	9.2	lung	19.5	AWD
5	M	44	D	Low anterior resection	1.1	1	1	R wedge	1	9.8	1	3	R wedge	1			19.5	AWD
6	M	56	D	Sigmoid colectomy	0.0	3	0.6, 0.5, 1.5	R & L wedge	Negative	26.4	8	5.5, 1.6, 1.5, 3.7, 0.7, 0.5, 0.5, 0.5	R & L wedge, cryo × 3	0.1, 1.5, 1, 1, 0.8, 1, 1, 1	7.0	liver, lung	17.2	DOD
7	F	43	C2	Low anterior resection	2.8	1	2.8	L lateral seg	1	18.2	5	2 to 6	Cryosurgery × 5	1	7.3	liver, lung	8.9	AWD
8	M	64	B2	APR	19.6	2	2, 2.3	L wedge	2, 1	15.1	2	6, 3	R segmentectomy, cryo	>1, 1	8.8	liver, pelvis	21.1	AWD
9	F	41	D	Right colectomy	18.3	2	3.2, 1	L lateral seg	1.7, 2.0	40.6	3	4, 2.5, 1.5	R lobectomy	2.3, 2.3, 2.3			40.5	ADF
10	M	39	D	Sigmoid colectomy	18.3	2	1.4, 1	R wedge	1.2, 1.2	24.7	1	2	R wedge	2.5	83.4	liver, abdomen	100.6	AWD

Pt = patient; APR = abdominoperineal resection; R = right; L = left; wedge = wedge resection; seg = segmentectomy; cryo = cryosurgical ablation; ADF = alive, disease-free; AWD = alive with recurrent disease; DOD = dead of recurrent disease.

Table 2.   CEA LEVELS

Patient Number	1	2	3*	4	5*	6*	7	8	9	10
Primary Colon Surgery										
Before	3	8	182	25	3.1		3	20	6	5
After	1.6	2	189	2	2.2	18	2.5	3	3	1.8
First Hepatic Surgery										
Before	42	25	189	325	3.1		2.5	11	5	13
After	1.5	10	4	2.9	2.2	18	1.5	4.2	2.9	2.5
Second Hepatic Surgery										
Before	13	23	12.4	34.5	2.2	226	42.4	8	7	4.6
After	2.2	3	2.9	4.1	2.2	1	33	5	2.7	2
Third Hepatic Surgery										
Before		200								12.4
After		1.4								3

Carcinoembryonic antigen (CEA) levels are in ng/mL.
* Primary colon surgery and first hepatic surgery were within 6 weeks in these 3 patients with stage D disease.

DISCUSSION

Colorectal cancer is the second most common form of cancer in the United States, with approximately 160,000 estimated new cases per year. Although many patients are cured, with primary colon resection a large number (range, 40%–80%) will develop recurrence of the disease.[24] For patients with recurrence involving only the liver, approximately 15,000 per year, surgical ablation offers the only chance for cure and is the accepted current therapeutic approach.[13] With experience, a high level of safety and efficacy of hepatic resections routinely is seen. Operative mortality after primary hepatic resection for tumor is less than 5%, and complication rates range between 10% and 60%.[2,8,25,26] It generally is accepted that primary liver resection can achieve long-term survival in 25% to 33% of patients with hepatic colorectal metastases.[5,27] In our patients, the 5-year actual survival was 32% and actuarial survival was 38% ± 7%. This is in contrast to a less than 2% 5-year survival with the natural history of the disease and less than 5% 5-year survival with current nonoperative care.[10,12,15] Disease-free survival was 16% at 5 years for our 95 resected patients, in agreement with disease-free survival rates of 15% to 25% at 5 years reported in the literature.[14,16,28]

Unfortunately, a majority of patients develop recurrence after hepatic resection for colorectal metastasis, most of which are identified in the first 12 to 18 months postoperatively.[3,16] The mechanisms of this failure may include inadequate margin at the first operation, missed lesion at the first operation, spread of disease at the time of the first operation, or simply natural progression of

micrometastatic disease from the primary tumor.[15] The incidence of recurrent disease after liver resection for colorectal metastasis is reported at 55% to 80%.[3,7,12,14–16] The liver is involved in 35% to 50% of patients,[1,6,7,12,15,16,18,19] with isolated hepatic involvement in 25% to 33% of patients.[1,6,7,12,16,19] Ten to 40% of these patients with isolated recurrence undergo second resections.[12,14,16,19,21] In our experience, 71% of patients recurred at a mean of 13 months, 55% involving the liver and 33% involving the liver alone. Nineteen percent of those with isolated recurrence underwent a second hepatic operation.

Intense interest in repeat surgical resection for recurrent hepatic metastases can be seen in the numerous reports in the surgical literature since 1984.[1,3,6,12–21,28–48] Eight of these case series provided data on the number of second hepatic operations in relationship to the number of initial hepatic operations performed at each institution in a similar time period ranging from 6 to 21 years.[3,7,12,16,19–21,34] In these 8 series, there were 248 second hepatic procedures (8%) compared with 3182 initial operations. Individual institutions reported from 5% to 16% incidence of repeat procedures compared with initial procedures. Six percent of our patients underwent repeat procedures. There are 30 patients reported who have undergone third hepatic procedures for colorectal metastasis in five reports.[1,7,16,19,28] The incidence of third hepatic procedures in relationship to second hepatic procedures was 8% as well, 30 of 368 cases. In our own experience, there were two of ten patients who underwent a third procedure.

The time interval from initial colon operation to first

hepatic operation was available for 53 individual patients from six case series,[1,6,7,12,17,20] with a mean of 13 ± 16 months (median 11 months). This compares with our experience of 14 ± 13 months (median 15 months). The time interval between first and second hepatic procedures was available for 80 individual patients in ten case series,[1,3,4,6,7,12,15,17,20,31] with a mean of 17 ± 12 months (median 12 months). In our experience, it was a mean of 17 ± 11 months (median 14 months). Others have reported very similar interval periods.[16,19]

Operative mortality for second hepatic procedures are available for 425 cases from 24 reports,[1,2,4,6,7,12,15, 17,18–20,29–34,42–45] with eight operative deaths (1.9%). In our experience, the operative mortality rate was 0% for 10 second resections compared with an operative mortality rate of 4% for 95 primary resections.

Data on postoperative complications are available in various forms in 15 reports.[1,4,3,6,7,12–21,31] Of 457 patients undergoing second operations, 113 patients (25%) had reported complications. The most common complications reported were hemorrhage in 5%, significant pleural effusion in 5%, and infections in 10% of patients (including abscess formation in 5% and pneumonia in 2.4%). Biliary leak was reported in 2.1% and biliary stenosis in 1%. Transient hepatic failure developed in 1.7%. These morbidity rates are similar to those seen in primary hepatic resections.[5,7,8,14,19,21] In our ten patients, six had complications that compared with two complications after their first hepatic operation. The mortality and morbidity after third hepatic resections are also relatively limited in our experience and that of others.[1,6,7,19]

Operative blood loss increased with repeat hepatic resections compared with primary resections in our experience. In the second hepatic operation, we used 32 units of packed erythrocytes, 12 units of fresh frozen plasma, and 6 units of platelets, compared with 21 units of packed erythrocytes in the first hepatic operation for these same ten patients. Similar experience with increased blood loss has been reported by others.[19,45] An operative field that is distorted by adhesions making for difficult exposure, intrahepatic anatomic variations induced by prior resections dictating variable planes of dissections, and hepatic parenchymal hypertrophy and friability are among several factors that are implicated in increasing the time required for repeat hepatic resection and the need for increased blood replacement products.

It appears that carcinoembryonic antigen levels contribute to optimal follow-up in patients who have undergone hepatic resection (Table 2). In many patients, especially those in whom carcinoembryonic antigen is not useful, serial CT scan has been useful. We also have found PET useful in following patients after hepatic re-

section.[22] Based on the time to recurrence, we believe this follow-up should occur at least every 6 months.

An improved prognosis for long-term survival with an aggressive surgical approach is best demonstrated when complete surgical resection with adequate tumor-free margins and absence of extrahepatic disease after resection is achieved.[15] Therefore, in an effort to identify patients who can appropriately be rendered disease free by surgical resection, preoperative staging of patients with recurrent hepatic colorectal metastasis should be aggressive to identify the number and distribution of lesions present. Our own group employs a combination of contrasted chest and pelvic CT, CT portography, ultrasound, bone scan, and whole body PET imaging. We recently reported that PET has been helpful in clarifying the presence or absence of intra- and extrahepatic colorectal metastases, differentiating surgical scar from recurrent tumor, and PET data have changed management strategies in up to 25% of our patients.[22]

The principles that apply to second-time resection are the same as those that are used to select the first time candidate: all known disease is resectable, adequate tissue margins are obtainable, there is adequate liver reserve function to tolerate surgery, and there are no medical diseases that would preclude surgery. In addition to the two key factors for a good outcome, no extrahepatic disease and ability to obtain 1-cm margins intrahepatically,[14,28] some authors believe the number of metastasis should be limited.[6,12,34] Based on the early recurrence in our two patients with more than three lesions who received second resection, we agree. Some authors recommend delaying second hepatic operation in patients with more than a single lesion to observe for the early development of widespread disease.[7,12,13] This is a reasonable approach. So far, there are no other prognostic indications identified from the time of the original colon operation or first hepatic resection.[14,28]

In our patients, survival after repeat hepatic resection for colorectal metastasis, admittedly with limited data, compares favorably with our experience after primary hepatic resections for isolated hepatic metastases (Fig. 1). Other groups have reported equivalent survival results when comparing primary and secondary resections of the liver for isolated colorectal metastases, with long-term survival as high as 32%.[28] Fifteen published case series on repeat hepatic surgery for colorectal metastasis[1,3,4,6,7,12,15,17,20,21,30–34] provided individual data on survival for a total of 124 patients undergoing a second hepatic operation for colorectal metastasis. Our ten patients were added to this for a total of 134 patients. The actuarial survival was 91% ± 3% at 1 year, 69% ± 5% at 2 years, 55% ± 5% at 3 years, 45% ± 6% at 4 years, and 40% ± 7% at 5 years (Fig. 3). Six patients were surviving
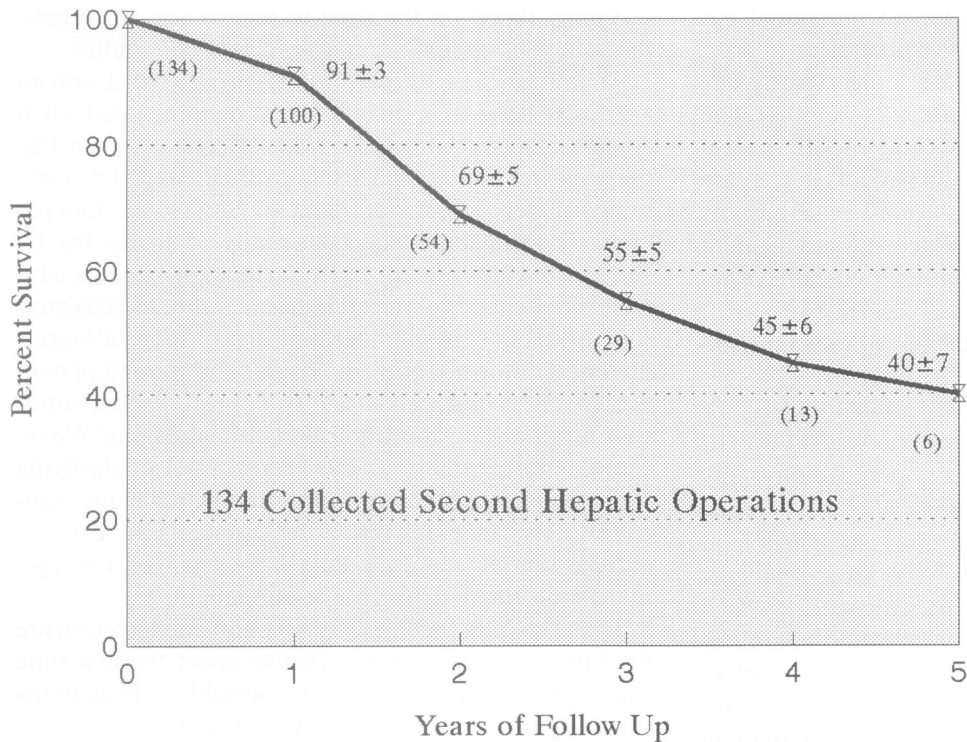
Figure 3. Survival curve for 134 patients undergoing second hepatic operations for colorectal metastasis. This represents our 10 patients together with 124 more collected from 15 reports in the literature, with individual follow-up available (see text for citation). The number of patients with available follow-up at each time point is shown in parentheses.

at 5 years of follow-up, including one of our own. These figures are remarkably similar to our experience after first-time resection and the experience of others.[2,5] The disease-free survival figures for our ten patients at 1, 2, and 3 years was 60% ± 16%, 60% ± 16%, and 45% ± 17%, respectively. Others have reported figures of 70%, 50%, and 21% to 36%, respectively.[7,19]

The pattern of failure after second liver resection for colorectal metastasis is provided for a total of 217 patients from 10 reports.[1,3,6,7,12,15,16,20,21,34] Recurrence occurred in 146 patients (67%). The liver was involved with recurrence in 104 patients (47%). Isolated hepatic involvement occurred in 62 patients (28%). In our ten patients, 60% recurred at a mean of 24 months (median 9 months). A median of 6 to 9 months to recurrence is reported by others.[12,21] The liver was among the sites involved in 50%, and the liver only was involved in 10%.

These data would suggest that results of repeat resection are not very different from those with initial hepatectomy. Review of the current literature and our own experience at Vanderbilt support second-time hepatic operation for recurrent colorectal metastasis. These resections can be performed safely, without greater risk than first-time resections, and offer a survival that is at least as good as first-time resections (Fig. 3). This experience and discussion helps to establish that repeat hepatic surgery is the best treatment option currently available for selected patients with recurrent colorectal metastasis to the liver.

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Discussion

DR. RONALD K. TOMPKINS (Los Angeles, California): Thank you, President Thompson, Secretary Copeland, Members, and Guests. This is an excellent paper with extremely accurate documentation of a very difficult procedure. I cannot imagine going back in for a third hepatic resection, even if I had been there the first two times. I think it would be very difficult.

The authors have included some things in the manuscript that they have not shown among the slides, and I would like to ask them some questions about it.

First of all, it seems that the median interval between the first and second operation and then the second and third operations grows successively shorter. And I wonder if they would comment on what they are accomplishing in the natural history of the disease by this aggressive approach. What is the role in their experience, and their advice, on the proposal that we should delay operation in patients in whom we have just discovered hepatic metastases, to see if other extrahepatic metastases will materialize in a few months?

This has been proposed by some; I think it is a highly controversial proposal, but I would like to know how they have looked at this and what their data might be.

Secondly, I think that the screening of these patients to rule out extrahepatic malignancy is an extremely difficult thing.