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Repeat Hepatectomy for Colorectal Liver Metastases

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Objective
The authors assess the long-term results of repeat hepatectomies for recurrent metastases of colorectal cancer and determine the factors that can predict survival.

Summary Background Data
Safer techniques of hepatic resection have allowed surgeons to consider repeat hepatectomy for colorectal metastases in an increasing number of patients. However, higher operative bleeding and increased morbidity have been reported after repeat hepatectomies, and the long-term benefit of these procedures needs to be evaluated.

Study Population
Sixty-four patients from a group of 243 patients resected for colorectal liver metastases were submitted to 83 repeat hepatectomies (64 second, 15 third, and 4 fourth hepatectomies). Combined extrahepatic surgery was performed in 21 (25%) of these 83 repeat hepatectomies.

Results
There was no intraoperative or postoperative mortality. Operative bleeding was not significantly increased in repeat hepatectomies as compared to first resections. Morbidity and duration of hospital stay were comparable to first hepatectomies. Overall and disease-free survival after a second hepatectomy were 60% and 42%, respectively, at 3 years and 41% and 26%, respectively, at 5 years. Factors of prognostic value on univariate analysis included the curative nature of first and second hepatectomies ($p = 0.04$ and $p = 0.002$, respectively), an interval between the two procedures of more than 1 year ($p = 0.003$), the number of recurrent tumors ($p = 0.002$), serum carcinoembryonic antigen levels ($p = 0.03$), and the presence of extrahepatic disease ($p = 0.03$). Only the curative nature of the second hepatectomy and an interval of more than 1 year between the two procedures were independently related to survival on multivariate analysis.

Conclusions
Repeat hepatectomies can provide long-term survival rates similar to those of first hepatectomies, with no mortality and comparable morbidity. Combined extrahepatic surgery can be required to achieve tumor eradication. Repeat hepatectomies appear worthwhile when potentially curative.

Surgical resection has become the treatment of choice of patients with isolated hepatic metastases from colorectal cancer. This is indeed the only form of treatment that offers a chance of cure, with 5-year-survival rates of 22% to 39%.[1-9] After resection, however, it is estimated that in 60% of the patients, the disease will recur,[6,10-13] and in approximately 30% of these cases, the disease will recur under the form of isolated liver metastases.[10-14] As safer techniques of hepatic resection have allowed the reduction of mortality and morbidity of major liver surgery in the past 10 years,[15,16] repeat hepatic resections for recurrence increasingly are being performed. The problem arises as to whether these procedures can bring an additional survival benefit and to whether the risk associated with them is acceptable. Like others,[12-14,17-28] we have advocated from our experience in a limited series the use of repeat resection in terms of expected risk-to-benefit ratio. However, a cumulative analysis of 150 repeat resections from the experience of 15 separate centers provided only 3 survivors at 5 years.[29] Even if 5-year-survival rates of 16% and 32% have been reported recently from two multi-institutional series,[7,21] the long-term benefit of such an approach is under scrutiny. In addition, a higher risk of intraoperative bleeding has been reported with repeat resections.[20] Finally, the criteria for the selection of patients with a reasonable hope of prolonged survival are not well established. We conducted a retrospective analysis of a 12-year experience in hepatic resection of colorectal metastases to define the long-term results of patients submitted to repeat hepatectomies and to determine the factors associated with survival.

PATIENTS AND METHODS

From January 1984 to June 1995, 243 patients underwent a liver resection for colorectal metastases in our unit. Of these, 64 (26%) underwent repeat liver surgery for recurrent or persistent disease, totaling 83 rehepatectomies (Table 1). There were 44 men and 20 women with a mean age of 56.3 years (range, 31–73). The primary tumor was a carcinoma of the colon in 45 patients (70%) and a carcinoma of the rectum in 19 patients (30%). Dukes' stage was A in 1 patient (2%), B in 13 patients (20%), and C in 50 patients (78%). After the colectomy, chemotherapy had been given in 37 (58%) of the 64 patients. Liver metastases were synchronous in 32 patients (50%). The mean interval between the colectomy and the first hepatectomy was 1.2 years with 67% of patients having the hepatectomy performed within 1 year (Table 1).

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Table 1. PAUL BROUSSE EXPERIENCE OF REPEAT HEPATECTOMY FOR COLORECTAL LIVER METASTASES: 64 PATIENTS, 147 LIVER RESECTIONS, 83 REPEAT HEPATECTOMIES (JANUARY 1984 TO JUNE 1995)

	Locally	Outside	Total
Hepatectomy			
First	48	16	64
Second	60	4	64
Third	15	0	15
Fourth	4	0	4
All	127	20	147
	Mean (range) (mo)	<1 yr	>1 yr
Colectomy to first hepatectomy	1.2 (0–9.5)	43	21
First to second hepatectomy	1.3 (0.3–5.1)	32	32
Second to third hepatectomy	1.8 (0.4–4.9)	5	10
Third to fourth hepatectomy	0.9 (0.4–1.7)	2	2

Characteristics of Tumor Disease in First and Second Liver Resections

Characteristics of tumor disease in first and second liver resections are summarized in Table 2. The proportion of patients with solitary metastases was 37% for first hepatectomies and 49% for repeat hepatectomies. Similarly, more than three metastases were present in 27% of the patients at the time of the first resection and in only 14% of the repeat hepatectomies. Extrahepatic disease was present in three patients (5%) at the time of the first liver resection (adrenal gland, 1 patient; lung, 1 patient; and ovary, 1 patient) *versus* 17 (20%) of 83 patients at repeat resection. The extrahepatic disease in this group was lymph node involvement in five patients, peritoneal deposits in three, tumor invasion of the stomach in two, pulmonary metastases in two, ovarian metastases in two, rectal recurrence in one, invasion of the diaphragm in one, and a tumoral thrombus invading the left portal vein in one patient.

Diagnosis of Recurrence after First Liver Resection

After the first liver resection, all patients were treated with systemic chemotherapy (an association of 5-fluorouracil and folinic acid in most cases). Patients were ob-

Table 2. CHARACTERISTICS OF TUMOR DISEASE AT REPEAT HEPATECTOMY COMPARED WITH FIRST RESECTION

	Hepatectomy			
	First	Second	Third–Fourth	All Repeat
No. of resections	64	64	19	83
Maximum tumor size				
≤30 mm	30 (47)*	43 (67)*	12 (63)*	55 (66)*
30–50 mm	19 (30)*	15 (24)*	3 (16)*	18 (22)*
>50 mm	15 (23)*	6 (9)*	4 (21)*	10 (12)*
No. of nodules				
1	24 (37)*	31 (48)*	10 (53)*	41 (49)*
2	12 (19)*	16 (25)*	2 (10)*	18 (22)*
3	11 (17)*	6 (9)*	6 (32)*	12 (14)*
>3	17 (27)*	11 (17)*	1 (5)*	12 (14)*
Mean serum CEA levels (IU/L)	21 ± 43	48 ± 170	26 ± 52	—
Mean serum CA 19-9 levels (IU/L)	41 ± 115	102 ± 333	11 ± 10	—
Extrahepatic disease	3 (5)*	14 (22)*	3 (16)*	17 (20)*

CEA = carcinoembryonic antigen; CA = carbohydrate antigen.
* Values are no. (%).

served every 4 months with liver function tests, abdominal ultrasonography, serum carcinoembryonic antigen and carbohydrate antigen levels. Colonoscopy was performed every year to exclude local recurrence of the primary tumor. Abdominal computed tomography (CT) scan, magnetic resonance imaging, or CT angioportography were reserved to confirm the diagnosis of recurrence or as part of the preoperative evaluation. A CT volumetric assessment was performed more recently in all cases in which a major hepatectomy was planned. With respect to the time of recurrence after first hepatic resection, the mean interval between first and second hepatectomy was 16 months with 50% of the patients reoperated on within 1 year (Table 1).

Selection of Patients

Repeat hepatectomy was considered in the absence of any medical contraindication to liver surgery when the liver recurrence was technically resectable and no unresectable extrahepatic disease was present as shown by CT scan of the chest and bone radionuclide scan. Patients with single, easily resectable recurrence after a prolonged disease-free interval underwent early surgery without chemotherapy. Patients with large or multiple lesions, with a short disease-free interval, or with extrahepatic disease received preoperative chemotherapy for 2 to 3 months. The aim in these cases was to limit tumor spread, to reduce tumor volume, and to exclude patients with rapidly progressive metastatic disease in whom repeat liver resection was unlikely to be of benefit. In seven patients (11%), the liver recurrence initially was considered as nonresectable because of the large size of the lesions, their ill location, multinodular tumor, or the presence of concomitant extrahepatic disease. Repeat liver resection could be performed in these patients after tumor reduction was achieved by prolonged chemotherapy as reported previously.[30]

Frequency of Repeat Hepatectomy for Colorectal Metastases

Of the 243 patients submitted to a liver resection, there were 179 patients with 1 hepatectomy (74%), 49 with 2 hepatectomies (20%), 11 with 3 hepatectomies (4%), and 4 with 4 hepatectomies (2%). The total number of liver resections in these 243 patients was 322. A noticeable evolution occurred during the 12 years of the study. Whereas repeat hepatectomies represented 11 (12%) of 93 overall resections in the period from 1984 to 1989, the proportion increased to 68 (30%) of 229 in the period from 1990 to 1995 (Fig. 1).

Operative Technique

The operative technique of liver resection in our unit has been described previously.[12] At operation, a careful search of the abdominal cavity was made for recurrent local disease, extrahepatic metastases, and peritoneal seedings. A complete examination of the liver was performed both by palpation and by intraoperative ultrasonography to confirm the number and size of the lesions, to define their relation with the intrahepatic vascular structures, and to look for occult liver metastases. Parenchymal

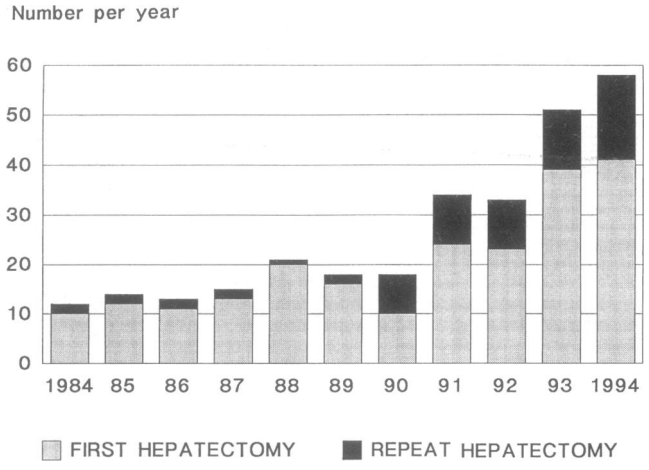

Figure 1. Evolution of the number of repeat hepatectomies as compared with first hepatectomies at Paul Brousse Hospital.

dissection was made using the ultrasonic dissector (CUSA, Cavitron Ultrasonic Aspirator, Valley Lab Inc, Boulder, CO), and segmental resections were used preferentially, provided a tumor-free margin of 1 cm could be obtained.

Repeat hepatectomies technically were more demanding than were initial resections for several reasons. Re-exposure of the liver was made difficult because of the frequent adhesions of the raw surface of the previous hepatectomy to adjacent organs, in particular to the diaphragm in right liver resections. Regeneration of the liver also induced changes in the shape of the organ and in the position of the vascular structures, especially after a first extended liver resection. Previous dissection of the hepatic pedicle and vena cava made vascular control more difficult to obtain. The liver often was more fragile as a consequence of both regeneration and chemotherapy. Operative time, therefore, often was increased as compared with first liver resections.

Postoperative Management

Systemic chemotherapy (5-fluorouracil, folinic acid associated or not to oxaliplatin[30]) was administered routinely after repeat liver resections either as adjuvant therapy (6–12 months) when rehepatectomy had been curative or as a treatment aiming to control tumor growth when resection had been palliative. In some of the latter cases, a third resection removing the remnant tumor was possible. Subsequent extrahepatic surgery was required after 13 repeat resections (16%), mainly for pulmonary metastases (Table 3). Patients were reviewed at 1 month and then every 4 months with evaluation of tumor markers, liver function tests, hepatic ultrasonography, and thoracic CT scan when pulmonary resection had been performed.

Statistical Analysis

Survival was calculated as the number of months from the date of the second hepatectomy until the last follow-up attendance or until death. Kaplan–Meier survival curves were obtained with a biomedical statistical package (Statistica 4.0, Statsoft, Tulsa, OK). The log–rank test was used to identify variables associated with survival. A p value < 0.05 was considered statistically significant. Multivariate analysis was performed using a Cox model, including variables that were significant on univariate analysis.

RESULTS

Type of Liver Resection

The proportion of anatomic (as opposed to wedge) resections was 55% for first procedures, 50% for second resections, and only 37% for third and fourth hepatectomies (Table 3). Curative resection could not be achieved in 16 repeat procedures (19%). Concomitant extrahepatic surgery was required in six second hepatectomies (9%) and in two third hepatectomies (14%) (Table 3).

Operative Mortality

There was no intraoperative mortality or postoperative mortality within the 2 months in the 64 patients (Table 4). The operative blood loss was higher during the repeat procedures as compared with the first hepatectomies, although the difference did not reach statistical significance. Accordingly, more than 5 blood units were required in 13% of repeat resections as compared with only 6% of first liver resections.

Postoperative Morbidity

Thirteen complications (20%) were observed after the 64 second resections and 3 complications after the 19 third and fourth resections (16%) (Table 4). There were three cases of postoperative hemorrhage, four cases of biliary leak, two cases of sterile fluid collections, three cases of abdominal infections, and four cases of pulmonary infections. Three patients needed reoperation (two for bleeding, one for a persistent pleural effusion). The complication rate was not significantly different from that observed after first hepatectomy (16%). The duration of the hospital stay also was similar (13.9 ± 8.1 *vs.* 13.3 ± 4.2 days). In the group of repeat hepatectomies, duration of hospital stay did not increase with the number of hepatectomies (Table 4).

Survival

Overall 3-, 5-, and 7-year-survival rates were 60%, 41%, and 34%, respectively, from the time of second liver

Table 3. TYPE OF HEPATECTOMY IN FIRST AND REPEAT LIVER RESECTIONS

	Hepatectomy			
	First	Second	Third–Fourth	All Repeat
Minor (<3 segments) [no. (%)]	34 (53)	42 (66)	13 (83)	55 (66)
Major (≥3 segments) [no. (%)]	30 (47)	22 (34)	6 (17)	28 (34)
Curative [no. (%)]	53 (83)	50 (78)	17 (89)	67 (81)
Noncurative [no. (%)]	11 (17)	14 (22)	2 (11)	16 (19)
Anatomic [no. (%)]	35 (55)	32 (50)	7 (37)	39 (47)
Wedge [no. (%)]	29 (45)	32 (50)	12 (63)	44 (53)
Concomitant surgery (no.)				
Digestive resection	—	3		3
Other resection	3	3	2	5
Subsequent surgery (no.)				
Pulmonary resection	4	10	2	12
Other resection	—	1	—	1
Total	7	17	4	21

resection with a median survival time of 46 months (Fig. 2). The respective figures for disease-free survival were 42%, 26%, and 19%, respectively. As a comparison, overall survival of the 243 patients of the study after a first hepatectomy was 87%, 54%, and 33% at 1, 3, and 5 years, respectively (Fig. 3). Of the 64 patients submitted to a second liver resection, 25 (39%) have died, and 39 (61%) are alive, of whom 23 are without recurrence with a median follow-up of 27 months. The present series includes nine patients alive at 5 years, of whom seven are without disease.

In patients with a third liver resection, cumulative survival from the date of the third resection was 47% at 3 years with a median survival of 32 months (Fig. 4).

Univariate Analysis for Survival

Factors Related to the Primary Malignancy

The location of primary colorectal cancer as well as the presence of metastatic lymph nodes, the Dukes' stage of the tumor, and whether chemotherapy had been given after colectomy did not influence significantly the survival after a second liver resection (Table 5).

Factors Related to the Metastatic Disease at the First Hepatectomy

Patients with metachronous liver metastases had better 5-year survival after rehepatectomy than did patients with synchronous metastases (50% *vs.* 35%), but the difference was not significant. When the interval between colectomy

Table 4. OPERATIVE MORTALITY AND POSTOPERATIVE MORBIDITY FOLLOWING REPEAT HEPATIC RESECTION

	Hepatectomy			
	First	Second	Third–Fourth	p Value
Operative mortality (<2 mo)	0/64	0/64	0/19	—
Operative blood transfusion (units) [mean (range)]	1.2 ± 1.8 (0–6)	2.0 ± 2.7 (0–12)	2.1 ± 2.8 (0–10)	NS
Complications (no.)				
Postoperative bleeding	1	3	—	NS
Biliary fistula	1	2	2	
Abdominal infection	3	2	1	
Fluid collection	2	2	—	
Pleuropneumopathy	3	4	—	
Total	10 (16%)	13 (20%)	3 (16%)	
Hospital stay (days)	13.9 ± 8.1	13.3 ± 4.2	13.1 ± 5.7	NS
Mean Range	7–63	7–25	7–30	

NS = not significant.

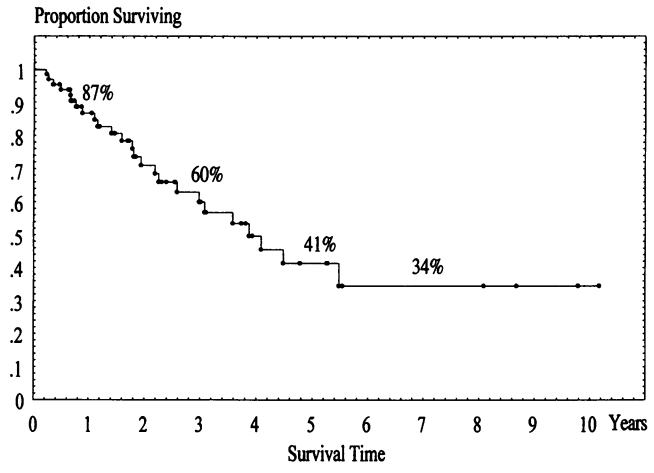

Figure 2. Cumulative survival of 64 patients with recurrent metastases of colorectal cancer after a second hepatectomy.

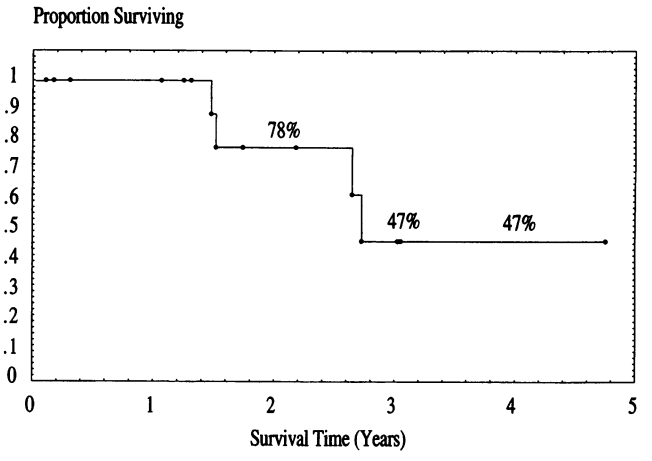

Figure 4. Cumulative survival of 15 patients with recurrent metastases of colorectal cancer after a third hepatectomy.

and the first hepatectomy exceeded 1 year, survival was better (56%) as compared with survival of patients with a shorter interval (37%), but the difference was not significant (p = 0.12). Concerning the methods of the first hepatectomy, 5-year survival was better when resection had been curative (53% *vs.* 0%, p = 0.04) and when an anatomic resection rather than a wedge resection had been performed (58% *vs.* 26%, p = 0.03) (Table 5).

Factors Related to the Recurrent Metastases

The 5-year survival was significantly better for patients with an interval of more than 1 year between the first and the second hepatectomy as compared with patients with an interval of less than 1 year (62% *vs.* 26%, p = 0.003) (Fig. 5).

With respect to the features of recurrent metastatic disease, patients with less than three nodules had better survival after a second resection than those with three nodules or more (49% *vs.* 9%, p = 0.002) (Table 6). The size of the lesions had no significant influence. Patients with serum carcinoembryonic antigen levels lower than 30 international units/L had better 5-year survival than those with serum carcinoembryonic antigen levels higher than 30 international units/L (54% *vs.* 21%, p = 0.03). When synchronous resectable extrahepatic disease was present, survival was significantly decreased at 3 years as compared with patients without extrahepatic disease (32% *vs.* 63%), and no patient was alive at 5 years as compared with a survival rate of 54% in patients without extrahepatic disease (p = 0.03) (see Table 6).

With respect to the type of second hepatectomy, 5-year survival was not significantly different whether an anatomic or a wedge resection had been performed (49% *vs.* 32%), but survival was markedly better when the resection was been curative as compared with patients in

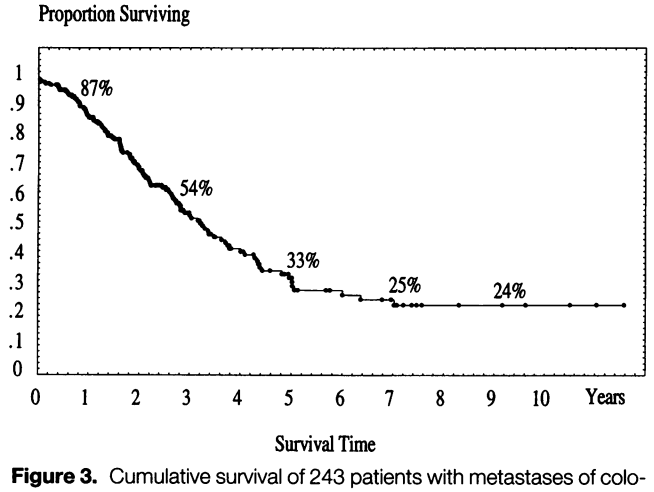

Figure 3. Cumulative survival of 243 patients with metastases of colorectal cancer after a first hepatectomy.

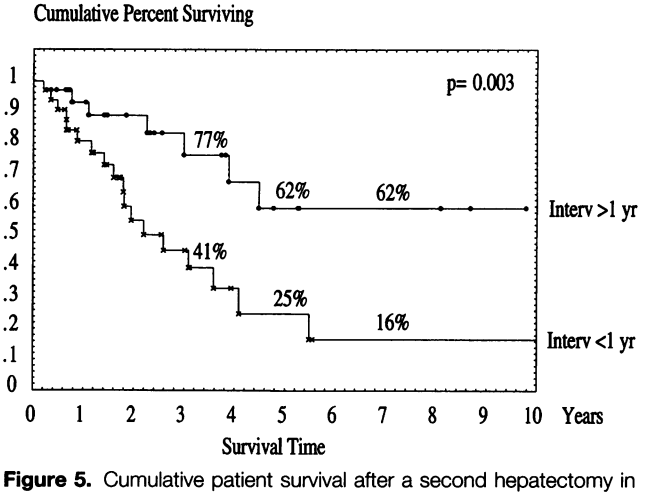

Figure 5. Cumulative patient survival after a second hepatectomy in relation to interval between first and second hepatectomies. (Full circle: more than 1 year; X: less than 1 year; log-rank p = 0.003).

Table 5. INFLUENCE OF CHARACTERISTICS OF PRIMARY MALIGNANCY AND FIRST HEPATECTOMY ON CUMULATIVE SURVIVAL FOLLOWING SECOND HEPATECTOMY

Prognostic Factor	No. of Patients	Survival Rate of Second Hepatectomy (%)		p Value
		3 yr	5 yr	
Primary malignancy				
Location				
Colon	45	55	38	0.32
Rectum	19	71	53	
Dukes				
B	13	46	28	0.12
C	50	60	43	
Metastatic lymph nodes				
Yes	42	57	41	0.40
No	21	64	42	
Postoperative chemotherapy				
Yes	37	52	34	0.11
No	27	75	50	
First Metastases				
Synchronous	32	52	35	0.18
Metachronous	32	69	50	
Interval of colectomy to hepatectomy				
<1 yr	43	55	37	0.12
>1 yr	21	72	56	
First hepatectomy				
Curative	53	67	53	0.04
Noncurative	11	50	0	
Anatomic	35	65	58	0.03
Wedge	29	48	26	

whom a noncurative resection was performed (48% *vs.* 0%, p = 0.002) (Fig. 6).

Multivariate Analysis for Survival

Two factors were associated independently to survival after the second resection: a delay between the first and second hepatectomy over 1 year (p = 0.009, risk ratio = 0.30) and whether the second hepatectomy had been curative (p = 0.008, risk ratio = 0.32).

DISCUSSION

The prognostic determinants of hepatic recurrence after a first liver resection presently are well known and include the number of liver metastases,[3,4,11,31-34] the size of the tumor,[35] a resection margin of less than 10 mm,[4,11,33,35] and the presence of extrahepatic disease.[8,11] The stage of the primary tumor,[8,34] the interval between the colorectal and the hepatic resection,[3,4] and the presence of bilateral as compared to unilateral disease[3,11,32,35] also have been associated with an increased risk of liver recurrence. These factors, however, are only rough indicators of prognosis, and commonly it is admitted, because of the potential survival advantage of surgical treatment, that patients in whom resection is possible should be operated on. Whether a similar attitude has to be adopted for liver recurrence after a first resection is still unclear.

A new liver resection may be proposed to patients with isolated hepatic recurrence or to patients with associated resectable extrahepatic disease. This may represent 10% to 15% of the total number of patients with resected colorectal metastases,[12,13,27] an estimate that can be made because isolated liver recurrence accounts for approximately 25% to 30%[10-14] of the 50% to 70% of patients with recurrent liver disease after a first hepatectomy.[6,10-13] Up until recently, hepatic recurrence after a first hepatectomy was an uncommon indication for further resection, limited to only 3% to 11% of patients having undergone initial resection.[29] In our experience of 322 liver resections performed for colorectal liver metastases in 243 patients, 25% of these resections were repeat hepatectomies. However, whereas repeat hepatectomies were performed sporadically in the first years of our experience, their frequency has been increasing from 12% before 1990 to 30% in the past 6 years. Indeed, as the results of hepatic surgery have improved dramatically in the past decade, several reports have appeared on the feasibility of a more

Table 6. INFLUENCE OF CHARACTERISTICS OF RECURRENT METASTASES AND SECOND HEPATECTOMY ON CUMULATIVE SURVIVAL FOLLOWING SECOND HEPATECTOMY

		Survival Rate of Second Hepatectomy		
	No Pts	3 yr	5 yr	p Value
Second metastases				
No. of nodules				
<3	47	75	49	0.002
≥3	17	28	9	
Size of tumor				
≤30 mm	47	52	27	0.78
>30 mm	17	50	29	
Serum CEA levels				
<30 IU/L	42	70	54	0.03
>30 IU/L	14	45	21	
Interval of first to second hepatectomy				
<1 yr	32	45	26	0.003
>1 yr	32	80	62	
Second hepatectomy				
Anatomic	32	62	49	0.13
Wedge	32	52	32	
Curative	50	68	48	0.002
Noncurative	14	15	0	
Extrahepatic disease	14	32	0	0.03
No extrahepatic disease	50	63	54	

* CEA = carcinoembryonic antigen.

aggressive attitude in favor of surgical treatment,[12-14,17-28] an approach that still needs to be evaluated both in terms of the risk of the procedure and the expected benefit of long-term survival.

Regarding the risks of repeat hepatectomies, the results of the present series confirm our previous reports on the possibility to perform rehepatectomy with no mortality and a morbidity comparable to the first resection. These results are in agreement with the overall mortality rate of 2% from a cumulative analysis on 311 published cases of repeat hepatic resections.[29] However, in contrast with the Repeat Hepatic Metastasis Registry in which a postoperative morbidity higher than that observed with first resections was noted,[21] the incidence of postoperative complications in our series (20%) was not significantly higher than that observed after first hepatectomies (16%). Previous studies have reported morbidity rates ranging from 15% to 52%.[12,17,20-22,25] This probably is because repeat procedures are associated with increased technical difficulties related to adhesions on the raw surface of the previous hepatectomy as well as to changes in the shape and consistency of the liver induced by regeneration. Also, some authors reported an increased risk of bleeding after repeat resections,[20,36] a factor known as the main determinant of mortality and morbidity after hepatectomy.[8,37] Similarly, the proportion of patients transfused with more than 5 blood units was increased in repeat resection as compared with first hepatectomies in our patients (13% *vs.* 6%), although the difference in the number of blood units transfused intraoperatively did not reach statistical significance. Adapted techniques of liver vascu-

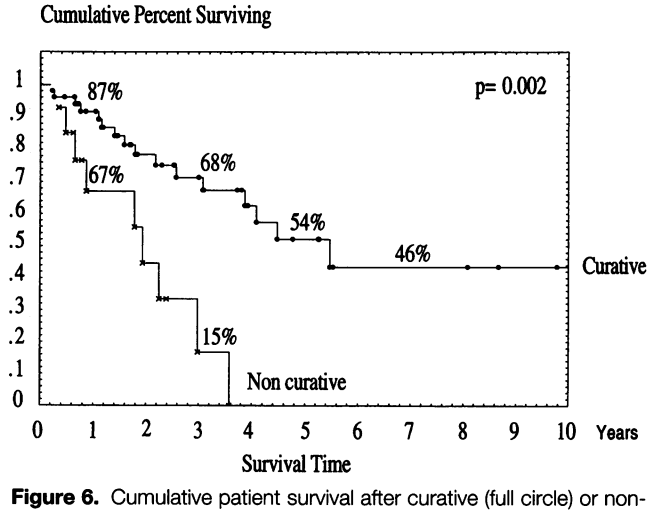

Figure 6. Cumulative patient survival after curative (full circle) or noncurative (X) second hepatectomy (log-rank p = 0.002).

lar control according to the size and location of the recurrence[15,38] may succeed in limiting the higher propensity to bleeding of repeat hepatectomies still further.

A prominent difference between first hepatectomies and repeat resections was the more limited amount of liver tissue resected during the latter procedures. Although major liver resections (three segments or more) represented 47% of first hepatectomies, they represented 36% of second hepatectomies and only 17% of third and fourth hepatectomies. It is clear that the extent of the new resection partly depended on the amount of liver tissue left at the first hepatectomy. We suggest, therefore, that the technique used for the first hepatectomy should integrate the possibility of a repeat resection and that the surgeon should limit the excision to the tissue that needs to be sacrificed because of carcinologic and vascular reasons. This attitude is further supported by the fact that the extent of hepatic resection does not influence the outcome of first or resected patients, providing that adequate margins (1 cm) are obtained and that all metastatic tissue is removed.[32] To achieve this goal, our policy was to favor anatomic resections according to the Couinaud classification of liver segments.[39] A deeper knowledge of the segmental anatomy of the liver[40] and the routine use of intraoperative ultrasonography[15,41,42] has eliminated the need of "blind" extensive resection, therefore limiting the amount of resected parenchyma. In addition, segmental surgery decreases the incidence of complications such as bleeding or infection in contact of ischemic margins of resection.[41] As opposed to some authors who reported more anatomic than wedge resections at second liver resections as compared with first hepatic surgery,[21] our proportion of anatomic resections was comparable for first and second procedures (55% and 50%, respectively), which was, therefore, slightly higher than for third and fourth hepatectomies (37%).

With regard to the selection of patients, we have considered that the indications for reresection should not be different from those for a first resection. The rationale was to offer to patients with recurrent resectable liver metastases the only chance of cure provided that the risk of morbidity and mortality was low. With such a policy, a 5-year-survival rate of 41% was observed, higher than in previous reports[7,21] and similar to that achieved after first resections in our unit. A trend toward a similar survival rate was observed after a third hepatectomy in 15 patients of this series.

The analysis of factors predicting survival in the present study shows that parameters concerning the primary malignancy were not determinant and that the outcome was related mainly to whether the first and second hepatectomies had been curative and to the time elapsed between the two procedures. As opposed to the results of the Repeat Hepatic Metastases Registry,[21] the present study shows that 5-year-survival rate is significantly better for those patients with an interval of more than 1 year between the two hepatectomies as compared with patients with an interval of less than 1 year (62% *vs.* 26%). These results may reflect the better prognosis of late as compared to early recurrences. While maximum tumor size of recurrent metastases did not seem to influence survival, the presence of more than two tumor nodules decreased significantly the chance of surviving as compared to patients with up to two nodules (9% *vs.* 49%). However, this factor was not significant on multivariate analysis, suggesting that it had no influence when the repeat hepatectomy was curative.

The presence of extrahepatic disease needs commenting on because in the present series, 14 patients (22%) who underwent a second liver resection had synchronous extrahepatic disease and 17 (26%) ultimately required extrahepatic surgery. Indeed, we did not consider disease outside the liver as a contraindication to a new hepatic resection, provided that surgical excision of the extrahepatic disease could be curative. In these 14 patients, the 3-year survival was decreased as compared with that of patients with recurrence limited to the liver (32% *vs.* 63%), and no patient is alive currently at 5 years (*vs.* 54% in patients without extrahepatic disease). Similar findings have been reported by the Registry with a 5-year survival, however, reaching 16% for patients with associated recurrence outside the liver.[21] Extrahepatic disease was not associated independently with decreased survival on multivariate analysis in our study, suggesting that there is no clear-cut argument to exclude rehepatectomy in selected patients. More patients and longer follow-up periods are needed to determine the possible benefit provided by repeat surgery in patients with associated extrahepatic recurrence.

For patients without extrahepatic disease, repeat liver resections for colorectal metastases definitely can offer prolonged survival, similar to first hepatectomies, provided that the surgery is curative.

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DISCUSSION

DR. ENCKE (Frankfurt, Germany): Thank you for this presentation and your large figures. I can only add our own small experience. I can confirm that the mortality and morbidity are extremely low, mortality was zero in our series and we had a morbidity rate of 13%. However, we only had 24 patients with isolated liver metastases as recurrences and we only operated in these patients. We do not perform an operation in those with extrahepatic disease. We reached a prolongation of survival for our second repeat hepatectomies in comparison to the group where it could not perform such an operation, but after 60 months, they all died finally, too. So we did not find this difference between those who lived longer in your series with second repeat hepatectomy in comparison to those with a first hepatectomy.

DR. JEEKEL (Rotterdam, The Netherlands): My question is also related to the inclusion of the patients with extrahepatic disease. I was curious in the last paper about the cryosurgery and now again you included the extrahepatic disease patients in your group. We would not treat those patients in my country. I think it is interesting you do, but if you exclude those patients, we have the 5-year survival of the overall group about 48% to 50%, which is not so different from the overall group of Dukes' A-B-C patients. So, why are these results so extremely good? Do you use other treatment as well as chemotherapy? I presume that you used chemotherapy as well, and I think it is very important to note that and to include it in your data. Is there any way to do this in a prospective manner, to use chemotherapy in addition to your treatment?

DR. BROELSCH (Hamburg, Germany): Congratulations for an excellent presentation. Many data were, however, actually difficult to follow. One question relates to the occurrence of extrahepatic disease. Does this extrahepatic disease occur after the first resection? Was it associated with intrahepatic recurrence preceding the second resection? I would agree with H. Jeekel