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Resection of Colorectal Liver Metastases

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Abstract. From 1960 to 1992 a total of 1718 patients with liver metastases from colorectal carcinoma were recorded. Of these patients, 469 (27.3%) underwent hepatic resection, which was performed with curative intent in 434 patients (25.3%). Operative mortality in this group was 4.4%, being 1.8% (2 of 114) during the last 3 years. Significant morbidity was observed in 16% of patients with a decrease to 5% (6 of 112) for the last 3 years. A 99.8% follow-up until November 1, 1993 was achieved. Excluding operative mortality, there are 350 patients with "potentially curative" resection and 65 corresponding patients with minimal macroscopic ($n = 19$) or microscopic ($n = 46$) residual disease. The latter group demonstrated a poor prognosis, with median and maximum survival times of 14.4 and 56.0 months, respectively. Among the 350 patients having potentially curative resection, the actuarial 5-, 10-, and 20-year survivals were 39.3%, 23.6%, and 17.7%, respectively. Tumor-free survival was 33.6% at 5 years. In the univariate analysis, the following factors were associated with decreased crude survival: presence and extent of mesenteric lymph node involvement ($p = 0.0001$); grade III/IV primary tumor ($p = 0.013$); synchronous diagnosis of metastases ($p = 0.014$); satellite metastases ($p = 0.00001$); metastasis diameter of > 5 cm ($p = 0.003$); preoperative carcinoembryonic antigen (CEA) elevation ($p = 0.03$); limited resection margins ($p = 0.009$); extrahepatic disease ($p = 0.009$); and nonanatomic procedures ($p = 0.008$). With respect to disease-free survival, extrahepatic disease ($p = 0.09$) failed to achieve statistical significance, whereas patients with primary tumors in the colon did significantly better than those with rectal cancer ($p = 0.04$). The presence of five or more independent metastases adversely affected resectability ($p < 0.05$). However, once a radical excision of all detectable disease was achieved, no significant predictive value of an increasing number of metastases (1–3 versus ≥ 4) on either overall ($p = 0.40$) or disease-free ($p = 0.64$) survival was found. Using Cox's multivariate regression analysis, the presence of satellite metastases, primary tumor grade, the time of metastasis diagnosis, diameter of the largest metastasis, anatomic versus nonanatomic approach, year of resection, and mesenteric lymph node involvement each independently affected both crude and tumor-free survival.

There is overwhelming evidence that resection of liver metastases from colorectal carcinoma provides an effective therapeutic approach [1–5] that can cure a substantial proportion of patients and may result in disease-free survival of 20 years and more [6–8]. The focus must now be shifted toward studying some of the more detailed aspects of this issue: (1) the proportion of patients with resectable disease in virtually unselected patient samples rather than in "surgical" series; (2) the importance of early diagnosis through aggressive screening and its effect on treatment; (3) the assessment of reliable indicators of prognosis and, more importantly, the identification of factors that preclude patient benefit and may consequently serve as contraindications; (4) the value of a re-resection in the event of tumor recurrence as a reflection of the importance of continuing follow-up investigations; and finally (5) the optimal technical approach. This article, in addition to presenting basic information on the largest single institution series worldwide, specifically addresses some of these questions.

This paper is dedicated to Gerd Hegemann, Emeritus Professor of Surgery, outstanding teacher of surgical thinking and practice.

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Material and Methods

Patients

A total of 1718 patients with hepatic metastases from colorectal carcinoma were recorded from 1960 through 1992 at the Department of Surgery, Erlangen University Hospital. The diagnosis was confirmed by surgical exploration in 1382 patients (80.4%), whereas 336 patients (19.6%) had external imaging only.

A group of 469 patients (27.3% of the entire sample, 33.9% of the subgroup explored surgically) underwent hepatic resection. Of these patients, 35 had deliberately palliative procedures: debulking for huge symptomatic lesions ($n = 17$), complete removal of significant hepatic disease despite minor but unresectable extrahepatic tumor ($n = 12$), tumor-reductive surgery preceding regional chemotherapy ($n = 6$). The remaining 434 patients underwent resection with curative intent, and they form the basis of this report. There were 229 men and 205 women with a median age of 59 years (range 26–91 years).

Treatment

Within the study group 195 patients (45%) underwent common anatomic resections. As defined by our recently published terminology [9], there were 53 right trisectorectomies, 97 right and 15 left hemihepatectomies along the "principal plane," and 30 (left) lateral sectorectomies. Thirty-one patients (7%) had uncommon sector-oriented procedures including 14 left trisectorectomies, 12 posterior sectorectomies, and 5 central hepatic resections. One hundred nineteen patients (27%) had segment-orientated resections with 15% to 70% reduction in total liver volume; and 89 patients (21%) underwent nonanatomic procedures.

In 74 patients (17%) en bloc excision of one or more *perihepatic* structures was carried out because of tumor adherence or suspected tumor invasion (right diaphragm 47; right adrenal gland 19; retrohepatic vena cava 2; portal vein bifurcation 1; bile duct confluence 2; omentum 8; small bowel loop 1; stomach 1). Major *extrahepatic* surgery in the sense of an anatomically separate procedure was simultaneously performed in 155 patients (36%). It consisted predominantly of combined removal of the liver mass and primary tumor as realized in 108 of the 189 patients (57%) with synchronous metastases.

In the remaining 81 patients (43%) with synchronous hepatic lesions, the primary procedure and liver resection were performed at separate operations. In one of these patients a huge cluster of metastases occupying most of the right hemiliver (specimen 4.25 kg) required a right trisectorectomy, with concomitant resection of the portal vein bifurcation done as the first operation, followed by a low anterior resection some weeks later. In the remaining 80 patients hepatic resection was postponed 2 weeks to 23 months, whereas it was carried out after 4 months to 6.5 years in the 245 cases with metachronously detected secondaries. Of these 325 patients, 14 underwent supplementary excision of a local recurrence, 3 patients had resection of a second malignancy (colon, renal, gastric), 18 patients had extrahepatic blood-borne secondaries removed (pulmonary 12, ovarian 2, cerebral 1, adrenal 3), and 8 patients underwent simultaneous excision of an omental deposit or limited peritoneal seeding. Another 9 patients had local recurrent disease, and 5 patients had other metastases removed after the primary procedure but prior to the actual liver resection.

In 1984 thirty-one patients entered a prospective randomized trial to assess the value of adjuvant regional chemotherapy. In 15 cases a catheter was inserted into the hepatic artery, and four courses of mitomycin C (8 mg/m^2 on day 1) and 5-fluorouracil (600 mg/m^2 on days 1–5) were administered at 4-week intervals. Apart from this trial, there was no adjuvant treatment protocol. Only 11 patients had adjuvant chemotherapy after diagnosis of their hepatic involvement, 4 of them prior to liver resection; and 10 with low and midrectum cancer, respectively, had adjuvant radiation therapy of the pelvis. Another 35 patients received chemotherapy after cancer relapse.

Follow-up Surgery

Sixty-four patients with initially curative liver resection underwent reoperation with curative intent for cancer relapse. A re-resection was ultimately performed in 51 patients and classified "potentially curative" in 47 instances. With two exceptions, these 47 patients had asymptomatic disease discovered on the basis of our follow-up protocol. Curative re-resections were predominantly accomplished for hepatic, pulmonary, or local recurrences; but they also addressed metastases in the adrenal gland, ovary, brain, and cutaneous or subdiaphragmatic implants following needle biopsy. The median interval between first liver resection and diagnosis of tumor recurrence was 13 months (range 2–33 months) in 47 patients with "curative" re-intervention, 17 months (range 2–67 months) in the 17 patients in whom this goal was ultimately not achieved, and 18 months (range 1–317 months) in 167 patients with no attempt at a "curative" reoperation.

Data Collection and Statistical Evaluation

Apart from four patients undergoing hepatic resection prior to 1969, the pathologic and clinical data were recorded prospectively. All patients but one were followed until November 1, 1993 or death.

To assess the proportion of patients with resectable disease, two subgroups of patients seen after 1980 were selected from the entire series in order to reduce diagnostic uncertainty as well as to minimize selection and referral bias. For patients with *synchronous* liver metastases, only inhabitants of Erlangen itself and surrounding villages were included (until recently no other unit to perform colorectal cancer surgery was available for these patients). Among patients with *metachronous* metastases, the analysis was restricted to patients who had already undergone their colorectal resection in our department; patients specifically referred for liver surgery after primary treatment elsewhere were analyzed separately.

Survival (endpoint: death, irrespective of cause) and tumor-free survival (endpoints: definite tumor recurrence *or* death) were estimated by means of the Kaplan-Meier product limited method and checked for statistical significance using the log-rank test. A univariate analysis was performed for (1) the entire group resected with curative intent, and (2) patients with a follow-up of more than 5 years (liver resection prior to November 1988). In addition, a stepwise multivariate regression analysis (BMDP 2L) was undertaken for the larger sample with respect to crude survival as well as tumor-free survival.

Results

Resectability

Analyzing the entire series, hepatic resection with curative intent was performed in 25.3% of cases. This proportion increased from 3.7% during the 1960s and 12.7% during the 1970s to 31.0% since 1980. Corresponding figures for procedures ultimately classified "curative" were 1.9%, 8.8%, and 26.8%, respectively. Hence the proportion of "curative" procedures among resections with curative intent increased from 50% to 87%.

If only the two selected patient groups described above are analyzed, resectability and proportion of curative procedures are for synchronous metastases 24.2% and 19.8%, and for metachronous lesions 23.8% and 22.0%, respectively (Table 1). Among patients specifically referred to our department, these figures were similar in cases of synchronous metastases, whereas they were 51.1% and 44.0%, respectively, in patients with metachronous hepatic involvement.

Focusing at the influence of various features, there is an obvious effect of the hepatic involvement as well as the extrahepatic disease. With respect to number of metastases, resectability was high in the case of one to four independent nodules with slightly superior results for solitary lesions. In patients with five to seven metastases a "curative" procedure was exceptional, whereas any number higher than nine was always connected with proved residual disease. Characteristics of the primary tumor were also associated with a different resectability chance. These effects are found in synchronous and metachronous metastases alike. A

Table 1. Resectability.

Parameter	Patients (no.)	Resection with curative intent No.	Resection with curative intent %	"Curative" procedures No.	"Curative" procedures %	Ultimately "curative" (%)
Years						
1960–1969	107	4	3.7	2	1.9	50
1970–1979	377	48	12.7	33	8.8	69
1980–1992	1234	382	31.0	331	26.8	87
Status						
Synchronous	926	189	20.4	151	16.3	80
Metachronous	792	245	30.9	215	27.1	88
Total	1718	434	25.3	366	21.3	84
Synchronous 1980–1992						
Erlangen inhabitants	293	71	24.2	58	19.8	82
Others	290	72	24.8	62	21.4	86
Metachronous 1980–1992						
Primary resection in Erlangen	345	82	23.8	76	22.0	93
Others	306	157	51.3	135	44.1	86

Table 2. Proportion of "curative" resection, 1980–1992: selected groups.

Parameter	Synchronous metastases Patients (no.)	"Curative" resection No.	"Curative" resection %	Metachronous metastases Patients (no.)	"Curative" resection No.	"Curative" resection %
No. of metastases						
1	58	30	51.7	110	50	45.5
2	30	13	43.3	35	13	37.1
3	21	10	47.6	21	5	23.8
4	10	4	40.0	11	3	27.3
5–7	21	1	4.8	27	4	14.8
≥8	153	—		141	1	0.7
Dukes system						
A	1	1	100	20	8	40.0
B	30	12	40.0	78	17	21.8
C1	72	17	23.6	122	30	24.6
C2	145	27	18.6	110	19	17.3
Unknown	45	1	2.2	15	2	13.3
Grading						
I	10	2	20.0	26	8	30.8
II	149	43	28.9	214	51	23.8
III	113	13	11.5	92	14	15.2
Other/unknown	21	—		13	3	23.1
Symptoms						
No	214	53	24.8	305	75	24.6
Unspecific	54	5	9.3	29	1	3.4
Liver-related	24	—		9	—	
Unknown	1	—		2	—	
Extrahepatic tumor						
No	192	52	27.1	179	67	37.4
Yes	101	6	5.9	166	9	5.4

particular important finding is the low proportion of curative resections in patients presenting with even uncharacteristic upper abdominal symptoms and the lack of resectability in case of "liver-related" clinical signs (Table 2).

Table 3. Postoperative complications.

Complication	No. lethal	No. nonlethal
Specific: liver-related		
Intraoperative hemorrhage	3	—
Postoperative bleeding liver	1	3
Unrecognized bile duct damage	1	—
Bile fistula	—	11
Periphepatic abscess	—	5
Liver failure	1	18
Liver + renal failure	2	—
Specific: non-liver related		
Postoperative bleeding at other site	—	5
Anastomotic leakage	3	11
Small bowel fistula	—	1
Chylous fistula	—	2
Abdominal wound infection	—	3
Perineal wound infection	—	4
General		
Deep vein thrombosis	—	2
Pulmonary embolism	3	2
Renal failure	1	1
Acute cardiac failure/myocardial infarction	4	—

Operative Mortality

Thirty-day mortality was 4.4%. It fell from 11.5% (6 of 52) during the first two decades to 3.4% (13 of 382) from 1980 onward. During the last 3 years mortality was 1.8% (2 of 114). Death directly related to hepatic resection was observed in eight patients (1.8%), resulting from massive intraoperative hemorrhage in three, postoperative bleeding and unrecognized bile duct damage in one each, and postresection hepatocellular or multiorgan failure following right trisectorectomy in three. There was no such case during the last 3 years. Mortality from a concomitant colorectal procedure was seen in three patients (0.7%) all dying from anastomotic leakage. The remaining eight deaths (1.8%) were related to general health problems, based on cardiac failure in four (two of them with proved acute myocardial infarction), acute renal failure in one, and pulmonary embolism in three. Two patients of the latter subgroup died after discharge from the hospital (Table 3).

Nonlethal Complications

Significant postoperative complications occurred in 68 of the 415 surviving patients (16%) with a decrease to 5% during the last 3 years. The complications were related to the liver resection in 37 cases (9%), to concomitant extrahepatic surgery in 26 instances (6%), and to nonsurgical problems in the remaining 5 patients (Table 3). Another 25 patients (6%) experienced a symptomatic right-sided pleural effusion as the only minor postoperative sequela. It resolved spontaneously in 8 cases but was treated in 4 patients by thoracocentesis and in 13 by chest tube placement.

Pathologic Classification

Minimal intrahepatic tumor, detected during the final steps of the operation, was left behind in 7 of the 434 patients. In an additional

Table 4. Destiny and tumor status at November 1, 1993.

Parameter	Curative resection (no.)	Nonradical resection (no.)	Palliative debulking (no.)	No liver resection (no.)
Patients	366	68	35	1249
30-Day mortality	16	3	3	77
Evaluable patients	350	65	32	1172
Status				
Alive, NED	128	—	—	—
Alive, WD	17	6	1	25
Dead, NED	20	—	—	—
Dead, DU	3	—	—	—
Dead, WD	181	56	31	1147
Lost to follow-up	1	—	—	2

NED: no evidence of recurrent diseases; WD: with recurrent disease; DU: disease unknown (no reliable information regarding recurrent disease).

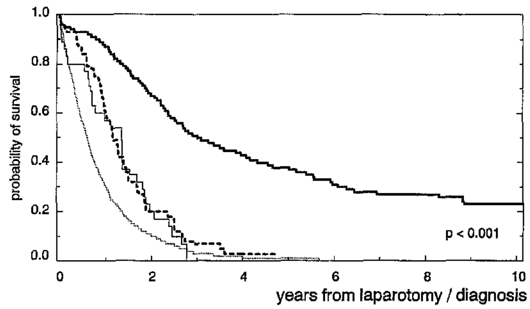

Fig. 1. Survival among 434 patients undergoing resection of liver metastases with curative intent (thick lines), divided into 366 potentially curative versus 68 nonradical procedures, operative mortality included. Thin lines indicate the two remaining patient groups undergoing deliberate palliative debulking (solid thin line; n = 35) or no resection (broken thin line; n = 1249) of hepatic metastases.

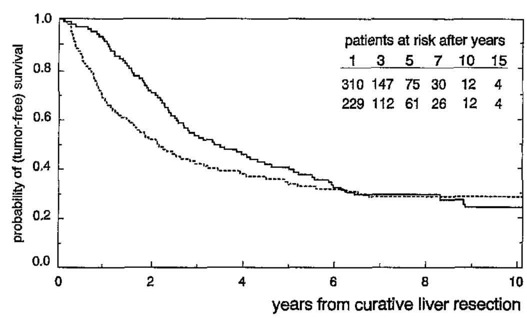

Fig. 2. Overall (solid line) and tumor-free (broken line) survival after potentially curative resection, operative (30-day) mortality excluded.

13 cases it became evident during surgery that some extrahepatic disease was not completely resectable.

The other 414 patients had all gross tumor removed, but 48 of them (12%) demonstrated positive margins on histologic examination (in the liver specimen 41, in an extrahepatic specimen 7). Therefore 366 procedures (88%) were classified "potentially curative resections" as defined by removal of all gross tumor with negative margins (even if minimal). Of this group, the specimen in 16 patients included tumor that histologically extended beyond the confines of the liver. Ten patients had invasion of adjacent structures, and three had lymph node metastases at the liver hilum, associated with invasion of the diaphragm in one case. The remaining three patients had tumor infiltration of the extrahepatic bile duct, the vena cava, and a tumor thrombus within the portal vein extending to its bifurcation, respectively.

Outcome and Tumor Status after Curative Resection

Excluding 30-day mortality, 350 patients survived their "curative" resection. As of November 1, 1993 there were 128 of these patients alive without evidence of disease, including 24 patients who had undergone a curative reintervention. Another 20 patients had died without definite cancer relapse including 9 with and 11 without a curative re-resection.

Of the 198 patients with definite cancer relapse, 17 were alive at 10 to 93 (median 30) months, and 181 had died as long as 115 (median 26) months from the time of hepatic resection. The survival period since diagnosis of recurrent disease ranged from 10 to 41 (median 19) months in those who have died and from 8 to 49 (median 22.5) months in the 15 still alive.

In the three patients operated on during the early 1970s the tumor status at death was unclear. One foreign patient was lost to follow-up the day of discharge from the hospital (Table 4).

Prognosis

Including operative mortality, the 3-, 5-, 10-, and 20-year survivals for the entire sample of patients undergoing liver resection with curative intent were 45%, 33%, 20%, and 15%, respectively. The crucial determinant of long-term benefit was completeness of tumor removal, as judged by operative assessment and subsequent histologic examination. Following procedures classified as "potentially curative," the 5-, 10-, and 20-year *actuarial* survival figures were 38%, 23%, and 17%, respectively with 75, 12, and 2 patients having survived these respective periods (Fig. 1). Excluding 30-day mortality, the precise figures ± double standard error (95% confidence level) were 39.3 ± 7.1%, 23.6 ± 11.9%, and 17.7 ± 22.7%, respectively. Correspondingly, the *actuarial* tumor-free survival at 5, 10, and 20 years was 33.6 ± 7.0%, 27.8 ± 14.2%, and 20.9 ± 26.2%, respectively (Fig. 2). Median survival was 39.6 months, and median tumor-free survival was 25.3 months. Among the 203 patients who had undergone surgery prior to November 1988 (i.e., with follow-up periods exceeding 60 months) *actual* 5-year survival and tumor-free survival were 36.9 ± 7.0% and 30.0 ± 7.2%, and the *actual* 10-year survival and tumor-free survival figures for 62 patients operated before November 1983 were 19.4 ± 10.0% and 17.7 ± 9.7%, respectively.

Of the 198 patients with "curative" resection but subsequent definite cancer relapse, 20 survived 5 years, and one has died close to 10 years later, accounting for 13.0% and 0.8% survival figures at 5 and 9 years, respectively. In contrast, none of the 68 patients with curative intent but nonradical resection has survived 5 years. Only 12 lived longer than 2 years, and two survived 4 years. The median survival time was 14.4 months (Fig. 1). Neither the distinction between 20 cases of macroscopic and 48 cases of microscopic residual disease nor the retrospective grouping of nonradicality due to "technical error" (n = 28) versus that due to "advanced disease" (n = 40) had a significant influence on prognosis. At present six patients in this group are alive 10 to 56 months after liver resection.

Table 5. Survival.

Parameter	Patients (no.)	Presently alive (no.)	Surviving > 5 years (no.)	Actual 5-year survival (%)	Median survival time (mo)	Actuarial survival (% at 1–10 years) 1	3	5	10	Log-rank test (p)
Patients										
Gender										
Male	182	70	42/112	38	36	92	51	38	19	0.29
Female	168	75	33/91	36	42	91	56	41	32	
Age										
< 60 Years	188	80	47/114	41	46	93	56	42	27	0.21
≥ 60 Years	162	65	28/89	31	34	89	50	36	18	
Primary tumor										
Localization										
Colon	189	86	38/102	37	42	91	55	42	28	0.27
Rectum	161	59	37/101	37	36	92	50	36	19	
Grading (Brothers)[a]										
Grade 1/2	251	109	61/154	40	47	93	56	42	25	0.013
Grade 3/4	73	19	14/49	29	30	88	43	29	18	
Mesenteric lymph nodes[b]										
Not involved	116	63	28/58	48	71	96	66	50	39	0.0001
Peripherally (C1)	120	41	31/83	37	38	94	53	37	18	
Centrally (C2)	96	31	13/55	18	28	84	37	29	—	
Mesenteric lymph nodes, synchronous metastases[c]										
Not involved	34	17	10/20	50	71	100	65	52	47	0.003
Peripherally (C1)	44	9	12/39	31	33	91	50	31	13	
Centrally (C2)	60	17	7/35	20	23	85	26	24	—	
Mesenteric lymph nodes, metachronous metastases[d]										
Not involved	82	46	18/38	47	53	94	67	50	32	0.11
Peripherally (C1)	76	34	19/44	43	41	96	54	42	27	
Centrally (C2)	36	14	6/20	30	46	83	54	37	—	
Metastases										
Time of diagnosis										
Synchronous	142	45	29/96	30	31	90	45	32	19	0.014
Metachronous	208	100	46/107	43	49	92	59	44	25	
Tumor-free interval for metachronous metastases										
< 12 Months	77	36	18/41	44	47	95	55	42	35	0.93
12–23 Months	66	31	17/37	46	55	91	65	50	28	
≥ 24 Months	65	33	11/29	38	44	91	57	41	14	
No. of metastases										
1 (± Satellites)	203	79	41/118	35	37	92	52	38	19	0.41
≥ 2 Independent metastases	147	66	34/85	40	41	90	55	41	32	
Satellite metastases										
No	301	135	70/171	41	47	93	58	43	28	0.00001
Yes	49	10	5/32	16	22	79	24	15	5	
Type of solitary metastases										
Solitary	180	74	38/105	36	45	93	55	40	23	0.002
Solitary + satellites	23	5	3/13	23	27	87	20	20	0	
Type of multiple metastases										
No satellites	121	61	32/66	48	50	94	61	47	36	0.0001
Multiple + satellites	26	5	2/19	11	18	73	26	12	12	
Distribution of multiple metastases										
Unilateral	90	42	22/53	42	48	90	61	43	36	0.73
Bilateral	57	28	12/32	38	33	91	44	36	24	
Critical number										
1–3 Metastases	318	131	63/182	35	39	91	53	38	22	0.40
≥ 4 Metastases	32	14	12/21	57	57	91	54	50	37	
Size of metastases										
< 5 cm	233	103	58/143	41	47	94	59	44	29	0.003
≥ 5 cm	117	42	17/60	28	29	86	42	30	15	
Extrahepatic disease										
No	303	130	68/177	38	42	93	56	41	26	0.009
Yes	47	15	7/26	27	29	81	33	26	0	
Preoperative CEA level[e]										
≤ 5 ng/ml	82	46	20/43	47	60	95	65	50	45	0.03
5.1–50.0 ng/ml	123	57	29/67	43	41	94	56	46	19	
> 50 ng/ml	74	27	11/35	31	32	93	45	29	—	

Table 5. (Continued)

Parameter	Patients (no.)	Presently alive (no.)	Surviving > 5 years (no.)	Actual 5-year survival (%)	Median survival time (mo.)	Actuarial survival (% at 1–10 years) 1	3	5	10	Log-rank test (p)
Treatment										
Time of resection of synchronous metastases										
Simultaneous	74	16	15/58	26	27	88	35	26	16	0.06
Delayed	68	29	14/38	37	37	93	55	40	26	
Margin of clearance										
1–9 mm	204	72	43/125	34	31	88	46	37	21	0.009
≥ 10 mm	146	73	32/78	41	51	97	64	43	28	
Limited clear margin										
1–4 mm	130	46	26/80	33	31	88	44	38	20	0.73
5–9 mm	74	26	17/45	38	32	86	50	36	24	
Type of resection										
Anatomic	291	134	63/154	41	44	92	57	42	24	0.008
Atypical	59	11	12/49	24	23	90	36	27	18	
Year of resection										
1960–1979	30	5	11/30	37	28	87	43	37	23	0.63
1980–1992	320	140	64/163	39	41	92	55	40	22	

[a]26 Patients not classified.
[b]18 Patients not classified.
[c]4 Patients not classified.
[d]14 Patients not classified.
[e]71 Patients not classified.

All but one of the 35 patients with deliberate palliative debulking died within 3 years of liver resection, the remaining patient being alive at 27 months. Despite considerably advanced hepatic disease, median survival was 16 months in this group. Among the 1249 patients who did not undergo liver resection, median survival time was 7.0 months. Apart from two cases lost to follow-up, all but 25 patients have died. Four patients survived for more than 5 years, the maximum survival time being 68 months. All four had initially presented with one or two liver metastases and without extrahepatic disease (Fig. 1).

Determinants of Prognosis: Univariate Analysis

The significance of clear margins is overwhelming ($p = 0.1 \times 10^{-17}$). Detailed analysis of various prognostic determinants was therefore restricted to patients who had undergone a potentially curative resection, and operative mortality was excluded (Tables 5, 6). If only patients undergoing hepatic resection prior to November 1988 are considered, the presence of mesenteric lymph node involvement or of satellite metastases as defined in our previous analysis [8] was a highly significant ($p < 0.01$) predictor of poor survival. The grade of the primary tumor, time of diagnosis of metastases, maximum diameter of metastases, margin of clearance, and type of liver resection proved to be of significant ($p < 0.05$) prognostic relevance.

Analyzing the entire sample, patient characteristics such as age and gender did not influence survival. The presence and distribution of positive mesenteric lymph nodes still provided a predominant indicator of prognosis. For the various subgroups analyzed, both survival and tumor-free survival were constantly superior for less advanced primary tumor stages according to the classification of Gabriel et al. into A, B, C1, and C2 cases [10]. In patients with metachronous metastases, however, the difference did not reach statistical significance. The grade of the primary growth was significant in terms of both survival and disease-free survival.

The time of diagnosis was significant in that (tumor-free) survival after resection for metachronously detected metastases was superior to that seen with synchronous metastases. The number of independent deposits or the distribution of multiple lesions both failed to affect prognosis. Survival of 32 patients from whom four or more individual tumor nodules were removed followed the same course as did survival of patients with one, two, or three metastases. There are 12 long-term survivors in the first group, nine of them living without recurrent disease at 5 to 14 years after liver resection. These patients had four to seven metastases removed that had been located as a cluster of deposits, randomly distributed unilateral disease, and bilateral involvement in three patients each. In all patients with unilateral tumor, the right hemiliver was affected. In contrast to the number of independent lesions, the presence of satellite metastases was associated with poor survival ($p = 0.00001$) and tumor-free survival ($p = 0.0001$) in the entire sample as well as in the subgroups with solitary and multiple metastases. These patients developed a higher proportion of pulmonary metastases with respect to initial relapse (39% versus 20%) as well as to final extent of disease (45% versus 23%). The diameter of the largest metastasis was a highly significant indicator of overall survival ($p = 0.009$) and significant in terms of tumor-free survival ($p = 0.015$).

Extrahepatic tumor (EHT) that was completely removed prior to or simultaneously with the hepatic resection was associated with significantly less favorable results. There are, however, seven tumor-free 5-year survivors despite EHT, five of whom remained free of recurrence for up to 8 years. Among these patients, the EHT consisted of local recurrence and histologically proved tumor infiltration of perihepatic structures in two patients each,

Table 6. Tumor-free survival.

Parameter	Patients (no.)	Presently alive free of disease (no.)	Surviving > 5 years free of disease (no.)	Actual 5-year disease-free survival (%)	Median disease-free survival time (mo)	Actuarial disease-free survival (% at 1–10 years) 1	3	5	10	Log-rank test (*p*)
Patients										
Gender										
Male	182	60	33/112	29	22	64	39	30	24	0.13
Female	168	68	28/91	31	28	70	44	37	33	
Age										
< 60 Years	188	72	38/114	34	25	67	44	36	31	0.44
≥ 60 Years	162	56	22/89	25	23	68	39	31	24	
Primary tumor										
Localization										
Colon	189	79	32/102	31	28	72	45	38	32	0.04
Rectum	161	49	29/101	29	20	62	37	29	23	
Grading (Brothers)[a]										
Grade 1/2	251	98	51/154	33	27	69	45	38	30	0.02
Grade 3/4	73	17	10/49	20	20	59	32	20	18	
Mesenteric lymph nodes[b]										
Not involved	116	56	25/58	43	49	74	52	48	41	0.0005
Peripherally (C1)	120	36	23/83	28	26	70	38	27	22	
Centrally (C2)	96	27	10/55	18	12	53	31	25	—	
Mesenteric lymph nodes, synchronous metastases[c]										
Not involved	34	15	9/20	45	44	77	54	45	45	0.003
Peripherally (C1)	44	8	8/39	21	21	61	32	20	14	
Centrally (C2)	60	15	6/35	17	11	47	23	23	—	
Mesenteric lymph nodes, metachronous metastases[d]										
Not involved	82	41	16/38	42	49	73	52	49	39	0.25
Peripherally (C1)	76	28	15/44	34	28	76	41	32	29	
Centrally (C2)	36	12	4/20	20	16	64	44	28	—	
Metastases										
Time of diagnosis										
Synchronous	142	40	23/96	24	20	59	35	27	22	0.004
Metachronous	208	88	38/107	36	31	73	46	38	33	
Tumor-free interval for metachronous metastases										
< 12 Months	77	30	16/41	39	27	72	44	35	33	0.84
12–23 Months	66	29	12/37	32	39	70	51	38	35	
≥ 24 Months	65	29	10/29	34	27	77	43	43	—	
No. of metastases										
1 (± Satellites)	203	69	32/118	27	25	67	41	32	25	0.56
≥ 2 Independent metastases	147	59	29/85	34	25	67	42	36	32	
Satellite metastases										
No	301	120	57/171	33	27	70	45	37	31	0.0001
Yes	49	8	4/32	13	11	49	19	13	7	
Type of solitary metastases										
Solitary	180	65	30/105	29	26	68	44	34	28	0.03
Solitary + satellites	23	4	2/13	15	15	61	20	14	0	
Type of multiple metastases										
No satellites	121	55	27/66	41	34	73	47	41	36	0.0006
Multiple + satellites	26	4	2/19	11	10	39	17	11	11	
Distribution of multiple metastases										
Unilateral	90	39	19/53	36	34	72	47	39	39	0.09
Bilateral	57	20	10/32	31	16	59	33	30	22	
Critical number										
1–3 Metastases	318	116	52/182	29	25	67	41	34	27	0.64
≥ 4 Metastases	32	12	9/21	43	28	69	48	34	34	
Size of metastases										
< 5 cm	233	91	46/143	32	30	72	46	36	31	0.015
≥ 5 cm	117	37	15/60	25	18	58	33	29	21	
Extrahepatic disease										
No	302	114	54/177	31	26	69	43	34	30	0.09
Yes	48	14	7/26	27	21	58	27	27	—	
Preoperative CEA level[e]										
≤ 5 ng/ml	82	44	19/43	44	59	74	60	50	47	0.008
5.1–50.0 ng/ml	123	51	23/67	34	26	65	44	40	27	
> 50 ng/ml	74	20	8/35	23	19	69	29	21	—	

Table 6. Continued

Parameter	Patients (no.)	Presently alive free of disease (no.)	Surviving > 5 years free of disease (no.)	Actual 5-year disease-free survival (%)	Median disease-free survival time (mo.)	Actuarial disease-free survival (% at 1–10 years) 1	3	5	10	Log-rank test (p)
Treatment										
Time of resection of synchronous metastases										
Simultaneous	74	14	12/58	21	13	55	26	21	17	0.09
Delayed	68	26	11/38	29	23	63	44	32	32	
Margin of clearance										
1–9 mm	204	64	35/125	28	20	64	38	31	25	0.03
≥ 10 mm	146	64	26/78	33	32	72	46	37	33	
Limited clear margin										
1–4 mm	130	40	22/80	28	18	64	36	33	23	0.68
5–9 mm	74	24	13/45	29	21	63	42	29	26	
Type of resection										
Anatomic	291	120	52/154	34	28	70	45	37	31	0.002
Atypical	59	8	9/49	18	13	53	27	20	15	
Year of resection										
1960–1979	30	5	8/30	27	20	60	37	27	23	0.58
1980–1992	320	123	53/173	31	26	68	42	34	28	

[a]26 Patients not classified.
[b]18 Patients not classified.
[c]4 Patients not classified.
[d]14 Patients not classified.
[e]71 Patients not classified.

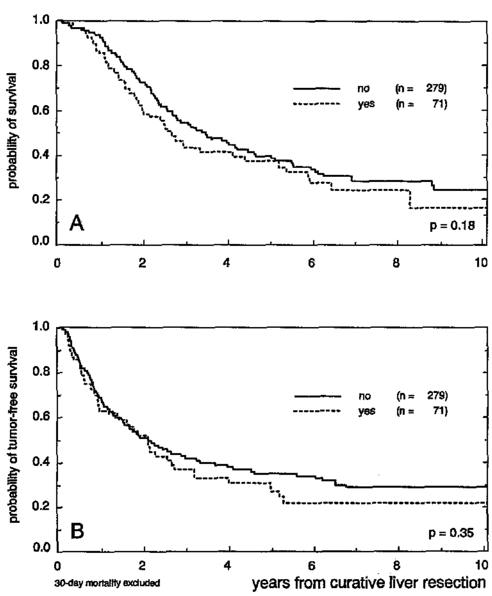

Fig. 3. Survival (**A**) and disease-free survival (**B**) for patients with four or more independent metastases and/or extrahepatic disease versus patients with one to three metastases and no extrahepatic disease.

and one patient had had a solitary lung metastasis removed 2 years earlier.

If patients with either extrahepatic disease or four or more individual metastases removed are combined in a group ($n = 71$) and compared to the remaining patients not affected by one of these two factors commonly regarded as "clear contraindications" ($n = 279$) (Fig. 3), no significant difference was detected in terms of survival ($p = 0.18$) or tumor-free survival ($p = 0.35$).

Among treatment-related parameters, the year of hepatic resection and the currently more aggressive policy toward metastatic disease did not adversely affect prognosis. Timing of resection in synchronous lesions was not significant despite a strong tendency in favor of the "delayed" group. Anatomic procedures were associated with much better outcome ($p = 0.008/0.002$). Correspondingly, a tumor-free margin of more than 10 mm resulted in superior survival ($p = 0.009$) and, though to a lesser degree ($p = 0.03$), disease-free survival.

Multivariate Analysis

The 15 factors analyzed in Tables 5 and 6 were entered into a Cox model for multivariate regression analysis. With enter and remove limits of $p < 0.1$ and $p > 0.15$, respectively, seven factors proved independently significant. Factors favoring survival included absence of satellite metastases, followed by grade I/II primary tumors (both $p < 0.01$), metachronous detection of metastases, small diameter of the largest metastasis, anatomic liver resection, liver resection in 1980 or later, and absence of mesenteric lymph node involvement (all $p < 0.05$). Regarding tumor-free survival, satellites and anatomic resection technique were ranked first and second, with the other factors following in a slightly different order (Table 7). Interestingly, no other feature contributed to either crude or tumor-free survival.

Follow-up Surgery

There were no operative death after re-resection of recurrent cancer. Actuarial survivals at 3 and 5 years from the time of diagnosis of recurrent disease (as well as of re-resection) were 67% and 41% (even though a few days later decreasing to 31%),

Table 7. Multivariate stepwise regression analysis (Cox model).

Factor	Favorable vs. poor	Improvement Chi-square	p
Survival			
Satellite metastases	No vs. yes	14.792	0.000
Primary tumor grade	I/II vs. III/IV	7.188	0.007
Time of metastasis diagnosis	Metachronous vs. synchronous	5.473	0.019
Size of metastasis	≤ 4.9 cm vs. ≥ 5.0 cm	4.839	0.028
Type of resection	Anatomic vs. non-anatomic	5.753	0.016
Year of liver resection	1980–1992 vs. 1960–1979	4.919	0.027
Mesenteric lymph node involvement	No vs. yes	4.542	0.033
Tumor-free survival			
Satellite metastases	No vs. yes	10.405	0.001
Type of resection	Anatomic vs. nonanatomic	10.259	0.001
Size of metastasis	≤ 44.9 cm vs. ≥ 5.0 cm	6.906	0.009
Mesenteric lymph node involvement	No vs. yes	7.181	0.007
Primary tumor grade	I/II vs. III/IV	3.961	0.047
Year of liver resection	1980–1992 vs. 1960–1979	3.733	0.053
Time of metastasis diagnosis	Metachronous vs. synchronous	3.645	0.056

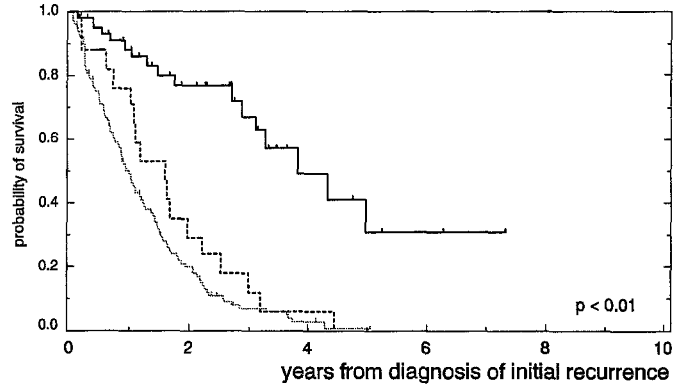

Fig. 4. Treatment of initial tumor recurrence. Survival in patients with initially curative liver resection and subsequent tumor recurrence (any mortality included), calculated from diagnosis of recurrent disease; curative re-resection was carried out within 4 weeks in 46 of 47 patients. Solid line: curative re-resection (n = 47); dashed line: nonradical/no re-resection (n = 17); dotted line: no attempt at re-resection (n = 167).

respectively, and disease-free survivals were 51% at 3 years and 40% at 5 years) if the second procedure was again classified "curative." If, however, macroscopic or microscopic disease was left behind, the 5-year survival was zero (Fig. 4). The three 5-year tumor-free survivors all underwent re-resection for intrahepatic recurrence, accompanied by a solitary lung metastasis in one patient and a biopsy-related skin metastasis in another. Another five patients, who are presently alive and free of disease more than 5 years after the initial liver resection had, in four cases, pulmonary metastases removed 41 to 56 months ago, and one patient was reoperated for a local recurrence 37 months ago. A third group of eight patients survived 5 years from initial liver resection, and 17 to 59 (median 39) months from reintervention but developed definite cancer relapse. Two of them had been reoperated for local recurrent disease and three each for new hepatic and pulmonary metastases, respectively. Resection of recurrent disease in other organs (adrenal gland, brain, ovary) was always followed by cancer progression and carried median and maximum survival times of 12 and 32 months, respectively.

Improvement of Prognosis with Time

To analyze the improvement of prognosis with time, the only endpoint was "definite cancer relapse" (i.e., a recurrence that again was completely removed was ignored, as was tumor-unrelated death). According to the Kaplan-Meier algorithm, 70%, 45%, 36%, and 32% of patients were initially likely to be free of disease after 1, 3, 5, and 7 or more years, respectively (bottom curve in Figure 5). As no definite cancer relapse was observed more than 7 years after the initial liver resection, the "free-of-disease curve" was level after this time. With every year of tumor-free survival, the curve shifted upward, with a 72% ultimate chance after 3 years, 88% chance after 5 years, and virtually 100% chance after 7 years of tumor-free follow-up (Fig. 5).

Discussion

Our overall results strengthen the increasing acceptance of hepatic resection as the preferred treatment of colorectal liver metastases. This approach carries a low operative risk and is associated with excellent postoperative quality of life and significant prognostic improvement.

Several centers have shown that liver resection during the 1990s is a well controlled procedure with a mortality approaching zero in some recent series [11–15]. In our own experience, overall mortality for patients who underwent resection since 1960 is gradually decreasing [2, 8]. It is now 4.4% but less than 2% for the 114 patients who had resection for colorectal metastases during the last 3 years. Death related to hepatic resection has not been observed since 1990. The mortality of a standard liver resection, performed by an experienced team in an otherwise healthy patient, can therefore be assumed to be 1% or less. Consequently, we are increasingly confronted with a twofold challenge: First, how far one may proceed in technically expanding procedures, eventually up to the stage of ante situ or ex situ resection [16]. Second, how liberal one can become in accepting patients with cardiovascular, pulmonary, and renal impairment for major hepatic surgery? This second consideration is, in our own experience, even more pressing, as one is occasionally faced with a desperate individual already refused by several other centers and searching for that last straw of hope. It may be much easier to blame the "objective" oncologic aspects of (a still unclear) tumor biology than to turn surgery down because of "risk" if it converts an otherwise chance of cure to nil.

Postoperative morbidity of hepatic resection has also been considerably reduced. Bleeding problems have virtually disappeared in noncirrhotic patients [9]. Septic complications or biliary leakage have become rare and when they do occur are effectively treated by percutaneous drainage and endoscopic stenting. In general, liver resection is better tolerated than are most primary colorectal resections, and recovery from surgery is usually fast and complete. The occasional reservation of medical physicians, withholding hepatic resection from a patient because of concerns of the immediate risk and the long-lasting sequelae involved, reflects

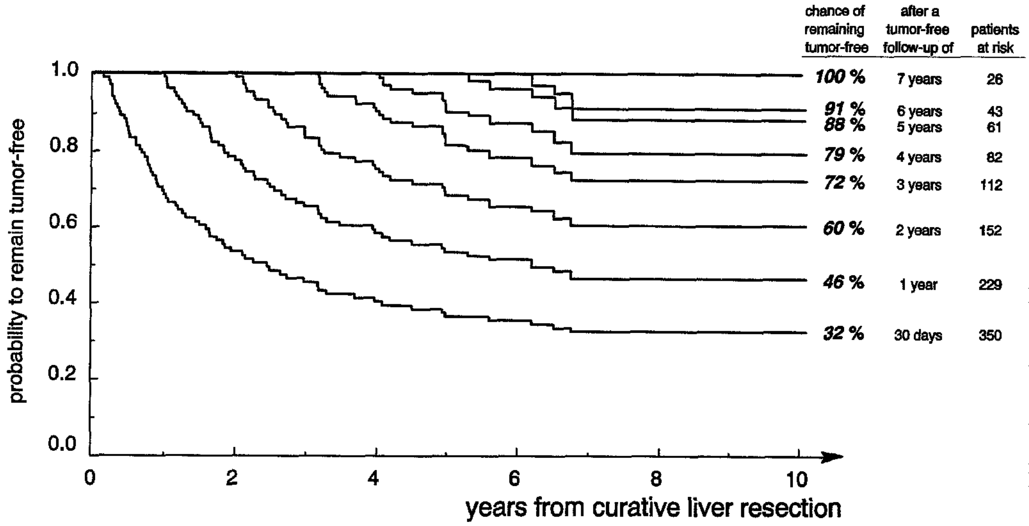

Fig. 5. Increase of the probability to remain free of a definite cancer recurrence after a tumor-free follow-up period of 1 to 7 years. Tumor recurrences that were completely removed by a curative re-resection are disregarded; deaths without recurrent disease are categorized as "lost to follow-up." Thirty-day mortality was excluded.

an inadequate appreciation of established surgical data. Assignment to chemotherapy as an alternative is a poor option. Any patients who can tolerate an aggressive chemotherapy protocol can, in general, tolerate liver resection as well.

The most important criterion for therapy is oncologic effectiveness. Five-year survival was 39% for patients undergoing radical procedures, with 34% tumor-free at this time. Corresponding figures in patients with a follow-up of more than 5 years are now 37% and 30%, respectively, which represents a substantial improvement over our previous analyses [2, 8]. Our current 5-year results are based on 75 and 61 patients, respectively, numbers that together with the two large multiinstitutional series [3, 4] clearly outweigh the world experience of untreated long-term survival. This finding makes, in connection with numerous other reports [1, 5, 11–15], any future demand for prospective trials on the general effectiveness of hepatic resection for metastatic colorectal cancer [17, 18] not only obsolete but unethical.

With respect to indicators of prognosis, this analysis essentially confirms our previous results [2, 8]. The increased number of patients with "curative" resection, and the growing proportion with a follow-up of 5 years and more, however, strengthens the statistical significance of these earlier findings. The investigation of patients with a minimum follow-up of 5 years, previously indicative only of mesenteric lymph node involvement [8], now also confirms the prognostic significance of tumor grade, time of metastasis diagnosis, satellite lesions, maximum diameter of metastases, margin of clearance, and the superiority of an anatomic operative approach. The large database in the total series adds the necessary statistical power to establish the prognostic relevance of such detailed aspects as the presence of satellites escorting solitary lesions, as well as to proving the impact of other variables, such as extrahepatic disease or preoperative carcinoembryonic antigen (CEA) level.

The correlation of many of the factors with a poor prognosis is easy to understand. The obvious presence of metastases at the time of colorectal resection indicates either late diagnosis of the primary tumor or, more likely, a rather aggressive growth pattern. In addition, as the risk of local failure is higher in the synchronous group, diminished survival becomes understandable. Larger size of hepatic lesions at the time of detection and high preoperative CEA levels may be partially related to biologic features but clearly reflect tumor mass and thereby a sort of diagnostic zero-time shift. Both these aspects make inferior survival plausible. Focusing on the aspect of tumor biology, poor primary tumor differentiation indicates "aggressive" behavior, as does mesenteric lymph node involvement [19]. As both these factors are associated with an increased probability of early and multifocal recurrent disease [A. Altendorf-Hofmann, unpublished data], their different effects in patients with synchronous and metachronous metastases become understandable. Whereas these two features in the first group should have a strong predictive value for prognosis, they are likely in the second group to influence resectability, or the underlying selection process, rather than the ultimate survival of patients with resectable metastases. A "biologic" indicator related to intrahepatic disease is the presence of satellite metastases. They are caused by portal vein invasion [20], which makes coincidental invasion of hepatic veins likely. Not only a inferior prognosis must be expected but also a high incidence of subsequent pulmonary metastases. This result, in fact, was observed in 45% of patients with satellite metastases compared to only 23% of other patients.

Some aspects are more difficult to interpret. For example, in contrast to results reported by others [3, 4], there was no significant influence of the time interval between primary procedure and liver resection in patients with metachronous metastases. Among the three groups analyzed in Tables 5 and 6 (< 12 months, 12–23 months, ≥ 24 months), many other factors such as primary tumor grade, mesenteric lymph node involvement, number and size of metastases, CEA level, or additional extrahepatic disease were well matched. All these lesions must have been present in the form of micrometastases, or were caused by surgical manipulation, at the time of primary operation. The subsequent stage of balance between microtumor and host immunology may last for different periods as a result of chance and is not necessarily due to a biologic difference. This view is supported by the fact that the chance of curative reoperation in case of cancer relapse was also not dependent on the time interval since the initial liver resection. Superior survival in patients operated since 1980 may by and large be attributed to improved imaging techniques and thereby the Will Rogers phenomenon [21], resulting in a significant influence reflected in the multivariate analysis. In the univariate test, however, this benefit of diagnostic accuracy is balanced by the contrary effect of more liberal indication criteria.

There has been little progress in the delineation of "contraindications" to hepatic resection. The distinction between solitary and two or more metastases as well as that of unilateral versus bilateral disease was initially thought to be of great importance for patient selection [22–28]. During the interim, these factors have been shown not be contraindications [7, 29] and may even have little to no prognostic significance [2, 8]. More relevant issues in this debate include extrahepatic disease, the maximum number of individual lesions, and the minimum margin of clearance [3, 28–32]. Extrahepatic disease is certainly the most serious concern. If unresectable, as is usually found, there is no point in removing a liver lesion for any reason other than for palliation of substantial symptoms. In our 35 patients, it has not led to long-term survival, although it has achieved improved quality of life in most patients. The median survival time of 16 months is also unexpected in view of the large tumor masses in this group. For tumors technically resectable, however, one may aggressively treat infiltration of adjacent structures, local recurrence, or a single pulmonary deposit. A distinct group includes those patients with multifocal lung involvement and hematogenous spread to third party organs. Including our re-resection experience, we have seen within the first group two patients with direct tumor invasion, four with pulmonary metastases, and three with local recurrence, who survived more than 5 years without definite tumor recurrence. In contrast, the second situation was unequivocally followed by further tumor progression and may well be out of the surgical domain. With respect to the maximum number of metastases, our previous finding of prognostic irrelevance [2, 8] has been substantiated. Patients with up to five randomly distributed metastases and seven nodules forming a localized cluster have survived more than 5 years without recurrent disease. Such long-term survival of patients with up to five resected metastases has meanwhile also been reported by others but, as in our series, was restricted to patients with complete tumor clearance [4, 33]. Indeed, a growing number of individual lesions, particularly if randomly distributed with bilateral involvement, may approach the technical limits of complete resectability rather than indicate a 180 degree switch in tumor biology.

The factor most influenced by surgical technique is the minimum margin of clearance required and desired. There is general agreement that a margin of 1 cm or more should be attempted [3, 4, 28, 30, 31], and there is a growing consensus that this judgment should be guided by routine application of operative ultrasonography [9, 20, 33]. To ascertain comfortable margins, we have long advocated, for small lesions, that the entire COUINAUD segment be removed, instead of performing a local wedge excision [34] and that it is best in general to rely on well established standard procedures if treating more advanced disease. The recent renewed advocacy of nonanatomic resections is difficult to understand, especially in view of the inferior results seen with this approach [28, 35]. The crucial question is whether one should keep removing tumors that, for reasons of size, number, or location, do not allow a 1 cm clear margin. Our data indicate that resection is sound. Not only was long-term (tumor-free) survival achieved in several patients with margins of 1 to 4 mm as well as 5 to 9 mm, but the multivariate analysis also failed to substantiate a prognostic significance of the extent of clear margins. A different finding by others [4, 30] is not truly contradictory, as in their series nonradical procedures are incorporated in the "low-margin" group, the obvious effect of which is clearly indicated by our Figure 1.

The possible effect of "referral and selection bias" was specifically addressed in our analysis. Referral bias has clearly increased over the last decade, as shown by the different "potentially curative resection" rate of metachronous metastases seen in patients deriving from our own colorectal service compared to those specifically sent for treatment of liver secondaries after primary resection elsewhere. Even in the first group, however, where referral bias can virtually be ignored, "curative" resectability, reflecting a combination of the extent of disease and the general condition of the patient, is 22%. Surprisingly, this figure is mirrored in patients from the Erlangen area admitted for primary large bowel cancer resection in whom preoperative imaging or operative exploration revealed synchronous liver metastases. The similar resectability figures in "referred" patients with synchronous metastases is due to the fact that these patients were usually not sent because of their hepatic involvement but for advanced local disease, advanced age, or poor general condition. The high resectability rate in the two less biased subgroups and the significant proportion of patients who underwent "curative" resection who had one or more features commonly referred to as clear contraindications to hepatic resection diminish the role of selection bias in this consecutive series.

Aside from a rather aggressive therapeutic approach, our high resection rate since 1980 may also be supported by a strict follow-up policy. CEA and CA 19-9 levels, abdominal ultrasonography, bi-directional chest radiographs, and endoscopy in patients with (low) anterior resection are performed at 3- to 4-month intervals for 2 years, 6-month intervals for the following 3 years, and on a yearly basis thereafter. With this practice, followed in nearly two-thirds of our patients, most liver metastases, even if large, have been discovered in the absence of specific clinical symptoms and were often found suitable for resection. In turn, among patients presenting with clearly liver-related clinical signs, resectability was exceptional. The significance of comprehensive follow-up investigations was also evident with respect to a successful reintervention after an initially curative liver resection. The latter was achieved in 47 of the 231 patients with tumor recurrence and resulted in a 41% five-year survival from the time of curative reintervention, which mirrors the outcome of initial liver resection. In 45 of these patients, however, the tumor recurrence was detected on the basis of follow-up routine rather than clinical signs.

In view of continuing improvement of imaging techniques and development of increasingly sensitive immunologic markers, optimal timing becomes an important issue. There is certainly a place for a "test of time" [15, 36], as surgical enthusiasm should be curtailed until the biologic behavior of metastatic tumor can be assessed. It is just as important to decide on surgical treatment early enough not to risk local unresectability or secondary spread to lymph nodes [25] and other organs [37]. As a rule of thumb, we advocate immediate surgery for any solitary liver lesion 3 cm in size if it is documented with two different imaging techniques, but we recommend a waiting period of 4 to 8 weeks for multiple lesions < 5 cm or in patients with extrahepatic disease if the delay does not compromise technical resectability.

Our 33-year experience in this field, initiated with the pioneering work of Hegemann and Mühe [38] and now marked by a large volume of consecutive patients, comprehensive follow-up, high resectability rate, and excellent survival data, forms a standard for quality control of the hepatic resection of metastatic colorectal cancer. A 5-year survival approaching 40%, with some 30% of patients free of disease, has also been reported by several other specialized centers [7, 11, 30]. Although the inferior results noted in some multi-institutional series [3, 4, 31] and in some earlier reports [22, 23, 30] may be partly related to less advanced imaging techniques, nonstandardized classification, or inclusion of non-radical procedures, they may also be due to a lack of specific surgical experience in some of the participating institutions. Consequently, current single institution results falling short of these general survival curves, when not explained by the more detailed analysis for several subgroups displayed in Tables 5 and 6, suggest the need for continuous reevaluation of local surgical practice. In a more general perspective, because optimal patient care is our premier goal, it reopens a debate as to whether hepatobiliary surgery should remain an inclusive part of general surgery, as it is in most institutions in Germany and several European countries, or should be only in the domain of centers and groups with a specialized interest and expertise in this field.

Afterthoughts

In 1988 Iwatzuki and Starzl predicted a period, 25 years into the future, when "the most important and practical application of the resectional techniques may be in the treatment of benign disease or for the treatment of mechanical complications from necrosis of malignant lesions caused by biologic or chemical therapy" [39]. The advent of genetic engineering and the potential of immunotherapy are indicative of the wisdom of this prophecy. It may well become reality that within our professional lives such intelligent therapeutic applications may supersede some of our rather "crude" surgical efforts. For the time being, however, the established and well refined technology of hepatic resection should be offered to virtually all suitable patients [40]. Increasingly sophisticated nonoperative treatment may serve as a supplement to improve results but cannot yet replace the still more effective surgical approach.

Résumé

Entre 1960 et 1992, un total de 1718 patients ayant des métastases d'un cancer d'origine colorectale ont été enregistrés. Quatre cent soixante-neuf patients (27.3%) ont eu une résection hépatique qui a été effectuée avec une intention curatrice chez 434 (25.3%). La mortalité opératoire a été de 4.4%, mais seulement de 1.8% pendant ces trois dernières années (2/114). La morbidité globale a été de 16%, et de 5% pendant ces trois dernières années (5/112). A la date du 1 Novembre 1993, on avait des nouvelles de 99.8% des patients. Après exclusion des patients décédés pendant l'intervention, 350 patients ont eu une résection «potentiellement» curatrice. Parmi ceux-là, 65 étaient le siège de tumeur résiduelle soit macroscopique ($n = 19$) soit microscopique ($n = 46$). Parmi ces derniers, le pronostic était moins bon car la médiane et le maximum de survie a été respectivement de 14.4 et 56 mois. Parmi les 350 patients ayant une cure «potentiellement» curatrice, la survie actuarielle à 5, 10 et à 20 ans a été respectivement de 39.3%, de 23.6% et de 17.7%. La survie sans tumeur a été de 33.6% à 5 ans. En analyse univariable, les facteurs suivants ont été associés avec une diminution de survie globale: présence de métastase lymphatique mésentérique étendue ($p = 0.0001$), tumeur primitive stade III/IV ($p = 0.013$), métastase synchrone ($p = 0.014$), métastases satellites ($p = 0.00001$), diamètre de métastase > 5 cm ($p = 0.003$), taux d'ACE élevé ($p = 0.03$), marges de résection limitée ($p = 0.009$), cancer extrahépatique ($p = 0.0009$), et intervention non-anatomique ($p = 0.008$). En ce qui concerne la survie sans tumeur, la présence de cancer extra-hépatique n'a pas atteint de signification statistique, alors que les patients avec un cancer primitif du côlon avaient un pronostic meilleur que ceux qui avaient un cancer du rectum ($p = 0.04$). La présence de cinq métastases indépendantes ou plus influençait la résequabilité en sens inverse ($p < 0.05$). Une fois qu'une résection radicale de toute maladie détectable a été faite, le nombre de métastases (1-3 *vs.* 4 ou +) n'avait plus de valeur prédictive sur ni la survie globale ($p = 0.40$) ni la maladie sans métastases ($p = 0.64$). En utilisant le modèle de Cox, la présence de métastases satellites, le stade de la tumeur primitive, le moment du diagnostic de métastases, le plus grand diamètre, de métastase, l'approche anatomique ou pas, l'année de la résection et la présence d'envahissement lymphatique mésentérique ont tous été des facteurs indépendants influençant la survie globale et la survie sans tumeur.

Resumen

En el período 1960 a 1992 registramos un total de 1.718 pacientes con metástasis hepáticas de carcinomas colorectales; 469 (27.3%) fueron sometidos a resección, la cual fue realizada con propósito curativo en 434 pacientes (25.3%). La mortalidad en este grupo fue 4.4%, siendo 1.8% (2 de 114) en los últimos 3 años. Se observó morbilidad significativa en 16% de los casos con una disminución a 5% (6 de 112) en los últimos 3 años. Hasta noviembre 1 de 1993, se logró un 99.8% de seguimiento. Excluyendo la mortalidad operatoria, hay 350 pacientes con resección "potencialmente curativa" y 65 pacientes con enfermedad residual macroscópica mínima ($n = 19$) o microscópica ($n = 46$). Este último grupo demuestra el pronóstico tan pobre con una sobrevida media y máxima de 14.4 y 56 meses, respectivamente. Entre los 350 pacientes que tuvieron una resección potencialmente curativa la tasa actuarial de sobrevida a 5, 10 y 20 años fue 39.3%, 23.6% y 17.7%, respectivamente. La tasa de sobrevida libre de tumor fue de 33.6% a 5 años. En el análisis univariable, los siguientes factores aparecieron asociados con disminución de la tasa cruda de sobrevida: presencia o extensión de la invasión ganglionar mesentérica ($p = 0.0001$), tumor primario grado III/ IV ($p = 0.013$), diagnóstico sincrónico de metástasis ($p = 0.014$). metástasis satélites ($p = 0.00001$), diámetro de las metástasis >5 cm ($p = 0.003$), elevación preoperatoria del CEA ($p = 0.03$), márgenes limitados de resección ($p = 0.009$), enfermedad extrahepática ($p = 0.009$) y procedimiento no anatómico ($p = 0.008$). Con respecto a la sobrevida libre de enfermedad, las lesiones extrahepáticas ($p = 0.09$) demostraron no tener significancia estadística; los pacientes con tumores primarios del colon evolucionaron significativamente mejor que los pacientes con cáncer rectal ($p = 0.04$). La presencia de 5 o más metástasis independientes afecta la resecabilidad ($p < 0.05$). Sin embargo, una vez lograda la resección radical de todas las metástasis, no se encontró un valor significativo de predicción según un número creciente de

metástasis (1-3 vs $\geq$ 4) sobre la tasa global de sobrevida ($p = 0.40$) o sobre la tasa de sobrevida libre de enfermedad ($p = 0.64$). En el análisis multivariable de regresión de Cox se encontró que los siguientes factores afectan en forma independiente la tasa cruda de sobrevida y la tasa de sobrevida libre de tumor: presencia de metástasis satélites, grado del tumor primario, momento del diagnóstico de las metástasis, diámetro de la mayor de las metástasis, abordaje anatómico vs no anatómico, año en que se efectuó la resección e invasión de los ganglios linfáticos mesentéricos.

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