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Hepatic Resection for Metastases From Colorectal Carcinoma — A Survival Analysis

G.R. Jatzko, P.H. Lisborg, H.M.Stettner and M.H. Klimpfinger

Between 1 January 1984 and 31 December 1992, 66 patients with hepatic metastases from colorectal carcinomas underwent liver resection. 40 of these patients had synchronous hepatic metastases, and liver resection was carried out simultaneously with radical resection of the primary tumour; in 26 cases metachronous metastases in the liver were surgically removed. 25 patients had an anatomical resection and the remainder underwent atypical resections. The postoperative mortality rate was 4.5% and the major complication rate was 19.7%. Univariate and subsequently multivariate analyses were used to predict the influence of various clinical, histopathological and surgical variables. The observed 5-year surival rate was 29.6% and the 5-year disease-free survival rate 13.9%. Furthermore, the observed median survival time was 24.7 months and the mean disease-free survival time was 16.7 months. Multivariate analysis showed that stage of primary (pTN) ($P = 0.043$), tumour grading ($P = 0.013$) and site of primary ($P = 0.007$) were factors which independently influenced 5-year disease-free survival whereas stage of primary (pTN) ($P = 0.008$), tumour grading ($P = 0.004$) and type of resection ($P = 0.035$) were identified as having independent influence on 5-year observed survival. We consider liver resection to be an effective form of treatment for patients with resectable liver metastases from colorectal carcinoma, although the overall chances for cure are generally not very promising. It appears that the biological behaviour of the primary tumour, in terms of tumour stage and grading, has the greatest influence on survival.

Key words: hepatic metastases, colorectal cancer, liver resection, multivariate analysis
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INTRODUCTION

SINCE Flanagan and Foster's report in 1967 [1] on hepatic resection of metastatic cancer, interest has increased in the surgical treatment of liver metastases, mainly from colorectal carcinomas. A reduction in postoperative mortality and morbidity for liver resection, associated with improvement in surgical and anaesthesiological techniques, has also encourgared this development. Indeed, it has been demonstrated that the prognosis for patients undergoing liver resection is better than that for patients with untreated liver metastases [2–4].

At present, hepatic resection is an accepted form of therapy for resectable metastases confined to the liver, which can be the only manifestation of tumour metastases over a long period of time [3–16]. Although the actual chance of being cured is generally poor, liver resection does prolong life considerably. All patients with hepatic metastases from colorectal carcinoma should, therefore, be evaluated for the possibility of liver resection.

In many cases, the only way to obtain acceptable survival rates is to carry out multiple surgical interventions, in particular, repeated hepatic resections [17]. It would, therefore, appear appropriate to distinguish between tumour-free survival and observed survival. In this study, clinical, histopathological and surgical factors were analysed to determine their influence on disease-free and observed survival.

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PATIENTS AND METHODS

Of a total of 833 patients who underwent surgery for colorectal carcinoma between 1 January 1984 and 31 December 1992, 163 had liver metastases. In 40 of these 163 cases (24.5%), the metastases could be resected simultaneously with the primary tumour. A further 26 patients were operated for metachronous hepatic metastases, 9 of them developing metastases within 1 year of resection of the primary tumour, and the remainder over a longer period. The mean age of the 66 patients included in the study was 65 years (±1.3 S.E.M.). The selection criteria for resection of hepatic metastases were the absence of extrahepatic disease, as well as hepatic resectability with clear resection margins, and sufficient residual liver in case of major resections. The liver resection was considered radical if the resection margins were histologically tumour-free. For simultaneous resection of primary colorectal cancer and hepatic metastases, a complication-free curative resection of the primary tumour, corresponding to a R0 resection according to the UICC [18] was a prerequisite. Hepatic resections were performed strictly in an elective setting.

All patients with a pre-operative diagnosis of hepatic metastases were evaluated using abdominal ultrasonography, computerised tomography (CT) and intra-operative

ultrasonography. In the last 5 years, all patients with colorectal cancer underwent intra-operative ultrasonography of the liver. Prior to this time, intra-operative ultrasonography was only performed for patients with liver metastases and when, despite a negative routine preoperative sonography, intra-operative palpation led to suspicion of liver metastases. In all cases where resectable metastases were diagnosed, a hepatic resection was performed.

Resection techniques employed were the finger fracture method, the ultrasonic dissector or both, with the Pringle manoeuvre being used during the parenchyma phase. Resection surfaces were sealed with fibrinous glue [19]. Table 1 shows the distribution of clinical, histopathological and surgical factors. The disease-free interval was defined as the time between resection of the primary tumour and diagnosis of hepatic metastases. The extent of hepatic replacement was expressed as a percentage of the total liver volume affected by metastases (H1 < 25%, H2 = 25–50%, H3 > 50%, as determined by intra-operative sonography), and in terms of the Milan stages [20, 21] namely I: H1 + solitary metastases, II: H1 + multiple metastases or H2 + solitary metastases, III: all other H2 and all H3 cases.

The surgical procedures carried out are listed in Table 2. Follow-up examinations every 3 months included liver function tests, CEA determination, chest X-ray, abdominal ultrasonography and colonoscopy. The mean follow-up time was 24 months. No patients were lost to follow-up.

Statistical methods

Disease-free survival was distinguished from observed survival to differentiate between the time taken for recurrent disease to develop and the actual survival time. Statistical analysis was carried out using the EGRET software package (Statistics and Epidemiology Research Corporation, Seattle, Washington, U.S.A.).

Survival rates were calculated by the Kaplan–Meier method [22], followed by univariate comparison with the log-rank test [23]. All variables were then simultaneously entered into the Cox proportional hazards regression model [24] to identify factors which independently influenced observed and disease-free survival. The stability of the model was confirmed by using a step-backwards and step-forwards fitting procedure. In the step-backwards approach, after initial simultaneous analysis, the least significant variable was repeatedly eliminated until a core of variables with independent influence remained. In the step-forwards approach, factors were entered into multivariate analysis according to their significance in the log-rank test. The next most significant factor was always added to the model and non-significant factors ($P > 0.05$) were eliminated. The variables identified as having independent influence on survival were identical in both procedures.

Table 1. Distribution of clinical, histopathological and surgical factors with 5-year disease-free and observed survival rates. A statistical comparison using the log-rank test

Prognostic factor	*n*	5-year disease-free survival (%)	*P*	5-year observed survival (%)	*P*
Gender					
Male	49	4.0	0.938	11.5	0.225
Female	17	13.4		51.3	
Age					
≤65	32	11.7	0.224	23.9	0.752
>65	34	15.6		32.9	
Site of primary					
Colon	30	31.9	0.007*	39.7	0.370
Rectum	36	0.0		20.0	
Stage of primary (pTN)					
1	1 Alive at 6 years			—	
2	14	21.8	0.143	34.6	0.012*
3	49	12.8		28.0	
Unknown†	2	—		—	
G-differentiation					
Well or moderate	55	13.4	0.455	34.5	0.086
Poor	9	14.3		28.6	
Unknown†	2				
Disease-free interval					
0 (synchronous)	40	10.7		26.7	
≤1 year	9	18.5	0.351	25.9	0.393
>1 year	17	26.2		43.8	
Distribution					
Unilobar	52	15.7	0.402	27.4	0.715
Bilobar	14	8.6		35.1	
Size of metastases					
≤50 mm	57	17.6	0.797	32.4	0.807
>50 mm	9	11.1		33.3	
Number of metastases					
Solitary	39	19.6		38.7	
Singular (2–3)	10	22.5	0.258	26.7	0.401
Multiple	17	7.6		14.5	
Resection margin					
≤1 cm	25	11.6	0.953	18.6	0.410
> cm	41	15.6		58.6	
Hepatic replacement					
h1	54	18.8		36.4	
h2	9	11.1	0.443	16.7	0.788
h3	3	33.3		33.3	
Milan stage					
I	35	22.8		37.5	
II	21	8.0	0.101	32.4	0.404
III	10	10.0		15.0	
Resection type					
Major	25	21.6	0.078	46.0	0.048*
Minor	41	9.8		20.3	

* Significant *P* values. † Operation of primary tumour performed at other hospitals, histology of primary tumour unknown.

RESULTS

There were no intra-operative deaths. 3 patients died in hospital in the postoperative period, corresponding to a mortality rate of 4.5%; all 3 patients had undergone simultaneous resections. One patient died of an ileus followed by multi-organ failure after a major liver resection, and the other 2 patients died of a stroke and pneumonia, respectively, after minor liver resections. Major complications were observed in 13 patients (complication rate 19.7%) and are listed in Table 3.

On average, operations lasted 215 min (range 180–310) for synchronous resections and 135 min (range 75–195) for metachronous resections. The mean number of blood units required intra-operatively was 3.2 (range 0–9) for synchronous resections and 1.5 (range 0–5) for metachronous resections.

Tumours recurred in 48 (72.7%) patients after a mean disease-free period of 16.7 months. For 25 patients (37.8%), the first site of relapse was the liver and for 4 patients (6%) the lungs; local tumours recurred at the site of primary tumour in just 1 case (1.5%), and a disseminated relapse was observed in 18 cases (27.2%). Re-operation was possible for 12 patients with a relapse

Table 2. Surgical procedures with temporal relationship to the resection of the primary tumour

	Synchronous	Metachronous
Extended right hepatectomy	0	1
Right hepatectomy	6	6
Extended left hepatectomy	1	0
Left hepatectomy	3	1
Left lateral hepatectomy	2	5
Atypical or wedge resection	28	13
Total	40	26

Table 3. Postoperative complications according to time and type of hepatic resection

Resection	*n*	Simultaneous	Metachronous	Major
Anastomotic leakage	2	2	—	2
Haemorrhage	2	2	—	1
Ileus	2	1	1	1
Pneumonia	2	2	—	—
Wound infection	2	1	1	—
Prolonged jaundice	1	1	—	1
Cerebrovascular stroke	1	1	—	—
Insufficiency of abdominal wall sutures	1	—	1	—
Total	13	10	3	5

affecting the liver alone, for 2 patients with isolated metastases in the lungs and for 1 patient with local recurrence. Thus, 15 of the 48 patients with tumour recurrence were re-operated on (31.25%).

The observed 5-year survival rate was 29.6% (Figure 1) and the 5-year disease-free survival rate was 13.9% (Figure 2). The median observed survival time was 24.7 months and the median disease-free survival time was 16.7 months. 2 of the 6 patients alive 5 years after the operation died at a later stage, namely 6 and 7 years after operation.

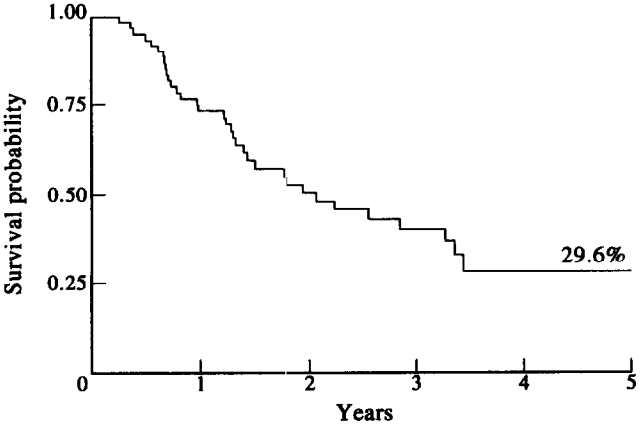

Figure 1. Observed survival curve following resection of hepatic metastases from colorectal cancer.

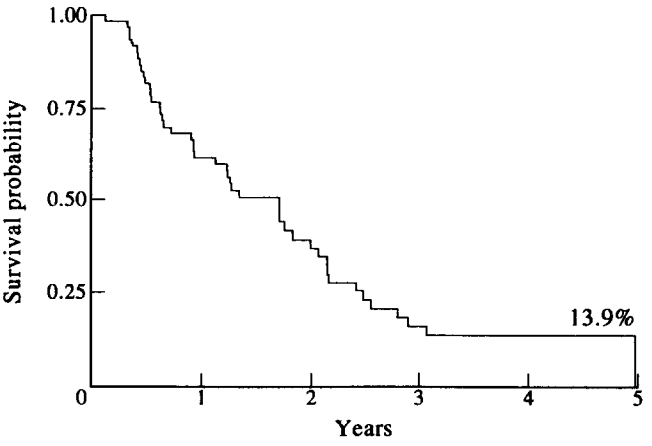

Figure 2. Disease-free survival curve following resection of hepatic metastases from colorectal cancer.

Univariate analysis

Among the factors considered (Table 1), stage of primary tumour and resection type had a statistically significant influence on 5-year observed survival but not on 5-year disease-free survival. The only factor to influence 5-year disease-free survival was the site of the primary tumour. No patient with liver metastases caused by rectal carcinoma remained 5-years disease-free. For all the other factors listed in Table 1, univariate analysis did not reveal any significant influence on patient survival.

Multivariate analysis

Multivariate analysis revealed that three factors, namely stage of primary tumour, tumour grading and primary tumour location, independently influenced 5-year disease-free survival. For 5-year observed survival, stage of primary, tumour grading and resection type independently influenced 5-year survival (Table 4).

Although tumour grading was not significant in univariate analysis, strong interactions with tumour stage were observed in multivariate analysis. This can be explained by the high number of moderately well differentiated primary tumours at tumour stage III (Table 5) with a correspondingly unfavourable prognosis. Due to this distribution, grading was not shown to have a significant influence in univariate analysis. However, when potential interactions with other factors, in particular tumour stage, were considered by carrying out a multivariate analysis, an independent prognostic influence of tumour grading could be identified.

Table 4. Multivariate analysis: factors with independent influence on survival

	Disease-free 5-year survival		Observed 5-year survival	
Detrimental prognostic factor	*P* value	Hazard ratio	*P* value	Hazard ratio
High stage of primary tumour	0.043*	2.4	0.008*	6.7
Poor differentiation	0.013*	3.8	0.004*	6.8
Minor resection	0.135†	1.8	0.035*	2.8
Primary rectal carcinoma	0.007*	2.8	0.936†	1.0

*Significant. † Non-significant.

Table 5. Interaction between the distribution of tumour stage and tumour differentiation

Tumour stage (pTN)		Tumour differentiation		
		Well	Moderately well	Poor
		n	*n*	*n*
I	(T1–2,N0)	—	1	—
II	(T3–4,N0)	2	10	2
III	(Tx,N1–3)	—	42	7

Two histologies of primary tumour unknown.

DISCUSSION

Liver resection for hepatic metastases from colorectal carcinomas is presently considered to be the best choice of treatment for a selected group of patients, with only a small number of metastases confined to the liver [5–16, 25–43]. Unfortunately, the proportion of patients suitable for this procedure is small, namely 14–30% of patients with synchronous or metachronous hepatic metastases [3, 5, 8]. Reviews of the literature indicate that a total of 35% of patients with colorectal carcinomas have liver metastases at the time of operation [14–25] or will subsequently develop them (8–25%) [2, 3, 5, 8]. Numerous studies on colorectal carcinomas have shown metastases in the liver to be one of the most important factors in determining patient survival. Whereas patients with untreated hepatic metastases, with a few exceptions, do not survive 5 years [2–5], a 5-year survival rate of 25–35% is possible after liver resection [4, 6, 8–12, 14, 26, 31–33, 35, 37, 39–41, 44–46]. The recent upsurge in the number of liver resections carried out is partly due to improved resection techniques, such as ultrasonic dissection, high-voltage electrocautery and the sealing of resection surfaces with fibrinous glue [19], as well as improved anaesthesiological and intensive medical care.

Nevertheless, the resection of hepatic metastases is burdened by a high rate of tumour recurrence. Nearly 35% of surgically treated patients (37.8% in our study) develop recurrence in the liver alone [3, 5], with other patients having recurring disease in the liver and other organs as well [5].

The results of the 66 patients who underwent radical liver resection for metastases from colorectal cancer at our institution can be considered favourable in the light of the 5-year observed survival rate of 29.6% and the mean survival time of 24.7 months. Data from reported series indicate that 5-year survival rates range from 23 to 40% [4, 6, 8–12, 14, 26, 31–33, 35, 37, 39–41, 44–46] and postoperative mortality ranges from 0 to 30% [3–5, 9, 10, 14, 19, 32, 36]. However, bearing in mind that the tumour-free 5-year survival rate is a mere 13.9% and the mean disease-free period only 16.7 months, the results are no longer very exciting, and reflect the actual situation of local treatment for what is probably a disseminated metastatic disease.

We have to accept that the chances of cure using surgical therapy alone are not very promising, and that neoadjuvant or adjuvant therapy modalities, such as pre-operative chemotherapy or active specific immunisation [47], will be necessary to improve long-term prognosis. However, an unchecked postoperative adjuvant chemotherapy trial failed to give effective results [48]. The results of a recently initiated phase 3 clinical trial of chemotherapy with 5-FU and leucovorin following potentially curative resection of liver or lung metastases from colorectal cancer will, therefore, be of particular interest (ENG trial EORTC 40923). Undoubtedly, hepatic resection for stage IV patients with no extrahepatic tumours produces better results than leaving the patients untreated, even if these are selected for their suitability for operation, or with other therapeutic schedules, for instance with systemic or intra-arterial chemotherapeutic regimens [26, 49].

In a few, even more selected series, 10-year survival rates of 15–22% have been reported [15, 16, 30, 50]. In our own series, there were too few patients to justify the calculation of long-term survival rates, but 2 patients who survived 5 years did die later of recurrent disease. When we consider our results, selected only by excluding residual tumours and including possible liver resections in terms of 5-year and long-term survival, it seems that almost all patients will succumb to their tumours. The length of observed survival is almost entirely due to repeated surgical interventions, as was the case for 22.7% (15/66) of our patients.

Nevertheless, the value of surgical treatment for lengthening the lives of patients with hepatic metastases is evident in our series, and has also been observed in other studies. Selecting subgroups of patients who will profit most from liver resection should become increasingly important.

In regard to prognostic variables, the results of studies are sometimes different and often conflicting in their statements because most studies are heterogeneous and analysed in different ways. Among the factors frequently evaluated, sex, age, site of the primary tumour, the pre-operative CEA level and type of hepatic resection are not very useful prognostic factors [10, 12, 13, 15, 20, 32, 35]. Other variables, such as the disease-free interval between primary treatment and liver resection, the proportion of the liver affected, the size and number of metastases, the lobar distribution uni- or bilobar, the extent of resection and even stage of primary tumour, were considered quite differently in univariate analysis [4, 6, 8, 9, 11, 12, 14, 30–35, 37, 38–41, 43–46]. Although only a few studies have analysed prognostic variables using multivariate analysis [3, 10, 13, 20, 21, 26], a positive histological resection margin or clearance of less than 1 cm has been consistently found to be one of the most important determinants of survival in these studies [3, 4, 12, 13, 20, 29]. Other independent factors in multivariate analyses were primary tumour stage [3, 10, 26], stage of hepatic metastases [20, 26], number of metastases [3, 13], maximum size of lesion (more than 8 cm) [3] and the disease-free interval before resection [3, 15, 40] (Table 6). The disease-free interval may correlate to host immune deficiencies and the biological behaviour of the tumour. Although the percentage of 5-year survival was greater for patients with a disease-free interval of longer than 1 year in this study, this was not statistically significant, as the vast majority of the patients underwent synchronous resections.

In our series, three factors were identified by multivariate analysis as independently influencing disease-free 5-year survival, namely tumour grading, stage of primary (pTN) and primary tumour location. Metastases in the liver from rectal carcinomas had a much worse prognosis after liver resection than colon carcinomas. For observed 5-year survival, stage of the primary tumour, grading and resection type were identified as factors independently influencing prognosis. In fact, stage of the primary as well as tumour grading are the main factors determining patients overall chances for survival in all conventional staging systems for primary tumours. It is, therefore, not surprising that these factors are also of value for prognosis of

Table 6. A review of literature on multivariate analysis identifying factors with independent influence on survival

	References						
	Fortner [10]	Ekberg [13]	Hughes [3]	Holm [20]	Stehlin [21]	Doci [26]	Present study
Radical surgery (R0 resection)	+	+	+	+	+	(+)	(+)
Stage of primary tumour	+	–	+	–	–	+	+
Stage of hepatic metastases	–	–	NA	+	NA	–	–
Number of metastases	–	+	+	–	+	–	–
Maximum size of lesion (>8 cm)	NA	–	+	–	–	NA	–
Disease-free interval before hepatic resection	–	–	+	–	–	–	–
Percentage of liver involvement	NA	–	NA	–	NA	+	–
Tumour grading	NA	–	NA	–	NA	NA	+

(+) only patients with radical surgery were analysed. NA, not analysed.

confined metastatic disease, if a resection for potential cure (R0) is possible. The negative influence of the rectum as primary tumour in multivariate analysis is only speculative. It could be that local recurrence is clinically recognised much later than liver metastases, and that liver resection is then performed under a false premise.

In conclusion, we believe that every patient with hepatic metastases should be evaluated for liver resection in the hope that they will be cured, provided that mortality and morbidity rates do not burden the prognosis for the patient. Of the various factors analysed for their influence on the prognosis, the biological behaviour of the primary tumour in terms of tumour stage and tumour grading has the greatest influence on survival.

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A Comparison of Two GM-CSF Schedules to Counteract the Granulo-monocytopenia of Carboplatin–Etoposide Chemotherapy

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In order to obtain the beneficial effects from granulocyte–macrophage colony-stimulating factor (GM-CSF) on granulo-monocyte recovery with the minimum dose and toxicity, we compared the effect of two different GM-CSF schedules (5 μg/kg/day subcutaneously, days 5 to > 18 versus days 12 to > 18 on the cytopenias which follow cytostatic treatment with carboplatin (400 mg/m² intravenous (i.v.) day 1) and etoposide (100 mg/m² i.v. days 1 to > 3). 13 patients entered the study for a total of 36 evaluable cycles. The cytostatic treatment produced a neutropenia that persisted for up to day 22 (absolute neutrophil count (ANC) < 1000/μl in 25% and ANC < 2000 in 50% of control cycles). Early GM-CSF administration markedly increased the leucocyte nadir and produced two waves of leucocytosis: an early one, linked to marrow reserve release and presumably of no value to the patients; and a delayed one, due to marrow precursor and progenitor cell proliferation, in which the granulo-monocytosis was associated with a marked eosinophilia. The delayed GM-CSF administration markedly increased the leucocyte nadir and accelerated granulo-monocyte recovery (with an only modest eosinophilia), so that chemotherapy could be repeated every 21 days in all the patients.

Key words: GM-CSF, cancer chemotherapy, neutropenia, dose intensity, carboplatin, etoposide
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INTRODUCTION

GRANULOCYTE–MACROPHAGE colony-stimulating factor (GM-CSF) stimulates the proliferation and differentiation of haematopoietic cells with an action that extends from the progenitors to precursors and mature cells of the granulo-monocyte lineage [1–5]. Its administration allows the severity and duration of granulo-monocytopenia, which follows cytostatic treatment, to be notably reduced [6, 7].

Generally, the administration of GM-CSF (or other growth factors) is started shortly after the end of cytostatic therapy, and