Surgical Treatment of Hepatic Metastases from Colorectal Cancer

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From 1980 to 1984, 48 patients were subjected to liver resection for hepatic metastases from colorectal cancer. The disease was staged according to the original staging system proposed by the authors: stage I, single metastasis involving less than 25% of hepatic parenchyma (21 patients); stage II, multiple metastases involving less than 25% of hepatic parenchyma or single metastasis involving between 25–50% (9 patients); and stage III, multiple metastases involving between 25–50% or more than 50% of hepatic parenchyma, irrespective of the number of metastases (18 patients). The extent of hepatic resection was generally related to that of liver disease; a typical lobectomy was performed in 28 patients and segmentectomies in 20. One patient died after operation (mortality, 2.1%), and major complications occurred in seven patients (morbidity, 14.9%). Morbidity was related to operatory blood loss: 45% of patients with blood replacement of more than 2000 cc developed major complications *versus* 5.4% with blood replacement of less than 2000 cc ($p < 0.05$). The actuarial 3-year survival for stages I, II, and III was 73%, 60%, and 29%, respectively ($p < 0.05$). Twenty-two patients (45%) have had recurrences, all stage III patients within 2 years of resection *versus* 28% of stage I patients (30 months disease-free survival, 49%). The liver only was the site of recurrence in 10 patients, distant sites in seven, and both liver and distant in five. Analysis of the different features of the primary tumor, the interval between bowel resection and detection of hepatic metastases, and the number and extent of liver secondaries demonstrated that prognosis after surgery was mainly related to the latter; they are considered in the staging system adopted in this study. It is a simple system and shows a good prognostic correlation. The results reported here are in agreement with those of the literature; the low mortality and morbidity and the survival benefit support the growing acceptance of surgery in treatment of hepatic metastases from colorectal cancer, in particular stage I patients. For the other stages, surgery should represent, when applicable, only the first step of a multimodality treatment.

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DURING THE PAST DECADE, the surgical treatment of hepatic metastases from colorectal cancer has become a widely accepted therapy. Several reports have documented the safety of this approach, and the results observed in selected groups are encouraging.[1-5] The 5-year survival of patients submitted to hepatic resection for single metastases of limited size has been quoted to be from 20%[6] to 42%,[7] but the frequency of patients with such a favorable situation does not exceed 15–18% of the totality of patients with metastases confined to the liver.[8-11] Of these, a larger percentage will potentially undergo a major hepatic resection, but long-term results are still controversial. Fortner et al.[2] have reported that the 3-year survival of patients with multiple metastases was essentially the same as for patients with solitary lesions. In contrast, none of the patients resected for multiple secondaries in the series of Wilson and Adson[7] survived for 3 years. More recently, Adson and van Heerden[3] suggested that at least 20–30% of patients with large hepatic metastases (single or multiple) could benefit in terms of duration and quality of life by major hepatic resection. The evident bias of results and opinions reflects the fact that the numbers of patients undergoing hepatic resection, reported by single institutions, are still small; series are often heterogeneous as regards the presence or absence of extrahepatic metastases, and criteria of definition of the metastatic disease are dissimilar among different institutions, so that series are usually incomparable.

Therefore, it is difficult to determine which patients are most likely to benefit from liver resections and to plan adjuvant treatments for those patients at high risk to develop recurrences. This is particularly evident for patients having more advanced disease than solitary metastasis of limited size. Therefore, the need of a common staging system is pressing.

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TABLE 1. *Classification of Hepatic Metastases, 1984*

H_1	Liver involvement equal to or less than 25%
H_2	Liver involvement between 25–50%
H_3	Liver involvement more than 50%
s	Single metastasis
m	Multiple metastases to one surgical lobe
b	Bilateral metastases
i	Infiltration of adjacent organs or structures
F	Impairment of liver function

TABLE 2. *Proposed Staging*

Stage	
I	H_{1s}
II	$H_{1m,b}$ H_{2s}
III	$H_{2m,b}$ $H_{3s,m,b}$
IV	(A) "Minimal" intra-abdominal extrahepatic disease (detected only at laparotomy)
	(B) Extrahepatic disease

A clinical classification of hepatic metastases was proposed by Gennari et al.[12] in 1982, and recently a staging system was proposed by the same authors.[13] The current study concerns the results observed in a consecutive series of 48 liver resections for hepatic metastases arising from colon and rectal cancers between May 1980 and October 1984. All patients were staged and classified according to the proposed classification (Tables 1 and 2).

Patients and Methods

From May 1980 to October 1984, 48 patients with hepatic metastases from colorectal cancer were submitted to liver resection at the Istituto Nazionale Tumori of Milan. There were 28 men and 20 women; the median age at the time of liver resection was 52 years for men (range: 33–75 years) and 53 years for women (range: 36–68 years).

In 35 patients, the diagnosis of hepatic secondaries was metachronous to the resection of colorectal primary; the median interval between the two events was 22 months (range: 3–60 months). In all these patients, resection of the primary was considered radical, but two of them had developed a local recurrence that was radically removed during the operation on the liver.

TABLE 4. *Distribution of Patients According to the Classification of Hepatic Metastases of Gennari et al.*[12]

	s	m	b	Total
H_1	21	4	3	28
H_2	2	8	2	12
H_3	3	3	2	8
Total	26	15	7	48

Hepatic metastases were detected synchronously with the primary in 13 patients. In all, the colorectal tumor was radically resected: synchronously in five, and after a median period of 6 months (1–22 months) in eight patients, four of which were resected elsewhere. The stage, grade, and location of the primary are summarized in Table 3; all were adenocarcinomas and were classified according to Dukes' classification.

Before liver resection, all patients were evaluated by echo-tomography, computerized axial tomography (CT), and angiography of the arterial and venous systems of the liver. To exclude additional distant metastases and/or local recurrence of the primary tumor, chest x-ray, barium enema, large bowel endoscopy, and, in patients previously submitted to abdominoperineal resection, pelvic CT scan were continually performed. Further instrumental examinations were indicated only by symptoms or biochemical abnormalities. Routine biochemical studies included hepatic enzyme serum levels as well as carcinoembryonic antigen (CEA) determinations. The extent of liver involvement was determined before operation by CT scan and compared with the intraoperatory examinations.

Distribution of the series according to the classification of Gennari et al. (Table 1) is reported in Table 4. It should be noted that only 44% of the patients had a single metastasis involving less than 25% of hepatic parenchyma, and that a relatively high percentage had extensive involvement of the liver.

Patients were grouped according to the proposed staging system (Table 2) to evaluate long-term results in numerically substantial series; the distribution by stage is reported in Table 5.

The surgical procedures performed are reported in Table 6. The extent of hepatic resection was generally related

TABLE 3. *Characteristics of the Primary Tumor*

Site	No. of Patients	Dukes' Grade	No. of Patients	Grading	No. of Patients
Rectum and sigmoid colon	34	B	15	Well differentiated	5
Left colon	8	C	23	Intermediate differentiation	20
Transverse colon	2	Unknown*	10	Poorly differentiated	6
Right colon	4	—	—	Unknown*	17

* Patients resected elsewhere.

TABLE 5. *Distribution of Patients According to the Staging System of Hepatic Metastases of Gennari et al.*[13]

Stage	No. of Patients
I	21
II	9
III	18

to the extent of liver disease. Wedge resections were preferred when the metastatic lesion was marginal or situated in the residual lobe (bilateral metastases). Surgery was considered radical when no gross residual disease was evident and if at least 1 cm of normal hepatic parenchyma surrounded the neoplasm.

Following resection, patients were regularly controlled every 2–3 months depending on geographic accessibility. CEA assay, liver function tests, and liver echotomography were routinely performed. In the absence of suspected relapse, chest roentgenogram and abdominal CT scan were performed at 6-month intervals. No patient was lost to follow-up, which was complete for all.

Survival and disease-free data were calculated by the life-table method as described by Peto et al.[14]; differences in the outcome of different stages were estimated by the Log rank test.[14] The heterogeneity among groups with different severity of complications was evaluated by comparing mean tables and by using analysis of variance.[15] All p values cited are two-tailed.

Results

There were no intraoperatory deaths. One patient died because of ischemic colitis (operative mortality 2.1%). Nonlethal major complications were observed in seven patients (morbidity 14.9%); they are listed in Table 7. In two patients, reinterventions for drainage of subphrenic abscess and hemostases were necessary. Transcutaneous drainage of the subphrenic abscess and of the biliary tree for a biliary fistula was performed in another three patients. Mild complications were observed in 16 patients (40%), *i.e.*, pneumonia, plural effusion, transient ascitis, and minor infection. Postoperative pulmonary and pleural complications were more frequent when a thoracophrenic approach was used (10/21) than when resection was performed by laparotomy (4/27).

TABLE 6. *Extent of Hepatic Surgery*

Surgical Procedure	No. of Patients
Right lobectomy	18
Extended right lobectomy	3
Left lobectomy	1
Left lateral segmentectomy	6
Segmentectomy	20

TABLE 7. *Postoperative Mortality and Morbidity*

	No. of Patients	%	Complications
Mortality	1/48	2.1	Ischemic colitis
Morbidity	7/47	14.9	3 subphrenic abscesses 2 biliary fistulas 1 pancreatic fistula 1 hemorrhage
Minor morbidity	16/40	40	Pneumonia and/or preural effusion and others

Estimated blood loss was equivalent to the blood replacement. The median loss was 1200 cc (range: 0–4100), but it varied according to the extent of liver resection: 1800 cc (range: 600–1800 cc) in extended lobectomy; 2000 cc (range: 600–4100 cc) in lobectomy; 600 cc (range: 0–3000 cc) in segmentectomies.

Morbidity was related to operatory blood loss (Fig. 1); six of 12 patients (45.5%) with blood replacement of more than 2000 cc developed major complications *versus* only two of 37 patients (5.4%) with blood replacement of less than 2000 cc. The mean blood loss of patients with major complications was 2100 cc *versus* 1500 cc and 1000 cc of patients with mild or no complications, respectively. Differences among the three groups were significant ($p = 0.007$).

Median postoperative stay in the hospital was 21 days (range: 9–74 days). The average stay of patients with no

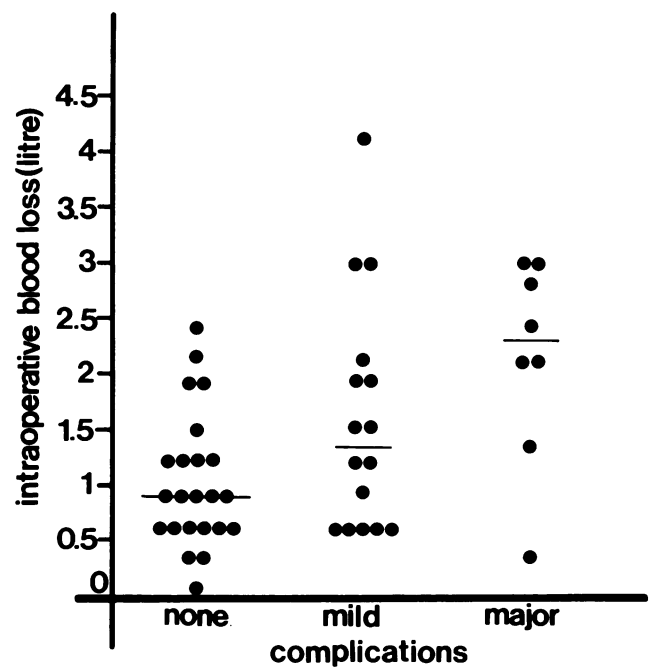

FIG. 1. Relation between intraoperative blood loss and postoperative complications. Analysis of variance confirmed that differences among groups were significant ($p = 0.007$). —— = mean blood loss.

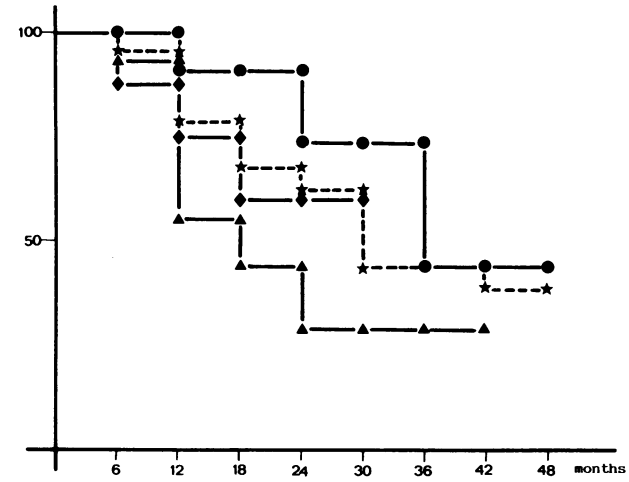

FIG. 2. Actuarial survival of patients subjected to hepatic resection according to stage. ●, Stage I (21 patients); ♦, stage II (9 patients); ▲, stage III (17 patients); ★, overall (47 patients, 1 operative death excluded). Statistical analysis: differences among figures—χ^2 (2df) = 6.06, $p < 0.05$; trend—χ^2 (1df) = 6.06, $p < 0.05$.

complications, and those with mild and major complications was 16, 26, and 40 days, respectively.

The overall median survival was 30 months with predicted 2-year and 3-year survivals of 62% and 53%, respectively (Fig. 2). The longest surviving patient was alive and without evident disease 48 months after liver resection. When survival was considered by stage, the predicted 3-year survival for stages I, II, and III was 73%, 60%, and 29%, respectively. The trend and the differences among these figures were statistically significant ($p < 0.05$). Site and Dukes' stage of the primary tumor, the interval between bowel resection and detection of hepatic metastases, and CEA levels before hepatic resection did not significantly affect the prognosis.

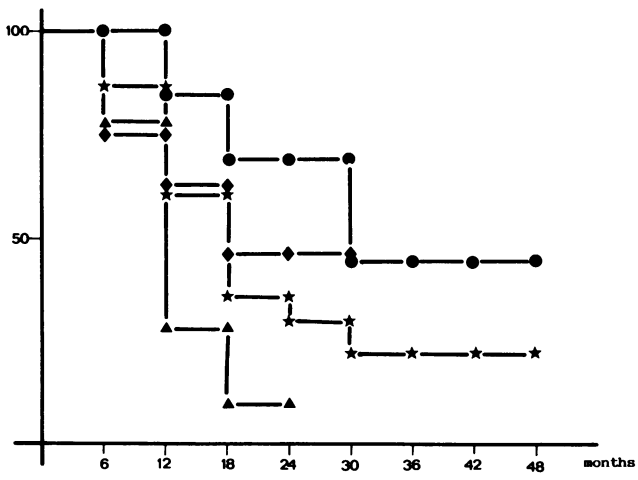

FIG. 3. Disease-free survival of patients subjected to hepatic resection according to stage. ●, Stage 1 (21 patients); ♦, stage II (8 patients); ▲, stage III (16 patients); ★, overall (45 patients, 1 operative death and 1 each stage II and III nonradical resections excluded). Statistical analysis: differences among figures—χ^2 (2df) = 9.57, $p < 0.05$; trend—χ^2 (1df) = 9.47, $p < 0.05$.

The overall median disease-free survival (Fig. 3) was 18 months with estimated 2-year and 3-year disease-free survivals of 46% and 28%, respectively. All stage III patients recurred within 2 years of resection, whereas six of 21 (28%) stage I patients have recurred; the actuarial figure of 49% disease-free survival at 30 months does not predict further decrease in this value. The median interval to recurrence was 15, 9, and 7 months for stages I, II and III, respectively. Out of 22 patients who developed recurrences, the liver only was the site of growth in 10 patients, distant sites in seven, and both liver and distant in five.

Discussion

The results reported in this paper are in agreement with those of the literature, and they support the growing acceptance of surgery as the primary approach to hepatic metastases from colorectal cancer. Hepatic resection for metastases can be done safely; the operative mortality ranges from 0[16,17] to 7%[2] and morbidity from 10[7] to 43%.[18] In the present series, one patient died after operation (2%), and seven developed major complications (15%). The average hospital stay after surgery has been reported as 11–12 days[3,4] and was 21 days in our series.

The good short-term results are enhanced by the survival benefit conferred by surgery; our median 30-month overall survival is in agreement with those reported by others.[3,17,18] The advantage seems evident if this figure is compared to the 6–12-month median survival of patients with unresected hepatic metastases.[8,19–21] The median survival of unresected patients with single metastasis is quoted as being from 4.5–6.2 months[9,22] to 11[8] and 16.7–21 months.[10,21] Since these patients represent the group with the most favorable prognosis, it may be concluded that hepatic surgery for colorectal metastases is the most effective treatment. Nevertheless, such comparisons should be considered with extreme caution because of the differences between surgical and nonsurgical series. In fact, only 25–30% of patients preoperatively eligible for surgery ultimately had all gross disease excised.[2,23] Thus, the extent of the disease in nonoperated patients is generally underestimated, even when the most modern investigations are employed. Moreover, comparison among different series is quite misleading because of the lack of criteria for staging the disease.

We can compare the results of our surgical series with those observed in a consecutive series of 191 patients with unresected liver metastases from colorectal cancer that were retrospectively staged according to present classification and staging systems (unpublished data). In these patients, the differences in the actuarial survival of stages

I, II, and III were statistically significant ($p = 0.02$). Only three patients (stages I and II) survived longer than 3 years.

A stage-by-stage comparison of the 2-year survival of resected and unresected patients (Table 8) evidenced the advantages gained by surgical treatment. The less optimistic comparison between survival of unresected patients and disease-free survival of resected patients (Table 9) supports the benefits of surgery in stages I and II but not the indication to operate on patients with more advanced disease. The median interval to recurrence in these patients with a poor prognosis was 7 months; they often underwent major hepatic resections or multiple segmentectomies and frequently developed postoperative complications that prolonged their hospital stay and were a source of important psychophysical distress. In agreement with others,[3,24] we feel that these negative aspects were balanced by the beneficial conviction of the patient to be cured and by the objective amelioration of quality of life. However, further analyses of the outcome of patients and a larger surgical series are required to clarify the problem.

In the present study, the different features of the primary tumor and liver metastases gave no evident suggestions; although Dukes' staging of the colorectal primary has been reported to be an important prognostic factor in patients resected for liver metastases,[1,2] it was a noninfluencing factor in ours as well as other studies.[23,25] Likewise, the interval between bowel resection and detection of hepatic secondaries, in agreement with others,[2,4,18,23] did not affect survival. Preoperative CEA levels were not correlated with the extent of liver disease or with the final outcome, as already reported.[2,16]

The extent of liver resection does not seem to influence survival.[2,4–6,23] As previously mentioned, our choice of the type of resection was related to the extent of hepatic metastases; thus, results of different surgical procedures are marked by the prognostic influence of stage.

Intraoperatory blood loss was correlated with the occurrence of postoperative complications; thus, it can be considered a predictive factor of morbidity but not necessarily a pathogenic cause. The type of resection and the anatomic and pathologic conditions of the liver may influence the amount of bleeding,[4] and a difficult hemostasis may significantly prolong the duration of anesthesia.

The results observed in the present surgical series are in general agreement with those reported in the literature. The main point of interest and differentiation from the other reports is our introduction of a very simple staging system that present analysis confirms as prognostically effective.

Several classifications have been proposed,[2,21,22,26–33] but none, ours included, have yet been adopted outside the confines of the proposing institutions. In fact, some do not consider quantitatively the extension of neoplastic liver invasion[32,33]; others propose a wide-ranging stage II, *i.e.*, stage II = liver involvement between 20–70% or 25–75%,[22,26–28,30,31] which includes a numerous and rather heterogeneous group of patients with difficult prognosis. Moreover, stage III would be restricted to a group of patients with disease often no longer curable. The staging system adopted in this study has a prognostic value and also allows planning of the therapeutic approach.

The role of surgery seems clear in stage I hepatic metastases, but, for other patients with hepatic metastasis from colorectal cancer, surgery probably represents, when applicable, only the first step of a multimodality treatment. Study of the postoperative outcome of these patients may represent a further contribution to the therapeutic strategy. A major contribution to the problem could be supplied by the acceptance of a worldwide common language.

TABLE 8. *Two-year Actuarial Survival of Resected and Unresected Patients by Stage of Hepatic Metastases*

	No. of Patients	Survival (%) Stage I	Stage II	Stage III
Resected	48	91	60	29
Unresected	191	17.5	11.7	4

TABLE 9. *Comparison between 2-year Disease-free Survival of Resected Patients and 2-year Survival of Unresected Patients*

	Survival (%) Stage I	Stage II	Stage III
Disease-free survival of resected patients	69	48	10
Survival of unresected patients	17.5	11.7	4

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