

Hepatic Resection for Metastatic Colon and Rectal Cancer

An Evaluation of Preoperative and Postoperative Factors

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Hepatic resection for metastatic colorectal cancer has been reported in over 700 patients. However, approximately 5000 patients each year are candidates for surgical excision. Since 1972, 25 patients have undergone hepatic resection for colorectal metastases at New York University. Potentially curable synchronous lesions were detected by preoperative liver chemistries and operative palpation. Patients were screened for metachronous lesions by serial liver chemistries and carcinoembryonic antigen (CEA) determinations; when clinical findings or laboratory findings were either positive or equivocal, then scanning techniques were used. Most patients had solitary lesions (20). Thirteen of 25 lesions were synchronous; 12 were metachronous. Anatomic lobectomy was performed in 13 patients (6 extended resections); and wedge resection was performed in 12. The operative mortality rate was four per cent; the 2-year survival rate, 65%; the 5-year survival rate, 25%. Hypertonic dextrose solutions were administered during and after operation. Postoperative albumin requirements ranged from 200 to 300 grams/day. Coagulation factors II, V, VII, and fibrinogen decreased after surgery to 30 to 50% of their preoperative levels. Subsequent elevation of these factors correlated with increased bile production and improvement in liver chemistries 10 to 14 days after operation. At present, hepatic resection for colorectal metastases provides the only potential method of salvage, offering a 20 to 25% long-term survival rate.

LOCAL CONTROL OF THE PRIMARY colorectal cancer may be inadequate to produce long-term survival. The liver is the most common site of blood-borne distant metastases. Hepatic metastases will occur in 50% of patients with colorectal cancer and is present at the time of initial presentation in 25% of patients.¹ Approximately 20,000 new patients are discovered each year with hepatic metastases from primary colorectal neoplasms. It is estimated that these lesions will be resectable in 10 to 20% of patients.² Based on a cumulative series, 25% of the patients whose hepatic metastases are resected can be salvaged.^{3,4} Since other adjunctive measures have

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not extended survival in prospective randomized clinical trials, surgical resection provides the only hope for cure in these patients at present. The collected data of authors in this country and abroad support hepatic resection as a standard form of treatment in patients with metastases from colorectal cancer.^{1-3,5-9}

Significant postoperative changes occur in hepatic function following major hepatic resection. The present study was undertaken to characterize these changes and to evaluate long-term survival following hepatic resection for metastatic adenocarcinoma of the colon.

Methods

Since 1972, 25 patients have undergone hepatic resection for colorectal metastases at New York University. Potentially curable lesions were sought by careful preoperative clinical evaluation and by operative palpation. Patients were screened for the presence of metachronous hepatic lesions by serial physical examination, liver chemistries, and carcinoembryonic antigen (CEA) determinations. Isotope and computed axial tomographic scans were performed when indicated by clinical or laboratory findings.

Results

The mean age of the patients studied was 58.3 years (range 35-78 years). There were 13 women and 12 men. The characteristics of the primary lesion and the pattern of hepatic involvement are listed in Table 1. Eighteen patients had primary tumors of the left colon or rectum. Most patients had solitary hepatic tumors (20); three additional patients with multiple metastases had unilobar involvement. Synchronous metastases were discovered

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TABLE 1. Tumor Characteristics and Pattern of Involvement

Characteristic	Number of Patients
Synchronous	13
Metachronous	12
Original Dukes Class B	4
Original Dukes Class C	8
Solitary	20
Multiple	5
Unilateral	23
Bilateral	2
Original site of carcinoma	
Left colon	11
Rectum	7
Right colon	5
Transverse colon	2

in 13 patients; metachronous metastases, in 12. In the latter group, the mean period from initial colon resection was 47 months (range 7–96 months), and the original Duke class was B in four and C in eight.

Wedge resection was performed in 12 patients; right hepatic lobectomy in seven patients, and right trisegmentectomy in six additional patients (Table 2). We studied the postoperative response of albumin, coagulation factors, and bile production in patients requiring major hepatic resection. Patients with wedge resections were not included in this analysis. Preoperative serum albumin levels (3.5 to 3.8 mg%) were maintained in these patients by exogenous infusion. Albumin requirements ranged from 200 to 300 gms for the first 5 postoperative days, and then 50 to 100 gms for the following 2 days. Serum levels decreased to less than 3.0 mg% when infusion ceased (Fig. 1). Serial evaluation of coagulation factors proved to be valuable as a guide to normalization of hepatic function. The prothrombin time, a measure of the extrinsic system in the blood coagulation cascade, is nonspecific and did not reflect individual changes in coagulation profile. An immediate increase on the first postoperative day was followed by a rapid return to normal (Fig. 2). The response of factors VII, V, II, and fibrinogen (factor I) varied. An immediate decrease from preoperative values was present on the first postoperative day in each factor. Factor VII decreased to 54% of preoperative levels initially. A gradual

TABLE 2. Type of Hepatic Resection

Type	Number of Patients
Wedge resection	12
Right	7
Left	3
Bilateral	2
Right lobectomy	7
Right trisegmentectomy	6

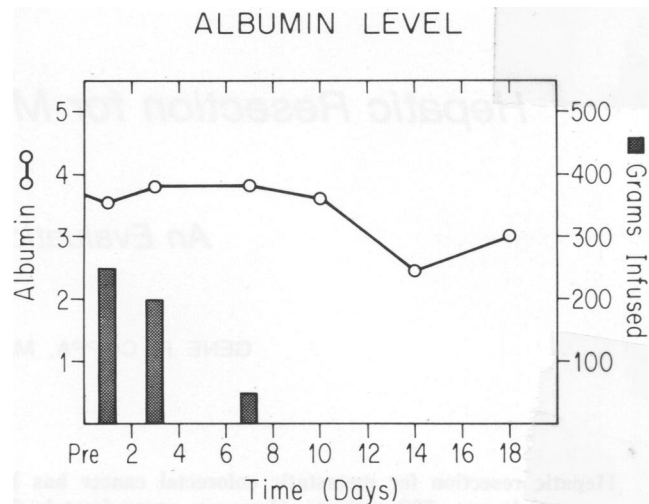


FIG. 1. The median postoperative serum albumin (mg%) and exogenous infusion (gm) in major hepatic resection.

rise was noted until preoperative levels were reached on the 18th day after surgery (Fig. 3). Factor V decreased to 42% of the preoperative level on the first postoperative day. Levels returned to the baseline level on the fourth postoperative day. A second decrease was noted on the 14th postoperative day, with a slow return to the preoperative levels (Fig. 4).

The response of factor II, the proenzyme prothrombin, correlated closely with clinical and biochemical return of hepatic function after major hepatic resection. The immediate postoperative decrease was 42% of the preoperative values. Levels remained low until the 10th postoperative day. A gradual increase to preoperative values occurred over the following 8 days (Fig. 5).

The initial fibrinogen decrease was 24% of preoperative

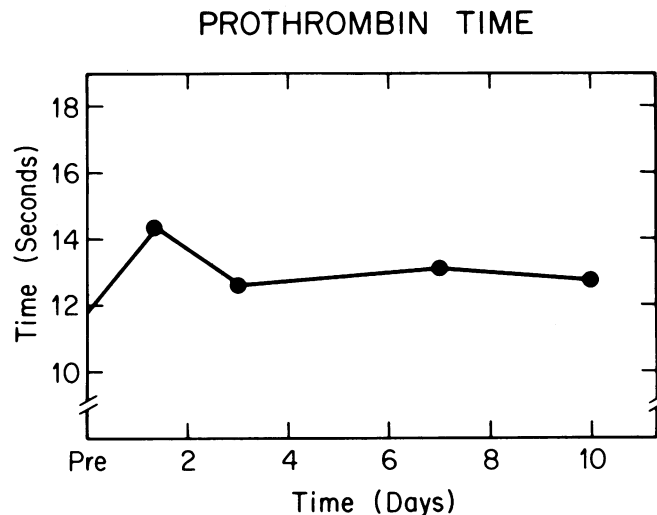


FIG. 2. The median postoperative prothrombin time (%) in major hepatic resection.

FACTOR VII

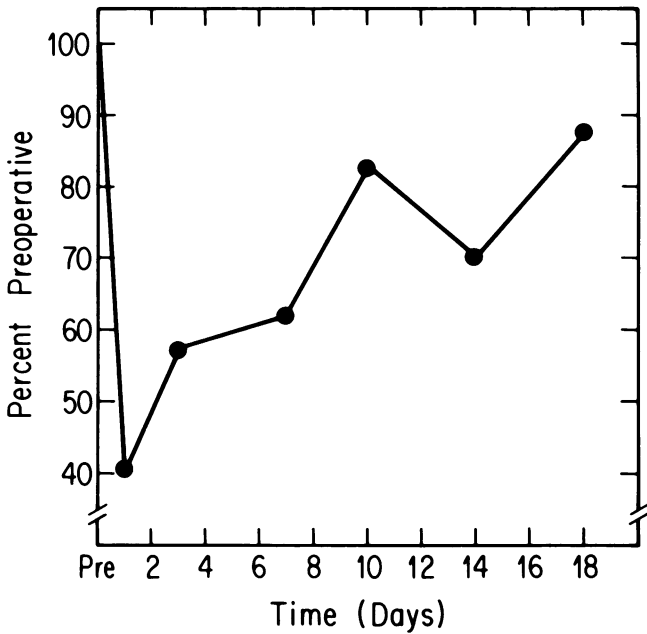


FIG. 3. The median postoperative factor VII (%) response to major hepatic resection.

levels. Fibrinogen remained at this plateau for 10 days and a secondary decline to 40% of preoperative levels occurred. Normal levels were reached in the third week after operation (Fig. 6). Despite these abnormalities in coagulation profile, clinical evidence of bleeding did not occur in any patient. The administration of fresh frozen plasma or fibrinogen was reserved for patients with coagulation factors less than 30% of preoperative levels.

FACTOR V

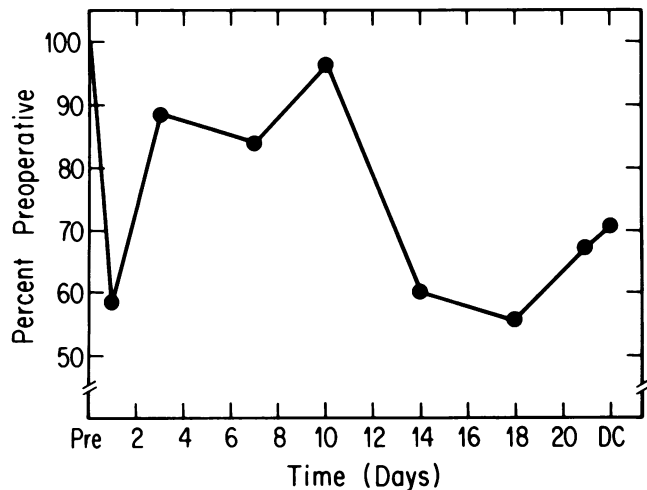


FIG. 4. Median postoperative factor V (%) levels after major hepatic resection.

FACTOR II

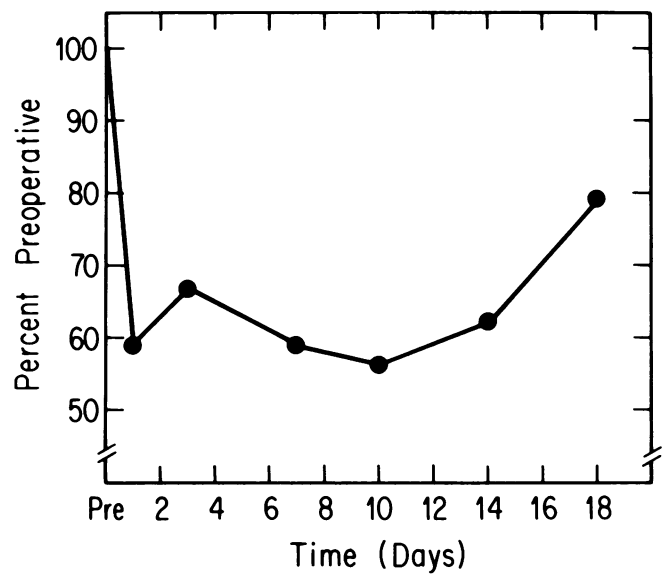


FIG. 5. The relationship of median factor II (%) levels to postoperative time (days).

The serum bilirubin reached peak levels on the seventh day. Decrease in serum bilirubin correlated with an elevation in hepatic bile production, as evidenced by an increase in bile duct drainage (median volume increase, from 51 cc to 238 cc). As Figure 7 illustrates, the median volume of extrahepatic drainage declined over this same period of time (270 cc to 25 cc).

Table 3 lists the major complications. There were four patients who developed subphrenic abscesses, one

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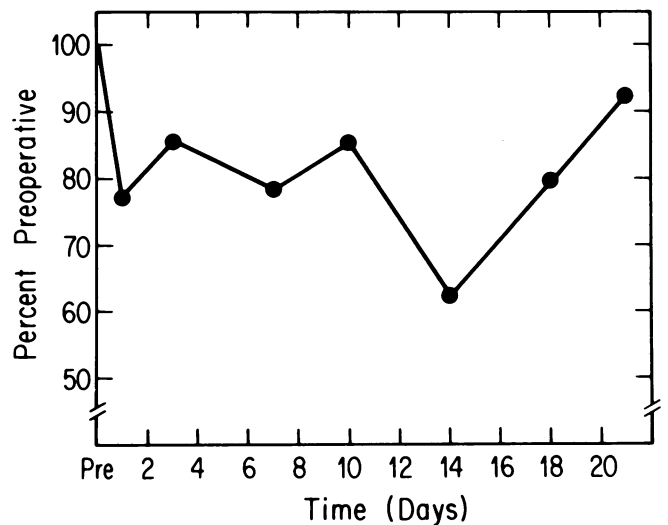


FIG. 6. Median postoperative fibrinogen (%) levels in patients after major hepatic resection.

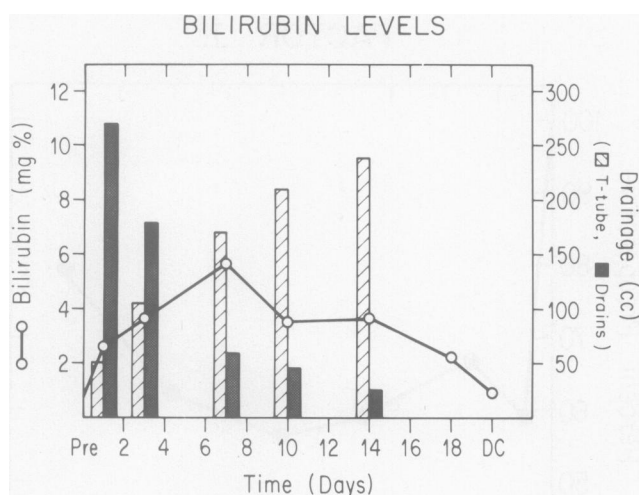


Fig. 7. The relationship of serum bilirubin (mg%) and biliary drainage (cc) to postoperative time.

of whom was associated with a prolonged biliary fistula which closed spontaneously. One patient, who died of hepatic insufficiency 35 days after right trisegmentectomy, is reported as the one operative death. The latter patient is excluded from the survival data. The operative mortality rate was four per cent.

The crude yearly survival and mean survival for these patients are presented in Table 4. Differences between time of discovery of metastatic disease (synchronous *versus* metachronous), number of lesions resected (solitary *versus* multiple), and type of resection (lobectomy *versus* wedge) are not statistically significant. The 5-year-survival rate was 25%, and 40% of all patients resected are alive and free of disease at the present. The mean duration of survival was 28.8 months.

Discussion

Although less than five per cent of all patients with hepatic colorectal metastases are candidates for resection, the possibility of extended survival justifies the pursuit and surgical therapy of these lesions.^{3,4} Recently, numerous reports have confirmed the feasibility of hepatic resection with acceptable morbidity and operative mortality rates (Table 5).

Early detection of these lesions remains elusive. Weight loss, anorexia, abdominal pain, jaundice, or nodular

TABLE 3. Postoperative Complications

Complication	No.
Subphrenic abscess	4
Respiratory	2
Wound infection	1
Biliary fistula	1
Death	1

TABLE 4. Survival Results for Hepatic Resection of Colorectal Metastases

Survival	Lobe	Wedge	Syn	Meta	Overall	No. of Patients
1 Year (%)	90	75	90	90	85	20
2 Year (%)	64	66	77	50	65	17
3 Year (%)	50	75	66	50	58	10
4 Year (%)	43	100	75	40	55	9
5 Year (%)	0	100	66	0	25	8
Mean (mos)	29.3	28	32	24.8	28.8	

hepatomegaly are the classical findings of metastases. However, these clinical signs of hepatic metastases are present in only 50% of patients and usually as a late finding. Unfortunately, abnormal liver chemistries may be manifested only when extensive disease is present. The overall accuracy of these tests is 60%.

Lactic dehydrogenase has been shown to be an accurate indicator of occult hepatic metastases.¹⁴ In evaluating synchronous liver involvement, radioisotope scanning is accurate in only 50% of patients;¹⁴ computed tomography, in approximately 85%.¹⁵ Intraoperative examination and palpation of the liver remains the most accurate method of determining liver involvement; however, it is applicable only to the synchronous hepatic lesions or to patients undergoing second-look or incidental laparotomy. Serial CEA determinations may detect 80 to 90% of patients with metastatic disease; however, elevation of serum CEA lacks specificity for patients with liver involvement by carcinoma of the colon and rectum.¹⁶

Surgical Treatment

In the late 19th century, isolated instances of hepatic resection for tumor were performed.¹⁷ Recent advances in anesthesia and a more thorough knowledge of intrahepatic architecture as emphasized in the early 1950s have accounted for the increasing use of hepatic resection to treat primary and secondary tumors of the liver.¹⁸⁻¹⁹ Originally only solitary metastatic lesions were felt to be resectable for extended survival. Recent cumulative data reveal 5-year survival rates of 30% for solitary lesions or unilobar multiple lesions and 10% for multiple bilobar lesions.^{3,21} Autopsy series have shown approximately 25% of all secondary hepatic tumors to be included in this category. Hepatic tumor size greater than 5 cm adversely affects the 5-year prognosis (27% *versus* 7.5%). Resection of both synchronous and metachronous lesions produced similar 5-year survival after liver resection (21% and 22%, respectively). The type of resection (wedge *versus* lobectomy) does not influence the survival in these patients and, thus, the goal of operative therapy

TABLE 5. *Hepatic Resection for Metastatic Colorectal Cancer Survival and Operative Complications*

Author	Number of Patients	Survival			Operative Complications	
		2-Year (%)	3-Year (%)	5-Year (%)	Mortality (%)	Morbidity (%)
Foster ³	284*	48	—	22	5	—
Wagner ¹⁰	141	61	46	25	4	—
Fortner ⁸	75	71	57	—	7	23
Bengmark ⁶	39	—	—	—	5	—
Muhle ⁵	38†	—	—	20	—	—
Morrow ¹¹	29	—	—	27	6	19
Present series	25	65	58	25	4	28
Thompson ⁹	19	—	—	17	5	—
Kortz ¹²	16	67	54	29	5	43
Taylor ¹³	16	—	42	—	—	—

* Collected review to 1978.

† Mixed primary cancers.

should be to remove sufficient hepatic parenchyma to encompass gross disease.³ The location of the resectable metastasis is the determinant of the extent of hepatic resection.

Intraoperative and Postoperative Management

After surgery, these patients should be evaluated for the presence of extrahepatic disease, the extent of hepatic metastatic involvement, electrolyte and nutritional status, and the presence of cirrhosis and hepatic insufficiency. The metabolic factors critical to low perioperative morbidity and mortality rates in patients undergoing major hepatic resections include: splanchnic fluid sequestration, glucose metabolism, and albumin requirements.

Splanchnic fluid sequestration accounts for a decrease in plasma volume as well as in red blood cell volume. This occurs during the operation and is at its worst in the first 4 to 8 hours after surgery. The extent of hepatic parenchyma resected correlates with the amount of fluid resuscitation needed.²² Pulmonary artery monitoring has been a significant advance in management and should be utilized during and after surgery for at least 24 hours. The increased demand for exogenous glucose is due to hypoglycemia produced by hepatic resection; it also correlates with the extent of resection. At least 50 gms of glucose are required in the first 24 hours.²² Frequent monitoring of urine (every 4 to 6 hours) and serum glucose (every 2 hours) while administering 10 or 25% dextrose through a central venous catheter is required. Preoperative intravenous hyperalimentation and the increase in endogenous insulin may cause potentialization of this problem. Hypoglycemia rarely extends for up to 3 weeks after the operation.

Maintenance of preoperative serum albumin levels also requires exogenous administration (Fig. 1). Decrease in hepatic albumin production produces the hypoalbuminemia seen in these patients. Other responses include

electrolyte imbalance, particularly dilutional hyponatremia, and metabolic alkalosis, which requires restriction of sodium and potassium supplements.

Nutritional factors must be maintained. Serial evaluation of coagulation profile is important, not only for maintenance of clotting parameters, but also as a guide to normalization of the hepatic function. The prothrombin time is an inadequate index of these changes, rising on the first postoperative day and rapidly returning to normal (Fig. 2). An initial decrease in factors VII, V, II, and fibrinogen occurs. Factor II is a sensitive indicator and continues to decrease until hepatic function normalizes (Fig. 3). All levels will return to preoperative levels in approximately 18 days. Postoperative administration of fresh frozen plasma and fibrinogen is reserved for those patients with signs of bleeding or with factors less than 30% of their preoperative levels.

Bile production is measured *via* bile duct drainage. Usually, a very small amount is noted in the first few days and is associated with a clinical and chemical rise in the bilirubin. Increased bile flow from the T-tube indicates a rise in bile production and manifests return of hepatic function. Several hundred milliliters of bilious and serosanguinous drainage from external drains may be expected in the first 4 to 7 days after surgery (Fig. 7).

Complications

Subphrenic abscess, wound infection, bile fistula, hemorrhage, renal failure with or without hepatic failure, pulmonary problems, wound infection, and coagulopathy are all reported problems that may occur in the postoperative period. The incidence of major complications ranges from 19 to 43% (Table 5). Postoperative mortality is usually due to deterioration of liver function as evidenced by rising bilirubin and persistent depression of coagulation factors.²³ Overall operative mortality ranges from four to seven per cent (Table 5).

Survival

The lack of a precise method of staging these patients has caused confusion concerning the natural history of this disease. Unselected, untreated patients have median survival of 9 months, and 2-year survival rate of 10%.²⁴ More recent studies of selected untreated patients with hepatic metastases from colorectal tumors revealed a median survival of 21 months for solitary lesions and 15 months for multiple unilobar lesions.¹⁰ Five-year survival in these latter two groups was three and zero per cent, respectively. Hepatic resection gives the greatest possibility of extended survival; in our patients, it provided a 25% crude 5-year survival rate.

Conclusions

Hepatic resection of metastatic disease from colorectal cancer provides a relatively safe and reliable method of controlling this disease. Twenty-five patients in whom hepatic resection was performed for colorectal metastases were studied. The operative mortality rate was four per cent. The mean duration of survival was 28.8 months. The 5-year survival rate was 25%. Careful monitoring of fluid management, glucose utilization, and albumin requirements is essential for low postoperative morbidity and mortality rates. In major hepatic resections, changes in coagulation profile, particularly factor II, correlate with normalization of hepatic function, as evidenced by decrease in serum bilirubin levels and increased bile production.

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