

Major Hepatic Resection for Metachronous Metastases from Colon Cancer

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Hepatic resection of metastatic colorectal cancer is being performed with increasing frequency. Reports describe wide variations in survival after resection of solitary or multiple metastases. In 23 consecutive patients having major hepatic resection for metachronous metastases from colorectal cancers, 18 patients had one, two, or three metastases and five had four or more individual metastases; the cure rate of one, two, or three metachronous metastases was comparable to reports of resected solitary simultaneous metastases. The median maximum diameter of metastases in patients both surviving and dead was 7 cm. Features separating surviving from dead patients were resection margins of at least 1 cm and fewer than four metastatic nodules. All patients with four or more hepatic metastases died of disease, 80% with further liver metastases. Only three of 18 (17%) patients with one, two, or three metastases developed further hepatic lesions. This study suggests that the biology of the hepatic metastatic disease is paramount; timing of the hepatic resection is of little importance. Delayed resection of suitable biologic situations does not impair survival opportunities, and early resection of inappropriate biologic situations with more than three hepatic metastases does not improve survival. Therefore, programs of early detection with the use of carcinoembryonic antigen (CEA) screening or "second look" operations will not increase cure rates.

HEPATIC RESECTION of solitary metastases of colorectal cancer has a proven role in those few patients having such isolated metastatic disease, but reports vary widely in recording the results of resection of multiple or solitary metastases. Five-year survival rates range between 21%¹ and 52%² for resected solitary lesions but between 0³ and 14%⁴ or even 25%⁵ for resected multiple lesions. Most series report on admixtures of synchronous and metachronous hepatic metastases or only synchronous metastases; results of resection of only metachronous has received little explicit documentation. Results of resection of isolated pulmonary metastases report all metachronous lesions and yield generally similar long-term results.⁶

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The biologic implications of these results have not been explored by most previous authors; thus, explicit criteria for resection of hepatic metastases are not well-formulated. After analyzing a series of major hepatic resections of metachronous colorectal metastases with a prolonged follow-up, we conclude that the timing of resection of favorable biologic situations was of little consequence but that the particular host-tumor biologic interaction that led to a defined pattern of disease was critical. Thus, the current basis for "second look" operations with intense follow-up of patients after colonic resection for cancer by means of serum markers or liver scans is fallacious and will not lead to improved cure rates when contrasted to a follow-up program based on less extensive or less frequent laboratory studies and with a focus on clinical examination. Our hypothesis emphasizes biologic pattern, not earliness of detection, as the genesis of curative operations for hepatic metastases from colorectal cancer.

Materials and Methods

Between 1966 and 1984, 23 consecutive patients in our combined personal experiences had hepatic resections for metachronous metastases from previous primary colon cancers with a minimum follow-up after hepatic resection of 6 months, and without an operative mortality. No patient was lost to follow-up. Eighteen patients had single, double, or triple metastases and five patients had multiple metastases. Fourteen were women and nine were men. Fifteen had right hepatic lobectomies, five had left hepatic lobectomies, and three had large wedge resections.

Four patients were presumed to have solitary metastases on diagnostic study and clinical and operative evaluation, yet on pathologic examination of the resected

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TABLE 1. Age, Pattern of Metastases, Type of Hepatic Resection, and Survival by Sex

	No.	Median Age	1, 2, or 3 Metastases		Resections						Survival NED Total	
					Right		Left		Right Wedge			
					No.	%	No.	%	No.	%		
Women	14	58 (45-73) yrs	10	71	7	43	4	29	3	29	5	36
Men	9	57 (50-70) yrs	8	89	8	89	1	11	0	0	6	67

liver were noted to have two or three closely adjacent nodules. Three of these patients are alive, free of disease, and all four were free of further hepatic metastases at last report, including the one patient dying of disease but without other hepatic metastases. Five patients had four or more separate lesions, usually multiple clustered nodules that appeared clinically and diagnostically solitary and led to exploration and resection. All five of these patients died of disease, 80% with further hepatic metastases. Thus, two groups were defined: patients with one, two, or three metastases (18) and patients with multiple metastases (5).

Formal lobectomies had hepatic tissue resected to the interlobar fissure or just short of it. Wedge resections were defined as removal of less than formally defined hepatic lobes or segments. The median weight of resections and their enclosed metastases were:

Wedge resection: 130 g (110-310 g)

Left lobectomy: 500 g (260-1,030 g)

Right lobectomy: 1,150 g (780-2,140 g)

Margins were measured grossly by the pathologist in the unfixed specimen and were described as negative if they were 1 cm or more and had no microscopic involvement. Positive margins were those with less than a 1-cm separation between the apparent edge of the metastatic nodule and the edge of the cut specimen, or those with microscopic involvement, all of which had less than a 1-cm gross margin.

All patients had no palpable hepatic metastases at original colonic resection and presented for surgery of the hepatic metastases because of symptoms or a palpable mass on physical examination and had no other apparent

metastases outside the liver and no evidence of local recurrence.

Results

Eleven patients are survivors, ten of them free of disease; seven living patients have survived longer than 24 months, six free of disease (Table 1). There was no difference in age, disease-free interval, or incidence of multiple metastases by sex. The sample size is too small to provide meaning to the described survival difference between men (67%) and women (36%).

Tables 2 and 3 indicate that there were no striking differences in age, sex, or surgical therapy between patients who had four or more metastases and those who had only one, two, or three metastases. Patients with one, two, or three metastases who died of disease or are now living were clinically similar except that a larger proportion of patients who survived had a prolonged disease-free interval.

Patients with multiple metastases, however, had a shorter disease-free interval and lived a shorter time than those patients with one, two, or three metastases who either lived or died (Table 3). Table 3 also demonstrates that patients living had roughly similar quantities of hepatic tissue removed which encompassed similar-sized metastases.

Patients with four or more hepatic metastases all died, 80% with further hepatic metastases; only three patients (17%) with one, two, or three metastases died with further hepatic lesions (Table 4).

Kaplan-Maier survival calculations through 3 years are presented in Fig. 1 for patients with one, two, or

TABLE 2. Sex, Age, and Type of Resection by Pattern of Hepatic Metastatic Nodules

Number of Metastases	No.	Sex		Median Age	Resection		
		Men	Women		R Lobe	R Wedge	L Lobe
Multiple	5	1	4	57 yrs (53-70)	4	1	0
One, two, or three	18	8	10	59 yrs (40-73)	11	2	5
Dead of disease	7	2	5	51 yrs (45-73)	5		2
Currently living	11	6	5	59 yrs (40-64)	6	2	3

TABLE 3. *Disease-free Interval, Survival, Margin of Resection, and Gross Pathology of Patients as a Function of the Pattern of Hepatic Metastatic Nodules and Survival*

Metastases	No.	Median Disease-free Interval	Median Survival	Margin		Median Specimen	Median Size (Largest Mass)
				-	+		
Multiple	5	10 mo (7-60)	13 mo (4-26)	2	3	950 g (110-1660)	7 cm (5.5-8.5)
One, two, or three	18	24 mo (11-180)	25 mo (2-168)	11	6	860 g (130-2,140)	7.3 cm (5.0-14)
Dead of disease	7	24 mo (13-66)	21 mo (8-38)	1	6	1,120 g (260-1350)	8.4 cm (5.5-10)
Currently living	11	24 mo (11-180)	28 mo (6-168)	10	0	850 g (130-2140)	7 cm (5.0-14)

three hepatic metastases and reveal a median survival of 38 months but cannot be calculated beyond that point since no deaths occurred after that interval. Table 5 presents actual survival figures every 6 months for 3 years and 4- and 5-year survivals and displays survival for our series and other series where data could be either extracted from the article or calculated by estimating from graphs. Some of these survival calculations are actual percentages, while other series describe actuarial projections of survival; all of the calculations excluded patients who died after surgery. In our series, all lesions were metachronous. The Wilson and Adson cases³ were both synchronous and metachronous; 75% of their metastases were less than 5 cm in diameter and 82% were wedge resections. In Wanebo's⁷ series, all patients presented with solitary synchronous lesions; 80% were wedge resections, but the size was not noted. The major hepatic resection series of Adson and Van Heerden¹ consisted of 11 patients with multiple and 23 patients with solitary metastases; all metastases were larger than 6 cm in diameter, and 25% of their patients had extra hepatic involvement. The number of separate nodules in their "multiple" category was not specified. Iwatsuki et al.² reported 24 patients, all with major resections and with actuarial predictions of survival, but data were not separated into solitary or multiple metastases or synchronous or metachronous. Foster⁴ collected a large number of patients with both multiple and solitary hepatic metastases from colon cancer but reported only 5-year survivals and did not elaborate on the extent of hepatic resection performed in these various institutions or the number of individual nodules that were classified

as multiple. Logan et al.⁸ separated their series into multiple and solitary lesions and included both synchronous and metachronous presentations. Fortner⁹ reported only actuarial survival predictions and included both synchronous and metachronous presentations without size descriptions. Rajpal et al.¹⁰ reported 30 patients who survived surgery after a variety of presentations and resections but presented only overall survival figures for a mixture of solitary and multiple metastases. A recent report by Kortz et al.²⁰ described all solitary lesions, both synchronous and metachronous. A more recent report by Fortner²¹ is similar to his earlier report but is now considerably larger.

Finally, two recent reports add much data to this literature survey and have significant implications for interpretation of the previous reports. Adson et al.⁵ summarized the entire experience of the Mayo Clinic, which includes their previous reports and adds an additional large number of cases to a total of 141. They report similar survival rates for solitary and multiple metastases of 25% but note that almost all patients with multiple lesions had less than three or four separate nodules that altogether averaged 4 cm in diameter for the largest lesion. They noted 5-year survival figures that were as good for masses larger than 4 cm in diameter, multiple and metachronous (37%), as for masses that were smaller than 4 cm, solitary and synchronous (26%).

In 33 patients with major hepatic resections, the presence of extrahepatic metastases precluded 5-year survival and produced a 3-year survival of only 11% and a 2-year survival of 36%, compared with 46%, 63%, and 72% survival for patients without extra hepatic metastases at the same time intervals, respectively.

August et al.,²² at the National Cancer Institute, reported 2- and 4-year survivals of 86% and 59% for cases of one, two, or three hepatic metastases but only 34% and 0% for cases with four or more hepatic metastases from colon cancer. They also found a relation between hepatic resection margins and survival: negative

TABLE 4. *Occurrence of Further Hepatic Metastases by the Pattern of Hepatic Metastatic Nodules Resected*

Metastases	No.	Died of or with Further Liver Metastases	
		No.	%
Multiple	5	4	80%
One, two, or three	18	3	17%

margin patients had 2- and 4-year disease-free survival of 36% and 24%, respectively, whereas patients with positive margins had a median disease-free survival of 7 months and 0% 2- and 4-year survivals; all four such patients lived beyond 2 years but with recurrent disease. They noted no 4-year survivors of patients with bilobar disease but a 28% 2-year survival and a median survival of 23 months in contrast to a median survival of greater than 54 months for patients with unilobar disease.

Discussion

Numerous recent reports in the literature attest to the fact that hepatic resections ranging from small wedge resections to trisegmental resections are associated with significant 5-year survival rates ranging from 12%⁴ to 42%,³ and even 52%² by actuarial projections, when performed for metastatic cancer of the colon and rectum, usually solitary lesions. Speculation as to the biologic basis of the results obtained is not often described, which leaves criteria for selection of suitable patients undefined in the literature. Two features in our series were associated with good survival; the presence of only one, two, or three metastatic lesions in the liver, and a margin of 1 cm or more between the metastases and the surgical resection line. No other patient characteristics, such as stage of primary cancer, age, sex, and size of metastases, were found to correlate consistently with survival. This suggests that the biologic behavior of the metastatic tumor or the tumor-host relationship was paramount and that only patients with one, two, or three metastases are potentially suitable for cure. That the disease-free interval was 10 months for patients with multiple lesions, all of whom died, 21 months for those with one, two, or three metastases who died, and 28 months for those patients with one, two, or three lesions who are alive also suggests a different biology for the favorable tumors. Thus, hepatic metastases from colorectal cancer that are favorable for resection seem to be more slowly progressive in their growth and delayed in their presentation within the overall categorization of metachronous metastases.

There is controversy about this assumption in the literature that records survival for patients with multiple metastases; only August et al.²² break down resected patients into actual numbers of metastases. If this subcategorization were performed, we expect that essentially all long-term survivors reported as having multiple metastases would have had fewer than four separate metastatic nodules. In our series, 80% of patients with four or more metastatic nodules developed further hepatic metastases, but only 17% of patients with only one, two, or three metastatic nodules did. Thus, there is an apparently unique biology to the latter patients;

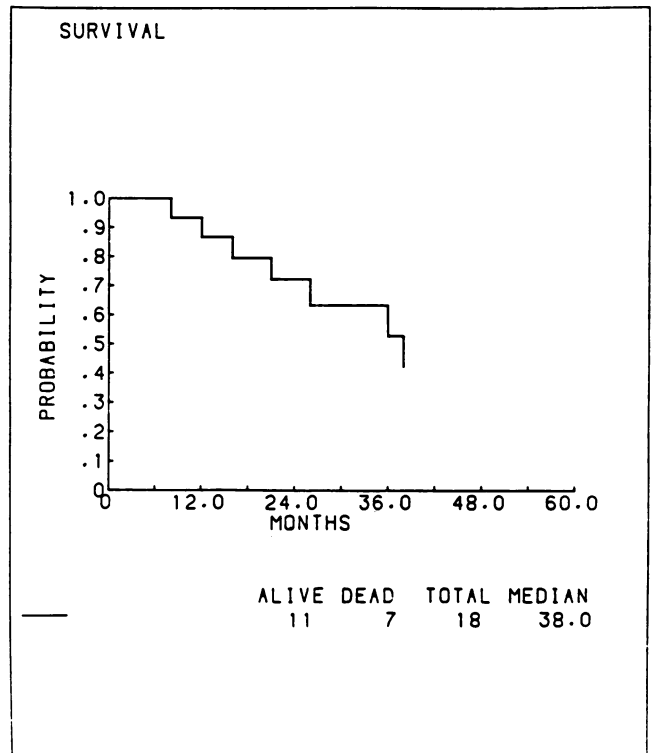


FIG. 1. Kaplan-Maier survival plot of one, two, or three metachronous hepatic metastases from colorectal carcinoma.

this is borne out by data from a large autopsy series¹¹ were, at death from hepatic metastases, 12% of patients with colorectal cancer had only a solitary hepatic metastasis and no other extra-hepatic metastatic lesions. In these unique biologic situations, the solitary metastasis apparently does not produce further metastatic disease and grows locally eventually to cause death. Apparently, only a single micrometastasis in the liver grew progressively. The supposition that one, two, or three hepatic metastases represent a unique biologic, rather than temporal, situation can be supported by several reports describing significant survival differences of untreated patients with hepatic metastases from colorectal cancer based on numbers of metastases. Goslin et al.¹² note a median survival of 24 months for patients with three or fewer metastases and 10 months for patients with four or more metastases. Twenty-six per cent of the former were still alive, but only three per cent of the latter were living, and none had resection. Wood et al.¹³ noted a 17-month mean survival for unresected patients with solitary metastases in contrast to an 11-month survival for those with unilobar but multiple metastases and a 3-month survival for those with bilobar and multiple metastases. Nielsen et al.¹⁴ noted mean survivals of 18 months for those with "few," 9 months for those with "several," and 5 months for those with "numerous" nodules. Pettavel and Morgenthaler¹⁵ recorded mean

TABLE 5. *Hepatic Resection for Colorectal Carcinoma with Metachronous Metastases to the Liver*

Survival (months)	Cady and McDermott		Wilson and Adson ³		Wanebo et al. ⁷	Adson and Van Heerden ¹		Iwatsuki et al. ²	Foster ⁴		Logan et al. ⁸	
	Multiple (5)	1, 2, or 3 (15)	Multiple (20)	Single (40)	Single (25)	Multiple (10)	Single (22)	(24)	Multiple (49)	Single (130)	Multiple (7)	Single (12)
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
6	80	100		95	92						100	100
12	60	93	65	83	84	86	84	91			83	89
18	20	79	45	72		71	83				20	86
24	20	71	32	62	68	67	55	73			20	86
30	0	55	25	55		50	39				0	86
36	0	55	18	47	36	50	33	73				83
48	0	33	8	37		40	19					80
60	0	40	0	42	28		21	52	14	31	0	

survivals of 22 months for patients with one small metastases, 11 months for multiple early metastases, and 5 months for patients with numerous nodules and objective evidence of liver disease besides the metastases. Adson et al.⁵ noted a median survival of 15 months for unresected multiple and 23 months for unresected solitary metastases.

That some patients will demonstrate only a solitary hepatic metastasis even up to the time of death and that solitary metastases consistently are associated with prolonged survival even without resection and that resection of such lesions, even when large, will result in significant cure rates argues for this presentation of metastatic colon cancer as a unique biologic, not temporal, event. In our series, the median diameter of such lesions was larger than 7 cm, relatively large metastases, with a median disease-free interval of 24 months; both of these features indicate that these lesions were not early: they had been present long enough that vast numbers of cancer cells had undoubtedly shed from these metastases into the general vascular circulation. Only 3 of 18 (17%) patients with one, two, or three metastases developed further hepatic metastases, while 80% of patients with multiple lesions did. This again illustrates the uniqueness of the biologic event of very few metastases.

Fisher's experiments with portal venous cancer cell injection in rats conclusively demonstrated the presence of latent nonprogressive hepatic micrometastases that required some hepatic injury to initiate progressive growth and destruction of the host. This concept can be extrapolated to suggest that patients with only one, two, or three hepatic metastases have had only a local host liver disturbance to permit progressive growth, while patients with multiple metastases apparently have had a more generalized breakdown in confinement of hepatic micrometastases.

Controversy arises in the literature regarding the need for early detection of hepatic metastases, with most authors urging frequent diagnostic tests to detect hepatic metastases as early as possible to permit early resection. Gilbertsen and Wangenstein¹⁷ developed the second

look operation as a technique to reduce the temporal lag in detecting intraabdominal metastases. In analyzing data from their asymptomatic second look operations, they noted one long-term survivor from the only resection of a solitary hepatic metastasis, but it was also noted that two of four patients were cured after resection for symptomatic presentation of an hepatic metastases, suggesting that the earlier detection of the second look operation offered no advantages.

Results of resection of large metastases after prolonged intervals following primary colon resection in our series also confirm that temporal factors play a minor, if any, role in increasing curability after hepatic resection, while the appropriate biologic setting of only one, two, or three metastases is essential. Our survival results for metachronous large metastatic lesions are identical with those for resection of smaller synchronous lesions reported by Wanebo et al.⁷ Sixty-five per cent of Wilson and Adson's series³ were synchronous metastases; 70% of the metastases were smaller than 4 cm in diameter and 90% were smaller than 5 cm, yet their reported survival results were identical to ours.

In Adson and Van Heerden's¹ report of major hepatic resections for metastases from colorectal carcinomas, the average size of the lesions was 10 cm, only four were smaller than 7 cm and none were smaller than 6 cm in diameter. Although 65% of their patients were listed as asymptomatic prior to hepatic resection, in no way can such lesions be considered clinically early. Their published survival curves of this group of large lesions resected by lobectomies were identical to those of their earlier series of small lesions removed by wedge resections.

These essentially identical survival results from a variety of reports (Table 5) after resection of metastases to the liver from colon cancer indicate that early detection and small size do not improve the survival potential of these patients and lend strong support to the concept that biologic appropriateness far outweighs the timing of hepatic resection. Delayed resection of suitable biologic situations does not impair survival, and early resection

TABLE 5. (Continued)

Fortner et al. ⁹	Rajpal et al. ¹⁰	Kortz et al. ²⁰	Fortner et al. ²¹				Adson et al. ⁵				August et al. ²²		
			Stage		Single	Multiple	Single	Multiple	Metachronous		1, 2, or 3	4 or more	
(17)	(30)	Single	I	II					(%)	(%)			Small
(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	
100	90							83	75			100	100
	81											100	80
	78											95	67
72	55	65	75			41	50	55	45			85	35
	47											73	35
72	42	54	66	58		41	50	40	38	42	38	58	35
	42	29	61			33	50	25	30			58	
		29	37	22		33	50	25	25	19	26	40	

of poor biologic situations with more than three metastases does not improve survival.

Therefore, programs of early detection by means of frequent, repetitive laboratory studies utilizing serum markers or radiologic tests using liver scans will not yield improved survival for treatment of hepatic metastases from colorectal carcinoma compared with follow-up programs of careful history taking and physical examinations, reporting of symptoms by patients, and less intense screening by biochemical or anatomic liver tests, perhaps at yearly intervals.

Hepatic resections of metastatic colon cancer should be performed for patients with one, two, or three lesions in one anatomic area regardless of the size of the lesions. The timing of such resections is of little consequence; therefore, some "test of time" after discovery of a synchronous metastasis is suggested as the most appropriate method of selecting biologically suitable candidates for major hepatic resections. Those patients with truly solitary, double, or triple metastases will remain as such, while the vast majority of patients who may initially appear with a solitary lesion will usually display their multiple metastases after an evaluation period of 2-4 or even 6 months. If only a small wedge resection of peripheral metastases discovered at the time of colonic resection is required, it would be appropriate to perform it at that time. To avoid unnecessary major right hepatic lobectomies, delay of a few months will enable recovery from the primary resection, analysis of suitability for hepatic resection, and appropriate diagnostic tests to rule out extra hepatic metastases or the more likely presentation of multiple hepatic metastases.

References

- Adson MA, Van Heerden JA. Major hepatic resections for metastatic colo-rectal cancer. *Ann Surg* 1980; 191:576-582.
- Iwatsuki S, Shaw BW Jr, Starzl TE. Experience with 150 liver resections. *Ann Surg* 1983; 197:247-253.
- Wilson SM, Adson MA. Surgical treatment of hepatic metastases from colo-rectal cancers. *Arch Surg* 1976; 111:330-334.
- Foster JH. Survival after liver resection for secondary tumors. *Am J Med* 1978; 135:389-394.
- Adson MA, Van Heerden JA, Adson MH, et al. Resection of hepatic metastases from colo-rectal cancer. *Arch Surg* 1984; 119:647-651.
- Wilkins EW Jr, Head JM, Burke JF. Pulmonary resection for metastatic neoplasms in the lung. *Am J Surg* 1978; 135:480-484.
- Wanebo HJ, Semoglou C, Attiyeh F, et al. Surgical management of patients with primary operable colo-rectal cancer and synchronous liver metastases. *Am J Surg* 1978; 135:81-86.
- Logan SE, Meier SJ, Ramming KP, et al. Hepatic resection of metastatic colo-rectal carcinoma. *Arch Surg* 1982; 117:25-28.
- Fortner JG, Kim DK, et al. Major hepatic resection for neoplasia: personal experience in 108 patients. *Ann Surg* 1978; 188:363-370.
- Rajpal S, Dasmahapatra KS, Ledesma EJ, et al. Extensive resections of isolated metastasis from carcinoma of the colon and rectum. *Surg Gynecol Obstet* 1982; 155:813-816.
- Pickren JW, Tsukada Y, Lane WW. Liver metastasis: analysis of autopsy data. In Weiss L, Gilbert HA. *Liver Metastasis*. Boston: GK Hall, 1982; 2-18.
- Goslin R, Steele G Jr, MacIntyre J. Factors influencing survival in patients with hepatic metastases from adenocarcinoma of the colon or rectum. *Dis Colon Rectum* 1982; 25:749-754.
- Wood CB, Gillis CR, Blumgart LH. A retrospective study of the natural history of patients with liver metastases from colo-rectal cancer. *Clin Oncol* 1976; 2:285-288.
- Nielsen J, Balslev I, Jensen HE. Carcinoma of the colon with liver metastases: operative indications and prognosis. *Acta Chir Scand* 1971; 137:463-465.
- Pettavel J, Morgenthaler F. Surgical oncology. In Pettavel J, Saegesser F. *The Treatment of Hepatic Metastases by Long-term Chemotherapeutic Infusions*. Baltimore: Williams and Wilkins, 1970.
- Fisher ER, Fisher B. Experimental studies of factors influencing the development of hepatic metastases XIII: effect of hepatic trauma in parabiotic pairs. *Cancer Res* 1963; 23:896-900.
- Gilbertsen VA, Wangenstein OH. A summary of thirteen years' experience with the second-look program. *Surg Gynecol Obstet* 1962; 114:438-442.
- Steele G Jr, Zamcheck N, Wilson R, et al. Results of CEA-initiated second-look surgery for recurrent colo-rectal cancer. *Am J Surg* 1980; 139:544-548.
- Tartert PI, Slater G, Gelernt I, et al. Screening for liver metastases from colo-rectal cancer with carcinoembryonic antigen and alkaline phosphatase. *Ann Surg* 1981; 193:357-364.
- Kortz WJ, Meyers WC, Hanks JB, et al. Hepatic resection for metastatic cancer. *Ann Surg* 1984; 199:182-186.
- Fortner JG, Silva JS, Golbey RB, et al. Multivariate analysis of a personal series of 247 consecutive patients with liver metastases from colo-rectal cancer. *Ann Surg* 1984; 199:306-316.
- August DA, Sugarbaker PH, Ottow RT, et al. Hepatic resection of colo-rectal metastases: influence of clinical factors and adjuvant intraperitoneal 5-fluorouracil via Tenckhoff catheter on survival. (In preparation.)