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Resection of the liver for colorectal carcinoma metastases: A multi-institutional study of indications for resection

Registry of Hepatic Metastases*

In an investigation of the indications for hepatic resection in the treatment of colorectal carcinoma metastases, the records of 859 patients who had undergone this procedure were reviewed. This patient group, from 24 institutions, was found to have a 5-year actuarial survival of 33% and a 5-year actuarial disease-free survival of 21%. The only factors that might by themselves be considered contraindications to hepatic resection are the presence of positive hepatic nodes, the presence of resectable extrahepatic metastases, or the presence of four or more metastases. Other factors that had a negative effect on long-term survival were margins of resection on the liver metastases less than or equal to 1 cm (S [5-year actuarial survival] = 23%), the presence of positive mesenteric nodes in the primary tumor specimen (S = 23%), and a disease-free interval of less than 1 year (S = 24%). The effect of any one of these factors was not great enough to contraindicate resection. However, combinations of prognostic factors must be considered before resection is recommended. The overall 5-year survival rate for this large series has been very satisfying. Decision making in the future must take into account such factors as number of metastases, extrahepatic involvement, and stage of the primary tumor.

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HEPATIC RESECTION is the only curative treatment currently available for colorectal carcinoma metastases to the liver, and it is estimated that every year approximately 6,000 to 12,000 patients in the United States are candidates for this procedure.[1,2] Previous studies suggest that the 5-year survival from this procedure is in the range of 25% to 35%.[2-22] However, at this time, only an estimated 1,000 hepatic resections are done each year in the United States (personal communication). The limited use of this procedure stems from three common beliefs: (1) Hepatic metastases are fatal regardless of treatment, (2) hepatic resection is effective only for solitary metastases, and (3) hepatic resection results in extreme morbidity and a high mortality rate. The third belief can be readily dismissed, as the mortality rate for hepatic resection has been addressed in several previous articles and is only about 5%.[3-6] This is a rate considered acceptable for a major surgical procedure. The purpose of this article is to evaluate the first two beliefs.

A collaborative effort involving 24 institutions intimately involved in hepatic resection provided data on a large series of patients in order to answer questions regarding the indications and contraindications to hepatic resection. Our results indicate that 5-year survival of patients is not unusual after hepatic resection and that multiple metastases, bilobar metastases, or large metastases are not, in themselves, contraindications to this procedure.

METHODS

Patient population. Eight hundred fifty-nine patients who had undergone curative hepatic resection for treatment of colorectal carcinoma metastases between 1948 and 1985 made up the study population. Patients who died postoperatively (within 30 days of operation) and patients who had gross tumor left in situ have been excluded. *Consecutive* patients from each of 24 recording institutions were reviewed and entered into a central data base. Two institutions recorded more than 100 patients, 3 institutions recorded 50 to 100 patients, 6 institutions recorded 20 to 50 patients, and 13 institutions recorded fewer than 20 patients. Confidentiality prevents our stating the exact number of patients from each hospital. However, we can confirm that each institution recorded all consecutive hepatic resections performed in the study period by participating surgeons. Chart review was governed by a standard data retrieval protocol. Investigators at each institution were asked to review their patient charts to complete the data form. The senior author (K. S. H.) visited the institutions where this was not feasible to directly review the patient charts. This resulted in approximately two thirds of the charts being reviewed by a single author. This same author also reviewed all data sheets before their entry into the computer in an effort to make this a uniform interpretation of retrospective data.

Data forms. A standard data form was designed to retrieve information on several aspects of the primary colorectal tumor, such as the date of primary resection, the location of the primary tumor, and the presence or absence of metastases to local lymph nodes. The form also recorded information on the status of the patient before undergoing hepatic resection, such as the date of diagnosis of the liver metastases, the carcinoembryonic antigen (CEA) assay before resection, and the presence of symptoms or signs of hepatic metastases (for example, nausea, abdominal fullness, abdominal mass, jaundice, and palpable hepatomegaly). Signs and symptoms of liver metastases were considered only in patients with liver metastases in situ more than 2 months after colon resection, to avoid confusion with symptoms of the primary tumor. In addition, information was recorded about the hepatic resection procedure, such as the date and type of resection, the presence or absence of extrahepatic disease, the presence of portal or celiac lymph nodes, the presence of contiguous spread (direct invasion or adhesion to adjacent structures), or the presence of discontiguous metastases (that is, simultaneous metastases outside the liver to the lungs, peritoneum, small bowell, etc.). The synchronous presence of the primary colon tumor was not considered a discontinuous metastasis, but an anastomotic recurrence after removal of a primary colon carcinoma was considered to be discontinuous extrahepatic disease. Data retrieved from the pathologic specimen included the number of metastases, the distance to the closest margin, and the largest diameter of each metastasis. Follow-up data recorded included the date of the most recent follow-up, the status of the patient (alive with disease, alive without disease, dead without disease, dead with disease), the site of initial recurrence after hepatic resection, and all other sites of recurrence after the initial site of recurrence.

Statistical analysis. The data base was maintained under the DBASE III data base management system on a microcomputer and uploaded to a main frame for analysis. The distribution of survival and disease-free survival was estimated with the standard Kaplan-Meier method. Disease-free survival was defined as time until death or recurrence, whichever occurred first. For patients who died of disease, if the date of recurrence was unknown the date of death was used for

Table I. Survival and disease-free survival for patients undergoing resection of isolated hepatic metastases

Factor	No. of pts	Survival (%)*	Disease-free survival (%)†
No. of metastases			
1	509	37	25
2	131	37	25
≥3	149	18	—
Pathologic margin on liver specimen			
Positive or <1 cm	203	23	13
>1 cm	107	47	33
Distribution of multiple metastases			
Unilobar	165	30	16
Bilobar	79	‡	‡
Stage of primary tumor			
Dukes' B (neg. mesenteric nodes)	226	47	28
Dukes' C (pos. mesenteric nodes)	317	23	18
Disease-free interval			
<1 mo	259	27	17
1 mo to 1 yr	206	31	22
>1 yr	333	42	26
Age (yr)			
<40	80	37	27
40-70	626	33	21
>70	92	31	18
CEA before liver resection (ng/ml)			
<5	45	47	42
5-30	126	30	19
>30	145	28	14
Size of solitary lesions (cm)			
<8	386	38	27
>8	101	27	21
Type of resection of solitary lesion			
Wedge	235	35	21
Anatomic resection	267	41	29

*5-Year actuarial survival
†5-Year actuarial disease-free survival
‡Not adequate numbers of patients to determine 5-year survival

the calculation of disease-free survival. Distributions of survival or disease-free survival were compared by means of the log rank test. If more than two groups were involved (such as free interval of less than 2 months, 2 to 12 months, more than 12 months) pairwise comparisons were made only if the overall test statistic was significant at the 0.05 level. In some cases results for merged groups were reported but the original significance test was based on group boundaries defined independently of the results. The multivariate analyses were based on the proportional hazards model of Cox.[23] Five-year survival and disease-free survival rates were estimated from the Kaplan-Meier curves and multivariate analyses. The curves themselves appeared to plateau around 5 years for sets with sufficient numbers of patients. In many cases the 5-year estimates are associated with wide confidence intervals, and this imprecision is mentioned. In some cases the estimation is so imprecise that estimates are not reported. Even for a data set as large as this, there are many comparisons of interest that can be made only with inadequate statistical power (for example, comparison of outcomes for stage C patients with two versus three metastases). We try to indicate when "negative" results are not conclusive because of inadequate statistical power.

RESULTS

Eight hundred fifty-nine patients were studied. Three hundred ninety-one have died. The patients still alive have a median follow-up time of 21 months, and 25% of them have been followed up for at least 40 months. The 5-year actuarial survival (S) for this group of 859 patients was 33%, with a 5-year actuarial disease-free survival (DFS) of 21% (Fig. 1.). Subgroups of patients were studied to evaluate the effects of various factors on prognosis. The patients were divided into three groups: (1) patients with metastases to the common duct or celiac nodes at the time of resection; (2) patients with extrahepatic, discontiguous metastatic disease at the time of resection; and (3) patients with resection of isolated hepatic metastases. All patients in all groups had undergone surgical removal of all gross disease.

Group 1. Common duct or celiac node involvement

The presence of metastases in the common duct or celiac nodes appears to be a significant determinant of survival after hepatic resection. Of the 24 patients with positive nodes, 17 had died and none have lived 5 years. Their survival distribution is significantly worse than that of patients without positive nodes ($p < 0.0001$).

Group 2. Extrahepatic discontiguous disease

This group does not include patients with a synchronous primary colorectal cancer in situ. Patients with extrahepatic discontiguous disease (other than common duct or celiac nodes) had a shorter disease-free survival than patients without such involvement ($p < 0.01$), but the survival distributions did not appear to differ. As data included only 37 patients with discontiguous involvement, we cannot conclude that survival is not impaired. The follow-up for this group of patients is also not sufficient to enable us to estimate 5-year survival or disease-free survival rates with reliability. To date, however, we have had no 5-year disease-free survivors among these patients.

Group 3. Curative removal of isolated hepatic metastases

The 798 patients who had curative removal of isolated hepatic metastases had a 5-year actuarial survival of 33% and a 5-year actuarial disease-free survival of 22%. Analysis of individual prognostic indicators for this group (Table I) revealed the following:

Margin of resection. Information on margin of resection was available for only a limited number of patients, but this factor appeared to be significant.

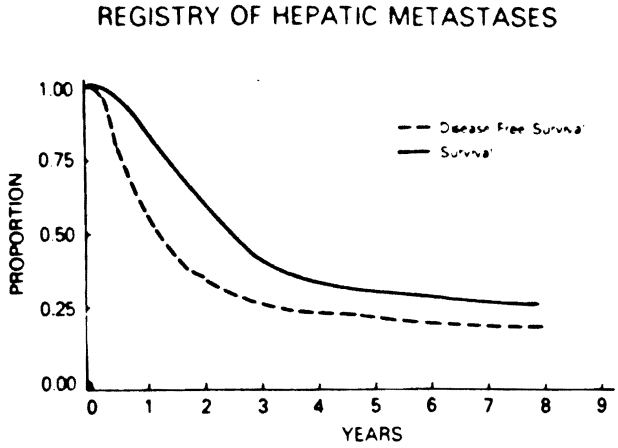

Fig. 1. Survival (——) and disease-free survival (- - - -) for 859 patients who have undergone hepatic resection for colorectal carcinoma metastases to the liver.

Patients with a margin that was greater than 1 cm ($n = 107$, S = 47%, DFS = 33%) had a significantly improved survival and disease-free survival when compared with patients with a pathologic margin of 1 cm or less ($n = 203$, S = 23%, DFS = 13%) ($p = < 0.01$).

Stage of the primary tumor. Patients with a stage B primary colorectal carcinoma ($n = 226$, S = 47%, DFS = 28%) had a significantly improved survival and disease-free survival when compared with patients with a stage C primary colorectal carcinoma ($n = 317$, S = 23%, DFS = 18%) ($p = < 0.001$).

Number of metastases. Patients with a solitary metastasis ($n = 509$, S = 37%, DFS = 25%) had a survival and disease-free survival similar to that of patients with two metastases ($N = 131$, S = 37%, DFS = 25%). Both of these groups seem to have an improved survival over patients with three metastases, patients with four or more metastases, and patients with multiple metastases (number of metastases not recorded). The numbers of patients with exactly three or four metastases are not sufficient for 5-year survival and disease-free survival rates to be reliably estimated separately for each group. For the combined group of 149 patients with three or more metastases, the actuarial 5-year survival was 18% and the 5-year disease-free survival was 7%. Even these figures are unstable, since only four of the 149 patients are alive after 5 years. Although it is difficult to draw adequate groupings with regard to number of metastases, patients with exactly there metastases have significantly poorer disease-free survival than those with a single metastasis

($p < 0.01$) or two metastases ($p < 0.01$). Patients with four or more metastases appear to do at least as poorly.

Distribution of metastases. Patients with multiple, unilobar metastases did not have a significantly improved survival ($p > 0.20$) or disease-free survival ($p > 0.40$) when compared with patients with multiple, bilobar metastases. There were only 75 patients with bilobar disease, and their follow-up is not adequate to enable us to reliably estimate a 5-year survival or disease-free survival for them (only two such patients are alive with more than 5 years' follow-up). Although we find no evidence that distribution is an important prognostic factor for patients with multiple metastases, definitive conclusions require longer follow-up of these patients.

Size of solitary metastases. Patients with a solitary metastasis that was less than or equal to 2 cm ($n = 113$, S = 35%, DFS = 24%), patients with a solitary metastasis 2 to 4 cm in diameter ($n = 130$, S = 37%, DFS = 27%), and patients with a solitary metastasis that was 4 to 8 cm in diameter ($n = 143$, S = 43%, DFS = 27%) appeared to have similar survival and disease-free survival. Patients with a solitary metastasis greater than or equal to 8 cm ($n = 101$, S = 27%, DFS = 21%) appeared to have a somewhat decreased 5-year survival and disease-free survival, though these differences were not statistically significant. Similar differences appeared to exist for patients with two metastases.

Symptoms of liver metastases. Patients with symptoms of metachronous metastases ($n = 93$, S = 32%) appeared to have a small but statistically significant reduction in survival when compared with patients without symptoms ($n = 226$, S = 45%) ($p = 0.05$).

CEA level before liver resection. Data on CEA level were available for a minority of patients. Patients with a CEA of ng/ml or less ($n = 45$, S = 47%, DFS = 42%) appeared to have an improved survival ($p = 0.08$) and disease-free survival ($p = 0.15$) when compared with patients with a CEA of 4 to 30 ng/ml ($n = 126$, S = = 30%, DFS = 19%) or patients with a CEA greater than 30 ng/ml ($n = 145$, S = 28%, DFS = 14%). Larger numbers and longer follow-up of patients in the group with a CEA of less than 4 ng ml are necessary to substantiate this trend.

Contiguous involvement of adjacent structures. Patients with contiguous spread of disease appear to have somewhat reduced disease-free survival compared with patients without contiguous spread ($p = 0.07$). The extent of follow-up for patients with contiguous spread is inadequate to estimate 5-year disease-free survival rates. (Only four of 104 such patients are alive without recurrence with 5 years follow-up.)

Disease-free interval. Patients with a disease-free interval greater than 1 year ($n = 333$, S = 42%, DFS = 26%) had a significantly improved survival ($p < 0.01$) and disease-free survival ($p < 0.02$) when compared with patients with a disease-free interval less than or equal to 1 year ($n = 214$, S = 24%, DFS = 16%). Patients with disease-free intervals less than 1 month had survival rates to similar to those with intervals of 2 to 12 months.

Age at liver resection. There were 74 patients younger than 40 years old and 88 patients older than 70 years. Although there was some suggestion that the older group had somewhat shorter survivals than those younger than 70, this difference did not approach statistical significance on this univariate analysis.

Surgical procedure for a solitary metastasis. Patients who underwent a major anatomic resection ($n = 267$, S = 41%, DFS = 29%) did not have a significantly improved survival or disease-free survival when compared with patients who underwent a wedge resection of a solitary metastasis ($n = 235$, S = 35%, DFS = 21%). However, when patients were considered by size of the solitary metastases and type of resection, a difference was suggested. The 54 patients who underwent a wedge resection for a solitary lesion greater than 4 cm in diameter had a decreased survival and disease-free survival when compared with the 177 patients who underwent an anatomic resection for a solitary lesion greater than 4 cm ($p < 0.02$). Patients with lesions less than 4 cm appeared to have similar survivals and disease-free survivals, regardless of whether a wedge or an anatomic resection was performed. Of patients with solitary lesions greater than 4 cm, those who underwent anatomic resection had more favorable prognoses with regard to Dukes' stage (51% C) and disease-free interval (37% synchronous) than did those who underwent wedge resections (69% C and 57% synchronous). We compared the procedures with Cox's proportional hazard regression model to adjust for stage and disease-free interval. The effect of surgical procedure appeared to persist as statistically significant, even after adjustment. The limited sample size for the number of factors included, however, renders the result less than conclusive.

The two subsets determined by size greater than or less than 4 cm for patients with solitary metastases were the only subsets for which procedures were compared. Hence this finding is not the result of excessive data manipulation. Nevertheless, the comparison is not based on random allocation of treatments

Table II. Natural history of colorectal liver metastases

Authors	Stage	Survival (m)	No. of pts	5-yr survivors
Patients with unresectable primary tumors				
Oxley and Ellis[24]	All	3*	25	0
Cady et al.[2]	All	4*	28	0
Nielsen et al.[26]	All	4.1†	65	0
Jaffe et al.[27]	All	4†	94	0
Patients with or without residual primary tumor				
Bengmark and Hafstrom[28]	All	6†	38	0
Abrams and Lerner[29]	All	7*	58	0
Baden and Anderson[30]	All	10*	105	1‖
Wood et al.[31]	Solitary	16.7*	15	1‖
	Multiple (localized)	10.6*	11	0
	Widespread	3.1*	87	0
Bengtsson et al.[32]	<25%	6*	5	0
	25%-75%	6*	13	0
	>75%	3*	7	0
Boey et al.[33]	Unilobar	9*	20	0
	Bilobar	6*	53	0
Goslin et al.[34]	>4	10*	87	0
	<4	24*	38	0
Lahr et al.[35]	Unilobar	12*	48	1‖
	Bilobar	4.5*	99	0
Finan et al.[36]	Solitary	15.5*	21	0
	Multiple	8*	65	0
Bacon and Martin[37]	All	11*	50	3
Stearns and Binkley[38]	All	8*	22	1‖
Patients with liver metastases only				
Wagner et al.[39]	Solitary	24*	39	—
	Multiple (unilobar)	16*	31	—
	Multiple (widespread)	11*	182	—
Nielsen et al.[40]	Few metastases	18†	20	
	Several	9†	5	0
	Widespread	5†	7	
Cady et al.[41]	All	13.8†	241	2‖
Oxley and Ellis[24]	All	12*	86	1‖
Jaffe et al.[27]	All	10*	13	1‖
		6‡	60	

*Mean survival
†Median survival
‡Metachronous
§Primary resected, no extrahepatic disease
‖Not proved at biopsy

and the groups may be prognostically different in ways we could not detect or appropriately adjust for.

Multivariate analysis. Multivariate analysis of the joint effects of the above factors on survival and disease-free survival was performed for patients without extrahepatic nodal or discontiguous involvement. Single-variable analyses, such as described above, are sometimes misleading because of the confounding effects of other variables. The multivariate analysis indicated that (1) stage of the primary tumor, (2) number of metastases, (3) presence of a metastasis greater than 8 cm in size, (4) disease-free interval before hepatic resection, and (5) age older than 70 were independent prognostic determinants of survival. All of these factors, except for age, were highly significant ($p < 0.01$) in the multivariate analysis. Age was of borderline significance ($p < 0.05$). The analysis indicated that there is a gradation of risk associated with an

Table III. Potentially resectable liver metastases left in situ* (condensed from Table II)

Stage	Survival: Median	Survival: Mean	No. patients	5-yr survivors
All†	6 - 12	6 - 13.8	673	9‡
Solitary			106	1§
Localized‖	6 - 24	18	142	1§

*Primary tumor sometimes left in situ (cannot differentiate from report).
Excludes apparently unresectable, such as "widespread,"[33, 34, 36] ">25%,"[35] "Bilobular,"[33, 34] "≥4,"[36] "multiple,"[36] and "several."[37]
†These series do not further subdivide extent of liver replacement.
‡Only three proved at biopsy.
§Not proved at biopsy.
‖Includes "localized,"[33] "<25%,"[35] "<4,"[36] unilobular,"[33, 34] and "few."[36]

increasing number of metastases: one, two, three, and greater than or equal to four. The analysis also indicated that the less favorable prognosis associated with the presence of a metastasis of at least 8 cm was not limited to solitary metastases; this probably was also the case for patients with two metastases. Large size does appear to have a detrimental effect, but even this set of data is inadequate, with the current limited degree of follow-up, to determine the exact nature of this interaction between size and number of metastases.

The predictions based on the multivariate model indicate that patients with stage C disease and three or more metastases do extremely poorly. In our data there are no patients with stage C disease and three or more metastases who have survived 5 years. The model predicts that the 5-year survival rate for stage C patients with three or more metastases is less than 10%, even if the disease is metachronous. For patients with synchronous stage C disease, who are either older than 70 or have a lesion greater than 8 cm, the predicted 5-year survival rate is less than 15%, regardless of the number of metastases. Patients with stage B disease and fewer than four metastases are predicted to have relatively good 5-year survival probabilities. These probabilities are reduced substantially for those with large metastases or for those older than 70 and are increased for those with metachronous disease. The predicted probabilities of 5-year survival and disease-free survival are limited in precision because of the limitation of follow-up of these patients.

DISCUSSION

Approximately 40,000 persons with colorectal carcinoma die of hepatic metastases each year. The only curative treatment currently available is hepatic resection. This study has demonstrated a 5-year survival rate of 33%, which should be compared with the numerous studies of the natural history of hepatic metastases for colorectal cancer that consistently show few or no patients surviving beyond 3 years. Of 1650 patients with untreated colorectal metastases to the liver reported in the literature (Table II)[24-43], there are only four who survived beyond 5 years with histologically documented metastases and an additional seven who survived beyond 5 years without biopsy proof of hepatic metastases. These 5-year survivors all ultimately died of hepatic metastases, and no chemotherapeutic regimen has improved this situation.

We can limit this literature review to disease that was potentially excisable by excluding what appear to be "unexcisable" metastases, such as "primary tumor left in place," "multiple liver metastases," and "widespread liver metastases," (Table III). This reduces the number of evaluable cases but does not remove any 5-year survivors. There are 11 5-year survivors here, but seven did not have hepatic metastases proved at biopsy and may not have had liver metastases at all. (Bengmark and Hafstrom[28] found a 5% to 8% rate of false-positive diagnoses of liver metastases by surgical palpation when biopsy was not performed.) We find, restrospectively, that there is a 1% to 2% 5-year survival rate in this collected series. When we include three case reports from the literature of long-term survival with biopsy-proved liver metastases[39, 42, 43] (all three with widespread and unexcisable metastases), we still have only 14 5-year survivors in the English-language literature, and all died eventually of cancer. Compare this with the 88 5-year survivors after hepatic resection reported here, 58 of whom remain free of disease to the present time.

In interpreting our results in terms of recommendations for which patients should undergo hepatic resections, we are implicitly employing a historical control group. It has been documented that patients with only a few metastases confined to the liver have a favorable natural history compared wtih all patients with hepatic metastases,[31, 39, 40] and no one doubts that patients who undergo hepatic resections are a selected subset. Nevertheless, the available published literature suggests that the 5-year survival rate even for this subset, if untreated, does not exceed 5% to 10% (Tables II and III). Hence we believe that the survival rates reported here indicate that hepatic resection has in fact resulted in patient benefit.

Despite the lack of efficacy of any other treatment, physicians continue to avoid hepatic resection. When it is considered that in the United States approximately

10,000 patients each year are candidates for hepatic resection and that only approximately 1,000 patients per year actually undergo resection, it is obvious that this procedure is shunned by the majority of physicians.

In evaluating the desirability of resection for an individual patient, one must take into account the risk of operative mortality, the likelihood that the patient's disease will be found removable and the likelihood that the patient will be in a prognostic subset for which a meaningful 5-year survival rate after resection is obtainable. It is generally reported that 50% or fewer patients operated on are found to be eligible for resection.[2-5] Increased ability to predict successful resection preoperatively awaits improved diagnostic methods. Even if the surgical mortality rate were 10%, a 5-year survival rate of 25% to 30% after hepatic resection still represents a rate of 22% to 27% when corrected for surgical mortality. Such rates make hepatic resection appear to be a worthwhile procedure, especially when we consider that operative mortality rates of much less than 10% are common in major centers. Nevertheless, it was our belief that the risk/benefit ratio could be improved if we could identify subsets of patients who did poorly after hepatic resection, as such patients could be spared the procedure. We also would like to reemphasize that this series represents prognostic factors in those patients *surviving* the resection. It is not the purpose of this article to discuss the morbidity and mortality of hepatic resection, as this has been addressed in several previous articles.[3-6] The individual surgeon must determine not only whether his patient falls into a good prognostic group after resection but also whether his patient can come through the procedure with an acceptable risk of morbidity and mortality. For example, though patients older than 70 years appear to have a good prognosis, not all patients more than 70 years old can withstand this major procedure.

We hoped that the results of this multi-institution review would help elucidate the indications and contraindications for hepatic resection. The numerous series that have appeared in the literature over the past 10 years have been relatively inconsistent in their conclusions because of the inability of any single institution to accumulate a large enough series of patients to answer questions definitively.[2-22] Though this is a retrospective collection of data that includes patients treated by many different surgeons at 24 separate institutions, all patients are similar in that they have undergone curative excision of all gross disease. We believe that this analysis has been successful, but even this large series leaves some questions unanswered. First, even a series as large as this is not sufficient to allow us to look adequately at combinations of factors or even some low-frequency subsets of a single factor. Second, in retrospective multi-institution studies that cover a long period of time substantial amounts of data on factors of interest are missing. Third, the patients who have undergone hepatic resection constitute a selected sample and the selection factors probably differ across institutions and years. This last point must be borne in mind as a caveat for interpretation of the prognostic evaluations. For example, the bilobar patients who underwent resection are not a random sample of "resectable" bilobar patients, but they may have been selected on the basis of factors that are not all identifiable, and these patients could have a better prognosis than those selected for resection in the future.

We have identified a number of factors that influence prognosis after hepatic resection. The only factors that might be considered by themselves as contraindications to resection are the presence of positive hepatic nodes, the presence of extrahepatic metastases (even if removable), or the presence of four or more metastases. Many other factors did act, however, as prognostic indicators and should be considered in combination in evaluation of the possible benefits of resection.

Those factors that have some effect on prognosis include the pathologic margin of the liver specimen. Patients with a greater than 1 cm margin had a 45% 5-year survival, whereas patients with a margin of 1 cm or less had a 23% 5-year survival. Data on margin width were unavailable for most of our cases. Hence we could not include this factor in our multivariate analysis. Margin should be taken into account as a stratification factor for a prospective review, and our analysis would suggest that a 1 cm margin be obtained whenever a liver resection is performed. At this time, however, this margin does not act as a contraindication to resection, even if a 1 cm margin cannot be obtained. There are not enough patients with a lesser margin for us to adequately estimate their 5-year survival rate, but there are 5-year survivors with such margins.

The stage of the primary tumor does have a strong effect on survival. Patients with stage B primary tumors do much better than patients with stage C primary cancer. Although the patients with a Dukes' C primary tumor do have a reasonable 5-year survival overall, our multivariate analysis suggests that those with multiple metastases and synchronous disease are not good candidates for resection. Further follow-up will help clarify this.

The disease-free interval does act as a prognostic

indicator. Patients with a longer disease-free interval have an improved survival when compared with patients with a brief disease-free interval. The presence of synchronous metastases is not in itself sufficient to exclude patients from hepatic resection, but this must be considered in conjunction with other factors.

The size of a solitary metastasis does seem to affect survival, in that patients with very large metastases (greater than 8 cm) will fare worse than patients with small metastases. The number of patients with very large metastases is not adequate to enable us to precisely estimate their 5-year survival rate; however, the actuarial estimate at this time is 25%. Hence it does not seem appropriate to employ this factor in itself to deny patients hepatic resection. Reanalysis with further follow-up may provide additional guidelines in the future.

CEA does appear to affect long-term survival but the manner of patients is small, and we would be cautious suggesting that low CEAs will lead to a better long-term survival.

The type of resection that should be performed has been debated in the past. The consensus has been that it is unimportant whether a wedge resection or a lobectomy is performed. The data from this registry are in general agreement with that conclusion. It would appear that patients who undergo a wedge resection will fare the same as patients who undergo a lobectomy when only small solitary metastases are considered. However, patients with large solitary metastases (greater than 4 cm) do seem have a worse prognosis when undergoing a wedge resection. Patients undergoing anatomic resections, however, have more favorable prognoses with respect to stage of disease and free interval. We attempted to adjust for this imbalance and still found that those patients undergoing wedge resection appeared to do worse. We think that this is due to an inadequate margin on the metastases, since it is difficult to do a large wedge resection without coming close to the tumor at some point during the dissection. When we consider our experience that anatomic resections are often less complicated and cause less blood loss than large wedge resections, we recommend that patients with large metastases (greater than 4 cm) undergo anatomic resection, even though this nonrandomized evaluation cannot be definitive. In addition to giving an improved pathologic margin, this also will most likely decrease complications and blood loss.

Our analysis provided no evidence that the presence of bilobar disease is a prognostic factor. There were only 79 such patients, however, and their long-term survival and disease-free survival cannot be estimated without further follow-up. At this time, however, we see no reason to take bilobar disease is a contraindication to resection.

Patients with metastatic disease in hepatic or celiac nodes have a significantly decreased survival despite node dissection. We think that these patients should not undergo hepatic resection, except as part of a trial with adjuvant therapy, since resection alone is not adequate treatment.

Patients with extrahepatic metastases resected simultaneously with liver metastases do appear to have survivals similar to those of patients who do not undergo extrahepatic resection, although with only 37 such patients we cannot say this conclusively. The disease-free survival of these patients is decreased, however. From the results of this review, we would recommend that patients who have simultaneous extrahepatic disease that is removable should undergo both liver resection and removal of the extrahepatic disease as part of a prospective trial of adjuvant therapy.

The number of metastases excised was also found to be an important prognostic factor. In this series, patients with three or more metastases did worse than patients with one or two metastases. The multivariate analysis suggested that prognosis decreases continuously as the number of metastases increases from one to five. That analysis suggests that stage C patients with multiple synchronous metastases are not good candidates for resection but that stage B patients with one to three metastases are. The precision of these predictions is limited by the small number of patients with multiple metastases and the amount of follow-up. We recommend that patients with three or more metastases should undergo resection only as part of a clinical trial and that for patients with two to three metastases the decision should take into consideration other factors, such as stage, disease-free interval, size, margin, and age. The effect of number of metastases should be reexamined in the future, with further follow-up of these patients.

Many of our patients underwent chemotherapy before and after hepatic resection. Agents included 5-fluorouracil, FUDR, methotrexate, and mitomycin C. Routes of administration included hepatic artery, portal vein, systemic vein, and intraperitoneal. In this retrospective review the variability between route of administration and drugs used was too great to permit us to come to a firm conclusion as to whether chemotherapy improved prognosis. It is beyond the capability of this analysis to confirm or deny the value of chemotherapy combined with hepatic resection; however, this question has been addressed by several of the

co-authors of this article in single-institution series. Fortner et al.[2] tried both intra-arterial and intraportal chemotherapy after resection, but in the absence of a concurrent control group no definite conclusion can be drawn regarding its efficacy. August et al.[5] found a suggestion of lessened survival with use of intraperitoneal 5-fluorouracil after resection, and this is currently undergoing a randomized trial at the National Cancer Institute. O'Connell et al.[44] administered intravenous 5-fluorouracil and semustine after hepatic resection and found no improved survival compared with a historical control. Currently there is no evidence that chemotherapy after hepatic resection will improve survival; patients should receive chemotherapy only as part of a randomized trial.

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