1656

Experience in hepatic resection for metastatic colorectal cancer: Analysis of clinical and pathologic risk factors

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Background. *The selection of patients for resective therapy of hepatic colorectal metastases remains controversial. A number of clinical and pathologic prognostic risk factors have been variably reported to influence survival.*

Methods. *Between January 1981 and December 1991, 204 patients underwent curative hepatic resection for metastatic colorectal cancer. Fourteen clinical and pathologic determinants previously reported to influence outcome were examined retrospectively. This led to a proposed TNM staging system for metastatic colorectal cancer (mTNM).*

Results. *No operative deaths occurred (death within 1 month). Overall 1-, 3-, and 5-year survivals were 91%, 43%, and 32%, respectively. Gender, Dukes' classification, site of primary colorectal cancer, histologic differentiation, size of metastatic tumor, and intraoperative blood transfusion requirement were not statistically significant prognostic factors ($p > 0.05$). Age of 60 years or more, interval of 24 months or less between colorectal and hepatic resection, four or more gross tumors, bilobar involvement, positive resection margin, lymph node involvement, and direct invasion to adjacent organs were significant poor prognostic factors ($p < 0.05$). In the absence of nodal disease or direct invasion, patients with unilobar solitary tumor of any size, or unilobar multiple tumors of 2 cm or smaller (stages I and II) had the highest survival rates of 93% at 1 year, 68% at 3 years, and 61% at 5 years. Unilobar disease with multiple lesions greater than 2 cm (stage III) resulted in 1-, 3-, and 5-year survivals of 98%, 45%, and 28%, respectively. Patients with bilobar involvement (multiple tumors, any size, or a single large metastasis) (stage IVA) had survival rates of 88% at 1 year, 28% at 3 years, and 20% at 5 years ($p < 0.00001$). Patients with nodal involvement or extrahepatic disease (stage IVB) experienced the poorest outcome with 1-, 3-, and 5-year survivals of 80%, 12%, and 0%, respectively ($p < 0.00001$).*

Conclusions. *The proposed mTNM staging system appears to be useful in predicting the outcomes after hepatic resection of metastatic colorectal tumors. (SURGERY 1994;116:703-11.)*

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ALTHOUGH IT IS CLEAR that hepatic resection for metastatic colorectal cancer can be performed quite safely, there is still controversy regarding patient selection.[1-3] Previous studies reported that 5-year survival rates (rarely observed without resection) range from 16% to 52%.[1-13] Many have addressed the influence of various clinical and pathologic parameters on the outcome of resective therapy, but the results vary considerably from study to study.

We have reexamined our 204 consecutive patients who underwent hepatic resection for colorectal metastases during the last 11 years to identify clinical and pathologic prognosticators.

Metastatic tumor characteristics were further examined by utilizing a TNM staging system modified from the International Union Against Cancer (UICC) and The American Joint Committee on Cancer (AJCC) recommendations for primary hepatobiliary tumors.[14] The results of this analysis will hopefully provide additional guidance identifying the patients most likely to benefit from surgical intervention and also help identify those at high risk for recurrence.

CASE MATERIAL AND METHODS

Patients. At the University of Pittsburgh Medical Center 204 patients underwent hepatic resection for metastatic colorectal carcinoma during an 11-year pe-

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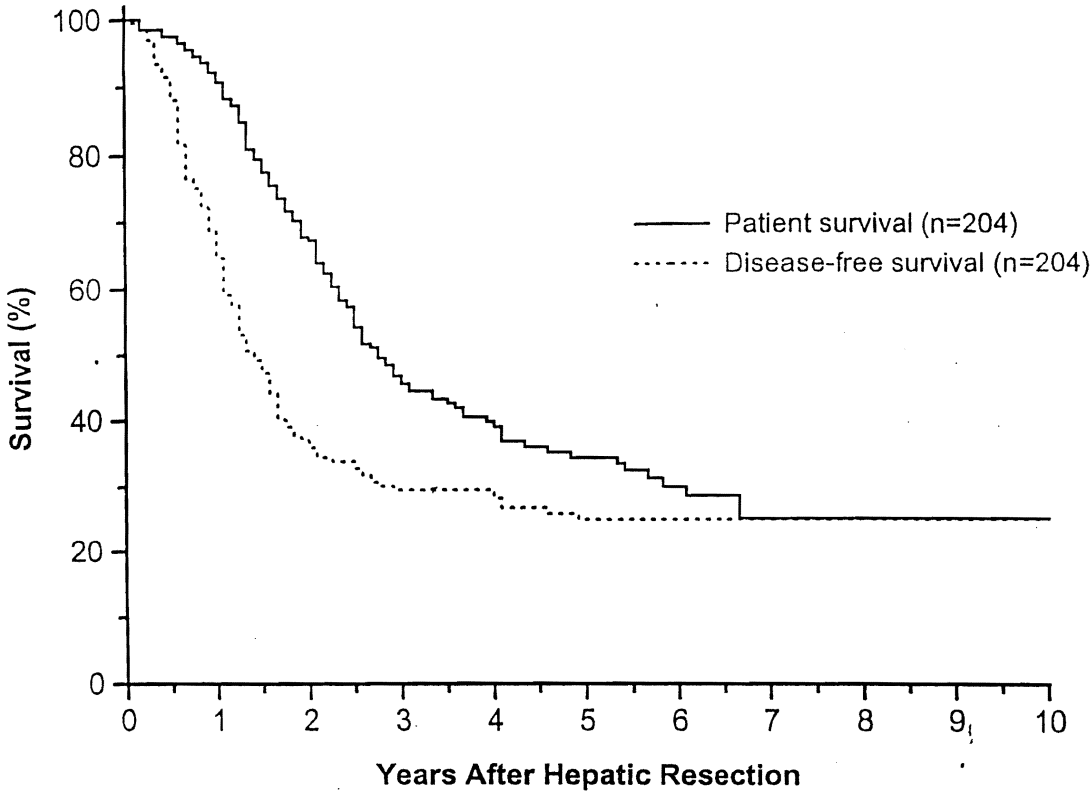

Fig. 1. Overall and disease-free survival rates of 204 patients after hepatic resection for metastatic colorectal cancer.

riod from January 1981 to December 1991. These were all attempts at curative resection. The 130 men and 74 women ranged in age from 28 to 79 years with a mean age of 58.5 years (median, 60 years). Patient follow-up as of December 1993 ranged from 24 to 130 months (median, 69 months).

The interval between resection of the colorectal primary tumor and hepatic resection ranged from −6 months (primary not discovered until after resection) to 228 months with a median of 16 months. Two patients had Dukes' A primary tumors, and 53 had Dukes' B. Dukes' C tumors comprised the largest group with 93 patients, and 56 patients had synchronous hepatic metastases. Most patients with Dukes' D tumors (synchronous metastases) underwent hepatic resection within the first 3 months; however, nine patients were not referred or evaluated until after this interval.

Major hepatic resections were performed in 171 patients (84%). Of the 115 patients having right or left lobectomies, 96 patients underwent standard lobectomies, 15 had wedge resections in addition to lobectomy, three patients had "extended" lobectomies, and one patient had multiple wedge resections with a right lobectomy. Fifty-five trisegmentectomies were performed with 47 right and 8 left.[8]

Ninety-one patients had solitary lesions, 15 of which had minor resections and 76 required either lobectomy ($n = 54$) or trisegmentectomy ($n = 22$). Multiple metastases were resected in the remaining 113 patients with 40 having four or more lesions (range, 4 to 11 lesions).

Methods. A retrospective review of all available inpatient and outpatient records including operative and surgical pathology reports was performed. Patient follow-up and outcome were documented by clinical visits, telephone interview, or correspondence.

The following clinical and pathologic risk factors were examined for prognostic influence: gender, age, interval between colorectal and hepatic resection, Duke's stage, site of colorectal primary tumor, histologic differentiation of the secondary tumor, number of metastases, tumor size (largest nodule diameter), unilobar or bilobar disease, type of hepatic resection, margin of resection, involvement of lymph nodes or contiguous structures, and intraoperative blood transfusion.

Statistical analysis. Survival time was calculated from the date of hepatic resection until death and disease-free survival from the date of hepatic resection until the time of tumor recurrence. Survival curves were generated by using the Kaplan-Meier (product-limit) method and were compared by using the generalized Wilcoxon (Breslow) test. Univariate Cox's proportional

Table I. Clinical risk factors and primary tumor characteristics for overall and disease-free survival

	No. of of patients	Overall survival (%)				Disease-free survival (%)			
		1 yr	3 yr	5 yr	Breslow	1 yr	3 yr	5 yr	Breslow
Overall	204	91	45	34		65	29	25	
Gender									
Male	130	92	47	34	$p = 0.361$	71	32	27	$p = 0.041$
Female	74	89	43	35		54	25	20	
Age									
<60 yr	96	93	51	41	$p = 0.037$	60	31	26	$p = 0.25$
≥60 yr	108	89	40	28		69	29	24	
Disease-free interval									
−6 to 3 mo	47	89	37	20	$p = 0.185$	59	24	24	$p = 0.116$
4 to 12 mo	42	88	48	36		55	30	30	
13 to 24 mo	49	86	41	35		60	27	21	
25 to 48 mo	43	98	46	37		72	29	18	
49 to 228 mo	23	96	65	52		91	45	40	
≤24 mo	138	88	42	31	$p = 0.045$	59	27	25	$p = 0.022$
>24 mo	66	97	52	42		78	35	26	
Primary stage									
Dukes' A and B	55	87	63	53	$p = 0.053$	77	41	34	$p = 0.033$
Dukes' C	93	92	40	28		60	26	20	
Dukes' D	56	91	37	26		60	25	25	
Site of primary tumor									
Anorectal	56	89	47	40	$p = 0.904$	64	37	26	$p = 0.536$
Sigmoid/left colon	105	93	47	31		65	27	24	
Transverse/right colon	43	86	40	34		64	25	25	

hazards model was used to calculate the relative risk (RR) of mortality and tumor recurrence and 95% confidence intervals. Patients alive as of December 31, 1993, were right censored at time of follow-up. A multivariate stepwise Cox's regression analysis (backward elimination method) was performed to identify factors that were independently associated with tumor recurrence and mortality. A p value <0.05 was considered statistically significant.

RESULTS

The overall survival was 91% at 1 year, 43% at 3 years, and 32% at 5 years (Fig. 1). Median survival was 33 ± 2.2 (±SE) months. There were no deaths within the first 30 days of operation and only two deaths (1%) within the first 120 days. As of December 1993, 72 of the 204 patients were alive and 50 patients were disease free at a mean of 65.1 ± 32.4 months (median, 62.5 months) after hepatic resection. Twenty-two patients were alive with recurrent disease at a mean of 20.7 ± 12.9 months (median, 18.5 months). Death with recurrent disease occurred in 124 (61%) patients. Eight (4%) patients died free of disease at a mean of 27.9 ± 30.9 months (median, 13.5 months) after hepatic resection.

Clinical risk factors and primary tumor characteristics. The actuarial overall and disease-free survival rates, stratified according to patient and primary tumor characteristics, are shown in Table I. Gender, incremental disease-free interval, site of primary tumor, and Dukes' stage were not correlated with patient survival. Patients older than 60 years of age and patients with a less than 24-month interval between colorectal and hepatic resection experienced a poorer outcome ($p < 0.05$).

When disease-free survival rates were examined, men appeared to have longer recurrence-free survival. Early primary tumor stage (Dukes' A or B) and more than 24-month interval between colorectal and hepatic resection were also found to be associated with longer disease-free survival. The remaining factors were not found to be significant predictors of disease-free survival when subjected to univariate analysis (Table I).

Pathologic risk factors for colorectal hepatic metastases. A number of hepatic metastasis features were found to affect patient and disease-free survival (Table II). The size (largest diameter) and differentiation of the metastatic tumor did not influence outcome when subjected to univariate analysis.

Patients with unilobar disease experienced superior patient and disease-free survival when compared with patients with bilobar disease ($p < 0.0001$). Of the 80 patients with bilobar disease, 52 (65%) had lesions requiring trisegmentectomy. The remainder underwent

Table II. Pathologic and operative risk factors for overall and disease-free survival

	No. of patients	*Overall survival (%)*				*Disease-free survival (%)*			
		1 Yr	*3 Yr*	*5 Yr*	*Breslow*	*1 Yr*	*3 Yr*	*5 Yr*	*Breslow*
No. of metastases									
1	91	89	56	45	$p = 0.003$	72	40	33	$p = 0.0003$
2-3	73	95	41	30		66	28	28	
≥4	40	88	29	19		46	10	3	
Tumor size*									
5 cm	79	94	51	38	$p = 0.231$	65	36	34	$p = 0.308$
5-9.9 cm	99	88	44	35		65	27	22	
10-20 cm	40	92	32	22		62	19	13	
Differentiation									
Well	53	91	51	40	$p = 0.932$	67	40	35	$p = 0.534$
Moderate to well	60	92	39	29		67	25	22	
Moderate to poor	89	90	46	33		62	23	20	
Tumor distribution									
Unilobar	124	92	55	44	$p < 0.0001$	72	35	31	$p = 0.0002$
Bilobar	80	89	31	19		53	18	15	
Hepatic resection									
Wedge, LLS	25	92	53	46	$p = 0.058$	76	55	49	$p = 0.014$
Lobectomy	115	91	49	39		69	30	24	
Trisegmentectomy	55	87	36	21		50	20	17	
Multiple wedge	9	100	33	0		67	11	0	
Resection margin									
>1 cm	95	89	55	42	$p = 0.005$	69	36	29	$p = 0.0062$
≤1 cm	92	92	43	32		63	29	25	
Involved	17	88	12	0		47	0	0	
Lymph node status									
Negative	198	90	47	35		65	30	26	
Positive	6	100	0	0		50	0	0	
Extrahepatic disease									
No	184	92	49	38	$p < 0.00001$	68	33	28	$p < 0.00001$
Yes	20	75	15	0		30	0	0	
mTNM stage									
Stage I and II	68	93	70	60	$p < 0.00001$	80	49	40	$p < 0.00001$
Stage III	43	98	49	33		72	34	26	
Stage IVA	67	88	31	22		55	19	19	
Stage IVB	26	81	12	0		38	0	0	

LLS, Left lateral segmentectomy.
*Greatest diameter.

extended lobectomy (3), lobectomy plus wedge resection (16), or multiple wedge resections (9).

A positive resection margin was associated with an extremely poor outcome with a patient survival rate of 88% and 12% at 1 and 3 years, respectively. Most patients with positive margins had major hepatic resections (seven lobectomies, eight trisegmentectomies), and 13 (76%) of 17 had bilobar disease. Patients with resection margins of 1 mm to 1 cm and greater than 1 cm had similar 5-year patient and disease-free survival rates.

The extent of hepatic resection was associated with disease-free survival ($p = 0.014$); however, it was only marginally associated with patient survival ($p = 0.058$). Most patients underwent right or left lobectomy ($n = 115$). The second largest group ($n = 34$) underwent either right or left trisegmentectomies. These two groups of major hepatic resections had 5-year survival rates of 39% and 21%, respectively. The bilobar tumor distribution of 16 patients required wedge resections in addition to lobectomy. The median survival in these patients was 18 months, which was considerably worse than the 43-month median survival rate for those requiring lobectomy alone ($p < 0.0001$). Patients with minor resections (wedge resection and left lateral segmentectomy) had expectedly higher 5-year patient and disease-free survival rates of 46% and 49%, respectively. Those who required multiple wedge (or segmental) resection ($n = 9$) fared significantly worse with a 3-year survival rate of only 33% and none at 5 years ($p < 0.05$). All of these patients had bilobar disease, and one third

Table III. Intraoperative transfusion and patient survival

	No. of patients	Actuarial overall survival (%)			Breslow	Hepatic resection type*			
		1 Yr	3 Yr	5 Yr		Wedge, LLS	RL, LL	RTS, LTS	Multiple wedge
No transfusion	40	90	52	46	$p = 0.776$	15	17	4	4
Transfused									
1-25 units	141	92	43	33	$p = 0.730$	6	88	45	2
1-5 Units	100	93	41	35		4	64	30	2
6-10 Units	29	93	55	41		2	19	8	
>10 Units	12	83	31	0			5	7	

*LLS, Left lateral segmentectomy; RL, right lobectomy; LL, left lobectomy; RTS, right trisegmentectomy; LTS, left trisegmentectomy.

had positive margins or involvement of adjacent structures.

The number of metastatic tumors in the liver was found to be associated with both disease-free and patient survival. Patients with solitary lesions fared best with a 5-year survival of 45%. Survival rates for patients with multiple tumors, especially those with four or more, were significantly less ($p < 0.003$). Of the 40 patients with four or more lesions there were four patients with positive margins and six patients with nodal involvement or extrahepatic disease. The majority (29 of 40, 73%) had bilobar disease, and 37 required major hepatic resections (22 lobectomies and 15 trisegmentectomies).

Data on intraoperative transfusion were available for 182 of the 204 patients. The mean transfusion requirement for hepatic resection in this series was 3.68 units (±4.1 units) of packed red blood cells with a median of 3 units. Forty patients (20%) did not receive a transfusion. Most of these patients underwent wedge resection, left lateral segmentectomy, right lobectomy, or left lobectomy (Table III). Almost all patients requiring blood (1 or more units) underwent major hepatic resections (78 right or left lobectomies, 45 trisegmentectomies). When subjected to univariate analysis, there was no significant difference in survival ($p = 0.776$). The 5-year survival rates of patients receiving 0, 1 to 5, and 6 to 10 units of blood were similar at 46%, 35%, and 41%, respectively.

Proposed modified TNM staging system. The interrelationship between tumor distribution, number of metastases, tumor size, and disease not confined to the liver was examined in accordance with a proposed TNM staging system for metastatic colorectal cancer (mTNM). (Table IV). Unilobar disease is confined to stages I through III, with bilobar disease and disease outside the liver comprising stages IVA and IVB, respectively. The actuarial patient and disease-free survivals correlated well with the proposed mTNM staging system (Fig. 2). Patients with stage I and II disease ($n = 67$) had the best patient and disease-free survival at 5 years of 61% and 40%, respectively ($p <$ 0.0001) (Table II). Patients with extrahepatic lymph node involvement or invasion of contiguous structures experienced expectedly poorer survival rates, and recurrent (or perhaps persistent) disease was ubiquitous.

Table IV. Proposed mTNM staging for hepatic colorectal metastases

	Classification		
Stage I	mT1	N0	M0
Stage II	mT2	N0	M0
Stage III	mT3	N0	M0
Stage IVA	mT4	N0	M0
Stage IVB	Any mT	N1	M0, M1
		N0, N1	M1

mT1, Solitary ≤2 cm; *mT2*, solitary >2 cm, unilobar; multiple, ≤2 cm, unilobar; *mT3*, multiple, >2 cm, unilobar; *mT4*, solitary or multiple, bilobar, invasion of major branch of portal or hepatic veins or bile ducts; *N1*, abdominal lymph node; *M1*, extra hepatic metastases or direct invasion to adjacent organs.

Multivariate analysis. Tumor size, unilobar or bilobar disease, and lymph node involvement were excluded from the multivariate analysis because the combination of these factors defines mTNM staging. They were excluded to avoid problems related to multicollinearity of risk factors.[15] The results of the multivariate analysis of mortality and tumor recurrence are shown in Tables V and VI, respectively. The following factors were found to be independently associated with tumor recurrence: number of tumors (four or more), involved margins, and mTNM stages IVA and IVB. Similar results were obtained when analyzing mortality. Involved margins and stages IVA and IVB disease were found to be independent prognostic factors. Stage III disease was also found to be significant, whereas the remaining factors previously examined were not found to be significant in a multivariate context.

DISCUSSION

A number of staging systems have been described for metastatic colorectal cancer to the liver.[16-19] Each has supportive data that have promulgated their use as sig-

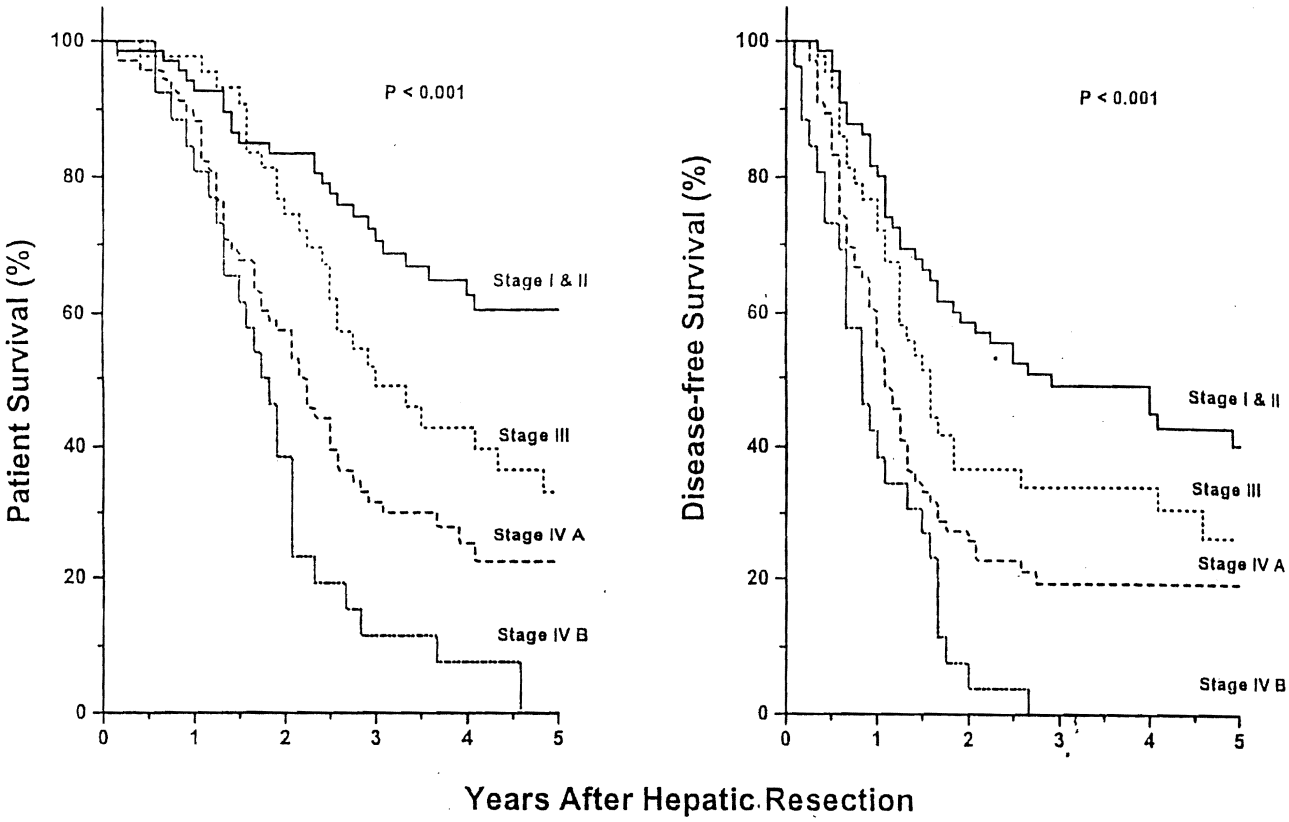

Fig. 2. Overall and disease-free survival rates after hepatic resection for metastatic colorectal cancer according to proposed mTMM staging system. (——, stages I and II (n = 67); . . . ., stage III (n = 43); – – – – stage IVA (n = 68); –●●– stage IVB (n = 26).

Table V. Relative risk of mortality with Cox's proportional hazards model

		Univariate 95% confidence limits			*Adjusted*	*Multivariate 95% confidence limits*		
Variable	*RR*	*Lower*	*Upper*	*p Value*	*RR*	*Lower*	*Upper*	*p Value*
Age (≥60 yr)	1.41	0.99	1.99	.037				
Interval (>24 mo)	0.73	.050	1.06	0.101				
Tumor no. (≥4)	2.24	1.43	3.49	<0.001				
Resection type								
RTS, LTS + multiple wedge	1.59	1.12	2.26	0.010				
Resection margin, involved	2.52	1.51	4.21	<0.001	1.90	1.12	3.21	0.017
Dukes' stage								
B	1.82	1.15	2.86	0.010				
C	2.02	1.23	3.32	0.005				
mTNM stage								
III	1.85	1.09	3.12	0.022	1.73	1.01	2.94	0.043
IVA	2.95	1.85	4.71	<0.001	2.69	1.67	4.34	<0.001
IVB	5.47	3.14	9.53	<0.001	5.20	2.97	9.09	<0.001

nificant prognosticators by their respective authors. Unfortunately, no system has been widely adopted to allow comparisons among studies. The application of Fortner's revised staging system to our series would result in the vast majority of patients being categorized as stage I because of the small number with regional or extrahepatic disease (stages II and III).[17] Our present analysis supports the further staging of disease confined to the liver (with complete extirpation) and its prognostic significance. Gennari et al.[18] and Doci et al.[19] suggested the use of a system more akin to TNM staging that took into account multiplicity and distribution, but

Table VI. Relative risk of disease recurrence with Cox's proportional hazards model

Variable	RR	Univariate 95% confidence limits			Adjusted RR	Multivariate 95% confidence limits		
		Lower	Upper	p Value		Lower	Upper	p Value
Tumor no. (≥4)	2.22	1.52	3.24	<0.001	1.84	1.25	2.70	0.002
Interval (>24 mo)	2.22	0.54	1.08	0.124				
Female gender	1.32	0.95	1.85	0.098				
Resection type								
RL, LL	1.72	0.94	3.15	0.081				
RTS, LTS + Multiple wedge	2.51	1.34	4.72	0.004				
Resection margin involved	2.60	1.55	4.38	<0.001	2.34	1.37	4.01	0.002
Dukes' stage								
B	1.58	1.05	2.39	0.028				
C	1.55	0.98	2.44	0.061				
mTNM stage								
Stage III	1.51	0.93	2.45	0.094	—	—	—	—
Stage IVA	2.25	1.47	3.43	<0.001	1.55	1.06	2.27	0.023
Stage IVB	3.96	2.37	6.62	<0.001	3.01	1.88	4.83	<0.001

the extent of liver involvement (percentage of parenchymal disease) was used rather than tumor size. We believed that tumor size, as measured in centimeters (maximum nodule diameter), and unilobar or bilobar involvement were more readily reproducible and applicable. After we analyzed the commonly reported potential risk factors influencing survival and recurrence, we applied a proposed mTNM staging system for hepatic metastatic tumors (Table IV). In our series of 204 patients the correlations to both overall and disease-free survival were shown to be highly statistically significant. In addition, the variables used in the staging system were all significant prognosticators when subjected to univariate analysis. The interrelationship among tumor size, multiplicity, and distribution is well illustrated by the proposed mTNM staging system, and it in turn reflects the influence of tumor burden on patient survival.

A number of studies have suggested that the presence of four or more metastases is a particularly adverse prognostic factor, but this has not been a consistent observation.[5, 7, 13, 16, 20-22] In our previous report[5] we had only seven patients with four or more lesions, and none survived more than 3 years. However, the results of this current analysis are statistically more compelling. The observed 20% 5-year survival rate of these patients argues against considering this an absolute contraindication to resective therapy. In contrast to the findings of Scheele et al.,[4] we found that bilobar distribution of metastases had a significant deleterious effect on overall and disease-free survival. Interestingly, 29 of 40 patients with four or more lesions had bilobar disease as did the majority of patients with large metastases (10 to 20 cm). Consideration of tumor size alone did not reveal prognostic significance, but the consequences of size with respect to tumor distribution and requirement for more extensive (bilobar) resections were observed to be important.

A multiinstitutional retrospective review from the Registry of Hepatic Metastases found that resection margins of less than or equal to 1 cm had a negative effect on long-term survival. It is notable that resection margins were not available for most patients in their series and patients with positive margins were grouped with those having margin widths of 1 cm or less.[7] When grouped separately we found no significant difference in survival rates unless the margin exhibited residual tumor. A positive resection margin was a powerful predictor of patient survival and recurrence in both a univariate and multivariate context. These observations were not surprising because residual tumor constitutes surgical treatment failure from the outset and outcome is expectedly poor.

Some reports have observed lower survival rates in older patients, but they did not approach statistical significance.[5, 7] Although we found that patients who were older than 60 years had somewhat poorer survival rates, the risk of recurrence was similar to those younger than 60 years of age.

The metastasis-free interval after resection of the colorectal primary tumor appears to be an important prognostic factor. The Registry of Hepatic Metastases study by Hughes et al.[7] found that a disease-free interval of less than 1 year was associated with inferior survival rates. Our analysis of incremental increases in disease-free interval revealed a trend for improved survival with increasing time. Patients with disease-free intervals of more than 24 months had superior overall and disease-free survival rates. It would appear that a longer metastasis-free interval connotes more favorable tumor biology and outcome.

In contrast to other previously reported studies we did not find metastatic tumor size, Dukes' stage, tumor differentiation, or amount of blood transfused to be significant prognostic factors.[6, 7, 11, 16, 19, 20, 23]

The data from this updated series of hepatic resections for metastatic colorectal cancer affirm our resolve to continue an aggressive surgical approach to this disease. In addition to examining the influence of traditionally reported prognostic factors we classified our patients with a simple mTNM staging system. The resultant analysis revealed this staging system to be a significant prognosticator for both survival and recurrent disease. Its application would more readily allow comparisons among studies and allow for prospective evaluation of the staging criteria and the role of adjuvant treatment strategies. Further refinements of staging criteria could evolve to include biologic, molecular, or genetic factors in addition to the anatomic extent of disease, which is the primary basis for TNM staging at present.

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DISCUSSION

Dr. James W. Williams (Chicago, Ill.). During the past 20 years or so a number of surgical investigators have collectively defined what we can expect from the biologic behavior of colon cancer when it spreads to the liver. What they have shown, I believe, is that a subset of colon cancers finds access to the portal bloodstream, lodges in the liver, finds a suitable environment, and can survive there in the absence of tumor anywhere else. Perhaps as many as 20% of patients who have colon cancer at some time during the course of their disease, either at autopsy or during the course of their illness, will have metastatic tumor isolated to the liver. This group and others have shown and this paper very eloquently illustrates that in a high percentage of patients the patient will be cured if you successfully remove the tumor.

The problem now is what to do with the group of patients with hepatic metastasis who we now can predict very accurately are not cured. One of the strengths of this paper is that it has shown that you can accurately predict which patients have a high risk of death from their primary disease despite a very skillful liver resection.

As surgeons who deal with this condition we now are at a crossroads or maybe at a time of new opportunities. With the molecular biologists describing various cytokines and biologicals that influence the immune system and the endothelial cells of our bodies, it is important for us as surgeons to be aware of some of this.

I want to illustrate what I think is enough of an unusual situation to justify a mini case report. The patient was a 48-year-old man who was found to have an obstructing colon cancer and 10 or 12 tumor implants throughout the liver. Clearly this patient had a limited chance of long-term survival.

We removed his tumors, which required a nonanatomic re-

section of the posterior segment of his right lobe, and 10 or 12 of these lesions were removed from the rest of his liver. He was started on an aggressive course of α-interferon and 5-fluorouacil. This was almost 4 years ago, and as far as we can tell this patient is free of cancer.

α-Interferon is a very potent drug that is able to clear a number of patients with chronic hepatitis B and to make them antigen negative, may be very effective in chronic hepatitis C, and has a number of effects on the immune system, endothelial cell function, and the expression of major histocompatibility complex molecules.

I am obviously not proposing this as a cure for cancer of the colon when it metastasizes outside the liver but just use this to illustrate the body of knowledge that is rapidly evolving in the laboratories of our basic scientist colleagues. As surgeons we must have the vision to exploit the potential of these powerful evolving molecules.

Dr. Ralph J. Doerr (Buffalo, N.Y.). In the patients who experience a recurrence after resective surgery for colorectal metastasis to the liver, one half of the patients again exhibit liver metastasis and one half have recurrences outside the liver. Could you tell us the pattern of failure in your patients and whether you undertook a second reresective effort? A number of reports have shown efficacy in reresecting a presumed isolated liver metastasis after initial curative resection.

With the poor survival data in the subset of patients who had contiguous involvement or lymph node positivity, would you recommend not resecting the liver in those patients? Perhaps when a gastroduodenal, periportal, or celiac lymph node is positive, the best course is to try another modality such as alcohol ablation or cryoablation.

Finally, is there any role for hepatic artery catheters in those otherwise desperate cases?

Dr. David Otta (Columbia, Mo.). I support Dr. Williams' comments. Our medical oncology colleagues have made significant progress with systemic chemotherapy. They have not conquered this disease, but certainly they are starting to see partial remissions with chemotherapy regimens such as 5-fluorouracil, α-interferon, and leucovorin.

You have presented nice data as to who is at high risk to fail surgical resection. If you can determine stage IV disease before operation with laparoscopy and computed tomographic scanning, would these patients benefit from preoperative chemotherapy and if they respond, would you then proceed with surgical resection?

Dr. Gayowski (closing). Dr. Williams asked how we treat patients whom we have identified at high risk for recurrence. In the past Dr. Iwatsuki and Dr. Starzl have advocated the use of chemotherapy for most patients after hepatic resection. Our previous experience suggested that patients receiving postresection therapy experienced improved survival and disease-free intervals. Now that we can identify patients who are at low and high risk for recurrence, I think we can develop better strategies to implement neoadjuvant therapy.

Unfortunately, we don't have very many chemotherapeutic agents that have consistently been shown to be efficacious for this disease. 5-Fluorouracil was mentioned, some of the new immunomodulators are coming into the forefront, and perhaps a combination of these therapies is warranted.

Patients identified as being at high risk for recurrent disease should receive some form of neoadjuvant therapy. Randomization to one form or route of therapy versus another would be appropriate. We do not believe that the null hypothesis is satisfied here, and a clinical trial should not include a null treatment arm.

I think we have all had anecdotal cases of patients who "haven't read the textbook" and survive in defiance of the odds and what we know from experience. This reflects the capricious nature of this disease and illustrates the many other aspects of tumor biology that we cannot see at the time of operation.

Dr. Doerr, in looking at patients who undergo resective therapy, roughly one half of our patients experienced recurrence in the liver and the other half had extrahepatic disease.

We had a small proportion of patients with isolated hepatic recurrence and a small number, probably three or four, underwent reresection for these. I don't have survival data for these patients readily available. We also had two patients with pulmonary metastases that were resected. One patient eventually succumbed to disease and one patient is still alive.

With respect to patients with nodal or contiguous disease, in Dr. Iwatsuki's early experience there was always an attempt to remove the tumor as long as it was confined or appeared to be confined to the liver. A lot of the contiguous disease cases had microscopic spread discovered after pathologic examination. In some cases surgical momentum dictated the outcome. There were a few young patients with nodal disease high in the hilum, and a decision was made to proceed with resection in an effort to offer some hope in an otherwise desperate situation. There were only six patients with positive nodes in the entire series. Ordinarily we would not proceed with resection in patients with lymph node metastases.

Dr. Otta, we have not used the staging system to stratify high-risk patients into a preoperative systemic chemotherapy protocol; however, this is an attractive proposal.

Letters to the editors

Staging of resectable colorectal liver metastases

To the Editors:

Dr. Gayowski et al.[1] have presented a consecutive series of 204 patients who underwent resection of colorectal liver metastases during an 11-year period. According to the summary, the procedures were "curative".

This analysis provides information on essential aspects such as length and completeness of follow-up, destiny and tumor status at the end of the study, and particularly the paramount question of macroscopic and microscopic tumor clearance. It confirms our own observation that (1) tumor recurrence after more than 5 years (7 years in our series) is extremely rare, (2) survival equals disease-free survival after this time, and (3) various factors proposed as absolute contraindications to resection such as four or more metastases and limited resection margins (as long as they are clear) may serve as qualifiers but not predictors of survival.[2,3] It also confirms the fact that histologically involved resection margins do preclude

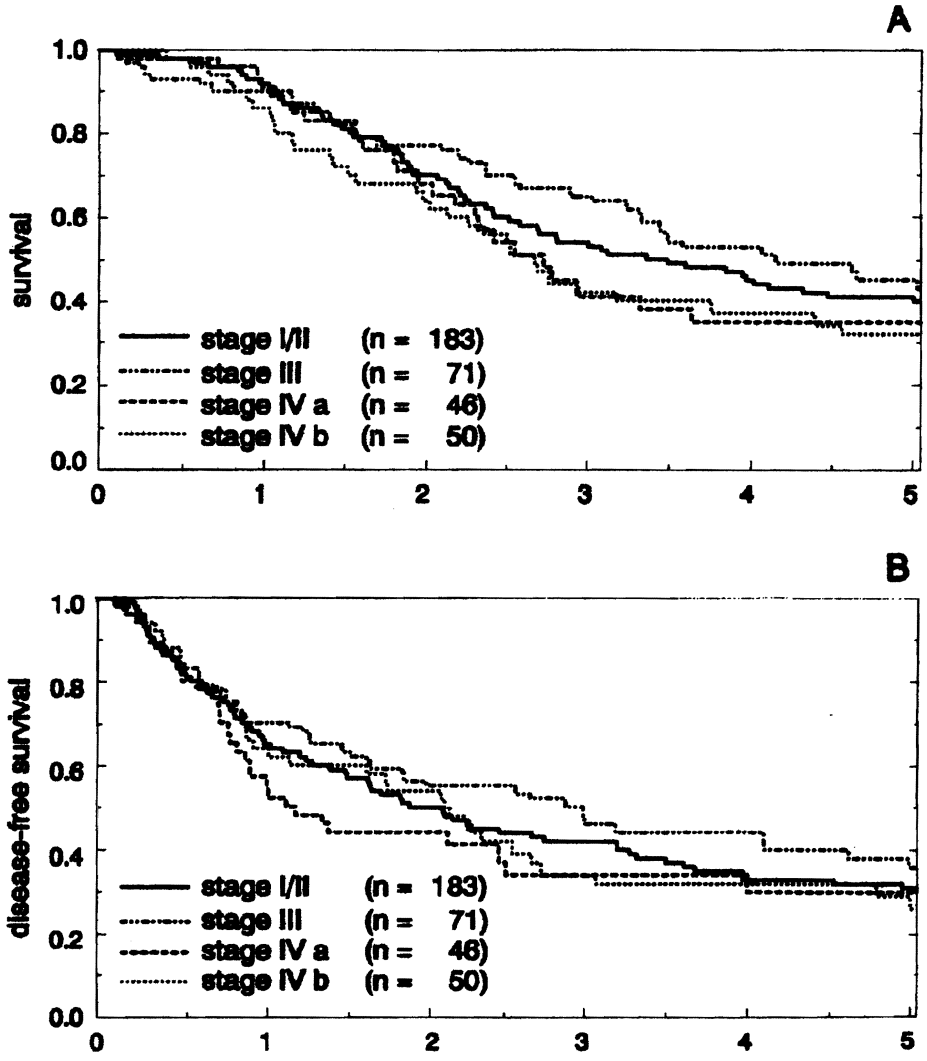

Figure. Survival (A) and disease-free survival (B) of 350 patients with curatively resected liver metastases according to Pittsburgh staging system (30-day mortality excluded).

5-year survival and result in very limited 3-year survival figures of 12%, which mirrors the natural history of comparable patients.[4]

These histologically nonradical procedures (17 patients) should have been removed from the further analysis because involved margins clearly contradict the Union Internationale Contre le Cancer classification of a "curative" procedure.[5] Their inclusion explains for weak results in various subgroups such as bilateral involvement (13 positive margins/80 patients) or trisegmentectomy (8 positive margins/55 patients) and makes statistically based conclusions on the biologic impact of these criteria less convincing.

The true problem of this article is the proposed staging system. Factors proven important in primary liver cancer, predominantly in patients with cirrhosis, are simply transposed to a completely different biologic condition, namely metastatic liver disease. Designed to create a widely acceptable framework for a more uniform data analysis, this proposal is likely to further increase the already existing confusion. The analysis of our own consecutive 350 patients who underwent macroscopically and microscopically complete R0 ("curative") resection fails to ascertain any validity of the new system in predicting either crude or disease-free survival (Figure, *A* and *B*). This is surprising because the overall results of the two series are quite similar. Their 5-year survival of 32% matches our 33% in 434 patients resected with curative intent, as does the percentage for patients with clear margins, which is 37% in Pittsburgh (extrapolated from Table II) as opposed to 39% in Erlangen. The similarly extrapolated 27% disease-free survival in Pittsburgh is not significantly different from 34% in our series.[2]

Because the proposed staging system appears irrelevant in our database, which presently comprises the largest single institution series worldwide, adoption by other groups may not solve the problem. Presumably a prospective data pooling by leading centers in the field, on the basis of a general consensus on inclusion and exclusion criteria (such as operative deaths, involved margins, positive hilar lymph nodes), and adding modern cytobiology features to traditionally collected criteria may provide a basis to minimize the Babylonian languish, terminology, and finally staging confusion among scientists and clinicians.

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11/59/67094

Reply

To the Editors:

We thank Dr. Scheele and his colleagues for their prompt reexamination of our proposed mTNM staging system on their large series of patients.

First, we would like to draw attention to our methodology section, which states that all procedures were attempts at curative resection. In our abstract summary "curative" was meant to refer to removal of all macroscopic disease, and we apologize if this was misleading or disinformative.

Second, we do not believe that exclusion of patients with microscopically involved margins (either parenchymal or in resected contiguous structures) would be appropriate. We agree that these represent surgical treatment failures; however, if we excluded our treatment failures from our analysis, then we are truly biasing our results. As many have experienced, surgical momentum often dictates the outcome of major hepatic resections, and even with removal of all macroscopic identifiable disease, we can expect "histologic nonradical" resections to occur, albeit with an acceptably low frequency. If we exclude these failures, then we are imposing bias in that the types of disease (bilobar) or extensive resection (trisegmentectomy) that are occasionally associated with positive microscopic margins (treatment failure) are excluded from analysis. We cannot ignore the biologic impact of the consequences of tumor number, site, and size with respect to our ability to completely extirpate these lesions.

Unfortunately, the application of our staging system did not appear to be useful in their series of patients, and hence its validity has been questioned. Their survival of stage I/II patients was approximately 40% at 5 years, significantly lower than our 60% rate. On the contrary, their reported survival of stage IV B patients (tumors with lymph node or extra hepatic involvement) was 30% at 5 years, as opposed to our 0% rate. We are surprised by the impressive survival rates of patients with hilar-perihepatic nodal metastases and/or contiguous or extrahepatic disease because these patients typically do not fare well.

What might have accounted for these differences? Although we look forward to seeing their new data (in press), we can only extrapolate from their previous publication (SURGERY 1990;110:13-29). In this report approximately one third of patients were treated with wedge resection and another 22% with segmentectomies, which we categorize as wedge resections. In addition, approximately one third of the patients had simultaneous colon and liver resection. This is in distinct contrast

to our series in which the use of wedge resection was exceptional (85% major hepatic resections) and simultaneous colon and liver resection was rare.

Smaller hepatic resections (wedge, segmental) might have underestimated the tumor stage, particularly when imaging techniques and intraoperative staging strategies were evolving during the 1960s and 1970s. Also, satellite tumor phenomenon was not addressed in our analysis, because we considered each lesion as independent. Hence, patients with a dominant lesion (larger than 2 cm) and multiple satellites in one lobe could be incorrectly classified as stage II in their series, again underestimating the staging.

Our proposed staging system is inadequate for the patients who undergo simultaneous colon and liver resection, because synchronous lymph node involvement in the colonic region (C1, C2) classifies all of the hepatic metastatic tumors in stage IV B. Hepatic metastases should be staged after the radical colectomy is completed. Nodal and extrahepatic disease in our proposed system refers only to the "metastases of metastases" phenomenon, rather than primary nodal disease or concomitant local primary invasion. If the 50 stage IV B patients in their series have a high incidence of remote extrahepatic disease (i.e., pulmonary), then the results are truly remarkable.

We fully agree that prospective data pooling and analysis are essential to evaluate staging criteria and refine or modify them further. The addition of cytobiologic features, as well as molecular or genetic factors, will help us better define the biologic phenomenon of colorectal metastases (if such a thing is indeed available now) and better elucidate the impact of surgical and/or adjuvant treatment strategies.

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Adequacy of stereotaxic breast biopsies

To the Editors:

I am responding to the article "Are Stereotaxic Breast Biopsies Adequate?" (SURGERY 1994;116:610-5).

First, Hernandez et al. arbitrarily define specimen "inadequacy" as rare or scant breast epithelium in one or two core fragments. The presence of breast epithelium may have *no* relationship to the mammographic lesion. For example, a perfectly "adequate" specimen may reflect fibrosis without ductal epithelium. Adequacy, as they define it, is clinically irrelevant.

Second, they confuse the terms *probably benign* with *indeterminate* lesions, which leads to interesting but misinformed discussion regarding the use of the technology. As most radiologists and informed breast surgeons are aware, the category of probably benign is used in a mammographic screening program to assign those lesions found at mammography with an approximate 1% or less likelihood of malignancy to periodic mammographic surveillance, *not* biopsy.[1] The designation of probably benign is not assigned to lesions for which the decision to biopsy has been made. In practice, most of these lesions for which biopsy is recommended are indeed indeterminate, given the few specific signs of malignancy available through mammography. It is emphasized that radiologists concentrate on recommending core biopsy only for lesions that otherwise would be managed with open surgical biopsy, excluding probably benign lesions where periodic imaging surveillance is a well-established management choice.[2] It is incorrect therefore that "before the advent of SCBB, most indeterminate mammographic lesions were observed rather than excised," as Hernandez et al. assert.

The scientific and fiscal validity of the procedure are not suspect, indeed quite the opposite. Parker et al.[3] demonstrated the reproducibility and reliability of this technique in a multiinstitutional study. One cannot call the use of excisional biopsy for all mammographic lesions for which biopsy is recommended as fiscally sound, given that there is generally only a 20% incidence of malignancy. Five biopsies to find one malignancy is unacceptable from anyone's perspective. In fact, the use of stereotaxic large-core breast biopsy instead of surgical biopsy would be "equally as accurate and would save the health-care system at least $1 billion a year."[4]

Third, uniformly obtaining only five core biopsy specimens is not currently clinically recommended. It is now well established that five cores is a *minimum* number and that larger lesions or lesions containing many calcifications require many more than five core specimens.[5]

Finally, I concur that frequently general surgeons are most experienced in the management of breast disease—when it exists. Importantly, surgeons are not trained in breast imaging or imaging guided procedures, as most radiologists are, and should become involved only at the appropriate clinical juncture. That is to say, a surgical referral should be generated when a mass or malignancy are proved or possible. This affords another area of cost saving in avoiding the layer of expense generated by unnecessary surgical referral when the mammographic lesion is found to be benign, as is most frequently the case.

The shifting paradigms of responsibility in breast disease diagnosis are understandably made with requisite suspicion and some level of animus. However, the transition is more effective when good communication and consultation are promoted. A multidisciplinary approach (incorporating at least the radiologist, pathologist, and surgeon) to the technology and the patient is in the best interests of all parties.

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