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An Analysis of 412 Cases of Hepatocellular Carcinoma at a Western Center

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Objective
Using a large single-institution experience at a Western referral center, the authors examine partial hepatectomy as treatment of hepatocellular carcinoma and relate treatment outcomes to clinical parameters, including the etiology of underlying cirrhosis.

Methods
Four hundred and twelve patients seen between December 1991 and January 1998 were identified in a prospective database. Data about the surgical procedure, perioperative complications, and long-term outcome were examined.

Results
One hundred twenty-six patients did not have underlying cirrhosis. Of the 286 patients with cirrhosis, 119 were the result of hepatitis B, 39 hepatitis C, 36 both B and C, 43 ethanol abuse, and the remainder other causes. Two hundred forty-three patients underwent surgical exploration, and 154 patients underwent hepatic resection. Seven (4.5%) died from the surgery. One hundred forty-three patients were treated by ablative methods. Patients with cirrhosis had smaller tumors but nevertheless had a lower resectability rate. Neither the presence of cirrhosis nor the etiology of the cirrhosis altered the perioperative morbidity or mortality rate. The greatest determinant of long-term outcome was resectability. The size of the lesion, an alpha-fetoprotein level >2000 ng/ml, and vascular invasion were also determinants of poor outcome. The presence of cirrhosis was a detrimental factor when analysis was stratified for size of tumor. The cause of cirrhosis did not influence the long-term outcome. The 5-year survival rate was 57% for patients with resected lesions <5 cm and 32% for patients with tumors >10 cm.

Conclusion
Partial hepatectomy is safe, effective, and potentially curative therapy for hepatocellular carcinoma. The presence of cirrhosis did not affect the surgical mortality rate but did affect the long-term survival rate. The cause of cirrhosis did not influence outcome. As treatment for small hepatocellular carcinomas, partial hepatectomy produces results similar to those of transplantation. For patients with large tumors who are poor candidates for transplantation, resection results in long-term survival in one third of patients.

Hepatocellular carcinoma (HCC), the most common solid-organ tumor worldwide, is responsible for >1 million deaths yearly.[1] Surgical excision of tumor is the only proven curative therapy.[2] The majority of cases of HCC occur in areas where viral hepatitis is endemic. In Japan, 75% of cases are associated with hepatitis C infection[3]; in China, hepatitis B infection is found in 80% of cases.[4] The majority of the published experience examining treatment for HCC is therefore understandably from the Far East, and the patients reported almost uniformly have underlying cirrhosis.[5–7] The experience in the West differs from this in several ways. The incidence of cirrhosis and HCC is much lower,[8] and a significant number of the patients with HCC do not have underlying cirrhosis. When cirrhosis is present, its etiology is more varied.[3] Because there are few screening programs, tumors are generally bigger at presentation,[9] making treatment potentially more difficult. In the West, liver transplantation is also a more accessible option, and therefore the relative merits of partial hepatectomy and liver transplantation as therapy are hotly debated.

The current study from a tertiary hepatobiliary cancer referral center with an extensive experience in partial hep-

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atectomy compares the results of partial hepatectomy in patients with and without cirrhosis. We examined the clinical experience from the last 6 years to define patient selection criteria for therapy and to evaluate treatment outcome for HCC at a Western cancer center. Also, we examined outcome data for the subset of patients who otherwise would have been candidates for liver transplantation in an attempt to provide data suitable for comparison with the results of transplantation for HCC.

MATERIALS AND METHODS

All patients seen at the Memorial Sloan-Kettering Cancer Center in the 6-year period between December 1991 and January 1998 were identified in the Department of Surgery's prospective hepatobiliary database. At the Memorial Sloan-Kettering Cancer Center, care for HCC is planned under the auspices of a multidisciplinary Hepatobiliary Disease Management Team, and new patients are discussed twice weekly at clinical-radiologic staging conferences. Four hundred twelve patients were considered for treatment in this period of time. Data for these patients were then extracted from the database, hospital and office charts, and patient interviews. Data examined included demographics (age, gender), pathology of liver lesion, pathology of nonneoplastic liver parenchyma, hepatitis serology, hospital course (including complications), and outcome. Follow-up was by personal contact with the patient, the patient's family, or the attending physician.

Definitions

Nomenclature for the extent of resection is that defined by Goldsmith and Woodburne.[10] An extended right hepatectomy is resection of Couinaud's segments[11] 4 through 8; an extended left hepatectomy is resection of segments 2, 3, 4, 5, and 8; a right lobectomy is resection of segments 5 through 8; and a left lobectomy is resection of segments 2 through 4.

Evaluation of liver function was by the Child classification.[12] Clinical staging of disease was performed using Okuda staging[13] and AJCC staging criteria.[14] These are summarized in Table 1. The 12 patients with fibrolamellar HCC seen in this period were excluded from analysis.

The presence of hepatitis C antibody was considered evidence for this virus as an etiologic factor for parenchymal disorder. The presence of hepatitis B surface antigen was considered proof of the hepatitis B virus as an etiologic agent. Hemachromatosis or alpha-1 antitrypsin deficiency was proven histologically.

Statistics

The chi square test or Fisher's exact test, where appropriate, was used for univariate comparisons. For univariate survival analysis, plots were by the Kaplan–Meier method and comparisons by the log-rank test. Multiple logistic regression was used to incorporate all the explanatory variables in the same model.[15] Using multiple logistic regression in the SPSS statistical package (Chicago, IL), prognostic factors were determined for the hazard rate of complications. Differences were considered significant at $p = 0.05$. All deaths within 30 days of surgery were considered to represent surgical mortality.

Table 1. DEFINITIONS

Child Score for Hepatic Disorder	Points		
Parameter	**1**	**2**	**3**
Albumin (g/dl)	>3.5	2.8–3.5	<2.8
Bilirubin (μmol/L)	<25	25–40	>40
Prothrombin time (s above normal)	<4	4–6	>6
Ascites	None	Mild	Moderate
Encephalopathy (grade)	0	I–II	III–IV

A = 5 or 6 points; B = 7–9 points; C = 9–15 points.

Okuda Staging for HCC	Points	
Parameter	**0**	**1**
Size of tumor	<50% of liver	>50%
Ascites	No	Yes
Albumin (g/dl)	>3	<3
Bilirubin (mg/dl)	<3	>3

I = 0 points; II = 1 or 2 points; III = 3 or 4 points.

AJCC Staging for HCC	
T1	Single, <2 cm, no vascular invasion
T2	<2 cm with vascular invasion, or >2 cm with no vascular invasion, or unilobar/multiple <2 cm with no vascular invasion
T3	>2 cm with vascular invasion, or unilobar/multiple >2 cm
T4	Bilobar/multiple or major vascular or adjacent organ invasion
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T1,T2 or T3 N+ M0
Stage IV	T4 or M+

RESULTS

Demographics

In the 6-year study period, 412 patients with HCC were seen at the Memorial Sloan-Kettering Cancer Center. The median age was 64 years. There were 293 men (71%) and 119 women (Table 2). Twenty-two percent of the patients were of Asian heritage. Two hundred eighty-nine patients (70%) had associated cirrhosis. Two hundred thirty-four patients underwent surgical exploration; 154 of them underwent resection. The age, gender, and ethnic distribution of

Table 2. CHARACTERISTICS OF PATIENTS UNDERGOING TREATMENT FOR HCC

	All Patients	Patients With Resection
Number	412	154
Age (mean ± SE)	61.4 ± 0.7	59.5 ± 1.2
Age (median [range])	64 (26–90)	63 (26–86)
Sex (M/F)	293/119	95/59
Asian n (%)	91 (22%)	32 (21%)
Cirrhosis	289	100
Cause of parenchymal disorder		
Hepatitis B	119	37
Hepatitis C	39	10
Both	36	10
ETOH	43	13
Other	52	30
Child classification		
A	342	144
B	54	9
C	16	1
Okuda stage		
I	212	77
II	189	73
III	11	4
Tumor size		
<2 cm	3	1
<5 cm	171	37
5–10 cm	130	54
>10 cm	108	62

the patients who underwent resection were similar to those of the entire population (see Table 2). Aside from the patients who were treated by partial hepatectomy, five patients were treated by intraarterial chemotherapy under an experimental protocol. One hundred thirty-nine patients were treated by ablative techniques, including cryotherapy, ethanol injection, or transcatheter arterial embolization. One hundred fourteen patients were treated by chemotherapy or supportive care. For outcome analysis, patients who received systemic chemotherapy were grouped with those who received supportive care, because there was little difference between these two groups in terms of survival.

Median survival for the 210 patients who have died was 7.6 months (range 0 to 70 months). Median follow-up for survivors is 20 months (range 1 to 72 months). For the 154 patients who underwent resection, the median survival was 13 months for the 72 patients who have died, and the median follow-up for survivors is 27 months.

The majority of patients had large tumors. Only three patients had tumors <2 cm. Two hundred thirty-eight patients (58%) had tumors >5 cm.

Etiology of Underlying Cirrhosis

Of the 289 patients with an underlying parenchymal disorder, 194 patients (67%) had liver damage from viral hepatitis. In 119 patients (41%), hepatitis B was the etiologic agent. In 39 (14%), the agent was hepatitis C, and in 36 (13%) it was both. In total, 54% of patients were hepatitis B carriers, and 26% were hepatitis C carriers. Ethanol abuse was the etiology for cirrhosis in 43 cases (15%). There were 10 cases of hemachromatosis and 2 cases of alpha-1 antitrypsin deficiency. The remainder of the cases were idiopathic. Only 17% of patients had hepatic function in the Child B or C category, reflecting the appropriateness of the referral pattern to a tertiary cancer center.

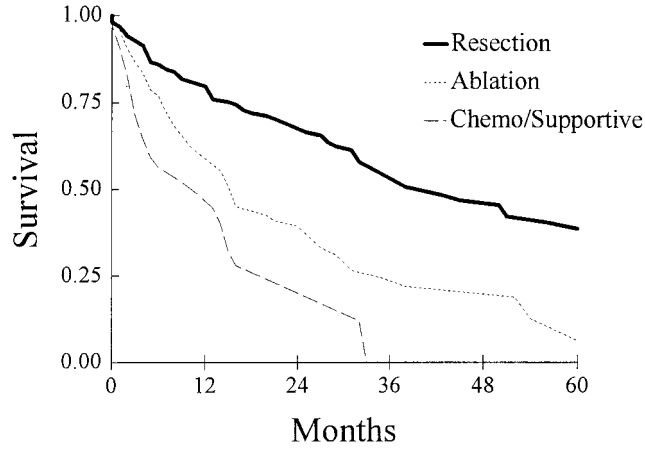

Figure 1. Survival of patients with HCC according to treatment.

Outcome of All Patients

By univariate analysis, the factors with the greatest influence on long-term outcome were resection as therapy ($p < 0.0001$), Child classification ($p < 0.001$), Okuda stage ($p < 0.001$), and presenting alpha-fetoprotein (AFP) level ($p = 0.004$). Factors not influencing outcome were gender, ethnicity, age, cirrhosis, or etiology of cirrhosis. In multivariate analysis using success of resection, size of tumor, AFP level, Child classification, and vascular invasion as covariates, the first four remained independent predictors of outcome. Success of resection ($p = 0.0001$, relative risk 0.6) and size <5 cm ($p = 0.02$, relative risk 0.6) were favorable characteristics; AFP >2000 ng/ml ($p = 0.05$, relative risk 1.2) and advanced Child classification ($p = 0.05$, relative risk 1.3) were unfavorable.

Survival as related to therapy is depicted in Figure 1. Median survival of patients who underwent resection was 39 months, with 1-, 3-, and 5-year survival rates of 81%, 54%, and 37%, respectively. For patients who underwent tumor ablation, median survival was 15 months and the 1-, 3-, and 5-year survival rates were 56%, 21%, and 7%, respectively. For patients treated with systemic chemotherapy or supportive care, the median survival was 9 months, with a 44% 1-year survival rate and no 3-year survivors. Resectability was found to have the greatest positive influence over outcome.

Outcome of Patients who Underwent Resection

Perioperative Results

The 154 resections included nine extended left hepatectomies (five in patients without cirrhosis, four in patients with cirrhosis). This series included 49 extended right hepatectomies (19 in patients without cirrhosis, 30 in patients with cirrhosis), 23 left lobectomies (12/11), 20 right lobectomies (8/12), 12 left lateral segmentectomies (1/11), and 41 segmental or subsegmental resections (9/32). The majority of resections (101/154, 66%) were lobectomies or more. Even for patients with cirrhosis, 57 of 100 resections were lobectomies or larger. This is because of the large size of the lesions encountered. Patients without associated cirrhosis were more likely to have a resection consisting of a lobectomy or more (81% *vs.* 59%, $p < 0.01$) (Table 3). This reflects the larger tumors encountered in patients without cirrhosis, as well as a willingness to perform nonanatomic resections in patients with cirrhosis in an attempt to preserve functional parenchyma.

There were seven perioperative deaths (4.5%). Three resulted from hepatic failure and one each from sepsis, pneumonia, gastrointestinal bleeding, and intraabdominal hemorrhage. Five of the deaths occurred in patients with cirrhosis (5%); two occurred in patients with no underlying parenchymal disorder (3.7%).

The median hospital stay was 13 days (range 1 to 60).

Of the patients without cirrhosis, 44% underwent resection, accounting for 73% of the patients who underwent surgical exploration (see Table 3). Patients with cirrhosis were less likely to undergo resection, although the tumors in patients with cirrhosis were significantly smaller (6 cm median *vs.* 10 cm; see Table 3). This probably reflects the healthy respect we have for potential complications after hepatic resection in patients with cirrhosis, and the resulting less-aggressive resectional approach in these patients. In patients selected for resection, however, the operative time, complication rate, and length of hospital stay were identical between patients with and without cirrhosis (see Table 3).

Seventy-eight perioperative complications occurred in 69 patients (45%); these are listed in Table 4. The most significant complications were intraabdominal, including hepatic insufficiency (n = 7, 5%), abdominal abscess or biloma (n = 14, 9%), and intraabdominal or gastrointestinal bleeding (n = 5, 4%). Cardiopulmonary complications were also common, including pneumonia (n = 6, 4%) and pneumothorax or pleural effusion requiring thoracostomy tube placement.

Long-Term Results After Hepatectomy

Table 5 lists the variables analyzed as potential predictors of adverse long-term outcome. Factors most influential on outcome by univariate analysis included preoperative AFP level (Fig. 2), surgical margin positive for tumor, vascular invasion (Fig. 3), and size of largest tumor. Factors not

Table 3. SURGICAL OUTCOME AS RELATED TO UNDERLYING PARENCHYMAL DISORDER

	n	Explored	Resected	Resected/All	Resected/ Explored	Mortality %	Lobectomy or more	Size of lesion (median [range])	OR time (min) (mean ± SE)	Complication %	Hospital Stay (days) (mean ± SE)
No cirrhosis	123	73	54	44%	73%	3.7%	81%	10 (3–26) cm	230 ± 17	43%	13 ± 1
Cirrhosis	289	161	100	34%*	62%*	5.0%	59%†	6 (2–20)cm†	225 ± 10	46%	13 ± 1
Hep B	119	65	37	31%*	57%*	3.0%	49%†	7 (1–20)cm†	215 ± 16	43%	11 ± 1
Hep C	39	16	10	26%*	63%	20%	60%*	5 (2–13)cm†	230 ± 25	40%	13 ± 3
Hep B+C	36	18	10	28%*	56%	0	31%†	5 (2–20)cm†	220 ± 30	40%	13 ± 4
Ethanol	43	23	13	30%*	57%	6.6%	80%	5 (2–20)cm†	211 ± 15	38%	11 ± 2
Other	52	39	30	58%	77%						

* $p < 0.05$ *vs.* no cirrhosis; † $p < 0.01$ *vs.* no cirrhosis

Table 4. COMPLICATIONS AFTER LIVER RESECTION FOR HCC*

	n
Cardiopulmonary	
Death	7
Arrhythmia	6
Pneumonia	6
Pneumothorax	2
Pleural effusion	3
Infections	
Abdominal abscess	9
Wound infection	5
Urinary tract infection	3
Venous catheter infection	2
C. difficile colitis	2
Gastrointestinal	
Hepatic insufficiency/failure	7
Biloma	5
Intraabdominal bleed	3
Portal vein thrombosis	2
Ascitic leak	2
Ileus	2
Gastrointestinal bleed	2
Enteric fistula	1
Dehiscence	1
Pancreatitis	1
Miscellaneous	
Deep venous thrombosis	2
Urinary retention	2
Renal insufficiency	2
Fall	1

* 69 patients, 78 complications.

found to influence long-term survival by univariate analysis included gender, ethnicity, advanced age, presence of cirrhosis, cause of cirrhosis, extent of resection, and number of tumors.

Some of the factors not found to predict outcome deserve further scrutiny. Although Child classification did not significantly predict outcome ($p = 0.09$), only a limited number of patients with Child B or C hepatic function status underwent resection ($n = 10$). None of these patients were long-term survivors. The lack of association between Child class and outcome probably reflects an inadequate sample size rather than biologic reality.

The presence of cirrhosis also did not at first glance seem to be associated with poorer outcome. The univariate comparison shown in Table 5 is an unfair one, however. In the patients who underwent resection, the tumors were significantly larger in patients without cirrhosis than in those with cirrhosis (median 10 cm *vs.* 6 cm; see Table 3). When the comparison of outcome as related to cirrhosis is stratified for tumor size (Fig. 4), the correlation of poor outcome with the presence of cirrhosis is significant ($p = 0.03$).

The influence of tumor size on outcome deserves further emphasis. The clinical experiences of liver transplantation for HCC are often compared with those of partial hepatectomy, even though most transplant programs treat only patients with small tumors. Figure 5 demonstrates the overall and disease-free survival rates for patients with resected tumors <5 cm and for those with tumors >10 cm. For those with tumors <5 cm, the overall 5-year survival rate is 57% and the disease-free survival rate is 44%. Even for those with large tumors (>10 cm), the 5-year survival rate is 32% and the disease-free survival rate is only 23%.

Multivariate analysis was performed using the variables deemed significant by univariate analysis as covariates (*i.e.*, positive surgical margin, AFP $>$ 2000 ng/ml, vascular invasion, and presence of cirrhosis). Positive surgical margin ($p = 0.03$, relative risk 2.0), AFP $>$ 2000 ng/ml ($p = 0.01$, relative risk 1.5), and vascular invasion ($p = 0.03$, relative risk 1.7) remained independent predictors of adverse long-term outcome.

DISCUSSION

For patients without cirrhosis, partial hepatectomy clearly is safe therapy. The surgical mortality rate for even the most extensive resection is uniformly $<5\%$ at major centers.[2,16–19] Even for the current study population with a median tumor size of 10 cm, resection in patients without cirrhosis resulted in a low surgical mortality rate of 3.7% and a 5-year survival rate of 42%. Partial hepatectomy is clearly the treatment of choice for HCC in the noncirrhotic liver.

It is also apparent that partial hepatectomy is becoming increasingly safe in patients with cirrhosis. Many publications have reported surgical mortality rates of 10% to 20% in patients with cirrhosis[19–21]; indeed, in the last publication from our institution, reporting 35 resections in patients with cirrhosis over a 20-year period (1970 to 1991), the surgical mortality rate was 14%.[22] The surgical mortality rate of 5% in the current series of 100 resections in patients with cirrhosis represents a significant improvement and is well justified by the 37% 5-year survival rate achieved in this population. It is also consistent with other recent series reporting surgical mortality rates of 4% to 7% in patients with cirrhosis.[6,16,17,23] Improvements in patient selection, anesthetic technique, and surgical conduct have combined to produce these recent improvements in the safety of hepatectomy in the setting of cirrhosis.

In selecting patients with cirrhosis for treatment, and particularly for surgery, baseline liver function is the most important factor influencing outcome. Many complex methods for estimating adequate liver reserve have been advocated, including tests that measure liver metabolic activity (*e.g.*, ICG clearance, galactose elimination, aminopyrine clearance).[24] Others have advocated assessing parenchymal fibrosis either directly by histologic evaluation or indirectly by measuring vascular resistance by means of hepatic venous wedge pressure.[17,25] We have not routinely relied on any of these evaluations for selecting patients for surgery or other therapy. Rather, we have found clinical staging scales

Table 5. EFFECT OF CLINICAL AND PATHOLOGIC PARAMETERS ON LONG-TERM OUTCOME AFTER RESECTION OF HCC

	Characteristic	n	1-yr Survival (%)	3-yr Survival (%)	5-yr Survival (%)	p
Gender	M	59	79	48	37	0.6
	F	95	81	53	40	
Asian	No	121	79	50	34	0.3
	Yes	33	79	62	35	
Age	<70	112	76	56	42	0.5
	≥70	42	85	41	27	
Cirrhosis	No	54	83	58	42	0.09
	Yes	100	77	47	37	
Cause of parenchymal disease						
	None	54	83	58	42	0.6
	Hep B	37	78	59	50	
	Hep C	10	69	69	51	
	Both	10	90	36	36	
	ETOH	13	85	40	14	
	Other	30	71	60	26	
Child class	A	144	81	53	40	0.09
	B	9	50	33	0	
	C	1	0	0		
Size of resection	<lobectomy	51	82	58	52	0.5
	≥lobectomy	103	79	50	35	
Size of lesion	<5 cm	38	86	66	59	0.04
	≥5 cm	116	79	48	33	
Number of lesions	1	113	81	49	35	0.5
	>1	42	76	54	48	
AFP level	<15 ng/ml	46	88	66	53	0.002
	>15, <2000	48	82	46	27	
	≥2000	29	62	18	18	
Margin	Negative	137	82	56	39	0.04
	Positive	17	52	32	32	
Vascular invasion	No	93	83	58	48	0.02
	Yes	61	72	41	23	

Analysis is a univariate analysis using log-rank Test for Data Comparison.

such as the Child classification[12] or Okuda staging[13] to be sufficient for selecting patients for safe surgery. The current study demonstrates that either of these scales is highly predictive for outcome. Further, when mainly patients of Child A classification are chosen for surgery, the surgical mortality rate is low. Given the current results, it is unlikely

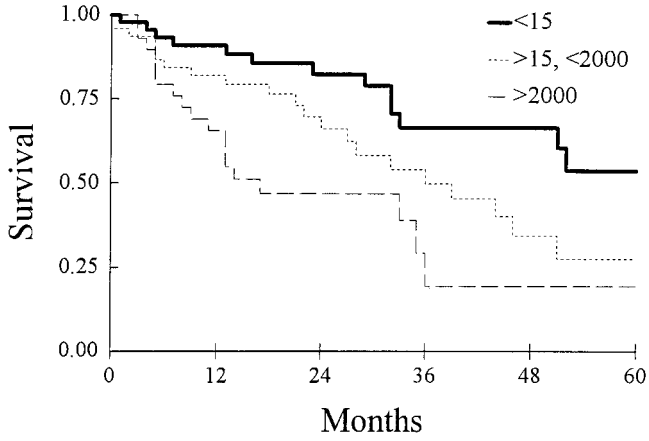

Figure 2. Survival of patients after resection of HCC as related to preoperative AFP levels (ng/ml) (p = 0.002).

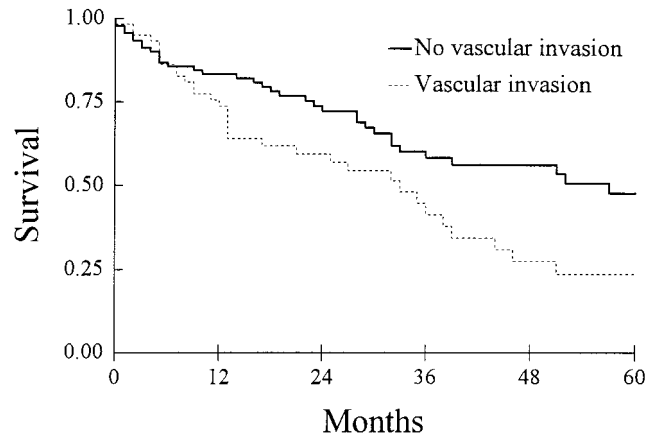

Figure 3. Survival of patients after resection of HCC as related to vascular invasion (p = 0.02).

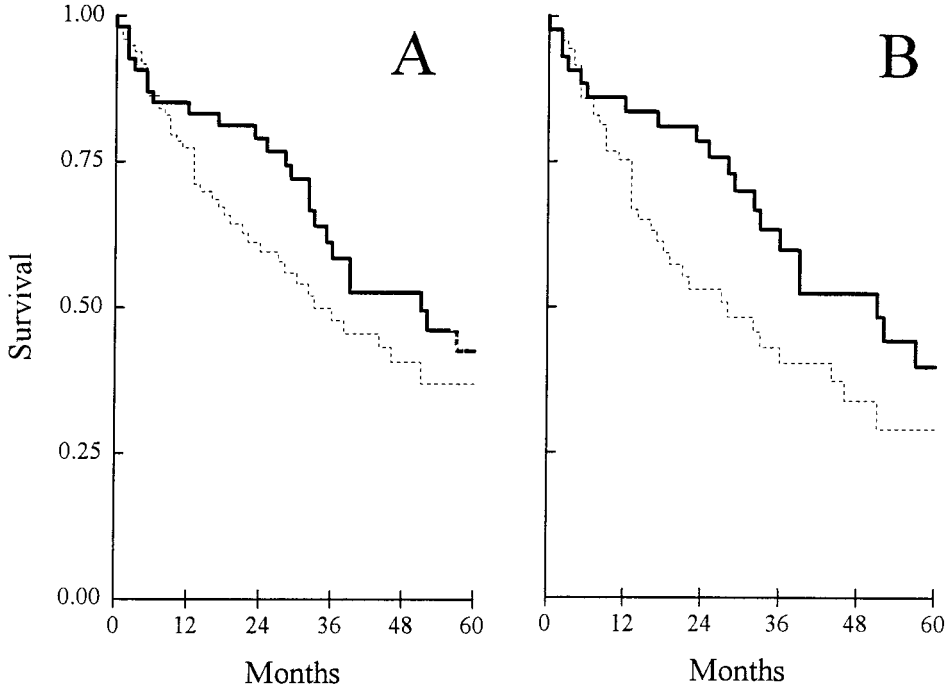

Figure 4. Survival of patients after resection of HCC as related to the presence (solid lines) or absence (dotted lines) of cirrhosis. (A) Results for all patients ($p = 0.09$); (B) results only for patients with tumors >5 cm ($p = 0.03$).

that more sophisticated tests will select patients with a better perioperative outcome for patients with Child A classification. It has been suggested by others that these tests will help select the few patients with Child B classification who may tolerate liver resection, but this has not been proven.

The current AJCC staging system[14] does not incorporate liver function as a staging criterion; this partly explains the reluctance of investigators to embrace this staging system.[26] Because liver function is such a major determinant of outcome, incorporating some measure of liver function into the clinical cancer staging system is essential for utility and widespread use.

There are theoretical reasons why the etiology of cirrhosis may affect treatment outcome and may be useful in patient selection. Epidemiologic studies indicate that the risk and pace of oncogenesis is highly related to the underlying parenchymal disorder. Data from long-term follow-up of patients with cirrhosis from hepatitis B indicate that the

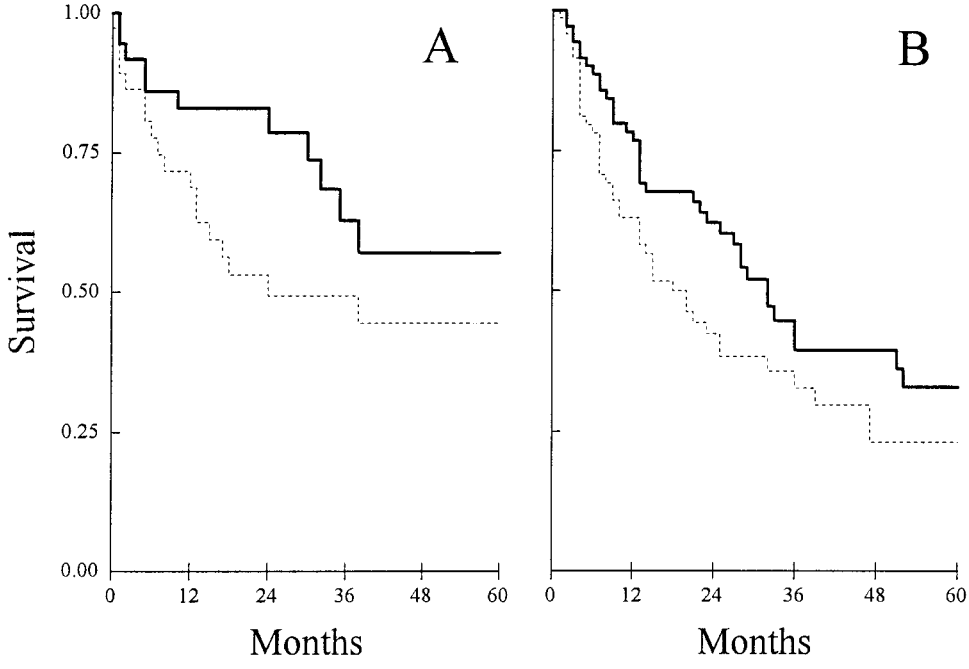

Figure 5. Overall survival rates (solid lines) and disease-free survival rates (dotted lines) of patients after resection of HCC as related to size of largest tumor. (A) Data for patients with largest tumors <5 cm; (B) patients with tumors >10 cm.

risk of developing HCC is approximately 0.5% per year.[4] Early studies seem to indicate that the risk of developing HCC in patients with cirrhosis from hepatitis C is much higher—5% per year.[3] It also appears that coinfection with both viruses,[27] or the combined influence of ethanol abuse and hepatitis C infection,[28] results in an even higher risk of cancer. Therefore, the risk of a second primary or multifocal disease could theoretically be related to the cause of cirrhosis.

The varied profile of etiologies of hepatic dysfunction seen at our center offers a unique opportunity to compare outcome based on the etiology of the underlying disorder. We found no difference in short-term or long-term outcome. The inability to detect a difference, however, may be the result of the small sample size of each subset of patients with each specific etiology of cirrhosis in this and other Western series.[2,17,29] In the series from the University of Barcelona,[17] for example, only six patients were infected with hepatitis B and 26 with hepatitis C. Even at a Western tertiary cancer referral center such as ours, which evaluates >500 new cases of primary and metastatic hepatic cancer each year and performs resections of approximately 300 such tumors yearly, there are inadequate numbers of patients with HCC to draw confident conclusions concerning the influence of underlying parenchymal disease on clinical course. Indeed, the largest Eastern study comparing the surgical results of patients with underlying hepatitis B and hepatitis C compared only 30 patients with hepatitis B and 96 with hepatitis C.[30] In that study, no difference in perioperative outcome or long-term recurrence was found, but the conclusions were also compromised by sample size.

Multicenter studies must be organized to examine the natural history of HCC depending on parenchymal disorder, incidence of second primary tumors, best screening methods, and potential adjuvant therapies to prevent recurrence. Follow-up from the current study and from other available studies is also too short to compare the outcome of hepatitis C-related HCC with that of HCC in other settings. This is because the serologic test for hepatitis C has been widely available only since 1991,[31] and HCC is generally a slow-growing tumor.[32]

It was initially surprising that the presence of cirrhosis did not statistically predict deleterious outcome, because cirrhosis clearly is associated with other causes of death, including liver failure and gastrointestinal bleeding. Other studies had found cirrhosis to be a significant predictor of outcome.[29] On reanalysis, it is clear that the lack of correlation of cirrhosis with poor outcome is the result of the significantly larger tumors encountered in patients without cirrhosis. When stratified according to tumor size, a detrimental influence of the presence of cirrhosis on long-term outcome is clearly documented (see Fig. 4).

The fact that vascular invasion is a dominant factor influencing outcome is not surprising. HCC has a great tendency for intravascular extension.[33] The intravascular tumor thrombus then becomes both a source for metastatic disease as well as a cause of vascular compromise and liver failure. Because the AFP level is highly correlated with vascular invasion ($p = 0.009$, chi square), it follows that AFP levels are highly predictive of outcome. This finding of a high correlation of AFP level with outcome has been reported by others.[29] Patients with vascular invasion or high AFP levels should be considered for adjuvant therapeutic trials.

Total hepatectomy and liver transplantation is the alternative, potentially curative option for the treatment of HCC.[18] Because patients with HCC often have cirrhosis, transplantation may not only rid the patient of tumor but will also treat the underlying hepatic dysfunction. Enthusiasm for transplantation as therapy has been particularly heightened by recent data demonstrating that 3-year survival can be expected in 50% to 70% of patients who undergo total hepatectomy and transplantation for HCC.[2,16,34,35] The morbidity and mortality rates associated with liver transplantation, however, are substantial. Although the surgical mortality rate is improving, with some centers reporting <5%,[2,16] most published reports have found rates of 10% to 20%.[19,35] Further, in many parts of the world where hepatitis and HCC are common, cultural prejudices against organ donation and a shortage of financial resources conspire to prevent widespread application of liver transplantation. Even in the United States, there are only approximately 4000 livers available for transplantation yearly.[36] It is difficult to justify the use of such a precious resource for patients with cancer, most of whom will have recurrence of the cancer despite liver transplantation. This explains why fewer than 100 transplantations are performed each year in the United States for cancers of any type.[36]

The published results of transplantation or of partial hepatectomy as treatment for HCC cannot easily be compared, however. Transplants for HCC have to date been offered mainly to patients with small tumors; few patients with tumors >5 cm undergo transplants, whereas patients who undergo partial hepatectomy generally have larger tumors. Because size is a major determinant of outcome, comparisons of the two therapies have been difficult. The sample size in the current study population allowed subset analysis of patients with tumors <5 cm, patients generally accepted as potential transplant candidates. In these patients with small tumors, the 3-year survival rate was 63% and the 5-year survival rate was 57%. The 3-year disease-free survival rate was 50% and the 5-year disease-free survival rate was 44%. These are results comparable to most recent series of transplantation. In the series from Bismuth et al,[2] the 3-year survival rate for tumors 3 to 5 cm after transplantation was 51%; the disease-free survival rate was the same. These data would indicate that partial hepatectomy is an effective therapy for HCC. The results are comparable to those of transplantation for small tumors, and the procedure may produce long-term survival even for patients with large tumors, where transplantation is not likely to be an option.

Although the patients who underwent ablative therapy

have a significantly better survival rate than those treated by chemotherapy or offered supportive care, these treatment groups are hardly comparable. Patients not offered ablative therapy are generally those with more advanced disease or those who have medical contraindications to interventional therapy. There is little doubt that ethanol ablation[37] or transcatheter embolization[38] can shrink tumors and, for small tumors, can eradicate the treated tumor. Of debate is whether this translates into a survival benefit.[38,39] For painful tumors, such ablation can provide symptomatic relief and is clearly justified. For asymptomatic tumors, a trial comparing ablations with chemotherapy or supportive care is sorely needed but will probably never be performed because of the biases of patients and investigators. Of greater interest, and certainly more feasible, is a study comparing ablative therapy with partial hepatectomy or liver transplantation for small tumors. It is clear that ethanol ablation as treatment for small HCC can produce long-term survivors.[37] In a series of 210 patients with cirrhosis and tumors <5 cm treated with ethanol injection, the 1-, 3-, and 5-year survival rates for those with solitary lesions were 88%, 47%, and 33%. How this or other ablative modalities will compare with surgical therapy for small tumors awaits random assignment trials.

These data would indicate that partial hepatectomy represents a safe, effective, and potentially curative therapy for HCC. For tumors >5 cm, resection is clearly the treatment of choice. For tumors <5 cm, although debate rages on concerning the relative efficacy of partial hepatectomy *versus* transplantation, much more relevant is an examination comparing surgery with ablative options. Further, effective adjuvant therapies are sorely needed. Studies of the effectiveness of therapeutic procedures or adjuvant therapies should stratify patients according to vascular invasion, size of tumors, AFP level, and presence of cirrhosis. The influence of the etiology of cirrhosis on the development of HCC, on the result of therapy, and on the recurrence of cancer needs to be studied in prospective trials. Because of the low incidence of HCC in the United States, these and other investigations should be approached in a multicenter fashion if useful results are to be obtained within our academic lifetime.

References

1. Fan ST, Lai EC, Lo CM, Ng IO, Wong J. Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. Arch Surg 1995; 130:198–203.
2. Bismuth H, Chiche L, Adam R, Castaing D, Diamond T, Dennison A. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. Ann Surg 1993; 218:145–151.
3. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. Semin Liver Dis 1995; 15:64–69.
4. Beasley RP. Hepatitis B virus: the major etiology of hepatocellular carcinoma. Cancer 1988; 61:1942–1956.
5. Okuda K, Liver Cancer Study Group of Japan. Primary liver cancers in Japan. Cancer 1980; 45:2663.
6. Lai EC, Fan ST, Lo CM, Chu KM, Liu CL, Wong J. Hepatic resection for hepatocellular carcinoma. An audit of 343 patients. Ann Surg 1995; 221:291–298.
7. Nagasue N, Kohno H, Chang YC, et al. Liver resection for hepatocellular carcinoma: results of 229 consecutive patients during 11 years. Ann Surg 1993; 217:375–384.
8. Wingo PA, Tong T, Bolden S. Cancer statistics, 1995. Ca Cancer J Clinicians 1995; 45:8–30.
9. Tsuzuki T, Sugoika A, Ueda M, et al. Hepatic resection for hepatocellular carcinoma. Surgery 1990; 107:511–520.
10. Goldsmith NA, Woodburne RT. The surgical anatomy pertaining to liver resection. Surg Gynecol Obstet 1957; 105:310–318.
11. Couinaud C. Bases anatomiques des hepatectomies gauche et droite reglées. J Chirurgie 1954; 70:933–966.
12. Wantz GE, Payne MA. Experience with portacaval shunt for portal hypertension. N Engl J Med 1961; 265:721–728.
13. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Cancer 1985; 56: 918–928.
14. Fleming ID, Cooper JS, Henson DE, et al. AJCC Cancer Staging Manual, 1997.
15. Cox DR. Regression models and life tables (with discussion). J R Statist Soc Br 1972; 187–220.
16. Schwartz ME, Sung M, Mor E, et al. A multidisciplinary approach to hepatocellular carcinoma in patients with cirrhosis. J Am Coll Surg 1995; 180:596–603.
17. Fuster J, Garcia-Valdecasas JC, Grande L, et al. Hepatocellular carcinoma and cirrhosis—results of surgical treatment in a European series. Ann Surg 1996; 223:297–302.
18. Iwatsuki S, Starzl TE, Sheahan DG, et al. Hepatic resection versus transplantation for hepatocellular carcinoma. Ann Surg 1991; 214: 221–229.
19. Ringe B, Pichlmayr R, Wittekind C, Tusch G. Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. World J Surg 1991; 15:270–285.
20. Suenaga M, Nakao A, Harada A, et al. Hepatic resection for hepatocellular carcinoma. World J Surg 1992; 16:97–105.
21. Sasaki Y, Imaoka S, Masutani S, et al. Influence of coexisting cirrhosis on long-term prognosis after surgery in patients with hepatocellular carcinoma. Surgery 1992; 112:515–521.
22. Vauthey JN, Klimstra D, Franceschi D, et al. Hepatic resection for hepatocellular carcinoma. Am J Surg 1995; 169:28–35.
23. Franco D, Capussotti L, Smadja C, et al. Resection of hepatocellular carcinomas: results in 72 European patients with cirrhosis. Gastroenterology 1990; 98:733–738.
24. Friedman LS, Martin P, Santiago JM. Liver function tests and the objective evaluation of the patient with liver disease. In Zakim D, Boyer TD, eds. Hepatology. Philadelphia: WB Saunders; 1996:791–833.
25. Bruix J, Castells A, Bosch J, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 1996; 111:1018–1022.
26. Nonami T, Harada A, Kurokawa T, Nakao A, Takagi H. Hepatic resection for hepatocellular carcinoma. Am J Surg 1997; 173:288–291.
27. Benvegnu L, Fattovich G, Noventa F, et al. Concurrent hepatitis B and C virus infection and risk of hepatocellular carcinoma in cirrhosis. Cancer 1994; 74:2442–2448.
28. Ikeda K, Saitoh S, Koida I, et al. A multivariate analysis of risk factors for hepatocellular carcinogenesis: a prospective observation of 795 patients with viral and alcoholic cirrhosis. Hepatology 1993; 18:47–53.
29. Stuart KE, Anand AJ, Jenkins RL. Hepatocellular carcinoma in the United States—prognostic features, treatment outcome, and survival. Cancer 1996; 77:2217–2222.

30. Takenaka K, Yamamoto K, Taketomi A, et al. A comparison of the surgical results in patients with hepatitis B- *versus* hepatitis C-related hepatocellular carcinoma. Hepatology 1995; 22:20–24.
31. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. Hepatology 1997; 26:34S–38S.
32. Okuda K, Musha H, Nakajima Y, et al. Clinicopathologic features of encapsulated hepatocellular carcinoma. A study of 26 cases. Cancer 1977; 42:1240
33. Kaneko T, Nakao A, Inoue S, Harada A, Nonami T, Takagi H. Intracaval endovascular ultrasonography for intracaval tumor thrombus. J Am Coll Surg 1994; 179:604–606.
34. Ojogho ON, So SK, Keeffe EB, et al. Orthotopic liver transplantation for hepatocellular carcinoma. Factors affecting long-term patient survival. Arch Surg 1996; 131:935–939.
35. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334:693–699.
36. Transplant data, 1998. UNOS database.
37. Livraghi T, Giorgio A, Marin G, et al. Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. Radiology 1995; 197:101–108.
38. Bismuth H, Morino M, Sherlock D, et al. Primary treatment of hepatocellular carcinoma by arterial chemoembolization. Am J Surg 1992; 163:387–394.
39. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med 1995; 332: 1256–1261.

Discussion

DR. JOHN S. BOLTON (New Orleans, Louisiana): Two assumptions have led to an attitude of therapeutic nihilism toward the patient with hepatocellular carcinoma and cirrhosis: one, cirrhotics with hepatocellular carcinoma have a prohibitively high operative mortality and, two, even when they can be safely resected, they have a lower survival rate than noncirrhotics.

This provocative paper challenges our underlying assumptions. It is not the first sizable Western single-institution series to do so, but it alone, probably with the series from Milan, Italy, is probably the largest series reported in the United States.

I do want to point out, though, that the adverse relationship between cirrhosis and hepatocellular carcinoma has not been repeated, and the take-home message here is not that hepatic resection for HCC in cirrhotics can be routinely done with operative mortality of plus or minus 5% and a 5-year survival of 37%. Despite having significantly smaller tumors, viral cirrhotics had a significantly lower chance of resection than noncirrhotics, and virtually all of the resected cirrhotic patients were a Child-Pugh score of 5 or 6, and they underwent less than or equal to three segment resections in the majority of cases. So there is a great deal of patient selection and surgical judgment being exercised here that we can all learn a lot from.

I have three questions:

How did you define cirrhosis in this series? In my opinion, I think it needs to be characterized in a bit more detail, and will greatly add to the information you are providing us with this morning.

Second, we are seeing an increasing number of patients referred after screening by hepatologists. These are high-risk patients with hepatitis B or C who are undergoing alpha-fetoprotein and ultrasound screening. What proportion of your cirrhotic patients were asymptomatic and detected by screening?

Third, for the 46 cirrhotic patients undergoing greater than three-segment resection, what was their operative mortality? And, again, can you substantiate the degree of their cirrhosis other than by Child-Pugh scoring? By that, I mean I have a Child-Pugh score of 5, I don't have cirrhosis, and I understand that these patients did have cirrhosis, but it would be nice to have it characterized in a bit more detail.

And one final comment: I would be a bit cautious about concluding that the number of tumors is not important. I think you have only a small amount of data to bring to bear on that point, and I think that needs to be looked at further in future studies.

DR. ANDREW KLEIN (Baltimore, Maryland): The authors have focused upon a very important aspect of liver biology, namely, does the etiology of chronic liver injury affect the outcome of treating liver cancer. This large clinical series of more than 400 patients provides important data and challenges some of the conventional wisdom on this topic.

Someone suggested that, given the ongoing risk of developing a malignancy in chronically damaged liver tissue, performing a liver resection in a patient with hepatocellular cancer and cirrhosis is akin to performing a partial colectomy in a patient who has colon cancer and ulcerative colitis. Nonetheless, the excellent results reported by Dr. Fong and the group from Memorial Sloan-Kettering indicate that there is indeed a role for liver resection in this setting.

I have three questions I'd like to ask.

First of all, patients with a viral etiology for their cirrhosis appear less likely to undergo a lobectomy at the time of resection compared to patients with alcoholic cirrhosis, although tumor size seemed to be relatively equivalent. Would you please comment as to whether this was related to the fact that those who had the viral hepatitis as a group had more advanced hepatocellular dysfunction, or perhaps some other explanation?

Secondly, given the expanding indications for offering antiviral therapy to patients with hepatitis C and cirrhosis and the supposition that this may indeed retard the development of hepatocellular cancer, are you recommending that postresection your patients with hepatitis C receive antiviral therapy in the form of ribavirin plus or minus interferon, or perhaps some other strategy?

And, finally, small prospective studies from both Milan and Barcelona have shown that cirrhotic patients with Stage 1 and Stage 2 liver cancer who undergo a total hepatectomy and liver transplantation show survival rates which are indistinguishable from those patients who have cirrhosis without a malignancy. The fact that long-term survival in these series exceed 70% to 75% has resulted in recent changes to our national organ allocation system, in which patients who have small liver cancer have priority for receiving an organ beyond what is afforded those who have cirrhosis and no tumor.

So my question is, even though you do not perform liver transplantation in your center, how do you decide in patients who have Stage 1 or 2 cancer whether to recommend a standard resection or liver transplantation?

DR. JEFFREY A. NORTON (San Francisco, California): I didn't see the paper, but I did see in the abstract that the mortality in patients with hepatitis C was 20% operative mortality. And I recently, because I'm at the VA now in San Francisco, am doing a lot of similar patients in liver surgery. And we have seen a higher incidence of mortality in hepatitis C as well.

So my question is really, is that a different operative mortality even in patients with good Child's classification? In hepatitis C, in my experience, they have had a worse outcome, and I can't really explain it. But the data that you present seemed to imply that as well, and I wish you would comment on that.

DR. OSAMA A. GABER (Memphis, Tennessee): I think that the questions that were asked by the previous discussants, I am very prudent to try to refrain because it is very clear that the definition of cirrhosis and the degree of liver failure should be disassociated when discussing this problem of hepatocellular carcinoma. Because in centers like ours where we do both the resections and the transplantation, clearly patients with Child-Pugh class 4 or 5 would not be candidates for the transplant if the resection can be easily done.

And, clearly, from your results—and I think it is something that all of us need to emulate—you can do these resections with very low morbidity and mortality. So I think that the issue is, and what Dr. Klein had indicated, is the survival of patients with small tumors after transplantation is excellent. So the question becomes really, how do you then divide the patients into resectable *versus* nonresectable?

I notice that you have a lot of patients that you didn't consider for resection, you didn't even take to the operating room, and I wonder how many of those were the patients that had a Child-Pugh class of 8 or 9. And were these patients then referred to transplantation—how many of them did you refer to transplantation? Because I think that it is very important to remember that transplantation does play a role in these patients, but it is in the patients with liver failure rather than just anatomic cirrhosis.

DR. YUMAN FONG (Closing Discussion): Starting off with Dr. Bolton's questions: first of all, he asked the definition of cirrhosis. On the resected patients, it's easy. It is a bridging fibrosis and inflammation in the pathology. On the nonoperated patients, it is usually radiologic criteria that we use, as well as biochemical criteria.

He asked how many of our patients presented asymptomatic from screening programs. Well, there are very few screening programs around the country, and the patients that are presenting with asymptomatic disease are generally those that are found to have changes in liver function tests on routine physicals, found to have viral hepatitis, have been followed by a hepatologist and then come to see us through the hepatologist who has been following the alpha-fetoprotein levels. That's why the cirrhotic patients actually had smaller tumors, because patients are getting fairly good care in the New York tri-state area. But still, that only amounted to about 10 to 15% of the patients. Most of them did not present from any sort of screening program.

The discussants asked about the size of resection as related to outcome, whether the patients with cirrhosis with large resections did poorly. On the contrary, patients with the cirrhosis that had three, trisegmentectomies, generally had huge tumors. And we are removing very little functional liver in those patients, and it really is the amount of functional liver removed that translates to poor perioperative outcome. And by and large, those patients had large resections for big tumors and did quite well.

In fact, in the cirrhotic patients, this is the patient population that we are willing to do wedge resections and nonanatomic resections, contrary to what we do in metastatic colon cancer or other cancers where we believe such resections to be bad cancer operations, so that we could preserve as much functioning liver parenchyma as possible.

Dr. Klein asked about the antiviral therapy after resection. We are not routinely sending patients for antiviral therapy because our local gastroenterologists do not believe that once patients have developed cirrhosis, that they are not strong believers in ribavirin and interferon, although in my mind that makes a tremendous amount of sense—not only for ribavirin and interferon, but for retinoids, for Cox-II inhibitors, because this is an ongoing inflammatory process. And for patients with hepatitis C, we know that the incidence of cancer, once patients develop cirrhosis, is about 5% per year. Therefore, developing second primaries or presence of multifocal disease that we haven't detected yet is very high. So screening and additional antiinflammatories should be considered, but should be considered in the context of clinical trials. And here is another area where a multicenter trial in this country should be set up so that we can go study this question in an academically feasible and fruitful way.

Staging of patients: most of our patients are not referred for a transplant, though most of the patients that were not explored for surgery had poor liver function, but most of them were also found to have macroscopic portal vein involvement and, clearly, half the patients were over age 65. Many factors led to our not believing them to be transplant candidates, but it is also a matter of referral pattern. In New York City, if a gastroenterologist sees a patient that he believes is a transplant candidate, usually the patient ends up at Mt. Sinai or NYU for transplant consideration. And those that are thought to be partial hepatectomy candidates come to see us.

Dr. Norton's question about hepatitis C and perioperative outcome: the reason I did not comment specifically on that is because there were only 10 patients with just hepatitis C, and two of them died postoperatively. And it is too small a number for me to definitively make any conclusions. My bias is that the hepatitis C patients do more poorly but, again, that's why we need a big epidemiologic study that is multicenter that allows us to address these questions.