Underlying Liver Disease, Not Tumor Factors, Predicts Long-term Survival After Resection of Hepatocellular Carcinoma

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Hypothesis: A subset of patients can be identified who will survive without recurrence beyond 5 years after hepatic resection for hepatocellular carcinoma (HCC).

Design: A retrospective review of a multi-institutional database of 591 patients who had undergone hepatic resection for HCC and on-site reviews of clinical records and pathology slides.

Setting: All patients had been treated in academic referral centers within university-based hospitals.

Patients: We identified 145 patients who had survived for 5 years or longer after hepatic resection for HCC.

Main Outcome Measures: Clinical and pathologic factors, as well as scoring of hepatitis and fibrosis in the surrounding liver parenchyma, were assessed for possible association with survival beyond 5 years and cause of death among the 145 five-year survivors.

Results: Median additional survival duration longer than 5 years was 4.1 years. Women had significantly longer median additional survival durations than did men (81 months vs 38 months, respectively, after the 5-year mark) (P=.008). Surgical margins, type of resection, an elevated preoperative α-fetoprotein level, and the presence of multiple tumors or microscopic vascular invasion had no bearing on survival longer than 5 years. However, patients who survived for 5 years who also had normal underlying liver or minimal fibrosis (score, 0-2) at surgery had significantly longer additional survival than did patients with moderate fibrosis (score, 3-4) or severe fibrosis/cirrhosis (score, 5-6) (P<.001).

Conclusions: Death caused by HCC is rare beyond 5 years after resection of HCC in the absence of fibrosis or cirrhosis. The data suggest that chronic liver disease acts as a field of cancerization contributing to new HCC. These patients may benefit from therapies directed at the underlying liver disease.

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Hepatocellular carcinoma (HCC) is one of the most common forms of cancer worldwide.1 Although the incidence of HCC in the United States is relatively low (<15 300 new cases each year), the incidence has increased throughout the last decade.1,2 More patients with HCC are being offered the option of resection because of improved methods of early detection of HCC, including α-fetoprotein (AFP) measurements and ultrasonography in patients with cirrhosis1,4 and improved patient selection, perioperative management, and surgical technique.5 Unfortunately, however, many patients do not benefit from hepatic resection for HCC because of recurrent disease within the first few years after surgery. Tumor-related factors known to predict recurrence and decrease survival duration include the presence of vascular invasion and large or multiple tumors.6,7

More controversial is the effect of chronic liver disease (cirrhosis) on outcome. Several studies have shown that the presence of underlying liver disease influences the survival duration of patients undergoing hepatic resection for HCC6,9 and that cirrhosis may predispose patients to multi-centric hepatocarcinogenesis.10 In 2 reports that included mainly patients with Child-Pugh class A cirrhosis, the presence of cirrhosis did not affect survival in multivariate analyses.11,12 None of these studies, however, provided a systematic analysis of the histopathologic state of the underlying liver disease (hepatitis activity and fibrosis stage).

The goal of this study was to identify the clinical factors, tumor factors, and underlying liver disease factors that predict further survival in patients who have
PATIENTS AND METHODS

A multi-institutional database of patients who underwent complete hepatic resection for any type of HCC between 1980 and 1995 was reviewed. All clinical records were reviewed on-site (D.M.N. and J.N.V.) with the assistance of translators with specialized hepatobiliary training if needed. Resections were performed at one of the following centers: The University of Texas M.D. Anderson Cancer Center (Houston), The University of Florida Hospitals (Gainesville), The Mayo Clinic (Rochester, Minn), Hôpital Beaujon (Paris, France), or Kyoto University Hospital (Kyoto, Japan).

Of the 591 patients in this database, we identified 145 (25%) who had survived for at least 5 years from the time of the resection. These 145 patients constituted the study population. Causes of death were available for all of the patients who died after the 5-year mark. Clinical factors investigated were age, sex, preoperative AFP level, and type of resection (removal of 1 lobe or more vs less than 1 lobe as defined elsewhere.14,15) Hepatitis B serology status was recorded, but hepatitis C could not be evaluated because many of the patients were treated before hepatitis C serology tests became available. All pathology slides were reviewed by 1 hepatobiliary pathologist (G.Y.L.). Pathologic variables included size of the surgical clearance (<10 mm vs ≥10 mm), tumor size (≤5 cm vs >5 cm), primary tumor classification according to the TNM classification system (T1-T4) in the American Joint Committee on Cancer manual, number of tumors (single vs multiple), and the presence of microvascular invasion. Underlying liver disease was assessed according to a previously described scoring system: fibrosis was scored as no or minimal fibrosis (0-2), moderate fibrosis (3-4), or severe fibrosis and cirrhosis (5-6). Necrosis and inflammatory changes characteristic of hepatitis were scored as mild (0-4), moderate (5-8), or severe (9-13).

Univariate and multivariate logistic regression analysis was initially performed to screen for important factors to explain the difference in the proportion of patients who survived fewer than 5 years vs those who survived 5 years or longer. The variables that were identified as statistically significant in univariate analyses were subsequently examined in multivariate logistic regression models. Further analysis was limited to the patients who survived 5 years or longer. The primary endpoint in the analysis was survival time after resection. The probability of survival was computed using Kaplan-Meier estimates. Long-term survival was reported as the number of months or years survived longer than 5 years after the surgery. The log-rank and Cox proportional hazards regression analyses were used to analyze the effects of clinicopathologic factors on long-term survival. To protect against overfitting the data in the multivariate Cox models, the number of candidate predictors for each multivariate model considered was constrained to approximately one tenth the number of events (deaths).16 Continuous predictors were dichotomized by using their medians or means as cutoff values. Associations between the clinicopathologic factors and fibrosis or hepatitis scores were investigated by using the χ² test (asymptotic or exact inference as appropriate) and Fisher exact test. Data analysis was implemented using S-Plus Professional for Windows Networks (MathSoft Inc, Seattle, Wash, 1999), and StatXact 3 for Windows (Cytel Software, Cambridge, Mass). P values equal to or less than .05 were considered statistically significant.

RESULTS

Of the 145 five-year survivors, 49 were women and 96 were men. The median age of the patients at the time of surgery was 63 years (range, 19-84 years, mean±SD, 60.6±12.0 years). The 10-year survival rate for these patients was 44% (95% confidence interval [CI], 33.4-60.6±12.0 years). The 10-year survival rate for these patients was 44% (95% confidence interval [CI], 33.4-60.6±12.0 years). The 10-year survival rate for these patients was 44% (95% confidence interval [CI], 33.4-60.6±12.0 years). The 10-year survival rate for these patients was 44% (95% confidence interval [CI], 33.4-60.6±12.0 years). The 10-year survival rate for these patients was 44% (95% confidence interval [CI], 33.4-60.6±12.0 years). The 10-year survival rate for these patients was 44% (95% confidence interval [CI], 33.4-60.6±12.0 years). The 10-year survival rate for these patients was 44% (95% confidence interval [CI], 33.4-60.6±12.0 years).

Univariate logistic regression analysis, tumor size (P=.008), AFP level (P=.01), microvascular invasion (P=.02), and surgical margins (P=.002) were simultaneous predictors of a difference in survival duration between those who survived fewer than 5 years and those who survived 5 years or longer. After adjusting for tumor size, surgical margins, and microvascular invasion, the estimated odds ratio (OR) of survival longer than 5 years was lower for patients with AFP levels higher than 28 µg/L (OR, 0.53 [95% CI, 0.33-0.86]) than for patients with AFP levels lower than or equal to 28 µg/L. After adjusting for tumor size, AFP level, and microvascular invasion, patients with surgical margins 10 mm or greater had an OR of 2.14 (95% CI, 1.32-3.47) for survival beyond 5 years compared with patients with surgical margins less than 10 mm. After adjusting for AFP level, microvascular invasion, and surgical margins, tumor size greater than 30 mm was associated with lower OR of surviving longer than 5 years (OR, 0.34 [95% CI, 0.23-0.68]). After adjusting for AFP level, surgical margins, and tumor size, the presence of microvascular invasion was associated with 0.35 (95% CI, 0.34-0.92) OR for surviving longer than 5 years after resection.
Among the 145 patients who survived 5 years or longer, neither preoperative AFP level (higher or lower than the median of &lt;28 µg/L; range, 0 to 49,380 µg/L), age ( &lt;60 or &ge;60 years), nor hepatitis B serology status predicted a survival duration longer than 5 years (Table 1). Hepatitis C serology could not be evaluated because the study included many patients who were treated prior to the advent of hepatitis C serologic testing. Sex, however, did predict survival; women had a median additional survival period of 81 months compared with only 38 additional months for men (P = .008). Patients who underwent resection of at least 1 lobe had a median additional survival duration of 83 months vs 41 months for patients who had less extensive resections.

This apparent difference, however, was not statistically significant (P = .15).

With regard to pathologic variables, tumor size was the only predictor of survival. Patients with large tumors ( &ge;5 cm) survived longer than did patients with smaller tumors (median additional survival time, 81 months vs 38 months, respectively; P = .03). Survival longer than 5 years was not influenced by primary tumor classification (T1-T4) (P = .25), number of tumors (P = .98), the presence of microscopic vascular invasion (P = .98), or the adequacy of resection margins (median additional survival for those margins with &lt;10 mm was 62 months vs 41 months for those with margins &ge;10 mm; P = .19) (Table 1). Overall and HCC-specific Kaplan-Meier survival curves for all patients are shown in Figure 1, and those for patients stratified by fibrosis score are shown in Figure 2. Overall survival was significantly better in patients with a fibrosis score of 0 to 2 than in those with a score of 3 to 4 (P &lt; .001) or those with a score of 5 to 6 (P &lt; .001) and not significantly different between those with a fibrosis score of 3 to 4 and those with a score of 5 to 6 (P = .51). When only HCC-related deaths were considered (n = 32), survival was again significantly different between patients with a fibrosis score of 0 to 2 and those with a score of 3 to 4 (P &lt; .001) or 5 to 6 (P &lt; .001) but not between patients with a fibrosis score of 3 to 4 and those with a score of 5 to 6 (P = .76). Patients with no or mild hepatitic activity (score, 0-4), survived longer (62 months) than did patients with moderate hepatitic activity (score, 5-8; 30 months), or patients with severe hepatitic activity (score, 9-13; 49 months) (P = .04).

Table 2 presents the clinicopathologic characteristics of the patients stratified according to fibrosis score (0-2 vs 3-6). Patients with a fibrosis score of 0-2 were more likely to be women (P = .008), to have undergone resection of 1 lobe or more (P = .02), and to have had large tumors (P &lt; .001) and low hepatitis scores (P &lt; .001).

The multivariate Cox proportional hazards model indicated that sex, age, and fibrosis score were simultaneous predictors of survival. After adjusting for age and fibrosis score, men had a higher risk of death than women (hazard ratio [HR], 2.07; 95% CI, 1.05-4.05; P = .04). After adjustments for sex and fibrosis score, patients aged 60 years or older had a greater risk of death than younger patients (HR, 1.83; 95% CI, 1.03-3.25; P = .04). After adjusting for age and sex, patients with a fibrosis score of 3 to 6 had a higher risk of death than those with a score of 0 to 2 (HR, 6.29; 95% CI, 2.14-16.39; P &lt; .001). The Hepatitis activity score could not be considered in the Cox model because few patients (n = 9) had high hepatitis scores among the subset with a fibrosis score of 0 to 2. However, a hepatitis activity score was negatively associated with survival duration (P = .04) and positively associated with fibrosis score (P &lt; .001).

Table 3 presents causes of death according to fibrosis score for the 52 patients who died during the study period. Only 3 patients with fibrosis scores of 0 to 2 (7%) died of HCC compared with 10 patients with scores of 3 to 4 (27%) and 19 patients with scores of 5 to 6 (31%). Progression of chronic liver disease accounted for only 4 (7%) of 52 deaths in this study and all were patients

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**Table 1. Clinicopathologic Features**

| Clinicopathologic Feature | Patients, No. (%) | Median Survival, † mo | P‡ |
|---------------------------|-------------------|----------------------|----|
| Age, y                    |                   |                      |    |
| &lt;60                    | 58 (40)           | 51                   | .14|
| &ge;60                    | 87 (60)           | 38                   |    |
| Sex                       |                   |                      |    |
| Female                    | 49 (34)           | 81                   | .008|
| Male                      | 96 (66)           | 38                   |    |
| α-Fetoprotein level, µg/dL|                   |                      |    |
| &lt;28                     | 64 (44)           | 40                   | .91|
| &ge;28                    | 61 (42)           | 49                   |    |
| Hepatitis B serology      |                   |                      |    |
| Negative                  | 83 (57)           | 49                   | .58|
| Positive                  | 49 (34)           | 30                   |    |
| Type of resection         |                   |                      |    |
| &lt; Lobectomy             | 76 (52)           | 41                   | .15|
| &ge; Lobectomy             | 69 (48)           | 83                   |    |
| T classification§          |                   |                      |    |
| T1                        | 19 (13)           | 60                   | .25|
| T2                        | 65 (45)           | 41                   |    |
| T3                        | 43 (30)           | 31                   |    |
| T4                        | 17 (12)           | 24                   |    |
| No. of tumors             |                   |                      |    |
| 1                         | 109 (75)          | 50                   | .98|
| &gt;1                      | 34 (23)           | 38                   |    |
| Tumor size, cm            |                   |                      |    |
| ≤5                        | 87 (60)           | 38                   | .03|
| &gt;5                      | 58 (40)           | 81                   |    |
| Microvascular invasion    |                   |                      |    |
| No                        | 53 (37)           | 50                   | .98|
| Yes                       | 91 (63)           | 33                   |    |
| Margin, mm                |                   |                      |    |
| &lt;10                     | 45 (31)           | 62                   | .19|
| &gt;10                     | 75 (52)           | 41                   |    |
| Hepatitis activity score  |                   |                      |    |
| 0-4                       | 73 (50)           | 62                   | .04|
| 5-8                       | 45 (31)           | 30                   |    |
| 9-13                      | 18 (12)           | 12                   |    |
| Fibrosis/cirrhosis score  |                   |                      |    |
| 0-2                       | 46 (32)           | 60                   | &lt;.001|
| 3-4                       | 37 (26)           | 30                   |    |
| 5-6                       | 62 (43)           | 29                   |    |
| Fibrosis/cirrhosis score  |                   |                      |    |
| 0-2                       | 46 (32)           | 61                   | &lt;.001|
| 3-6                       | 99 (69)           | 26                   |    |

* Percentages may not add up to 100% because of missing data.
† In addition to 5 years postresection.
‡ Log-rank test.
§ TNM staging system according to the American Joint Committee on Cancer manual.

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References:

1. **Table 1.** clinicopathologic features

2. **Table 2.** clinicopathologic characteristics of the patients stratified according to fibrosis score (0-2 vs 3-6).

3. **Table 3.** causes of death according to fibrosis score for the 52 patients who died during the study period.

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with fibrosis scores of 5 to 6. Table 4 presents causes of death according to hepatitis activity scores. Thirteen (41%) of 32 deaths from HCC occurred in patients with low hepatitis activity scores (0 to 4).

**COMMENT**

We developed a multi-institutional database of 591 patients who had undergone hepatic resection for HCC, from which we identified 145 patients (25%) who had survived at least 5 years. The large number of patients, the extended follow-up, and the wide spectrum of liver disease provided unique insight into the role of underlying liver disease in long-term prognosis after resection of HCC. Patients with minimal or no fibrosis (score, 0-2) had excellent additional survival time and were unlikely to die of HCC. Patients with moderate or severe fibrosis/cirrhosis, however, were still at increased risk of death of HCC after 5 years.

Factors predicting recurrence of HCC after resection have been documented. Fuster et al\textsuperscript{17} showed that recurrence rates within the first 3 years after resection were higher among patients with large tumors (\textgtr 3 cm), vascular invasion, and multiple tumors. Other large single- or multi-institution studies have indicated that large tumor size\textsuperscript{3,18-20} vascular invasion\textsuperscript{6,11,12} high preoperative AFP level, and multiple tumors\textsuperscript{21} predicted a worse outcome. Among the patients selected for our study, tumor factors typically associated with impaired survival after resection of HCC did not predict an adverse outcome beyond 5 years.

Previous studies have noted the effect of underlying liver disease on long-term survival after resection of HCC. Shirabe et al\textsuperscript{22} showed that patients with better liver function, demonstrated by preoperative indocyanine green retention, were more likely to live 10 years after surgery than were patients with poor liver function. Yamanaka et al\textsuperscript{23} found that patients with hepatitis C–related chronic liver disease were more likely to develop HCC 3 or more years after resection. These authors concluded that the “carcinogenic potential” of the chronically damaged liver was responsible for the appearance of these new lesions.

There are 2 possible explanations for the adverse effect of existing fibrosis on additional survival after 5 years. First, patients with advanced fibrosis or cirrhosis are more likely to develop recurrence of the primary HCC and subsequently die of the disease; second, fibrosis and cirrhosis may represent a field of cancerization associated with the development of a new metachronous HCC after resection. Kosuge et al\textsuperscript{24} found that HCC recurrence rates
HCC would begin developing new HCCs, while those without cirrhosis continued to die of HCC. The multivariate analysis indicates sex as an independent risk factor of survival, suggesting that factors other than fibrosis such as estrogen status and tobacco or alcohol abuse may contribute to the difference in the risk for HCC.

We found that long-term prognosis was better among those who had tumors greater than 5 cm; 80% of large tumors were found in patients with moderate or severe fibrosis or cirrhosis (P = .008). The multivariate analysis indicates sex as an independent risk factor of survival, suggesting that factors other than fibrosis such as estrogen status and tobacco or alcohol abuse may contribute to the difference in the risk for HCC.

Our finding that women with HCC survived longer than men after the first 5 years was also observed in the recent National Cancer Database report on HCC, in which better encapsulation of tumors in women was cited as a possible reason for the better prognosis. In our study, women constituted 50% of the patients with minimal or no fibrosis but only 26% of patients with moderate or severe fibrosis or cirrhosis (P = .008). This observation is consistent with findings from a recent study that found that the male-female ratio for occurrence of HCC in the absence of fibrosis was 1:1 but, for occurrence of HCC in patients with fibrosis or cirrhosis, it was 3:1. The multivariate analysis indicates sex as an independent risk factor of survival, suggesting that factors other than fibrosis such as estrogen status and tobacco or alcohol abuse may contribute to the difference in the risk for HCC.

There is molecular evidence that second primary tumors are found in the presence of cirrhosis. Sakamoto et al studied a presumed recurrent HCC after resection in a patient with chronic active hepatitis B and found that hepatitis B virus DNA integration in the 2 tumors was distinctly different, indicating their differing clonal origin. The theory of field cancerization has been proposed to characterize the pathologic and genotoxic changes found in tissues near tumors. These changes are often the result of “preconditioning” by various carcinogenic agents.

Our study, detailed histologic assessment of underlying liver disease indicates that fibrosis may be a marker of risk associated with field cancerization in HCC.
both large tumors and fibrosis scores of 0 to 2. There seems to be a small subset of patients with HCC who have large solitary tumors that in the absence of vascular invasion have a uniquely favorable prognosis. This subset has been previously described and we have been able to identify this group of patients within our database. In 1981, Knodell et al20 proposed a histology activity index to quantify the extent of necrosis and inflammation associated with hepatitis and the structural changes associated with portal fibrosis in patients with chronic active hepatitis. In 1995, Ishak et al13 modified this index to separately score hepatitis (score, 0-13) and fibrosis (score, 0-6). In our study, the presence of fibrosis correlated most strongly with the risk of continued hepatocarcinogenesis. Low hepatitis activity scores do not predict patients at risk for HCC as liver fibrosis scores do. Among 32 deaths of HCC, only 3 (9%) occurred in patients with low fibrosis scores, while 13 (41%) occurred in patients with low hepatitis scores (P = .06). Further, no or minimal hepatitis activity was noted in 36% of patients with a score of 3 to 6 at risk for HCC (Table 2). These findings validate the use of 2 separate scorings in chronic liver disease.

In the absence of effective adjuvant chemotherapy, the current treatment recommendation after resection of HCC is observation, with the options of repeated resection or, rarely, transplantation. In our study, late deaths from progression of chronic liver disease were rare (7%), and most of the deaths (51%) were from HCC. To prevent relapse, the ideal treatment after resection should combine adjuvant chemotherapy to avert recurrence and chemopreventive therapy to prevent new HCC. Recent studies show promise for the chemoprevention of HCC in patients with chronic active hepatitis. In a controlled study, Nishiguchi et al31 showed that interferon alfa could be effective in the prevention of new HCC in patients with hepatitis who were at risk for HCC. Another randomized study by Muto et al32 showed a 28% reduction in the incidence of new HCC in patients who had been treated with the acyclic retinoid polypropenoic acid after definitive treatment of HCC by resection or percutaneous ethanol injection. These preliminary studies support the investigation of novel agents in chronic liver disease and systematic scoring of underlying liver disease. Based on our findings, patients with a fibrosis score of 3 to 6 should undergo close long-term surveillance after resection of HCC. If possible, they should be enrolled in chemoprevention trials since they are at continued risk of dying of HCC.

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22. William C. Chapman, MD, Nashville, Tenn: In this retrospective study, the authors assess factors associated with further long-term survival in a cohort of 145 patients who have already survived 5 years following liver resection for hepatocellular carcinoma (HCC). Their analysis suggests that surgical margins, the level of AFP elevation, tumor multifocality, and microscopic vascular invasion, among other factors, are unassociated with long-term survival in this group. Instead, fibrosis or cirrhosis appears to be the most important factor associated with tumor recurrence and death.

23. I do have difficulty interpreting some of these data that I hope the authors can clarify. By not including outcomes during the first 5 postoperative years, we have to speculate somewhat on the conclusions of this study. For example, is there a bias introduced because patients with unfavorable pathologic features have already died within the first 5 years of follow-up? Part of this is semantics in terms of declaring that these factors are unassociated with long-term survival. If tumor factors were to have caused patients to die in the first 5 years, then can we accept the conclusion of this paper that they are not important in long-term survival? If I don’t think so. So, what I think the authors are trying to tell us is that if patients survive 5 years following liver resection, then chances are they’re cured from their original tumor and the greatest risk at this point is that a second primary tumor will develop and this is most likely to occur in patients with active hepatitis, fibrosis, and cirrhosis. While sophisticated studies can help to distinguish second primary tumors from recurrent tumors, unfortunately we don’t know the status of tumors in this regard in the current study. A second potential unknown variable in this multicenter study involves the inclusion of Eastern and Western patients in the same data set. We know that the tumor biology and long-term outcomes appear to be different in these 2 patient groups, with Eastern patients having a more favorable outcome than Western patients. This may be related to screening programs and tumor resection at an earlier stage of the disease.

24. I would agree strongly with the authors that our current HCC staging system is flawed and does not predict long-term outcomes in patients with HCC. The status of the non–tumor-bearing liver does need to be incorporated into our pathologic staging system. Dr Vauhney is heading up this effort within the joint commission (AJCC) and perhaps he can update us on how this is likely to be incorporated.

25. I have 3 questions for the authors. (1) Could you tell us about the variables of importance during the first 5 years for patients in this study group? Did pathologic variables, including surgical margins, vascular invasion, and tumor stage, make a difference in survival during this period? (2) Please tell us of the relative patients included from Japan compared with the United States and France, what were the pathologic features of this subgroup, was there a similar breakdown of pathologic staging, presence of hepatitis, fibrosis, and cirrhosis, and were similar procedures performed compared with the remainder of patients? (3) And finally, should we perform a preoperative liver biopsy of the non–tumor-bearing liver prior to liver resection to help us select treatment strategies? In particular, in patients with more advanced fibrosis or cirrhosis, should we consider liver transplantation instead of resection? Outcomes following liver transplantation in properly selected patients with cirrhosis and early stage HCC have now been demonstrated to be equivalent to patients with similar underlying liver disease but without malignancy, with 5-year survival rates of greater than 70%. You’ve demonstrated to us that a problem is the field effect and it would seem to me that the best method for eliminating the field effect is total hepatectomy. There are obvious issues that must be resolved, including donor waiting times and organ availability, but I would appreciate your thoughts on when you consider liver transplantation in your patients with HCC.

26. Theodore X. O’Connell, MD, Los Angeles, Calif: I wonder if the long-term effects you see in the difference in survival have anything to do with the patient originally having a tumor or not having a tumor. That is, is it simply due to their underlying cirrhosis and chronic active hepatitis that they die of progressive liver disease or do they develop completely new or unrelated tumors? Another way to ask this question is, do you have any data, any comparisons, of long-term survival in patients who did not have tumor but who do have cirrhosis, essentially adding another arm to the study? Do they seem exactly like your patients with tumor and cirrhosis? I wonder if the long-term effects you see in the difference in survival have anything to do with the patient originally having a tumor or not having a tumor. That is, is it simply due to their underlying cirrhosis and chronic active hepatitis that they die of progressive liver disease or do they develop completely new or unrelated tumors? Another way to ask this question is, do you have any data, any comparisons, of long-term survival in patients who did not have tumor but who do have cirrhosis, essentially adding another arm to the study? Do they seem exactly like your patients with tumor and cirrhosis? I wonder if the long-term effects you see in the difference in survival have anything to do with the patient originally having a tumor or not having a tumor. That is, is it simply due to their underlying cirrhosis and chronic active hepatitis that they die of progressive liver disease or do they develop completely new or unrelated tumors? Another way to ask this question is, do you have any data, any comparisons, of long-term survival in patients who did not have tumor but who do have cirrhosis, essentially adding another arm to the study? Do they seem exactly like your patients with tumor and cirrhosis?
that, as has been discussed by others, each of these hepatocellular carcinoma syndromes are going to behave differently. Hepatitis C is clearly going to behave, I believe, in a much different fashion with patients having multifocal disease and long-term problems than may have been the case with the other types or other associated hepatocellular carcinomas. And finally, the new serology for hepatitis C has been available since 1992, so that would mean that all resections since 1987 who had 5-year survivals should give us some estimate of what percentage of these patients in fact had hepatitis C. So, I'm wondering again if the author could share with us the hepatitis C component in this whole population I suspect that may be the population of patients who continued to die after the 5-year observation.

Robert C. G. Martin II, MD, New York, NY: I have a couple of questions. Recent publications have classified these patients with other classifications also, primarily the Childs-Pugh and Okuda class. Did you break those down at all and were those a predictor at all in 5-year survival? In addition to that, in your discussion of chemotherapeutic agents, would you update us or discuss some of the recent prospective randomized trials of the use of I-131 and also of the use of retinoids to prevent second primary tumors.

Joseph Buell, MD, Cincinnati, Ohio: Some of the larger transplant centers such as Mount Sinai and the University of Chicago, noted for hepatic transplantation for hepatitis C, have discovered up to a 20% to 40% incidence of undiagnosed HCCs at the time of total hepatectomy. And with the increase of hepatitis C in the overall population and the probably forthcoming increased incidence of hepatitis C and hepatoma, we should use your data, which is both interesting and excellent in determining these patients who might be best served by transplantation and total hepatectomy.

In our experience at the University of Chicago, we noted only 4 recurrences out of approximately 52 liver transplantations for tumor. So, these data can be used to identify patients who might forego resection, and undergo TACE therapy or chemoembolization, a therapy that we've adopted at the University of Cincinnati and Henry Bismuth has adopted for patients undergoing total hepatectomy and transplantation with the use of marginal organs, for example, organs from older patients or split liver transplantation. Incorporating these organs into the donor pool, we can provide transplantation to patients who would not normally receive an organ. So I ask what your opinion might be of the TACE therapy or chemoembolization and potential use of marginal organs to provide therapy.

Dr Vauthey: I will provide answers in aggregate for several questions. I'd like to emphasize the purpose of this database first. We have established this database using uniform definitions across nations, across continents, hopefully to better understand hepatocellular carcinoma (HCC) and the broad spectrum of associated chronic underlying liver disease.

To answer the question as to the survival of the group that did not make the 5-year mark, the factors affecting survival in that group were the usual factors of survival for HCC. Vascular invasion was number 1. Other factors were number of tumor and size of tumor. There was also an effect of underlying liver disease on overall survival for patients with fibrosis scores of 5 and 6.

As to a comparison between Eastern and Western patients, we have done that within the main database but not for survivors after 5 years to avoid the statistical limitation of small numbers. In Japan, patients present with smaller tumors as a result of ultrasonographic screening of chronic liver disease. The disease is strongly associated with viral hepatitis, as you know, and underlying liver disease is more severe. We have data on hepatitis serology on 230 patients that were operated after 1991. And up to 85% of the patients in Japan have hepatitis positive serology. B only, C only, or a combination of both. In the West, the disease is less strongly associated with viral hepatitis and only about 50% of the patients have positive hepatitis serology for B or C or both. Interestingly, no difference in survival was noted between Eastern or Western patients or with regard to hepatitis serology status.

The third question was regarding what we're going to do with the data and whether we're going to do a preoperative liver biopsy to make our decision regarding transplantation. In my opinion, there should be no competition between transplantation and resection in this disease. There are patients who are clearly candidates for transplantation. There are defined criteria for this: if a patient has HCC, and if the tumor is 5 cm in size or less and single or if there are up to 3 tumors, up to 3 cm, and there is advanced underlying liver disease, this patient would be referred to a transplant center. On the other hand, there is a large group of patients who still need to be considered for resection, and in fact the vast majority of the patients go to resection since there are only about 100 liver transplantations performed in this country per year for malignant disease. So, we're left with a large pool of patients, and we have to decide about treatment.

The effect of cirrhosis is undeniable. It cannot be dissected out easily from the data before 5 years because of the strong adverse effect of tumor occurrence on survival. However, looking at the patients beyond 5 years, a fibrosis score of 3 to 6 is a predominant factor driving the prognosis and the data strongly suggest that these are new HCCs. Preliminary controlled studies have suggested a benefit from treatment with interferon and retinoid for the chemoprevention of new HCC. I think it is time that hepatologists and medical oncologists and surgeons get together and investigate this further in a multidisciplinary fashion. And this study indicates the need for this and establishes fibrosis as a marker of the ongoing risk for HCC.

The issue of vascular invasion: It is hard to predict whether there is vascular invasion or no vascular invasion in these patients preoperatively unless there is gross vascular invasion. If there is vascular invasion of the main branch of the portal vein, however, in a young patient, we would still resect the disease if it can be completely resected because there may be a small subset of patients that can benefit from resection.

As to the cause of cirrhosis in these patients, besides hepatitis serology and hemochromatosis, this can be a very subjective issue and was not included in the analysis. As to the number of patients with Child-Pugh B cirrhosis, it accounted for only about 10% of patients with cirrhosis and did not affect prognosis.