PAPER

Critical Appraisal of the Clinical and Pathologic Predictors of Survival After Resection of Large Hepatocellular Carcinoma

Timothy M. Pawlik, MD, MPH; Ronnie T. Poon, MD; Eddie K. Abdalla, MD; Daria Zorzi, MD; Iwao Ikai, MD; Steven A. Curley, MD; David M. Nagorney, MD; Jacques Belghiti, MD; Irene Oi-Lin Ng, MD; Yoshio Yamaoka, MD; Gregory Y. Lauwers, MD; Jean-Nicolas Vauthey, MD; for the International Cooperative Study Group on Hepatocellular Carcinoma

Hypothesis: A subset of patients with hepatocellular carcinoma (HCC) with a diameter of 10 cm or larger may benefit from hepatic resection.

Design: Retrospective study of a multi-institutional database.

Setting: Five major hepatobiliary centers.

Patients: We identified 300 patients who underwent hepatic resection for HCC 10 cm or larger.

Main Outcome Measures: Clinical and pathologic data were collected, and prognostic factors were evaluated by univariate and multivariate analyses. Patient survival was stratified according to a clinical scoring system and pathologic T classification.

Results: The perioperative mortality rate was 5%. At a median follow-up of 32 months, the median survival was 20.3 months, and the 5-year actuarial survival rate was 27%. Four clinical factors—α-fetoprotein of 1000 ng/mL or higher, multiple tumor nodules, the presence of major vascular invasion, and the presence of severe fibrosis—were significant predictors of poor survival (all $P<.05$). Patients were assigned a clinical score according to the following risk factors: 1, no factor; 2, one or two factors; or 3, three or four factors. On the basis of the clinical score, patients could be stratified into only 2 distinct prognostic groups: no factor (score of 1) vs 1 or more factors (score of 2 or 3) ($P<.001$). In contrast, when patients were stratified according to pathologic T classification, 3 distinct groups were identified: T1 vs T2 vs T3 and T4 combined ($P<.001$). Fifty-six percent of the patients with a clinical score of 2 and 20% of patients with a clinical score of 3 actually had T1 or T2 disease on pathologic examination.

Conclusions: Patients with large HCCs should be considered for liver resection as this treatment is associated with a 5-year survival rate exceeding 25%. Clinical predictors should not be used to exclude patients from surgical resection because these factors do not reliably predict outcome.

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HEPATOCELLULAR CARCINOMA (HCC) is one of the most common malignancies worldwide. In many Eastern countries, patients with HCCs are often diagnosed as having small tumors because of the widespread implementation of multiple screening modalities.[1] Large HCCs—tumors with a diameter of 10 cm or larger—are, however, not uncommon, especially in regions in which screening is not routine.[2-4] In particular, the incidence of a large HCC is especially high in patients younger than 40 years.[5,6] A large HCC is a significant risk factor for intrahepatic and extrahepatic spread and is believed to decrease disease-free survival and overall survival.[3,7-9] Unfortunately, patients with large HCCs are generally not considered candidates for liver transplantation, percutaneous ethanol injection, transcatheter arterial chemoembolization, or radiofrequency ablation.[10-13] Hepatic resection, therefore, remains the only tenable treatment option for these patients. Resection of a large HCC, however, is a surgical challenge that can entail a greater operating time, blood loss, and risk of postoperative liver failure.[14,15]

Because of the increased difficulty involved in resecting a large HCC, as well as the perceived poor prognosis of patients with tumors exceeding a 10-cm diameter, reports of hepatic resection for a large HCC are limited.[2,15-21] The role of hepatic resection for a large HCC remains unclear. In the current study, using an international multi-institutional experience, we evaluated 300 patients with a large HCC who underwent surgical resection in an attempt to clarify the clinicopathologic factors that influence long-term prognosis.

Author Affiliations are listed at the end of this article.
Group Information: The authors of this article comprise the International Cooperative Study Group on Hepatocellular Carcinoma.

METHODS

Between April 1, 1981, and September 30, 2000, 300 patients with an HCC with a 10-cm or larger diameter underwent resection at the following 5 major hepatobiliary centers: The University of Texas M. D. Anderson Cancer Center, Houston; Mayo Clinic, Rochester, Minn; Beaujon Hospital, Paris, France; Kyoto University Graduate School of Medicine, Kyoto, Japan; and Queen Mary Hospital, Hong Kong, China. Tumor size was defined as the largest diameter of the tumor specimen. Patients with a tumor size 10 cm or larger are the topic of this study. Prior to surgery, all patients were evaluated with a baseline medical history and physical examination; serum laboratory tests; computed tomographic or magnetic resonance imaging scan of the abdomen and pelvis; and a chest radiograph. All patients with an HCC who underwent resection had no clinical, radiographic, or intraoperative evidence of extrahepatic disease at presentation.

The following data were collected for each patient: demographics; laboratory data (α-fetoprotein [AFP] level and hepatitis serologic test results); tumor histologic features, number, and location; operative details; disease status; date of last follow-up; and date of death. Data were recorded as clinical features, present or absent; age, younger than 60 years vs 60 years or older; AFP lower than 1000 ng/mL vs 1000 ng/mL or higher; and number of tumors, single vs multiple. Microscopic vascular invasion was defined as the presence of tumor emboli within the central vein, the portal vein, or large capsular vessels or involvement of the branches of the portal vein or the hepatic veins.[22,23] Major vascular invasion was defined as gross invasion of the right or left main branches of the portal vein or the hepatic veins.[24] Tumor grade was assessed using the nuclear grading scheme outlined by Edmondson and Steiner.[25] Grades 1 and 2 were considered low-grade HCC, and grades 3 and 4 were considered high grade. The degree of fibrosis was scored according to the classification of Ishak et al,[26] where Ishak 0 to 2 was no or minimal fibrosis; Ishak 3 to 4, incomplete bridging fibrosis; and Ishak 5 to 6, complete bridging fibrosis and nodules. Resection was classified as less than a hemihepatectomy (eg, segmentectomy or subsegmentectomy), hemihepatectomy, or extended hepatectomy (≥5 liver segments). Patients were pathologically staged according to the sixth edition of the American Joint Commission on Cancer (AJCC) staging manual[27] (**Table 1**). The clinical data and pathologic resection specimens were each reviewed on site by 2 sets of the investigators (R.T.P., D.M.N., and J.N.V., and I.O.N. and G.Y.L).

All data are presented as percentages of patients or the median value. Statistical analyses were performed using univariate tests (χ^2) to test for differences in variables with regard to survival. Factors that appeared to be significantly associated with survival were entered into a Cox proportional hazards model to test for significant effects while adjusting for multiple factors simultaneously. Actuarial survival was calculated using the Kaplan-Meier method. Differences in survival were examined using the log-rank test. $P<.05$ was considered statistically significant.

Table 1. AJCC/UICC Classification Scheme for HCC (Sixth Edition)*

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Solitary tumor without vascular invasion		
T2	Solitary tumor with vascular invasion or multiple tumors ≤5 cm in diameter		
T3	Multiple tumors >5 cm *or* tumor involving a major branch of the portal or hepatic vein(s)		
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum		
Stage grouping			
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIC	Any T	N1	M0
IV	Any T	Any N	M1
Fibrosis score (F)			
F0	Fibrosis score 0-4 (no fibrosis to moderate fibrosis)		
F1	Fibrosis score 5-6 (severe fibrosis to cirrhosis)		

Abbreviations: AJCC, American Joint Commission on Cancer; HCC, hepatocellular carcinoma; UICC, International Union Against Cancer.
*Adapted from Green et al, eds.[27]

RESULTS

Table 2 lists the clinical features of the 300 patients in the study. There were 222 men (74.0%) and 78 women (26.0%), for a male-female ratio of 2.8:1. The median patient age was 55 years (age range, 13-87 years). The preoperative liver function according to the Child-Pugh[28] classification was rated as Child-Pugh A in 241 patients and Child-Pugh B in 22 patients. A Child-Pugh classification was unavailable in 48 patients. This study included no patients with disease classified as Child-Pugh C as such patients were not offered resection. Most patients had solitary tumors (63.3%) and positive hepatitis B serologic test results (62.7%). The median preoperative AFP was 500 ng/mL (range, 2-2.2 million ng/mL). At the time of operation, the extent of hepatic resection was less than a hemihepatectomy in 122 patients, a hemihepatectomy in 141 patients, and an extended hepatectomy in 37 patients.

Recently the AJCC staging system was updated and simplified[22] (Table 1). The cut-off value for tumor size in the prognostic classification is 5 cm, and the influence of tumor size is limited to patients with multiple tumors. Another important feature of the new AJCC staging system is the provision of a separate reporting of fibrosis in every case of resected HCC. Patients with severe fibrosis-cirrhosis (Ishak 5 to 6 disease classification score, complete bridging fibrosis and nodules) have their disease scored as F1, whereas patients with moderate (Ishak 3 to 4 disease classification score, incomplete bridging fibrosis) or no or minimal fibrosis (Ishak 0 to 2 disease classification score) have their disease scored as F0.[27] Although patients were similarly distributed among the T1 and T2 subgroups, there was a slight predominance of patients in the T3 subgroup (Table 2). In contrast, only 29 patients (9.7%) had T4 disease. On final pathologic staging, 208 patients (69.3%) had some component of vascular invasion: 159 patients (53.0%) had microscopic vascular invasion, and 49 patients (16.3%) had major vascular invasion. Equal numbers of tumors were classified as low grade and high grade. The grade was unavailable for 3 patients. With regard to coexisting fibrosis, most patients (69.3%) had their disease scored as F0: 130 patients (43.3%) with Ishak 0 to 2 disease classification score and 78 patients (26.0%) with Ishak 3 to 4 disease classification score. Seventy-eight patients (26.0%) had severe fibrosis (Ishak 5-6 disease classification score) and had their disease scored as F1.

Fifteen patients died within 30 days of resection, for a perioperative mortality rate of 5.0%. At a median fol-

Table 2. Clinicopathologic Features of 300 Patients*

Variable	No. (%) of Patients
Age, y	
<60	189 (63.0)
≥60	111 (37.0)
Sex	
Female	78 (26.0)
Male	222 (74.0)
Child-Pugh classification[28]	
A	241 (80.3)
B	22 (7.3)
Unavailable	37 (12.4)
Hepatitis B status	
Negative	93 (31.0)
Positive	188 (62.7)
Unavailable	19 (6.3)
α-Fetoprotein level, ng/mL	
<1000	145 (48.3)
≥1000	122 (40.7)
Unavailable	33 (11.0)
Tumor No.	
Solitary	190 (63.3)
Multiple	110 (36.7)
Vascular invasion	
Absent	92 (30.7)
Present	
Microscopic	159 (53.0)
Major	49 (16.3)
Edmondson-Steiner grade[25]	
Low grade (I and II)	155 (51.7)
High grade (III and IV)	142 (47.3)
Unavailable	3 (1.0)
Degree of fibrosis, Ishak score[26]	
0-2	130 (43.3)
3-4	78 (26.0)
5-6	78 (26.0)
Unavailable	14 (4.7)
AJCC T category	
T1	67 (22.3)
T2	87 (29.0)
T3	117 (39.0)
T4	29 (9.7)
Type of surgical resection	
Less than a hemihepatectomy	122 (40.7)
Hemihepatectomy	141 (47.0)
Extended hepatectomy (≥5 liver segments)	37 (12.3)

Abbreviation: AJCC, American Joint Commission on Cancer.
*For a more detailed description of scoring, see the "Methods" section.

low-up of 32 months (range, 0.2-208 months), the median survival was 20.3 months (95% confidence interval [CI], 16.5-24.0 months) (**Figure 1**). The 1-, 3-, 5-, and 10-year overall survival rates were 64.9%, 36.7%, 26.9%, and 17.8%, respectively. The longest-living survivor was alive and disease free at 17.3 years of follow-up.

Statistical analysis revealed several factors that influenced survival. On univariate analysis, an AFP of 1000 ng/mL or higher, multiple tumor nodules, the presence of vascular invasion, and the presence of severe fibrosis were all significant predictors of poor survival. Patients with an AFP of 1000 ng/mL or higher had a median survival of 12.7 months, compared with 28.2 months for those with AFP lower than 1000 ng/mL ($P=.003$) (**Figure 2**A). Multiple tumors on presentation were also associated with a poor prognosis. Whereas patients with solitary tumors had a median survival of 29.8 months, those with multiple tumors had a median survival of 14.1 months ($P<.001$) (Figure 2B). Similarly, the presence of severe fibrosis and the presence of vascular invasion were powerful predictors of survival. Patients with severe fibrosis (F1) had a median survival of only 12.7 months compared with 24.0 months for patients classified as being F0 ($P<.001$). Both microscopic and major vascular invasion predicted poor survival (**Figure 3**). Patients with major vascular invasion had a median survival of only 9.1 months compared with 24.0 months for patients without major vascular invasion ($P<.001$) (Figure 3A). Of those patients who did not have major vascular invasion (n=251), a subset (n=159 [63.3%]) had microscopic vascular invasion on final pathologic examination. Patients with microscopic vascular invasion had a median survival of 16.1 months compared with 44.3 months for patients without microscopic vascular invasion ($P<.001$) (Figure 3B). Univariate analysis revealed no significant difference in survival based on age, sex, hepatitis status, Child-Pugh classification, or tumor grade.

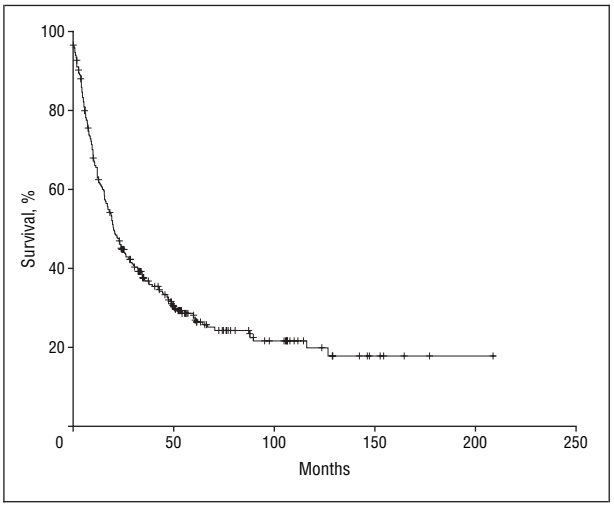

Figure 1. At a median follow-up of 32 months (range, 0.2-208 months), the overall long-term median survival for patients with a hepatocellular carcinoma 10 cm in diameter or larger was 20.3 months. The 1-, 3-, 5-, and 10-year survival rates were 64.9%, 36.7%, 26.9%, and 17.8%, respectively.

On multivariate analysis, AFP level, vascular invasion, tumor number, and the presence of severe fibrosis remained independent predictors of poor survival. Patients with AFPs of 1000 ng/mL or higher had a greater likelihood of death than those with lower AFP levels (hazard ratio [HR]=1.55, 95% CI=1.15-2.08, $P=.004$). Patients with major vascular invasion had more than a 50% increase in their mortality risk (HR=1.71, 95% CI=1.15-2.55, $P=.009$). The presence of multiple tumors (HR=2.25, 95% CI=1.17-4.30, $P=.02$) or severe fibrosis (HR=2.19, 95% CI=1.08-4.49, $P=.03$) also was associated with significantly higher mortality. As noted in **Table 3**, 1-, 3-, and 5-year survival rates were all adversely affected by each of the aforementioned factors.

Using the 4 independent variables—AFP level, major vascular invasion, tumor number, and degree of fibrosis—a clinical score was devised in an attempt to stratify patients with regard to prognosis. Patients lacking all 4 risk factors were assigned a score of 1, patients with 1 or 2 risk factors were assigned a score of 2, and

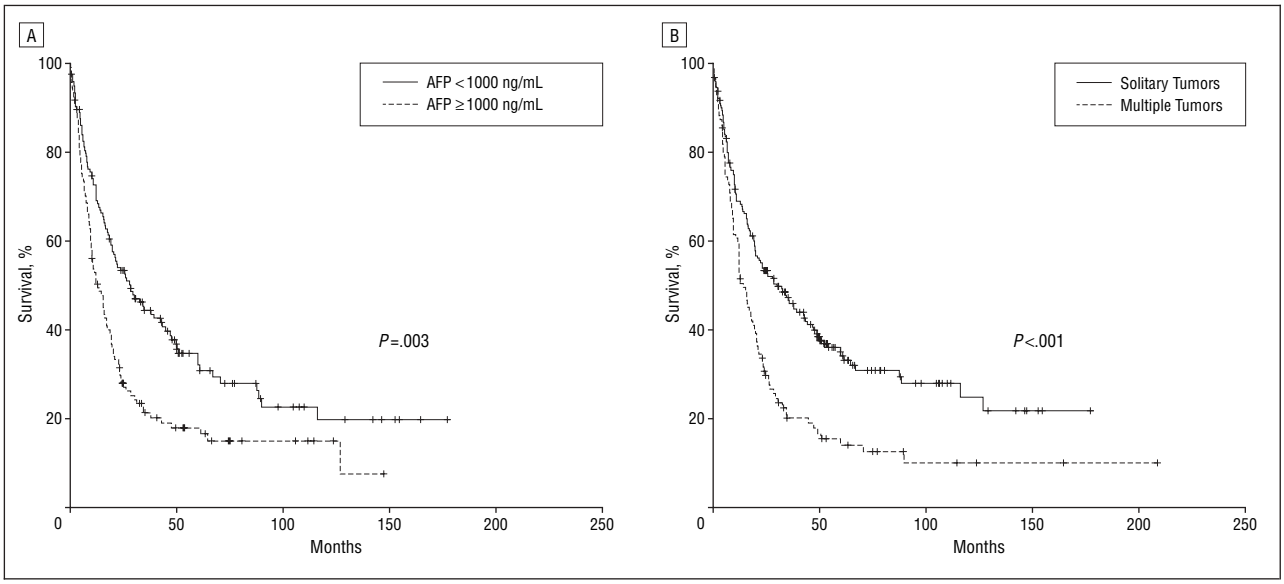

Figure 2. The α-fetoprotein (AFP) level and number of tumor nodules both adversely affected the overall survival. A, Patients with an AFP of 1000 ng/mL or higher had a significantly worse survival compared with patients with lower AFP levels. B, Similarly, patients with multiple tumors had a significantly shorter median survival compared with patients with only a solitary tumor.

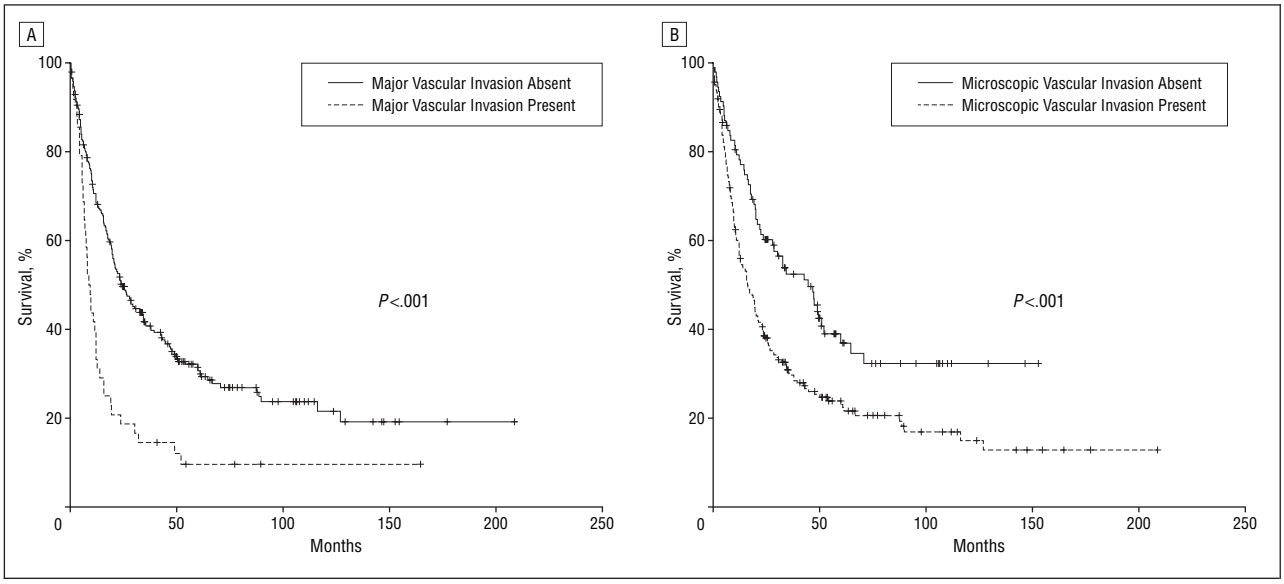

Figure 3. Both microscopic and major vascular invasion predicted poor survival. A, Patients with major vascular invasion had a median survival of only 9.1 months. B, Those with microscopic invasion had a median survival of 16.1 months. In contrast, patients who were completely free of vascular invasion had a median survival of 44.3 months.

patients with 3 or 4 risk factors were assigned a score of 3. The difference in survival between patients with a score of 1 and patients with a score of 2 or 3 was statistically significant (**Figure 4**). Patients with a score of 1 had a longer median survival (59.7 months) compared with either patients with a score of 2 (19.0 months) or patients with a score of 3 (10.4 months) ($P<.001$, score 1 vs score 2 and score 3). In contrast, there was no significant difference in the survival between patients with a score of 2 and patients with a score of 3 ($P>.05$). The 5-year survival rates for patients with scores 1, 2, and 3 were 49.2%, 19.0%, and 14.3%, respectively ($P<.001$).

To assess our clinical scoring system, patients were also stratified by the T category of the AJCC staging system, which is the generally accepted classification scheme used after resection. The AJCC staging system is based on postresection pathologic findings and includes microscopic vascular invasion as a criterion, which was omitted from our scoring system as it cannot be reliably determined by preoperative needle biopsy and is not useful in a preoperative clinical scoring system. Survival by AJCC T category is shown in **Figure 5**. The T classification stratified patients into 3 distinct T categories (T1 vs T2 vs T3 and T4 combined), rather than the 2 subsets (score 1 vs score 2 or 3) seen with the clinical scoring system. Under the AJCC system, patients with T1 tumors had a significantly better outcome than patients with T2 tumors while patients with T2 tumors had a significantly

Table 3. Factors Used in Formulating the Clinical Score*

Variable	Survival, %			Overall Median Survival, mo	Hazard Ratio	*P* Value
	1-y	3-y	5-y			
α-Fetoprotein level, ng/mL						
<1000	69.8	44.5	35.2	28.2	1.55	.004
≥1000	52.0	21.4	16.6	12.7		
Major vascular invasion						
Absent	68.9	40.8	30.8	24.0	1.71	.009
Present	37.5	14.6	9.7	9.1		
Tumor No.						
Solitary	68.3	46.0	35.1	29.8	2.25	.02
Multiple	57.9	20.3	14.1	14.1		
Degree of fibrosis, Ishak score[26]						
0-4	67.3	43.0	33.8	24.0	2.19	.03
5-6	52.3	22.7	12.1	12.7		

*For a more detailed description of scoring, see the "Methods" section.

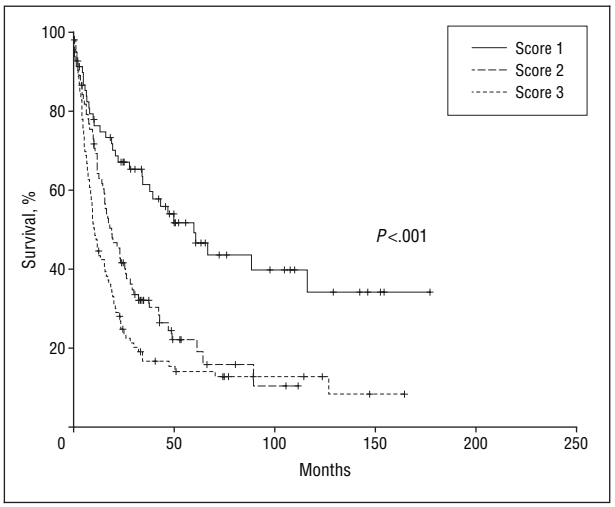

Figure 4. A clinical scoring system was devised in an attempt to stratify patients with regard to their prognosis. Patients lacking all 4 risk factors (an α-fetoprotein ≥1000 ng/mL, major vascular invasion, multiple tumors, and severe fibrosis) were assigned a score of 1, patients with 1 or 2 risk factors were assigned a score of 2, and patients with 3 or 4 risk factors were assigned a score of 3. Patients with a score of 1 had a longer median survival (59.7 months) compared with either patients with a score of 2 (19.0 months) or patients with a score of 3 (10.4 months) (both $P<.001$). For a more detailed description of the scoring method see the "Methods" section.

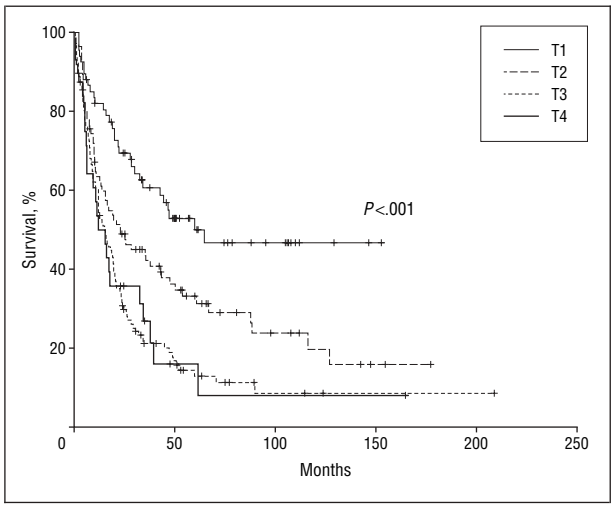

Figure 5. Survival according to the American Joint Commission on Cancer Staging T-classification system. Patients with T1 tumors had a significantly better outcome than did patients with T2 tumors ($P<.001$), while patients with T2 tumors had a longer median survival than did patients with T3 or T4 tumors ($P<.001$). Patients who had T3 and T4 tumors had a similar poor long-term prognosis.

longer median survival than patients with T3 or T4 tumors (T1: 64.7 months vs T2: 23.1 months vs T3: 15.6 months and T4: 12.1 months) (both $P<.001$). Within each T category, patient survival could also be stratified by F score (**Table 4**). The relationship between the clinical scoring system and the AJCC T classification system is outlined in **Table 5**. Although the clinical scoring system was able to accurately identify most patients with a favorable pathologic T category (87% of the patients with a score of 1 were either T1 or T2), it was less successful in predicting which patients had an unfavorable T category (only 43.9% of the patients with a score of 2 were either T3 or T4 and 80% of the patients with a score of 3 were either T3 or T4). That is, an advanced clinical score (ie, score 2 or 3) did not always correlate with an advanced pathologic T category (ie, T3 or T4), especially for patients with only 1 or 2 clinical risk factors.

COMMENT

Small liver cancers are increasingly recognized owing to the screening modalities used for early detection of patients at high risk for HCC. Despite this, the size of resected HCC lesions has remained unchanged in most countries, and most HCCs are still discovered at an advanced stage.[3,29,30] In Japan, the proportion of HCC tumors larger than 10 cm in diameter still ranges from 10% to 20%.[3,31] The incidence of large HCC is especially high in younger patients, with a large HCC accounting for 32% of resectable tumors in patients younger than 40 years.[5] In most patients who have large HCCs, the lesion is far advanced at the time of detection, and long-term prognosis is generally considered poor. Delayed diagnosis may be one explanation for why large HCC tumors are so advanced on the initial examination. However, some investigators have argued that there are specific biological features particular to large HCCs that lead to their ag-

gressive nature. For example, Nagasue et al[32] reported that aneuploidy was more frequent in large than in small HCCs; others, however, have disputed this finding.[33,34] In the current study, there was no preponderance of high nuclear grade in large HCC tumors. Rather, equal numbers of tumors were classified as having a low or high nuclear grade (51.7% and 47.3%, respectively).

The Liver Cancer Study Group of Japan[3] has reported that HCC tumor size and survival rate after liver resection are inversely correlated. Additionally, some investigators have noted that outcome after resection for a large HCC is extremely poor.[35] Patients who have a large HCC have been reported to be more likely to die of recurrence in the remnant liver or from distant metastasis, and some authors have reported few 5-year survivors.[7,35,36] More recent studies, however, have described patients with a large HCC who underwent resection and survived long periods following intervention.[2,15,21,37] Lee et al[15] reported 1-, 3-, and 5-year disease-free survival rates of 42%, 30%, and 28%, respectively. Similarly, Zhou et al[37] described a 26.2% 5-year survival rate for patients with 10-cm-diameter or larger HCC tumors. In the current study, we report 1-, 3-, and 5-year survival rates of 64.9%, 36.7%, and 26.9%, respectively, for HCC tumors that are 10 cm in diameter or larger. The similarity in long-term outcome between the current study and recent previous reports serves to emphasize that resection of a large HCC can provide durable long-term survival. In fact, in both the current study and that by Zhou et al,[37] more than 17% of patients were still alive at 10 years' follow-up.

A clear understanding of the clinicopathologic factors that influence the long-term prognosis following hepatic resection for a large HCC is important in helping to decide who should be offered surgical intervention. In the current study, an AFP of 1000 ng/mL or higher, multiple tumor nodules, the presence of vascular invasion, and the presence of severe fibrosis were all significant factors affecting survival (all $P<.05$). Other studies have similarly reported that elevated AFP levels predict poor overall survival for patients with a large HCC,[17] and previous European and Japanese reports have emphasized the importance of preoperative AFP levels by incorporating the AFP level into clinical prognostic scoring systems.[3,38] Although the exact mechanism by which AFP levels may worsen prognosis remains unknown, some authors have suggested that high AFP levels may suppress the ability of the immune system to destroy cancer cells.[39,40] Similar to the level of AFP, the number of tumor nodules may reflect the overall tumor burden within the liver. Multiple tumors can be caused by either intrahepatic metastases or multicentric carcinogenesis. In the current study, the presence of multiple tumors (HR=2.25, 95% CI=1.17-4.30, $P=.02$) was one of the strongest independent predictors of poor survival. The adverse effect of the number of tumors on prognosis is reflected in the current AJCC staging system, which stratifies patients with multiple tumors greater than 5 cm to the T3 category.

Vascular invasion is a known prognostic factor after resection of HCC.[8,22,41] In the present study, patients with vascular invasion had a significantly shorter median survival compared with those without evidence of vascular invasion. In particular, patients with major vascular invasion had a very short median survival of only 9.1 months. Tsai et al[42] noted an association between tumor size and increasing rates of both microscopic and macroscopic vascular invasion. Although most patients in the current study had vascular invasion (69.3%), almost one third of the patients who had a large HCC did not have any evidence of vascular invasion—either major or microscopic. The fact that tumor size is often a marker for vascular invasiveness[43,44] may explain why size often fails to affect survival in studies that control for vascular invasion.[45] Given this, prognosis based solely on tumor size clearly does not apply to most patients who have an HCC. Tumor size, per se, therefore, should not be used as the sole criterion to exclude patients from surgery who have an otherwise resectable tumor.

Table 4. Survival According to the AJCC T Category System Stratified by Fibrosis Score

AJCC T Category	Fibrosis Score*	No. of Patients	Median Survival, mo	*P* Value
T1	F0	50	76.4	.003
	F1	15	21.6	
T2	F0	61	37.9	.01
	F1	25	10.8	
T3	F0	75	20.1	.03
	F1	32	12.7	
T4	F0	22	16.1	.71
	F1	6	5.3	

Abbreviation: AJCC, American Joint Commission on Cancer.
*The fibrosis score was unavailable for 14 patients. For a more detailed description of scoring see the "Results" section.

In the present study, a clinicopathologic scoring system was devised in an attempt to identify which patients with a large HCC benefited the most from surgical resection. The clinical scoring system was not based solely on noninvasive clinical and radiologic parameters since the assessment of major vascular invasion and fibrosis was based on pathologic findings. Although major vascular invasion and severe (F1) fibrosis can often be identified preoperatively, accurate identification of these features prior to surgery can be limited. Major vascular invasion can be underestimated owing to limitations of imaging techniques, while fibrosis can be underscored because of the inadequacy of the core liver biopsy.[46] Our clinical scoring system therefore represents a best-case scenario for the clinical assessment of patients prior to surgery. Despite this, our data showed that a score based on potential preoperative clinicopathologic factors was markedly inferior to the AJCC staging system. Undoubtedly, a clinical scoring system based on only true clinical factors would be an even worse approximation of outcome. Thus, we contend that clinical predictors of outcome should not be used to categorically exclude patients from surgical resection.

The current AJCC staging classification for HCC does not use tumor size as a prognostic criterion except in patients with multiple tumors.[22,27] As shown in the current study, patients with a large HCC can still be stratified into subcategories based on AJCC criteria, including T category (Figure 5) and F score (Table 4). In other words, tumor size itself does not universally portend a poor prognosis. In fact, our data suggest that relatively good out-

Table 5. Relationship Between Clinical Scoring System and AJCC T Category*

Clinical Score	Total No. Patients	No. (%) of Patients			
		T1	T2	T3	T4
1	69	28 (40.6)	32 (46.4)	2 (2.9)	7 (10.1)
2	82	15 (18.3)	31 (37.8)	29 (35.4)	7 (8.5)
3	100	5 (5.0)	15 (15.0)	66 (66.0)	14 (14.0)
Unavailable	49	19 (38.8)	9 (18.4)	20 (40.8)	1 (2.0)

Abbreviation: AJCC, American Joint Commission on Cancer.
*For a more detailed description of scoring see the "Results" section.

comes can be obtained with surgical resection for large (≥10-cm-diameter) T1 and even T2 tumors. Kosuge et al[43] also reported good survival in a subset of patients with large tumors. In that study, the 5-year recurrence-free survival rate among patients with HCC tumors 8 cm in diameter or larger and no vascular invasion was 73%. These data emphasize that morphologic criteria such as tumor size do not accurately predict outcome following surgical treatment of HCC. In fact, the sixth edition of the AJCC staging for liver cancer confirms that median survival exceeds 5 years following resection of large solitary tumors (5-10 cm and even >10 cm in diameter) without vascular invasion (T1 tumors). This staging system was validated and this specific finding confirmed by Poon and Fan[47] in Chinese patients with an HCC who have a medical history of hepatitis B. In the present study, we show that, rather than tumor size, other factors such as major or microscopic vascular invasion, the number of tumors , and adjacent liver fibrosis dictate long-term survival.

CONCLUSIONS

The present study indicates that hepatic resection can be performed safely and lead to long-term survival in a subset of patients with large HCCs. Patients with an AFP of 1000 ng/mL or higher, multiple tumors, major vascular invasion, or severe fibrosis, however, have significantly shorter survival after resection. Clinical scoring systems that use these factors can help identify those patients who are most likely to benefit from resection. However, this information should not be used to exclude from surgical consideration patients with a large HCC who have an otherwise resectable lesion. Future studies should strive to identify molecular markers that define the underlying biology of HCC better than the currently available clinicopathologic factors.

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Author Affiliations: Department of Surgery, University of Texas M. D. Anderson Cancer Center, Houston (Drs Pawlik, Abdalla, Zorzi, Curley, and Vauthey); Departments of Surgery (Dr Poon) and Pathology (Dr Ng), University of Hong Kong Medical Center, Queen Mary Hospital, Hong Kong, China; Department of Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan (Dr Yamaoka); Department of Gastroenterological and General Surgery, Mayo Clinic, Rochester, Minn (Dr Nagorney); Department of Surgery, Beaujon Hospital, Paris, France (Dr Belghiti); and Department of Pathology, Massachusetts General Hospital, Boston (Dr Lauwers).
Correspondence: Jean-Nicolas Vauthey, MD, Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 444, Houston, TX 77030 (jvauthey@mdanderson.org).
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DISCUSSION

John Brems, MD, Burr Ridge, Ill: This is the largest review of resection of large HCCs from a consortium of 5 large hepatobiliary institutions in the literature. In this study, 300 patients were identified who underwent surgical resection for HCCs that were greater than 10 cm in diameter. From this study 4 clinical factors were identified that were significant predictors of survival. However, the authors concluded, and I would agree, that the size of HCC should not exclude patients from surgical resections. This is an important study because we have little to offer these patients with large HCCs. They are not candidates for liver transplantation, and ablated modalities do not appear to help these patients. In addition, we have no useful systemic therapies to offer these patients. Therefore, surgical resection is essentially the only good option for these patients. The problem is deciding who should undergo resection. The authors have attempted to answer this question. An interesting aspect of this study was that 70% of the patients had minimal or no fibrosis in the remaining liver remnant. This means despite having a large HCC, the remaining liver remnant was essentially normal with little or no fibrosis. This is probably the most important predictor of perioperative morbidity and mortality. I noticed in the demographics that 63% of the patients had hepatitis B as their underlying liver disease. I suspect many of these patients were carriers of hepatitis B and did not have chronic active hepatitis B. Studies have shown that patients who are carriers of hepatitis B have very little fibrosis in the remaining liver remnant and, consequently, have better functional reserve. The groups that tend to do worse are the patients who are alcoholics and the patients with hepatitis C. I was wondering if the authors could elaborate on how many of their patients with hepatitis B were carriers. Additionally, do they perform any preoperative studies in patients to evaluate the functional reserve of the remaining liver remnants such as ICG [indocyanine green] clearance or calculating CT [computed tomographic] liver volumes of the remaining liver remnant?

Second, with large HCCs, especially in the right lobe, it can be difficult to mobilize the liver. I was wondering what their indications were for using an anterior approach vs a posterior approach to these tumors. I have found the anterior approach to work very well in attempting to resect large tumors in the right lobe of the liver. When these tumors are medially rotated, they tend to tear the hepatic veins and there can be a lot of bleeding in a difficult place to control. I was wondering what their experience was and what they advocated as far as performing an anterior vs a posterior approach to resection of large tumors in the right lobe of the liver.

Third, as I mentioned in this study, fibrosis in the remnant portion of the liver appears to be an important predictor of how the patients will do after liver resection. I was wondering what they think the role of laparoscopy is for both assessing the tumor and for biopsying the liver remnant to determine the degree of fibrosis.

Last, since this is a group of patients for which we have little to offer besides liver resection, I was wondering what they do with the patient who they feel cannot be resected because of either advanced fibrosis or some other factor that they feel would make them a prohibitive risk. For example, do they consider these patients for live liver donor transplantations?

Dr Vauthey: As indicated in the article, we defined as hepatitis B–positive serology those patients who had hepatitis B core antibody and hepatitis B surface antigen, so these patients were not only carriers. We used this definition because the risk of HCC is increased not only in patients with hepatitis B surface antigen positive but also in patients who are hepatitis B core antibody positive.

Regarding the evaluation of the functional reserve, these patients come from a multicenter retrospective study from the United States, Hong Kong, Japan, and France. These patients were evaluated differently at the different centers. In the East surgeons have used ICG in preparation for resection to sort out the bad actors and patients with more advanced disease. In the West ICG was not used. In spite of this, the results regarding morbidity and mortality were similar. So, this reflects the complexity of the selection of patients with cirrhosis or chronic liver disease before liver resection. At our center for a right-sided hepatectomy we typically do not use ICG and we use just the Child-Pugh score. If a

patient is Child-Pugh A+ and has no overt portal hypertension (splenomegaly and/or hypersplenism), we perform preoperative portal vein embolization if the future liver remnant is less than 40% of the total estimated liver volume. We measure portal vein pressure prior to portal vein embolization.

Regarding the anterior approach, we have used the anterior approach increasingly for several reasons. Many of these large tumors are attached to the diaphragm, many of them are friable, and the anterior approach offers the option of dissecting completely the vena cava prior to the mobilization of the right lobe, thus, minimizing the difficulty associated with poor exposure.

Concerning the assessment of the fibrosis, a biopsy specimen of the underlying liver is unreliable and, in fact, there was a recent article in *Hepatology* by the Beaujon group in Paris indicating variability in the interpretation of fibrosis (Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology*. 2003;38:1449-1457). We use laparoscopy in these patients, and we still believe that there is great value in gross assessment of the liver prior to proceeding with any resection in these patients.

Finally, liver transplantation remains contraindicated in patients with a large HCC because of the high risk of vascular invasion associated with most large tumors. The patient who was presented here earlier was a young patient with hepatitis B– and C–induced cirrhosis and, in fact, we tried very hard to transplant this patient. We sent him to our colleagues at the University of Florida and tried to find him a marginal liver. I was convinced that this solitary large HCC had a favorable biology also based on the tumor biopsy specimen indicating a well-differentiated tumor. The patient was turned down based on tumor size, and we proceeded with a resection. I think living-related liver transplantation might be a viable option in a subset of patients with a large HCC if we could better predict favorable biology.

Scott Helton, MD, Chicago, Ill: Dr Vauthey, I want to congratulate you and your group on providing additional valuable information, and for those of you who do not know, Nic and this group are really responsible for modifying the sixth edition of the AJCC staging system for liver cancer. As you know, predicting outcomes for patients with HCC is difficult and that is why we see this proliferation of new staging systems combining clinical and pathologic systems as you have done for the sixth edition of AJCC. As you alluded to in your discussion, one factor that may predict outcome is the region in the world in which the patient is born and treated because there are both diagnostic as well as selection and treatment factors that may predict their outcomes. I have 2 questions in that respect. First, did you include the region, Asia, United States, and Europe in your univariate and multivariate analysis as a predictor of survival? Second, did you compare your new clinical system with CLIP [Cancer of the Liver Italian Program], CUPI [Chinese University Prognostic Index], or the new Japanese staging system to establish whether yours is even more predictive of survival than those more recent ones?

Dr Vauthey: Regarding first the complexity of the mix of patients, we presented a paper at the Society for Surgery of the Alimentary Tract earlier this year looking specifically at this subject and at whether hepatitis predicts survival. In fact, there is a variable mix of advanced liver disease for each country of origin (Pawlik TM, Poon RT, Abdalla EK, et al. Hepatitis serology predicts tumor and liver-disease characteristics but not prognosis after resection of hepatocellular carcinoma. *J Gastrointest Surg*. 2004;8:794-805). If you look at the Japanese patients, they have small tumors, severe fibrosis, and less vascular invasion. If you look at the Chinese patients, they have larger tumors, less severe fibrosis, but more vascular invasion. On balance, fibrosis and vascular invasion are 2 risk factors affecting survival. In the multivariate analysis controlling for these factors we found out that hepatitis serology or country of origin did not influence survival.

Regarding the second question, CLIP score or other staging systems, such as Barcelona Cancer Liver Clinic staging: the CLIP score is probably the best clinical predictor of survival for unresectable patients with advanced liver disease because it has been established prospectively and validated in the West and in the East. As for patients who are resectable, I believe we should use a staging that is based on the biology of the HCC. There was a consensus conference sponsored by the American Hepato-Pancreato-Biliary Association on this a couple years ago in Boston and the AJCC/UICC sixth edition staging was recommended for the assessment of prognosis in patients undergoing surgery (resection or transplantation) for hepatocellular carcinoma (Henderson JM, et al. HPB 2003; 5:243-250).

Anton Bilchik, MD, Los Angeles, Calif: The low morbidity and high survival rate for such large tumors in compromised livers are extremely impressive. Two questions. During the 20-year period of the study there have been radical changes in chemotherapy, imaging, and surgical technique. Can you comment on how these changes may have impacted the results? Is the primary focus of the study to define the factors that influence survival or to define the role for resection for large HCC?

Dr Vauthey: I think the only modality besides transplantation and resection that have a bearing on survival is chemoembolization, but it provides a minimal benefit, and only a small subset of these patients had preoperative chemoembolization. As you know, chemotherapy is really not effective.

William Chapman, MD, St Louis, Mo: I, too, would like to congratulate this group on their investigations into an important area, and I think one of the important points of this article is to stress the fact that resection remains a useful option in patients with HCC with careful selection. I think this is a carefully selected group, and I had a couple of questions. Only 26% of the patients had even severe fibrosis. I do not know what percent of those patients actually met the definition of cirrhosis. In the article you mention that 80% of the patients had Child A classification, but I think that is a little confusing because I do not think we typically think of a noncirrhotic patient in terms of the Child classification. So this is really—I wonder if you are comparing in some ways apples and oranges to patients that might be considered for transplantation. Are these the same groups? I would agree with you that in patients who do not have cirrhosis, resection should be the first choice. Second point I would just mention, there are selected patients, just to be sure the point is made, where chemoembolization can have dramatic results and whether or not those patients had then downstaged, particularly those with cirrhosis, whether those patients then might be considered for transplantation—I think is still an open question. I would agree with you that ablation is not an option in these patients.

Dr Vauthey: I would agree with you there is a selection bias. This is a series of resectable patients. There is an overlap between resection and transplantation and the size of this overlap remains unclear. The article emphasizes favorable biology irrespective of size. The Mount Sinai group in New York has recently shown that tumors greater than 5 cm have a greater than 80% survival at 5 years after transplantation if the tumor has no vascular invasion and this emphasizes favorable biology irrespective of size not only after resection but also after transplantation (Roayaie S, Frischer JS, Emre SH, et al. Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 centimeters. *Ann Surg*. 2002;235:533-539). So, this article is about biology. While treatment methods evolve, I think the staging reflects the biology of the tumor.