Tumor Size Predicts Vascular Invasion and Histologic Grade: Implications for Selection of Surgical Treatment for Hepatocellular Carcinoma

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Vascular invasion and high histologic grade predict poor outcome after surgical resection or liver transplantation for hepatocellular carcinoma (HCC). Despite the known association between tumor size and vascular invasion, a proportion of patients with large tumors can be treated surgically with excellent outcomes. Clarification of the association between tumor size, histologic grade, and vascular invasion has implications for patient selection for resection and transplantation. The objective of this study was to examine the relationship between HCC tumor size and microscopic (occult) vascular invasion and histologic grade in a multicenter international database of 1,073 patients who underwent resection of HCC. The incidence of microscopic vascular invasion increased with tumor size (≤3 cm, 25%; 3.1-5 cm, 40%; 5.1-6.5 cm, 55%; >6.5 cm, 63%) ($P < 0.005$). Both size and number of tumors were important factors predicting vascular invasion. Among all patients with tumors 5.1 to 6.5 cm, microscopic vascular invasion was present in 55% compared with 31% for all patients with tumors 5 cm or smaller ($P < 0.001$). Among patients with solitary tumors only, microscopic vascular invasion was significantly more common in tumors measuring 5.1 to 6.5 cm (41%) compared with 27% of tumors 5 cm or smaller ($P < 0.003$). Tumor size also predicted histologic grade: 36% of tumors 5 cm or smaller were high grade, compared with 54% of lesions 5.1 to 6.5 cm ($P = 0.01$). High histologic grade, an alpha-fetoprotein level of at least 1000 ng/mL, and multiple tumor nodules each predicted occult vascular invasion in tumors larger than 5 cm. The high incidence of occult vascular invasion and advanced histologic grade in HCC tumors larger than 5 cm, as well as biologic predictors of poor prognosis, should be considered before criteria for transplantation are expanded to include these patients. (*Liver Transpl 2005;11:1086-1092.*)

Hepatic resection and liver transplantation are aggressive, extirpative approaches to the treatment of selected patients for hepatocellular carcinoma (HCC) and are the only known potentially curative treatment options for this disease. Resection and transplantation are largely complimentary, not competing, treatments—resection for patients with preserved liver function and transplantation for patients with compromised liver function. Within each group, selection of patients for surgical therapy is currently based on morphologic criteria such as size, number of tumors, and degree of underlying liver disease.

After resection, long-term survival can be expected in patients with solitary tumors regardless of size, especially when underlying fibrosis is minimal.[1] In fact, size has no significant impact on survival when microscopic vascular invasion is absent, as survival after resection of T1 tumors larger than 10 cm in diameter is similar to survival following resection of T1 tumors less than 5 cm.[1] Similarly, long-term survival can be expected when multiple tumors without vascular invasion are completely resected.[1]

The establishment of strict morphologic criteria has significantly impacted the outcome after liver transplantation for HCC. Before the adoption of these criteria for transplantation, results with liver transplantation were poor. Recurrence rates ranged from 60% to 70%,[2,3] and the 5-year survival rate was less than 30%.[4,5] Since the implementation of more stringent selection criteria, survival rates after liver transplantation have been similar to those after resection for

Abbreviations: HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; HR, hazard ratio; FNA, fine-needle aspiration.

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Received March 29, 2005; accepted April 4, 2005.

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Presented at the International Hepato-Pancreato-Biliary Association 6th World Congress, Washington, DC, June 3, 2004.

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Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/lt.20472

patients without cirrhosis who have lesions of similar stage.[6,7] Specifically, survival data obtained from Milan and Barcelona revealed 4-year survival rates of 75% after liver transplantation,[8,9] based on careful selection of patients with specific morphologic criteria: only patients with HCC and cirrhosis who had three or fewer tumor nodules that were 3 cm or less in maximum diameter or a single tumor 5 cm or less and no clinically apparent signs of vascular invasion were considered acceptable for transplantation.[10] Although these arbitrary criteria were determined based on the small series from Mazaferro et al.,[9] no patients in that series had evidence of microscopic vascular invasion in the explanted tumor specimens, which may not represent the spectrum of tumors treated based on these criteria. The recognition, however, that tumor size and tumor number impact outcome has led to the adoption of these criteria worldwide for liver transplantation.

Subsequent studies[1,11,12] have shown that vascular invasion—macroscopic or microscopic—is one of the strongest predictors of tumor recurrence after liver transplantation. Llovet et al.[8] reported that microscopic vascular invasion detected at pathologic examination of the explant specimen was associated with no disease-free survivors at 3 years, whereas 94% of patients without macro- or microscopic vascular invasion were disease-free after 3 years.

Since microscopic invasion cannot be determined preoperatively, tumor grade has been investigated as a possible surrogate marker of microscopic vascular invasion. In an analysis of tumors less than 5 cm, Esnaola et al.[13] reported that tumor size greater than 4 cm and high-tumor grade predicted microscopic vascular invasion in patients with HCC who were candidates for liver transplantation. Others have also shown that tumor grade is an important prognostic factor after liver transplantation.[14-16] In fact, several studies have directly correlated tumor grade with prognosis after resection or transplantation.[17-20] For example, Jonas et al.[14] reported that the 5-year survival rate after liver transplantation for HCC was 84% in patients with well-differentiated tumors, compared with only 41% in patients with poorly differentiated tumors.

Currently, patients with solitary tumors without evidence of major vascular invasion are considered for surgical treatment based on the presence or absence of underlying liver disease. Absent underlying liver disease, major resection is considered appropriate. In the presence of severe cirrhosis, transplantation has been proposed for selected patients with solitary tumors up to 6.5 cm in maximal diameter.[10,21] There is concern, however, that allocation of organs to patients with large tumors (>5 cm) will negatively impact outcome because of the increasing incidence of (microscopic) vascular invasion and advanced histologic grade in tumors as size increases. Using both the Milan criteria[9] (5-cm cutoff for solitary tumors) and the recent University of California San Francisco[10] proposal (6.5-cm cutoff for solitary tumors) as a guideline for the analysis, the objective of the current study was to examine the association between tumor size, tumor number, histologic grade, and the incidence of vascular invasion in HCC. More importantly, we sought to identify predictors of microscopic vascular invasion in patients with large (>5 cm) HCC.

Patients and Methods

Between January 1986 and September 2000, 1073 patients with HCC underwent resection at five major hepatobiliary centers: The University of Texas M. D. Anderson Cancer Center (Houston, TX), Mayo Clinic (Rochester, MN), Beaujon Hospital (Paris, France), Kyoto University Graduate School of Medicine (Kyoto, Japan), and Queen Mary Hospital (Hong Kong, China). The clinical data were reviewed on site by J.N.V., D.M.N., and R.T.P., and the pathologic resection specimens were reviewed on site by G.Y.L. and I.O.N. Only patients with HCC who had no clinical, radiographic, or intraoperative evidence of extrahepatic disease and who underwent an attempt at curative resection were included in the study. The following data were collected for each patient: demographics; laboratory data (alpha-fetoprotein [AFP] level and hepatitis serology); tumor size, number, histologic grade, and location; presence of vascular invasion (major and microscopic); and operative findings. Data were recorded as follows: clinical features, present or absent; age, younger than 60 years vs. 60 years or older; AFP level, less than 1000 ng/mL vs. 1000 ng/mL or greater; and tumor number, single vs. multiple. Tumor size was defined as the largest diameter of the tumor in the resected specimen. In patients with multiple tumors, the largest lesion was used as the index lesion. Tumor grade was assessed using the nuclear grading scheme outlined by Edmondson and Steiner, with tumor grade categorized as low, intermediate, or high.[22] Tumor grade was defined by the poorest degree of differentiation identified within the tumor upon pathologic analysis of the entire resected specimen. The degree of fibrosis of the hepatic parenchyma was graded according to the established classification scheme of Ishak et al.[23]: Ishak grade 0, no fibrosis; Ishak grade 1 or 2, minimal fibrosis; Ishak grade 3 or 4, incomplete bridging fibrosis; Ishak grade 5 or 6, complete fibrosis or cirrhosis. Vascular invasion was defined by the findings on final pathologic analysis. 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 lobar or segmental branches of the portal vein or the hepatic veins.[1,24] Major

vascular invasion was defined as gross invasion of the right or left main branches of the portal vein or the hepatic veins.[25]

All data are presented as percentages of patients or the median value. Statistical analyses were performed using univariate tests (chi square). Where reported, multivariate analyses were performed by entering factors that appeared to be significant on univariate analysis ($P \leq 0.10$) into a Cox proportional hazards model to test for significant effects while adjusting for multiple factors simultaneously. A P-value < 0.05 was considered significant.

Results

Table 1 shows the clinicopathologic features of the 1073 patients in the study. There were 805 men and 268 women, for a male-to-female ratio of 3:1. The median patient age was 59 years (range, 5-88 years). The majority of patients had solitary tumors, and the median tumor size was 6.0 cm (range, 0.3-27.0 cm). Most tumors were intermediate or high grade. Only 15% of patients had low-grade tumors. A minority of patients had cirrhosis (25%).

Table 1. Clinical and Pathologic Features of Patients (n = 1073)

Variable	Number of Patients (%)
Age, yrs	
<60	546 (51)
≥60	527 (49)
Sex	
Male	805 (75)
Female	268 (25)
Child-Turcotte-Pugh classification*	
A	849 (89)
B	100 (10.5)
C	1 (0.5)
Alpha-fetoprotein level*	
<1000 ng/mL	688 (71)
≥1000 ng/mL	283 (29)
Tumor size	
≤3 cm	260 (24)
3.1–5.0 cm	228 (21)
5.1–6.5 cm	89 (9)
>6.5 cm	496 (46)
Tumor number	
Single	877 (82)
Multiple	196 (18)
Edmondson-Steiner grade	
Low (grade I)	161 (15)
Intermediate (grade II)	435 (41)
High (grade III or IV)	477 (44)
Ishak score	
Ishak 1–4	804 (75)
Ishak 5–6	269 (25)
Hepatitis status*	
Hepatitis negative	254 (24)
Hepatitis B	584 (54)
Hepatitis C	155 (15)
Co-infection	75 (7)

* Information not available for all patients.

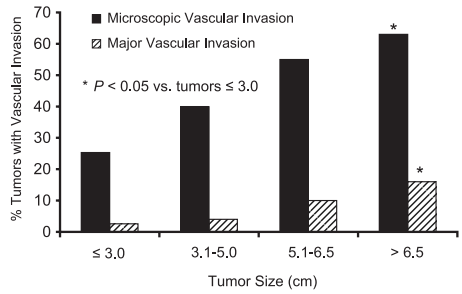

Figure 1. Incidence of microscopic and major vascular invasion stratified by tumor size.

The overall incidence of major vascular invasion was 9.4% (n = 101) and the incidence of microscopic vascular invasion was 49% (n = 528). As tumor size increased, the incidence of major vascular invasion increased: 3 cm or smaller, 3%; 3.1 to 5 cm, 4%; 5.1 to 6.5 cm, 10%; larger than 6.5 cm, 16% ($P = 0.001$). Similarly, the incidence of microscopic vascular invasion increased with tumor size as follows: 3 cm or smaller, 25%; 3.1 to 5 cm, 40%; 5.1 to 6.5 cm, 55%; larger than 6.5 cm, 63% ($P = 0.005$) (Fig. 1).

The rates of microscopic and major vascular invasion in patients with either solitary or multiple tumors are shown in Table 2. Patients with multiple tumors with a maximal tumor size larger than 6.5 cm had a higher incidence of microscopic vascular invasion compared to patients who had solitary tumors of a similar size (Table 2). Patients who had solitary tumors measuring 6.5 cm or smaller, however, had the same incidence of microscopic vascular invasion (29%) as patients who had less than three tumor nodules, none of which measured greater than 5 cm in size. The incidence of microscopic vascular invasion was 31% for all tumors measuring 5 cm or less, compared with 55% for all tumors measuring 5.1 to 6.5 cm ($P < 0.001$) (Fig. 2). Of note, solitary tumors measuring 5 cm or less had an incidence of microscopic vascular invasion of 27% compared with 41% for solitary tumors measuring 5.1 to 6.5 cm ($P < 0.003$). Solitary tumors measuring greater than 6.5 cm had an incidence of microscopic vascular invasion of 58% ($P < 0.005$ compared with solitary lesions measuring 5 cm or less or compared with solitary tumors measuring 5.1 to 6.5 cm).

Tumor size was also associated with histologic grade.

Table 2. Association of Vascular Invasion and Tumor Number Stratified by Tumor Size

Tumor Size	Microscopic Vascular Invasion (%)			Major Vascular Invasion (%)		
	Solitary	Multiple*	*P* Value	Solitary	Multiple*	*P* Value
≤3 cm	28	42	0.38	3	8	0.12
3.1–5.0 cm	39	42	0.87	3	13	0.02
5.1–6.5 cm	54	59	0.24	5	22	0.04
>6.5 cm	58	76	0.03	14	20	0.09

* For multiple tumors, tumor size refers to the dimension of the largest single lesion.

As tumor size increased, the incidence of low-grade tumors decreased and the incidence of high-grade tumors increased. Overall, tumors 5 cm or smaller were more frequently low grade (19% for tumors ≤5 cm vs. 12% for tumors >5 cm) ($P = 0.006$), and tumors larger than 5 cm were more frequently high grade (37% for tumors ≤5 cm vs. 47% for tumors >5 cm) ($P = 0.004$). The incidence of high-grade tumors was 36% for tumors 5 cm or smaller, compared with 54% for tumors 5.1 to 6.5 cm ($P = 0.01$). In addition, large (>5 cm) tumors that were intermediate- or high-grade had a significantly greater likelihood of being associated with microscopic vascular invasion compared to small (≤5 cm) intermediate- or high-grade tumors or large (> 6.5 cm) low-grade tumors (each $P < 0.05$ vs. > 5 cm intermediate- or high-grade tumors) (Fig. 3). Whereas only 30% of patients with intermediate- or high-grade tumors measuring 5 cm or less had evidence of microscopic vascular invasion, the rate of microscopic vascular invasion was 66% in intermediate- or high-grade tumors measuring 5.1 to 6.5 cm ($P < 0.001$).

To identify predictors of microscopic vascular invasion in patients with HCC larger than the current 5-cm size limit specified by the Milan criteria, a separate analysis was performed. A total of 486 patients were excluded from this separate analysis because of tumor size 5 cm or less, and 85 patients were excluded because of the presence of major vascular invasion. Of the 502 patients in this analysis (all with tumors > 5 cm, none with major vascular invasion), 287 (57%) had microscopic invasion on pathologic review. Statistical analysis revealed several factors that were significantly associated with microscopic vascular invasion in tumors larger than 5 cm. On univariate analysis, high histologic grade (Table 3), preoperative AFP level of at least 1000 ng/mL, the presence of tumor invasion of an adjacent organ, multiple tumor nodules, and tumor size were each associated with the presence of microscopic vascular invasion. Patients with a preoperative AFP level of at least 1,000 ng/mL were more likely to have microscopic vascular invasion on the final pathology review (64%) than were patients with an AFP level of less than 1000 ng/mL (43%) ($P < 0.001$). Similarly, microscopic vascular invasion was more common in tumors that were

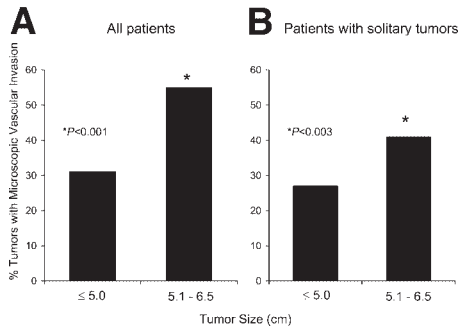

Figure 2. (A) The incidence of microscopic vascular invasion in tumors between 5 cm and 6.5 cm (55%) was nearly double the incidence in tumors 5 cm or smaller (31%). (B) This difference persisted when only solitary tumors were considered (41% vs. 27%, respectively).

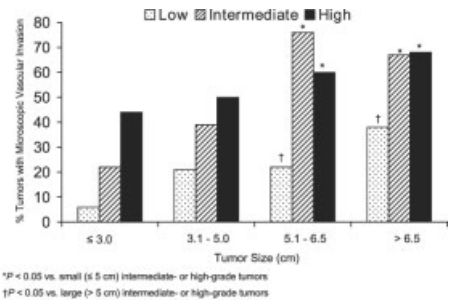

Figure 3. Histologic grade stratified by tumor size and rate of microscopic vascular invasion.

found at the time of the operation to be invading adjacent organs (78% vs. 48%) ($P = 0.03$). Microscopic vascular invasion was also more prevalent in patients who had multiple (65%) rather than solitary (44%) tumors ($P = 0.05$). Even in this subgroup of patients with large tumors, the incidence of microscopic vascular invasion increased with increasing size: 5.1 to 6.5 cm, 55%; 6.6 to 10 cm, 58%; 10.1 to 15 cm, 63%; larger than 15 cm, 76% ($P = 0.009$).

On multivariate analysis, grade, preoperative AFP level, number of tumor nodules, and tumor size remained independent predictors of microscopic vascular invasion (Table 4). Patients with incrementally larger tumors (hazard ratio [HR] = 1.5, 95% confidence interval = 1.3-1.8, $P = 0.001$) and high-grade tumors (HR = 1.7, 95% confidence interval = 1.3-2.2, $P = 0.006$) had an increased risk of microscopic vascular invasion. An AFP level of at least 1000 ng/mL (HR = 2.1, 95% confidence interval = 1.5-2.6, $P = 0.011$) and the presence of multiple tumors (HR = 1.8, 95% confidence interval = 1.3-2.5, $P = 0.03$) were also associated with microscopic vascular invasion.

Discussion

Careful allocation of organs has been a guiding principle in transplantation to optimize benefits to patients who undergo transplantation and to avoid transplanting patients unlikely to derive a benefit from the treatment. Tumor size is an important predictor of outcome after surgical treatment for HCC most likely because tumor size acts as surrogate marker for the presence of microscopic vascular invasion.[12,14] Although several factors may contribute to a poor prognosis after liver transplantation, vascular invasion is one of the most important.[1,8,13,14,26,27] While major vascular invasion can be identified preoperatively in the majority of cases, microscopic vascular invasion is impossible to rule out before transplantation. Although tumor size can be identified preoperatively, the use of tumor size alone to prioritize patients for transplantation is problematic, as survival after resection of T1 tumors greater than 10 cm in size is not significantly different than survival after resection of small T1 tumors.[1] Thus, recognition of surrogate markers of microscopic vascular invasion that can be obtained in the preoperative/pretransplant setting could improve selection of patients for surgical treatment of larger HCCs, possibly even expanding the pool of patients most likely to benefit from transplantation despite the presence of large tumors.

Although increasing tumor size is believed to be associated with microscopic vascular invasion, only a few studies have examined in detail whether there is a correlation between tumor diameter and vascular invasion.[12,14] In the current study, we showed definitively that the frequency of microscopic vascular invasion dramatically increased as tumor size increased (Fig. 1). In fact, the incidence of microscopic vascular invasion was almost twice as high in tumors larger than 5 cm (61%) as in smaller tumors (32%) and continued to increase with increased size even larger than 10 cm. More than half (55%) of patients with tumors 5.1 to 6.5 cm in size had microscopic vascular invasion on final pathologic examination. Importantly, the incidence of vascular invasion in solitary tumors 5.1 to 6.5 cm (41%) was significantly greater than the incidence in solitary tumors less than 5 cm (27%). Although tumor size was based on pathologic assessment, current imaging techniques allow for the accurate preoperative determination of tumor size. Recognition of the relationship between tumor size and vascular invasion and consideration of the substantially higher incidence of vascular invasion in larger tumors may be an important factor in

Table 3. Association between Microscopic Vascular Invasion and Grade in Patients with Tumors Larger than 5 cm Without Evidence of Major Vascular Invasion (n = 502)

	Tumor Grade		
Microscopic Vascular Invasion	Low, % (n)	Intermediate, % (n)	High, % (n)
Absent (n = 215)	73 (45)*	38 (78)	39 (92)
Present (n = 287)	27 (17)	62 (126)	61 (144)*

* $P < 0.001$.

Table 4. Factors Predictive of Microscopic Vascular Invasion in Patients with Tumors Larger than 5 cm Without Evidence of Major Vascular Invasion: Multivariate Analysis (n = 502)

Prognostic Factor	Hazard Ratio	95% CI	*P* Value
High-grade tumor	1.7	1.3–2.2	0.006
Large tumor size	1.5	1.3–1.8	0.001
AFP ≥ 1000 ng/mL	2.1	1.5–2.6	0.011
Multiple tumors	1.8	1.3–2.5	0.03
Tumor invasion into adjacent organ	1.1	0.70–1.5	0.22

Abbreviations: CI, confidence interval; AFP, alpha-fetoprotein.

clinical decision-making and treatment selection for resection and/or allocation of organs for transplantation.

Tumor grade has been shown to influence survival after resection for HCC.[14-16,28,29] Data in the transplantation literature suggest that patients with poorly differentiated large HCC do worse than patients with moderately- or well-differentiated tumors.[14,30] In the current study, tumor size was a significant predictor of advanced tumor grade. Almost half (47%) of the patients with tumors larger than 5 cm had a high histologic grade.

Similar to the findings in the current study, proponents of the University of California San Francisco criteria noted a higher incidence of vascular invasion and high-grade lesions in patients with tumors larger than those permitted by the Milan criteria.[31] Although no survival difference between the groups selected using the Milan vs. University of California San Francisco criteria was noted in the study by Yao et al.,[31] the median follow-up time was short (only 2 years), and the conclusions were based on actuarial, rather than actual, survival data. Because transplantation in patients with larger tumors may result in significantly shorter disease-free and overall survival, further studies with longer follow-up are needed before the universal adoption of an increased size limit for liver transplantation.

Tumor size alone may not be a contraindication to transplantation. Roayaie et al.[32] reported recurrence-free survival rates of greater than 80% for patients with tumors larger than 5 cm with no pathologic evidence of vascular invasion. This finding is consistent with other reports of excellent survival after resection of any size T1 tumor.[1] Patients with vascular invasion, however, were significantly more likely to have recurrence and had a worse overall survival.[1,32] These findings underscore the fact that vascular invasion, rather than tumor size, ultimately dictates prognosis.

In the current study, we identified specific factors that help identify the cohort of patients with tumors larger than 5 cm who are at a higher risk for vascular invasion. Specifically, microscopic vascular invasion was significantly more common in patients with high-grade tumors, an elevated AFP level, or multiple tumors. These data suggest that rather than using size alone as a strict selection criterion, biologic parameters such as grade, AFP level, and multicentricity should be considered. In particular, when patients with tumors larger than 5 cm are considered for liver transplantation, it must be recognized that the histologic grade of the tumor is the most powerful predictor of occult vascular invasion (HR = 3.66).

Percutaneous fine-needle aspiration (FNA) biopsy can be an accurate way to preoperatively characterize HCC grade. The risks of FNA can be minimized at specialized centers that routinely perform this procedure using appropriate techniques.[33] Durand et al.[34] reported that the sensitivity and accuracy of FNA biopsy were 90% and 91%, respectively. The incidence of needle tract seeding was 1.6%, and no recurrence was observed after local excision.[34] The utility of FNA, however, remains controversial as the heterogeneity of histologic grade within a single tumor may limit the overall accuracy of FNA. Despite this, some centers[15] are currently using preoperative FNA tumor grading as the major criterion to establish whether a patient with HCC is fit for transplantation and are not considering tumor size and number of nodules as absolute selection criteria. Using well- or moderately-differentiated histologic grade as the main selection criteria, Cillo et al.[15] reported a 5-year actuarial survival rate of 75% and a recurrence-free survival rate of 92%. FNA tumor grading may have a lesser impact on selection for resection in patients with large HCC, as organ allocation is not an issue.

In conclusion, to optimize the use of surgical treatments for HCC, current selection based on morphologic criteria of size and number of tumors alone may need to be modified to correctly identify patients who are most likely to benefit from resection or transplantation. The emphasis on increasing the upper limit of tumor size while ignoring other biologic parameters such as grade warrants further scrutiny. Data from this study as well as others[14] suggest that vascular invasion is predicted by additional factors beyond tumor size, such as higher preoperative AFP level, multicentricity, and most importantly, high histologic grade. Based on the cumulative data, liver transplantation for HCC larger than 5 cm may therefore be most appropriate for patients with a low AFP level, solitary tumors, and low tumor grade. The role of percutaneous biopsy for grading prior to resection or transplantation requires study, particularly given the finding that grade was the most powerful predictor of occult vascular invasion. Careful consideration of existing data from large series such as this may help to guide future studies aimed at expanding criteria for surgical resection and transplantation of HCC.

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