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Spectrum and significance of microscopic vascular invasion in hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide, and it has been difficult to treat successfully [1]. At present, surgical resection and liver transplantation are the mainstays of treatment with curative intent [2,3]; however, less than 25% of patients with HCC are eligible for hepatic resection or transplantation at the time of diagnosis [4,5], frequently because of advanced disease with intrahepatic or extrahepatic vascular spread. In addition, tumor recurrence rates are high after potentially curative surgery [6–8]. The high incidence of recurrence after surgical treatment is the most crucial factor limiting patients' long-term survival. Currently, vascular invasion with hematogenous spread and occult metastases is considered the major cause of tumor recurrence after hepatic resection and liver transplantation [7–10].

In HCC, vascular invasion can be either macroscopic with microscopic vascular invasion or microscopic alone (Fig. 1). Macroscopic vascular invasion is a well-established negative prognostic factor in HCC. In patients with resectable HCC, the presence of macroscopic tumor thrombus in portal or hepatic veins indicates a poor prognosis [11]. When patients with HCC undergo liver transplantation, those with macroscopic or large-vessel tumor invasion invariably suffer tumor recurrence [12]. In recent years, the role of microscopic vascular invasion, a relatively early-stage event of HCC

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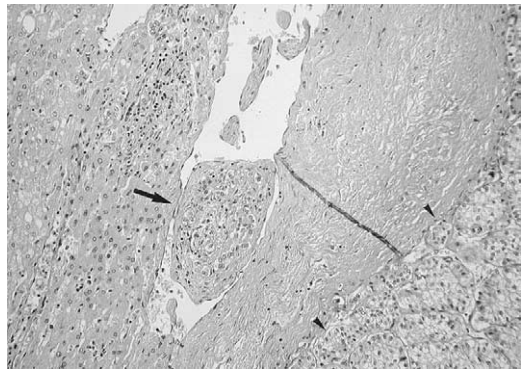

Fig. 1. Hepatocellular carcinoma (*arrowhead*) with presence of microscopic vascular invasion (*long arrow*) in the surrounding noncancerous area (hematoxylin-eosin, original magnification×100).

vascular invasion, was emphasized [10,13,14]. Studies have shown that microscopic vascular invasion is an important prognostic factor for postoperative recurrence and survival after resection or liver transplantation of HCC.

In a recent study, the authors [14] evaluated the clinical significance of microscopic vascular invasion in patients with resectable HCC. Among 322 patients undergoing curative resection for HCC, 50 (15%) had macroscopic vascular invasion and 190 (59%) had microscopic invasion. Of 37 patients with tumor sizes of less than 2 cm, 15 (40.5%) had microscopic vascular invasion. The presence of microscopic vascular invasion was significantly associated with preoperative serum α-fetoprotein levels, tumor size, tumor number, and absence of tumor capsule. Increasing tumor size correlated with a higher incidence of microscopic vascular invasion (Fig. 2). Microscopic vascular invasion is an independent predictor of postresection tumor recurrence and survival. In addition, the survival rate of patients with microscopic vascular invasion was lower than that of patients without invasion and higher than that of patients with macroscopic invasion (Fig. 3). Microscopic vascular invasion affected patient outcome in the authors' subsequent study, which controlled for tumor size. Analyses of the authors' 327 patients with HCC (59 patients having macroscopic vascular invasion were not enrolled) indicated that when these patients were stratified using tumor size, the survival differences still held, albeit in a small number of patients, and patients with microscopic vascular invasion tended to have a decreased survival time when compared with patients with no vascular invasion. The differences become significant in patients with tumor sizes of more than 5 cm and in patients with tumor sizes of 2 to 5 cm with a wide surgical margin (>1 cm; Fig. 4).

A recent report on HCC in patients who underwent liver transplantation revealed similar findings. Kirimlioglu et al [15] indicated that 48% of 212

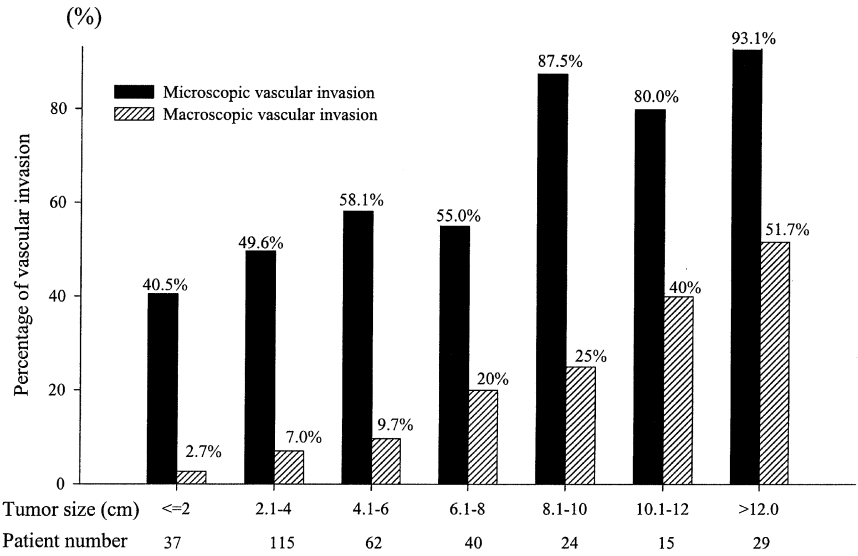

Fig. 2. Frequency of microscopic and macroscopic vascular invasion in 322 patients with hepatocellular carcinoma stratified according to tumor size. (*From* Tsai TJ, Chau GY, Lui WY, et al. Clinical significance of microscopic tumor venous invasion in patients with resectable hepatocellular carcinoma. Surgery 2000;127:603–8.)

nonfibrolamellar native livers with HCC, which were removed at the time of liver transplantation, showed microscopic vascular invasion, and 19% showed macroscopic vascular invasion. Vascular invasion is the strongest predictor of tumor recurrence after liver transplantation. Microscopic invasion correlates with tumor nodule number, tumor size, presence of giant cells, degree of tumor necrosis, and degree of differentiation.

Tumor spread in HCC progresses from capsular invasion to intrahepatic metastasis, with the portal vein acting as an efferent vessel [16]. There is a strong correlation between the frequency of vascular invasion and the presence of intrahepatic metastasis. It is apparent that microscopic vascular invasion occurs early in the progression of HCC [17]. The mechanism by which HCC progression results in microscopic vascular invasion is not exactly known. A recent report indicated that in patients with HCC, a high level of preoperative serum vascular endothelial growth factor is a predictor of tumor microscopic vascular invasion [18]. Because HCC is characterized by high vascularization and because the vascular endothelial growth factor is an important mediator of angiogenesis, it is likely that angiogenesis has a role in the development of vascular invasion in HCC.

The liver has a unique circulatory system, with the portal vein as the main tributary of the gastrointestinal tract. Tumor cells spreading in the portal venous system eventually implant within the liver and develop into recurrent tumor. As tumor size increases, or because of surgical manipulation, HCC spreads via the portal vein to the remainder of the liver. Vascular invasion of

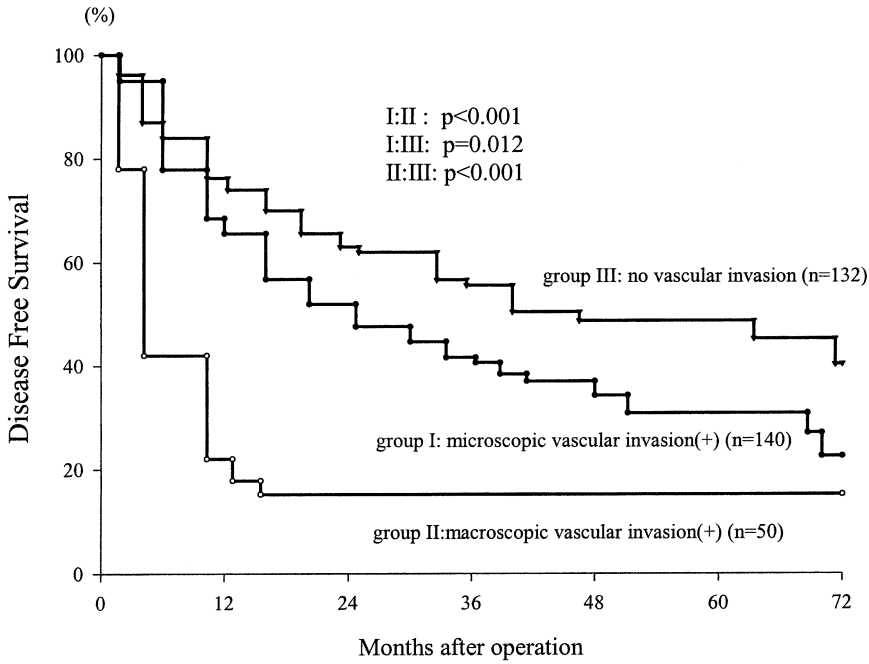

Fig. 3. Disease-free survival curves in three groups of patients with hepatocellular carcinoma according to the status of tumor vascular invasion. *P* values show a significant difference among the three curves. (*From* Tsai TJ, Chau GY, Lui WY, et al. Clinical significance of microscopic tumor venous invasion in patients with resectable hepatocellular carcinoma. Surgery 2000; 127:603–8.)

the hepatic vein indicates and is associated with an increased incidence of extrahepatic recurrence.

Hematogenous spread may be responsible for early recurrence of HCC; however, Schlitt et al [8] have reported that tumor recurrence after transplantation occurs within a wide time range (43 days to approximately 8.5 years). This observation suggests that, in some patients, hematogenously spreading tumor cells may persist in a dormant state for long periods of time before growing into detectable tumor nodules.

Although microscopic vascular invasion is a predominant factor related to postsurgical recurrence, its presence cannot be determined until results of a histologic work-up of the resected specimen are known. Because most tumors for which surgery is contemplated may co-exist with invasion, it is mandatory to use effective treatment strategies to eradicate tumor cells that may already exist in the vessels and to decrease the possibility of tumor cells spreading during tumor manipulation. It has been proposed that intrahepatic spread of hepatic tumors follows the pattern of step-by-step dissemination [19]. Tumor recurrence after resection is almost inevitable in patients with tumor thrombus in the main portal trunk [20]; however, in

patients with only microscopic vascular invasion, the potential for curative resection exists. Tsai et al [14] showed that in patients with microscopic invasion only, a 5-year disease-free survival rate of 31% can be achieved after hepatic resection. Accordingly, to decrease the potential adverse effects of microscopic vascular invasion, the following measures may be important to achieve a successful resection and increase the chance of cure: (1) perform an anatomic resection; (2) ligate the portal pedicle of the resected segment early, before parenchymal transection; (3) avoid unnecessary manipulation of the liver; and (4) obtain an adequate surgical margin [21]. For patients with single, nodular HCCs smaller than 5 cm in diameter and extranodular tumor growth, Yamamoto et al [22] reported that the rate of tumor microscopic vascular invasion is 34%. They further stated that systematized hepatectomy with Glisson's pedicle ligation and transection at the hepatic hilus, and resection of the sector in which tumors are located and supplied by the ligated pedicle are effective in decreasing tumor recurrence and prolonging survival. These results support the hypothesis that removal of the entire portal territory of one or more neoplastic segments with early extrahepatic ligation of the portal pedicle benefits patients with HCC, who subsequently have decreased postoperative tumor recurrence.

At present, microscopic vascular invasion has not yet been uniformly reported in the pathologic staging of HCC. In the TNM staging of HCC, the T classification is based on the size of the largest tumor nodule, the number and location of tumor nodules, and the presence of vascular or adjacent organ invasion. For the vascular invasion factor, the Liver Cancer Study Group of Japan's staging system [23] calls for the reporting of macroscopic vascular invasion only. The American Joint Committee on Cancer and the International Union Against Cancer staging systems for HCC [24] have specifically recommended the inclusion of gross and/or histologic tumor involvement of vessels. A criticism of this system is its inadequacy in predicting survival; it is also unnecessarily complex [25,26]. To further stratify patients adequately with respect to prognosis, several recent proposals address the problem of revision of the current TNM staging system by weighing microscopic vascular invasion more strongly [26–28]. Recently, Vauthey et al [26] proposed a simplified model of TNM staging based on vascular invasion (including major vascular invasion and microvascular invasion), tumor number, and tumor size, which incorporates the effect of fibrosis of liver on survival. In this study, the analysis of microscopic vascular invasion identified a subset of patients with single tumors and no vascular invasion (sT1) who had a favorable prognosis irrespective of tumor size, suggesting unique tumor biology.

The frequent presence of microscopic vascular invasion in HCC underlines the need for strict criteria in the selection of patients for liver transplantation. Recent reports clearly have indicated that vascular invasion, including macroscopic and microscopic invasion, was the most important negative factor associated with tumor recurrence after transplantation

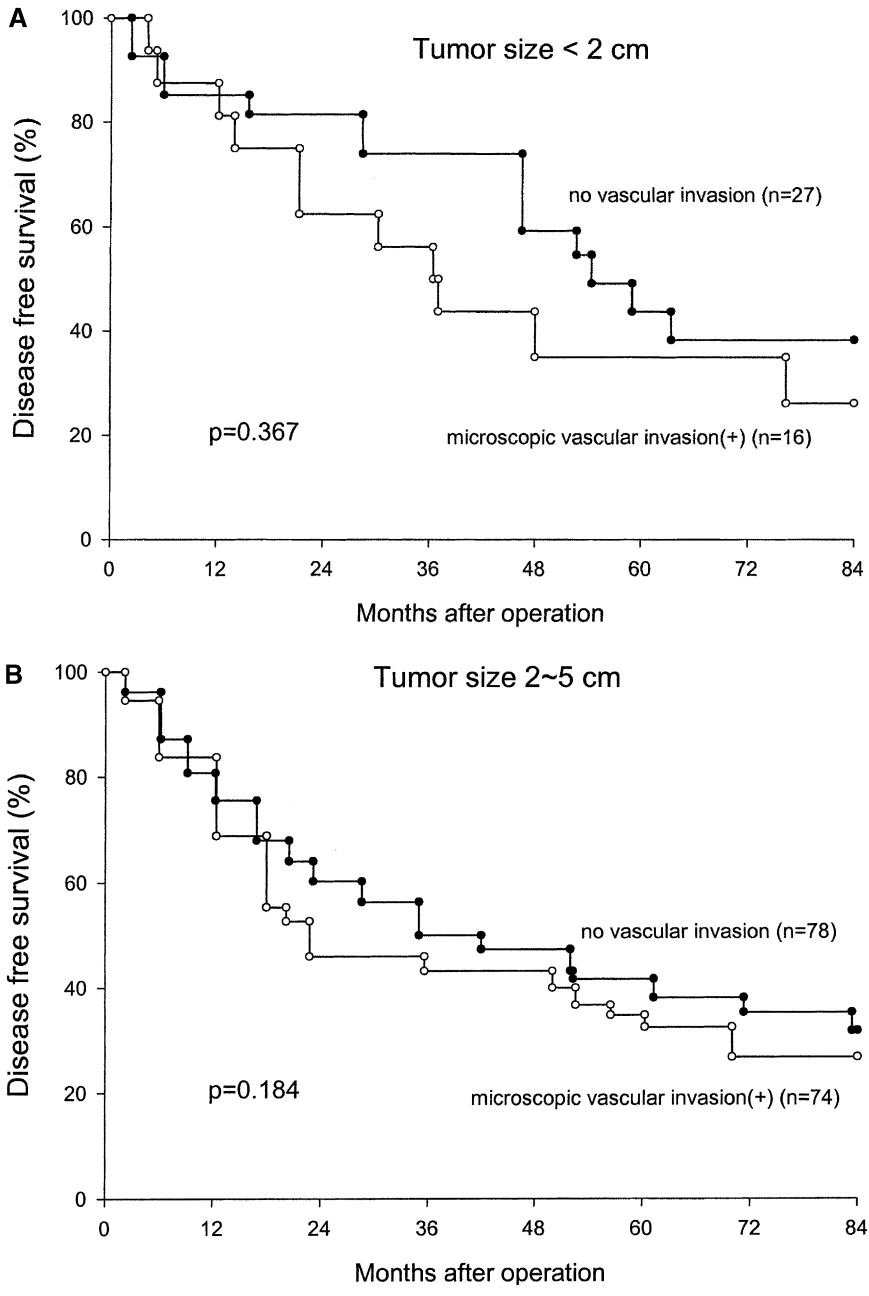

Fig. 4. Effects of microscopic vascular invasion in patients with hepatocellular carcinoma with (A) tumor size of <2 cm, (B) tumor size of 2–5 cm, (C) tumor size of 2–5 cm and surgical margin of >1 cm, and (D) tumor size of >5 cm.

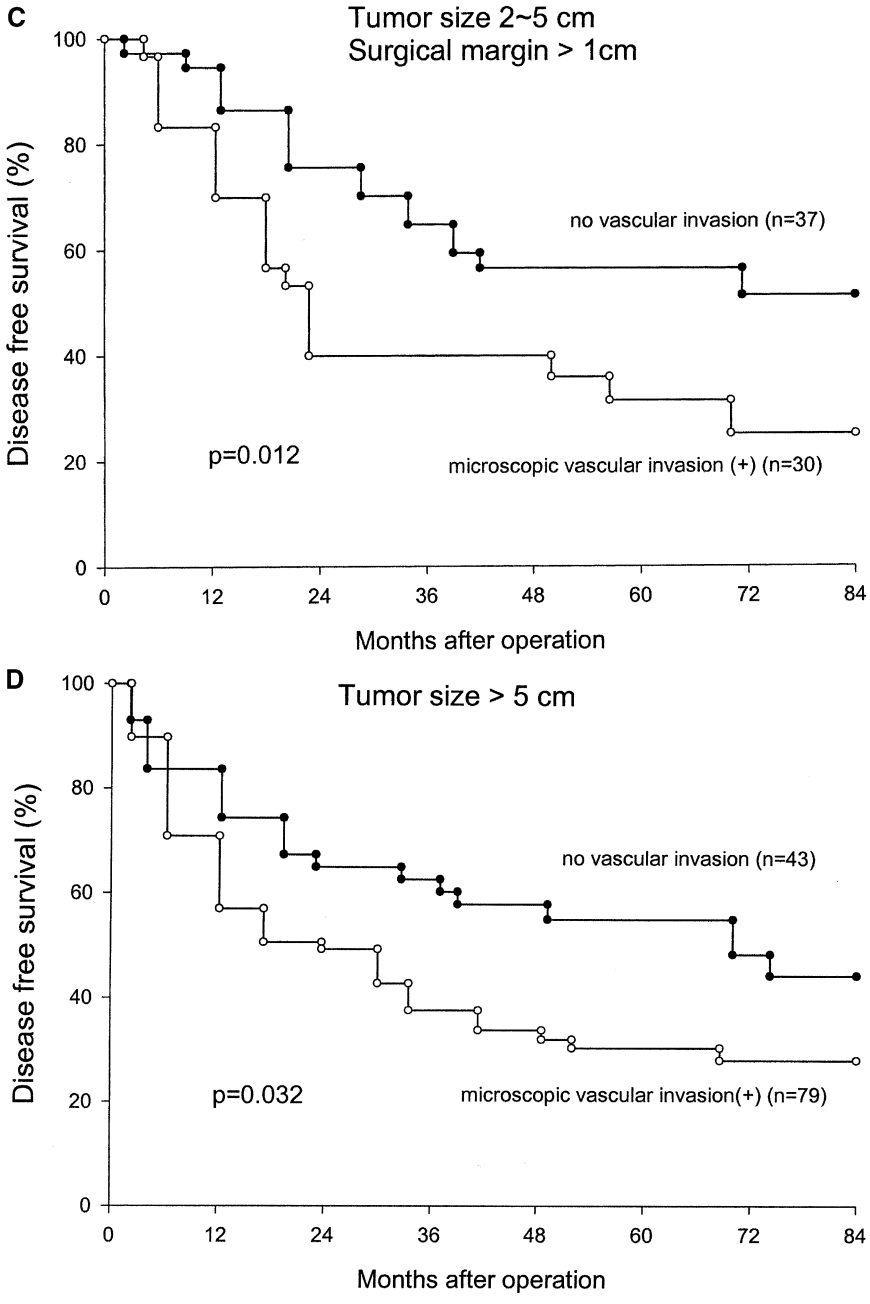

Fig. 4 (*continued*)

[13]. Patients with known vascular invasion should not be subjected to liver transplantation. It is also true that the larger the tumor, the more likely it is that vascular invasion will be present (see Fig. 2); however, some small tumors may have microscopic vascular invasion and carry a worse potential outcome than large tumors without vascular invasion. Currently, there is no reliable way of determining preoperatively which tumors have no vascular invasion and, because of the scarcity of organ donations and the disadvantage of immunosuppression in the presence of circulating tumor cells, proper selection of patients with small tumors (single HCC tumors of <5 cm or three nodules of <3 cm) for liver transplantation is necessary. For hepatic resection, which presently carries a very low operative mortality rate because of advances in surgical techniques and perioperative management [4], tumor size should not be regarded as a selection criteria, and resection of large tumors, where a complete resection is possible, remains justified [29]. A preoperative test that could identify vascular invasion or, possibly more important, identify circulating tumor cells [30], could allow more appropriate selection of patients who would benefit from liver transplantation or hepatic resection.

Considering the high frequency of microscopic vascular invasion in HCC, the development of effective postoperative adjuvant therapy is necessary to further improve patient survival. The protocols currently being used for adjuvant systemic chemotherapy after liver transplantation suggest some survival benefit [31,32]. For patients who undergo hepatic resection, postoperative systemic adjuvant chemotherapy with epirubicin has provided discouraging results, especially in patients with cirrhosis [33,34]. The possible role of postresectional intraportal therapy, with therapeutic agents administered directly into the portal venous system, in the treatment of patients with a high probability of tumor vascular invasion has not been reported. Prospective randomized clinical trials are needed to clarify the possible therapeutic benefit of this approach for this subgroup of patients with HCC.

In conclusion, microscopic vascular invasion is an important event in the biology of HCC and correlates with a higher risk of recurrence after resection. A better understanding of the development of vascular invasion and its clinical implication will improve the selection of patients at risk for microscopic vascular invasion and help target therapy to prevent recurrence following surgery.

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