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Original contribution

Histologic classification of microscopic portal venous invasion to predict prognosis in hepatocellular carcinoma

Nobuhiro Fujita MD[a], Shinichi Aishima MD, PhD[a,*], Tomohiro Iguchi MD, PhD[a], Yohei Mano MD[a], Akinobu Taketomi MD, PhD[b], Ken Shirabe MD, PhD[b], Hiroshi Honda MD, PhD[c], Masazumi Tsuneyoshi MD, PhD[a], Yoshinao Oda MD, PhD[a]

[a]*Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan*
[b]*Department of Surgery and Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan*
[c]*Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan*

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Summary Portal venous invasion is one of the most important prognostic factors after surgical resection of hepatocellular carcinoma. Microscopic portal venous invasion can be evaluated histologically. We examined 280 hepatocellular carcinomas with microscopic portal venous invasion (n = 125) or without it (n = 155) for 3 characteristics: the number of invaded portal vessels, the maximum number of invading carcinoma cells, and the farthest distance from the tumor. Univariate analysis of overall and disease-free survival revealed that the number of invaded portal vessels and the number of invading carcinoma cells were poor prognostic factors. Therefore, we classified patients with microscopic portal venous invasion into 2 groups: a high–microscopic portal venous invasion group, in which there were multiple invaded portal venous vessels (≥2) and more than 50 invading carcinoma cells (n = 57), and a low–microscopic portal venous invasion group, in which microscopic portal venous invasion was observed but with invasion of only a single portal venous vessel or fewer than 50 invading carcinoma cells (n = 68). The high–microscopic portal venous invasion group showed significantly higher α-fetoprotein levels, larger tumor size, and higher frequencies of poorly differentiated histology, capsule infiltration, and intrahepatic metastasis compared with the low–microscopic portal venous invasion group ($P = .0496$, $P < .0001$, $P = .0431$, $P = .0180$, and $P = .0012$, respectively). The high–microscopic portal venous invasion group showed poorer overall survival and disease-free survival rates than the low–microscopic portal venous invasion group ($P = .0004$ and $P = .0003$), and the high–microscopic portal venous invasion group was an independent prognostic factor for disease-free survival ($P = .0259$). We proposed a new definition for classifying microscopic portal venous invasion and documented the necessity of definite histologic evaluation of it.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm in the world and is especially common in East Asia and sub-Saharan Africa [1-3]. Despite recent advances in surgical techniques and preoperative management, patient

* Corresponding author.
E-mail address: saish@surgpath.med.kyushu-u.ac.jp (S. Aishima).

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survival remains unsatisfactory because of the incidence of recurrence after hepatic resection [4]. Portal venous invasion is the most frequent vascular invasion in HCC [5] and is closely related to intrahepatic recurrence [4]. It has been shown that blood flowing into the HCC is fed mainly via arterial tumor vessels as a result of neovascularization [6,7]. Such blood flowing into the HCC is drained mostly via portal veins around the tumor, especially in advanced HCC [8,9]. These results can explain why tumor cell invasion is observed more frequently in portal veins than in terminal hepatic veins [5,8].

Portal venous invasion has been identified as one of the most important prognostic factors regulating survival or recurrence after surgical resection of HCC [4,5,10-12]. Portal venous invasion can be divided into macroscopic and microscopic. Macroscopic portal venous invasion indicates the presence of tumor thrombus in the major branches of portal veins upon gross examination of a resected specimen. Microscopic portal venous invasion (MPI) indicates the presence of clusters of cancer cells in the portal veins upon histologic examination. The prognostic difference between macroscopic and microscopic vascular invasion has been described [13,14]. Tsai et al [13] reported that the patient survival rate in HCCs with macroscopic vascular invasion was lower than that in HCCs with only microscopic vascular invasion after resection. In addition, Vauthey et al [14] proposed a new, simplified staging for HCC based on vascular invasion, tumor number, and tumor size. In this staging, they also divided vascular invasion into microscopic and macroscopic; the latter was a poor prognostic factor. However, little is known about the concrete estimated MPI or the relationship between the degree of MPI of HCC and clinicopathologic findings including prognosis. The purpose of the present study was to investigate MPI in detail and to propose a new histologic classification of MPI in HCC.

2. Materials and methods

2.1. Patients

We obtained data on 319 patients who had undergone hepatectomy and been diagnosed with HCC from the files of the Department of Anatomic Pathology of Kyushu University (Fukuoka, Japan) between June 1992 and November 2003. Any cases with preceding therapy and a noncurative operation were excluded from this study. Portal venous invasion was evaluated based on the classification of the Liver Cancer Study Group of Japan [15]. *Macroscopic portal venous invasion* was defined as macroscopically observable tumor invasion of (or tumor thrombus in) second-order or more proximal branches of the portal vein. *MPI* was defined as microscopically observable tumor invasion of (or tumor thrombus in) distal to the second-order branches of the portal vein but not of the second-order branches. We macroscopically compared the resected specimen with preoperative radiologic evidence (computed tomography or magnetic resonance imaging) and intraoperative findings and determined second-order or more proximal branches of the portal vein. Macroscopic portal venous invasion was observed in 39 cases, and these cases were excluded from this study. As a result, 280 patients who were diagnosed as having HCC with MPI (n = 125) or without MPI (n = 155) were evaluated.

Table 1 summarizes the clinicopathologic characteristics of the 280 HCC patients we investigated. After the initial operation, ultrasonography and dynamic computed tomography were performed every 3 months in addition to a monthly measurement of α-fetoprotein. The median follow-up period was 1969 days (range, 30-5712 days).

We could not obtain written informed consent from all of the patients, so we removed identifying information for all samples before analysis for strict privacy protection. This procedure was in accordance with the Ethical Guidelines for Human Genome/Gene Research enacted by the Japanese Government. This study was approved by the Ethics Committee of Kyushu University (No. 22-27).

2.2. Histologic evaluation of MPI

All the resected specimens were sliced by a series of axial incisions approximately 3 to 5 mm apart. In all cases, the

Table 1 Summary of clinicopathologic findings of HCC

Clinical data	
Sex (male/female)	221/59
Age (y)	65 ± 0.5
HBsAg (+) (%)	19.6
HCVAb (+) (%)	68.6
Child-Pugh classification (A/B/C)	227/45/8
α-Fetoprotein (ng/mL)	17.0 ± 127.2
Pathologic data	
Tumor size (cm)	2.8 ± 0.1
No. of nodules (single/multiple)	217/63
Differentiation (well/moderate/poor)	31/196/53
Capsule formation (%)	68.6
Capsule infiltration (%)	61.8
Septum formation (%)	70.4
Serosal invasion (%)	43.9
MPI (%)	44.6
Hepatic venous invasion (%)	13.6
Bile ductal invasion (%)	3.9
Intrahepatic metastasis (%)	23.9
Liver cirrhosis (%)	43.9
No. of slides per centimeter of tumor dimension	2.3 ± 0.1
Surgical data	
Type of resection (major resection [a] (%))	36.8
Operation time (min)	290 ± 5.9
Blood loss (mL)	885 ± 63.2

NOTE. Continuous values are expressed as median ± SE. Abbreviations: HBsAg, hepatitis B virus antigen; HCVAb; HCV antibody.

[a] Segmentectomy, lobectomy, or extended lobectomy.