Early Detection and Curative Treatment of Early-Stage Hepatocellular Carcinoma

MASATOSHI KUDO
Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Osaka, Japan

The method for early detection of hepatocellular carcinoma (HCC) has been well-established in Japan by means of regularly screening patients at risk for developing HCC by using imaging and tumor markers. An important issue is the accurate characterization of nodular lesions found in cirrhotic livers. This problem has been addressed by development of imaging modalities such as ultrasonography angiography with intra-arterial injection of CO_2, computed tomography during hepatic arteriography, and computed tomography during arterial portography. It is most important to differentiate the typical hemodynamic patterns of low-grade dysplastic nodule including arterial hypovascularity with preserved portal perfusion from those of HCC characterized by arterial hypervascularity with decreased portal perfusion. At present, these findings are easily obtained by contrast-enhanced phase-invasion harmonic imaging, which is a noninvasive ultrasound technology. Radiofrequency ablation is an efficient technique to curatively treat early-stage HCC. The 5-year survival rate of RFA at our institution is 76%. Although local recurrence rate after curative RFA is as low as 6.2%, the intrahepatic distant metastasis is as high as 85% at 5 years. The prevention of intrahepatic distant recurrence by maintenance interferon therapy is thus very important. The 5-year survival rate and first, second, and third recurrence rates after curative RFA in patients who had maintenance interferon therapy were much better than those in patients who did not receive interferon therapy after curative RFA. In conclusion, recent progress in screening, diagnostic, and therapeutic strategy for early-stage HCC has improved the prognosis of patients with HCC. Furthermore, advances of prognostic staging system, such as Japan Integrated Staging score, facilitate the management of HCC.

Early detection and characterization of hepatocellular carcinoma (HCC) are important in improving prognosis of patients with HCC. To characterize such nodular lesions correctly, evaluation of intranodular hemodynamics is of value, because pathologic findings or malignancy grades of HCC are closely related to intranodular hemodynamics. In addition, curative treatment and prevention of recurrence after curative treatment are other important issues.

In this article, the methods for early detection of HCC and its differentiation from premalignant and/or borderline lesions as well as curative treatment including maintenance interferon therapy are described.

Early Detection of Hepatocellular Carcinoma

In Japan, the screening protocol for early detection of HCC has been established during the past 2 decades. Patients with chronic viral hepatitis/liver cirrhosis caused by HBV or HCV infection are regarded as high risk for developing HCC. Regular follow-up by ultrasonography (US) every 3 months and measurements of tumor markers including alpha-fetoprotein, its activity to bind with *Lens culinaris* agglutinin A and protein induced by vitamin K absence or antagonist-II every month, have made it possible to detect HCC in an early stage. However, it has brought about another problematic issue that the more frequently US is performed, the more small nodular lesions are detected in the liver, along with increasingly more lesions not diagnosed as overt HCC. This is a very important problem that needs to be addressed and solved.

Differential Diagnosis of Overt Hepatocellular Carcinoma, Early Well-Differentiated Hepatocellular Carcinoma, and Low-Grade Dysplastic Nodule

Intranodular Hemodynamics of Overt Hepatocellular Carcinoma

Because afferent blood vessels of an overt HCC are from the hepatic artery, intranodular hemodynamics in

Abbreviations used in this paper: CT, computed tomography; CTAP, computed tomography during arterial portography; CTHA, computed tomography during hepatic arteriography; HCC, hepatocellular carcinoma; JIS, Japan Integrated Staging; LGDN, low-grade dysplastic nodule; PEIT, percutaneous ethanol injection; RFA, radiofrequency ablation; US, ultrasonography.

1542-3565/05/$30.00
PII: 10.1053/S1542-3565(05)00712-3

HCC are characterized by arterial neovascularization and absence of portal venous flow.[1,2] In contrast, the hemodynamic pattern of a premalignant lesion (low-grade dysplastic nodule [LGDN]) or a borderline lesion manifests itself with poor arterial vascularity and the presence of portal supply or an increase thereof.[3,4] The imaging diagnosis of HCC and premalignant lesions is based on such characteristics of intranodular hemodynamics.

Angiography is not always efficient in demonstrating arterial hypovascularity or portal venous flow in small nodules less than 1.5 cm in diameter, as previously reported. Rather, US angiography and computed tomography during hepatic arteriography (CTHA) are more sensitive in detecting intranodular arterial vascularity. Computed tomography during arterial portography (CTAP) also is a sensitive tool in detecting portal perfusion within a nodule,[5,6] enabling differentiation of overt HCC from a premalignant lesion. Likewise, color Doppler imaging is useful in detecting afferent portal venous flow in premalignant lesions.[7] Recently, contrast-enhanced US with intravenous injection of a contrast agent, Levovist (Schering, Berlin, Germany), has been reported to be useful in evaluating portal perfusion within the nodule, leading to improved differentiation of LGDN from overt HCC.[8–12]

Hemodynamics of Well-Differentiated Hepatocellular Carcinoma in an Early Stage

Most well-differentiated HCCs in an early stage do not stain on angiography or retain iodized oil within the tumor, thereby making the diagnosis difficult.[6] It is also well-known that some well-differentiated HCCs in an early stage are fed by the portal vein, not by the hepatic artery, unlike typical HCCs.[13–15] Therefore, some hypovascular HCCs (early-stage HCCs) show no perfusion defects on CTAP and might look like benign nodules with "benign-appearing" patterns of the vasculature.[9] Color Doppler imaging also picks up afferent portal flow signals.[7,16] With the exception of these nodules having a benign-appearing hemodynamic pattern, the diagnosis of HCC is possible even in its early stage by a combined use of tomographic vascular imagings, including US angiography, CTHA, and CTAP.[6,13,17]

Role of Harmonic Imaging in the Characterization of Hepatocellular Carcinoma and Low-Grade Dysplastic Nodule

Detection of Arterial and Portal Flows in Hepatocellular Carcinoma

Contrast-enhanced harmonic imaging[8,10,11,18] detects intratumoral vascularity in more than 95% of HCCs; no blood signals are observed only in the remaining 5%. Likewise, 98% of HCC nodules show hypervascularity and/or isovascularity on dynamic computed tomography (CT). Therefore, the detection rate of intratumoral vascularity is not different between contrast harmonic US and CT.[8,10]

In the hypervascular HCCs, contrast-enhanced harmonic US images tumor vessels originating in the periphery and infiltrating into the center of tumors and having irregular branches. Most HCCs show heterogeneous or homogeneous staining of tumor parenchyma, which is hyperechoic on the gray scale background in comparison with surrounding liver parenchyma. Perfusion defects in the postvascular phase, as a result of fast washout from the nodule, are other characteristics of these HCCs.

Low-Grade Dysplastic Nodule

Contrast-enhanced harmonic US in the early arterial phase depicts no blood vessels in any LGDNs. In the late vascular phase and postvascular phase, it can detect isovascular staining in 75% and hypervascular staining in 12.5% of them, pointing to a portal venous supply in them. The sensitivity and specificity of LGDN pattern are 75% and 100%, respectively, with the positive and negative predictive values of 100% and 99%, respectively. In contrast, dynamic CT images low attenuation only in the arterial phase in all the dysplastic nodules; it is accompanied by isoattenuation in the portal and delayed phase in 75% of LGDNs. Therefore, the rate of detecting intranodular vascularity in LGDNs is comparable between contrast-enhanced harmonic US and dynamic CT.[8,10] Recently, pure arterial phase imaging, a novel contrast US technique, clearly showed portal venous flow within the LGDN, which is proved by CTAP.

Radiofrequency Ablation

Radiofrequency ablation (RFA) is a new therapeutic technique in which dielectric heating caused by radiofrequency waves (460 $\pm$ 5 Hz) in the region around the electrode inserted in a lesion almost fully coagulates and necrotizes liver tumors.

RFA uses an expandable or cool-tip electrode needle, and single coagulation is able to necrotize a total area of about 3–4 cm. Accordingly, curative ablation for a tumor measuring 3.0 cm or less can be completed with a single treatment session. The current indications are 3 or fewer tumors measuring 3 cm or less or a solitary tumor with a major axis of 5 cm or less. Because local occlusion of hepatic blood flow, by using a balloon or transcatheter arterial embolization, increases the coagulated area in RFA, this combination has been used successfully.