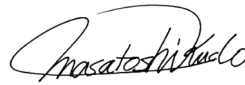**Editorial**

Early Hepatocellular Carcinoma: Definition and Diagnosis

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Editor *Liver Cancer*

Early hepatocellular carcinoma (HCC) can be described as "early" according to its pathological characteristics as well as its clinical characteristics. Taking the pathological approach first, the term "early" implies that a lesion is at a relatively early stage of carcinogenesis and prognosis is still good. Well-differentiated HCC is not necessarily early HCC. According to the clinical approach, the term "early" is used to differentiate HCC diagnosed in its early developmental stage from that diagnosed at more advanced stages. The clinical approach to diagnosing early HCC is used preferentially in the United States and Europe and, in general, this conceptualization of early HCC refers to tumors smaller than 3 cm and three or fewer in number at stage A (early stage) with respect to Barcelona Clinic Liver Cancer staging, although it sometimes includes solitary tumors up to 5 cm in size, as defined in the Milan criteria. Both very early and early stage tumors are relatively small, but both are hypervascular in the arterial phase and are regarded as classic HCC.

The pathological approach, however, defines early HCC as HCC in the early stage of carcinogenesis (generally ≤2 cm) that is often hypovascular with irregular boundaries on diagnostic imaging and contains portal elements without significantly affecting the original structure of the liver. The pathological characteristics of HCC include its multistep progression from a low-grade to a high-grade dysplastic nodule, to early HCC, and eventually to classic hypervascular HCC [1](fig.1). Accordingly, the accurate diagnosis and proper treatment of early HCC, a precursor of classic (typical) HCC, is extremely important. Therefore, I will discuss here the pathological aspects of early HCC.

According to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer developed by the Liver Cancer Study Group of Japan [2], early HCC is defined as follows. Early HCC exhibits focal structural abnormalities such as acinar or pseudoglandular structures, broken or irregular trabecular alignment, and/or obvious invasion of the stromal tissue. Cellular atypia is usually unremarkable, but the nuclear–cytoplasmic ratio is increased due to decreased amounts of cytoplasm. The cytoplasm also shows eosinophilia or basophilia. The cell density may be more than twice that of the surrounding non-cancerous liver tissue. In addition, lesions often exhibit fatty changes or clear cell changes. Because the cancer cells of early HCCs do not grow expansively, they instead proliferate by replacing ad-
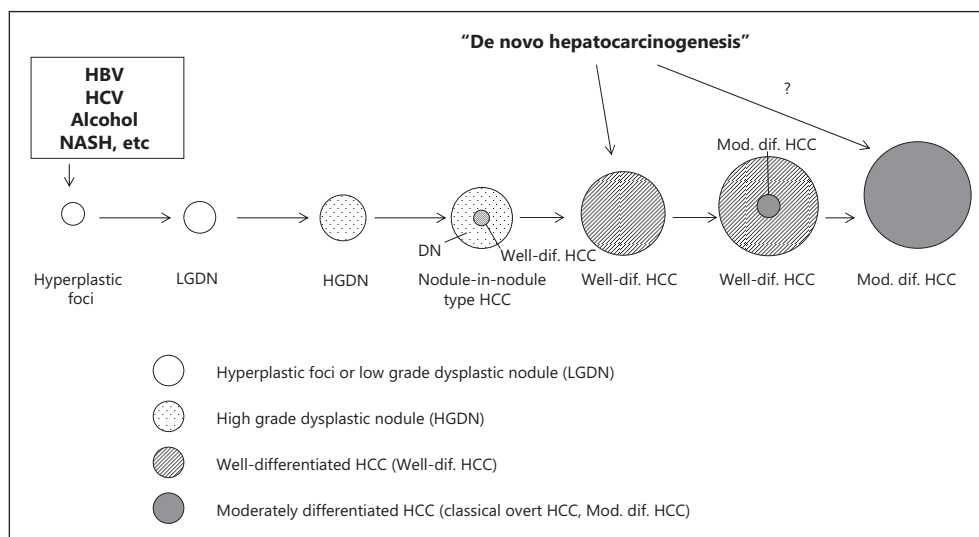
Fig. 1. Schematic representation of multistep progression of human hepatocarcinogenesis. HBV= hepatitis B virus; HCV=hepatitis C virus; NASH=nonalcoholic steatohepatitis.

jacent hepatocytes in a trabecular arrangement at the boundary with surrounding liver tissues, resulting in a poorly demarcated margin. Macroscopically, the lesions are classified as small nodules with indistinct margins [3]. These criteria for early HCC have already gained international consensus [4] and have been incorporated into the World Health Organization's latest "blue book" on digestive system tumors [5]. In addition, several molecular markers for the pathological diagnosis of early HCC have been identified, including heat-shock protein 70 (HSP70) [6], glypican-3 (GPC3) [7], glutamine synthetase (GS), cyclase-associated protein 2, and Bmi-1. Using HSP70, GPC3, and GS markers in combination, the sensitivity and specificity of early HCC diagnosis can be as high as 72 and 100%, respectively [8].

However, accurate differentiation of early HCC from dysplastic nodules is possible only when stromal invasion is found in resected specimens. In other words, differential diagnosis between early HCC and dysplastic nodules is often not possible without the findings of stromal invasion on biopsy. Differentiating between these two types of lesions with imaging used to be challenging, even when using computed tomography (CT) during hepatic arteriography/CT during arterial portography (CTHA/CTAP).

However, the subsequent introduction of gadolinium (Gd)-ethoxybenzyl (EOB)-diethylenetriamine pentaacetic acid (DTPA)-enhanced magnetic resonance imaging (Gd-EOB MRI) has proven to be a major breakthrough in the diagnosis of early HCC. Gd-EOB-DTPA is endocytosed into liver cells via organic anion transporter 8 [9, 10]. Because early HCC appears on Gd-EOB MRI images as a hypointense nodular lesion and a dysplastic nodule appears as an iso- or hyperintense lesion on the hepatobiliary phase, the diagnostic accuracy of early HCC is now generally ≥95% [11–13]. Moreover, previous studies have followed up the natural course of hypovascular nodules with hypointense signals on the Gd-EOB MRI hepatobiliary phase and reported that, even if early HCC is ruled out on biopsy, there is a high probability that this type of hypovascular nodule will undergo hypervascular change and transform into typical HCC [14–16]. In other words, even if biopsy excludes early HCC, hypovascular nodules that are hypointense on the Gd-EOB MRI hepatobiliary phase may be regarded as early HCC. At any rate, such lesions can be considered as nodular lesions with a high potential to transform to HCC.

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Reflecting this clinical background, the HCC clinical practice guidelines used in Japan [17] already include a specific algorithm for the diagnosis and treatment of early HCC, whereas the HCC clinical practice guidelines used in the United States and Europe (AASLD and EASL-EORTC guidelines [18, 19]), as well as those in other Asian countries [20], do not contain criteria for the diagnosis and treatment of early HCC. This is a clear indication that, compared with other countries, HCC screening and diagnostic skills are well advanced in Japan, owing in large part to the sophisticated nationwide surveillance system for HCC [21]. Developing measures to identify hypervascular HCCs while they are still curable is currently the biggest challenge facing the United States, Europe, and other Asian countries, where effective nation-wide surveillance systems for HCC have not been established. In contrast, the current focus in Japan, where small hypervascular HCCs are routinely diagnosed, is to differentiate early HCC correctly from dysplastic nodules and to develop effective treatment for early HCC defined in accordance with its pathological conceptualization. It is not an overstatement to say that the large gap between Japan's HCC screening/diagnostic capabilities and those of other countries manifests as a large difference in awareness and management of early HCC.

In conclusion, we sincerely hope that other countries will follow the Japanese approach and develop effective nationwide surveillance systems for HCC and join us in constructive dialog aimed at improving the diagnosis and treatment of early HCC.

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