Imaging studies for detection of early stage hepatocellular carcinoma

Department of Diagnostic Radiology, National Cancer Center Hospital, Tokyo
Kenichi Takayasu, M.D.

Background

The screening program of high risk group for hepatocellular carcinoma (HCC) with ultrasonography and alpha-fetoprotein measurement has enabled early detection of small HCC less than 3 cm. At the same time, a vague nodular lesion with indistinct margins less than 1.5 cm has been frequently encountered\(^1\)\(^-\)\(^3\). Most of these lesions are associated with overt HCC in an identical liver, and are shown as hypodense or hypovascular lesion on dynamic CT or angiography\(^4\)\(^-\)\(^6\). These features contrast with overt HCC, most of which show hyperdense or hypervascular lesion with an enhanced ring formation.

Classifications of nodular hepatocellular lesions

To establish a common histological criteria for the various hepatocellular nodules, a new classification was proposed by the Liver Cancer Study Group of Japan in 1992\(^7\). They divided into six categories: large regenerative nodule, adenomatous hyperplasia (AH), atypical AH, early HCC of the well-differentiated type (early HCC), well-differentiated HCC, and moderately or poorly differentiated HCC.

Subsequently, a new classification for nodular hepatocellular lesions was introduced by the International Working Party of the World Congress of Gastroenterology in 1994\(^8\). In this classification, four categories are proposed: low-grade dysplastic nodule, high-grade dysplastic nodule, well-differentiated HCC, and HCC. Therefore AH and atypical AH corresponded to low-grade and high-grade dysplastic nodule, respectively, the term of early HCC was recommended to be discontinued. The most difficult point among the two classifications was how to categorize early HCC into the high-grade dysplastic nodule or small HCC. Big confusion has occurred in the field of pathology and radiology.

In 2000, a guide book of Pathology and Genetics, Tumours of the Digestive System was published from the World Health Organization (WHO)\(^9\), in which the term of early HCC is used on a parallel with
dysplastic nodule, mainly due to the lack of objective phenotypic or genotypic marks to definitively differentiate early HCC from AH and/or atypical AH. Recently, the novel study, in which early HCC could be differentiated from AH and atypical AH with heat–shock protein 70 (HSP70) as a sensitive molecular marker, was reported in 2003\(^10\). With this marker, the differential diagnosis of precancerous lesions and early HCC could be more precise in clinical settings.

In the present paper, the hepatocellular lesion was defined as early HCC when the following criteria was satisfied: increased cell density twice that of the surrounding tissue in addition to structural abnormality and stromal invasion\(^2\) \(^7\).

**Multistep progression of hepatocarcinogenesis**

Clinical and pathological study revealed multistep progression of hepatocarcinogenesis: from AH to early HCC, nodule–in–nodule type HCC, and finally to overt HCC\(^3\) \(^11\). As another pass way, de novo progression is also presumed. Spontaneous regression is also recognized during follow–up period of some nodular lesions.

**Implication of enhancement or staining of nodular hepatocellular lesions**

For the radiologist and hepatologist who are concerning treatment of HCC, whether the lesion with no tumor stain is enhanced or not by follow–up dynamic CT, MRI and/or US is very important. Once the lesion evolved in chronic liver disease shows enhancement partially or entirely, it suggests that the lesion obtains malignant potential and some treatment is necessary.

Hemodynamic study with combination of angiography and CT showed the good correlation between blood supply and grade of malignancy of hepatocellular nodules\(^2\).

**Images of early HCC**

Ultrasonography demonstrates a small lesion without mosaic appearance or halo. The lesions were hypoechoic in 50\%, hypechoic in 40\%, and mixed echoic in 10\% in our study. The hypechoic feature sometimes reflects steatosis of tumor cells and the hypoechoic may be due to the homogeneously compacted cells or hyperplastic change.

The overall sensitivity of CT for early HCC was 56\%; 24\% on unenhanced CT, 31\% in the arterial dominant phase of contrast enhanced CT, and 51\% in the parenchymal phase\(^9\). Enhancement of early HCC in the arterial dominant phase was seen in only 5\%. The most common pattern among detected
early HCCs on CT was iso-iso-hypo dense pattern in 22%, followed by hypo-hypo-hypo pattern in 19%, among others. The lesions with hypo density on unenhanced CT tended to have moderate to high degree of fatty change within it.

The combination study of angiography and helical CT is helpful in assessing tumor number and characterizing tumor nature in a candidate patient for surgery. CT arterial portography (CTAP) and CT hepatic arteriography (CTHA), the catheter inserted in the superior mesenteric artery and in the proper hepatic artery, respectively, are used to evaluate the hemodynamics of portal blood flow and hepatic arterial flow within the lesion. CTAP disclosed 66% of early HCC as a hypo dense nodule and 34% as iso dense (not detected, suggesting the lesion having portal supply within it). While, CTHA showed 55% of lesions with hypo density, 30% with iso, and only 15% with hyper density. Twenty seven percent of lesions were shown as hypo attenuating on both CTAP and CTHA, suggesting that these early HCCs received relatively lower blood supply from the portal and arterial blood flow than the surrounding parenchyma\textsuperscript{13}. The findings were much different from those of small overt HCCs.

On T1 weighted images, 53% of early HCC were iso intense and 45% were hyperintense, and on T2-weighted images, 85% of them were iso intense\textsuperscript{14}.

Hepatic arteriography was able to detect only 9% of early HCC \textsuperscript{15}.

**Images of adenomatous hyperplasia and atypical adenomatous hyperplasia**

The mean diameter of these lesions decreased: 0.8 cm in AH and 1.2 cm in atypical AH which were significantly smaller than that of early HCC (1.4cm). The detection rates for a total lesion of AH and atypical AH were 23% on US, 4% on CT, 40% on CTAP, and 25% on CTHA\textsuperscript{16}. The features on CT and CTHA were almost similar to those of detected early HCC; a hypo attenuating nodule.

**Images of nodule-in-nodule type HCC (previously called as an early advanced HCC)**

When dedifferentiated component (moderately differentiated HCC) emerging within a well differentiated HCC (early HCC) grows expansively, the lesion often demonstrates a nodule-in-nodule appearance. The arterial dominant dynamic CT disclosed that the central portion alone becomes hyperdense and the peripheral portion iso- or hypodense, and in the parenchymal phase the entire nodule became hypodense\textsuperscript{17}. In other words, the CT density behavior of central and periphery portions of nodule-in-nodule HCC was similar to that of isolated early HCC and isolated advanced HCC,
respectively.

T1-weighted images showed central hypo- and peripheral hyperintensity, and T2-weighted image should central hyper- and peripheral iso- or hypointensity, which features were seen in one third to one-half of this tumor. Dynamic MRI with Gd-DTPA demonstrated similar findings to those of dynamic CT.

**Natural course of borderline lesion and/or early HCC**

The borderline lesion and/or early HCC demonstrated as hypo-hypo/iso-hypo dense pattern on unenhanced, arterial and parenchymal phases of dynamic CT, respectively, were periodically followed up mainly on CT without any treatment. Our recent study revealed that approximately 40% of 60 hypodense nodules changed to hyperdense. Malignant transformation occurred directly from borderline lesion and/or early HCC to overt HCC, or via a subsequent progress of nodule-in-nodule type HCC in some lesions.

**Conclusions**

The differential diagnosis of early HCC from the precancerous lesions, is still difficult by histopathology alone due to very well differentiated histology with little atypia in early HCC. But is could be possible with recent development of molecular technology. Meanwhile, the imaging modality contributes to differentiate early HCC from nodule-in-nodule and overt HCCs and to study the natural course of hepatocarcinogenesis.

**References**