■ REVIEW ■

Hepatocarcinogenesis in Liver Cirrhosis: Imaging Diagnosis

Hepatocellular carcinoma (HCC) frequently occurs in association with liver cirrhosis, as chronic liver disease is one of the most important factors in carcinogenesis. In addition to HCCs, recent reports of pathologic studies of resected specimens from cirrhotic liver describe associated small nodular lesions such as regenerative nodule, dysplastic nodule (adenomatous hyperplasia), and dysplastic nodule with subfocus of HCC (early HCC). In hepatocarcinogenesis of the cirrhotic liver, a regenerative nodule might be the first step in the development of HCC, going through phases of dysplastic nodule, early HCC and early advanced HCC in a multistep fashion. Fortunately, recent advances in various imaging techniques have facilitated the verification of these nodules. In this review, new nomenclature of small hepatocellular nodules, and detection and characterization of hepatic nodules in carcinogenesis with various imaging techniques are described with focus on the premalignant lesions and early stage of HCC. In addition, the efficacy of various imaging techniques for diagnosing them is discussed. Although the terms and definitions of these nodules are still variable and controversial, familiarity with the concept of these borderline lesions is important.

Key Words : Liver neoplasms; Liver cirrhosis; Ultrasonography; Tomography, X-ray computed; Magnetic resonance imaging

Byung Ihn Choi

Department of Radiology and Institute of Radiation
Medicine, Seoul National University College of
Medicine, Seoul, Korea

Received : February 7, 1998

Accepted : February 25, 1998

Address for correspondence

Byung Ihn Choi, M.D.
Department of Radiology, Seoul National University
Hospital, 28, Yongon-dong, Chongno-gu, Seoul,
110-744, Korea
Tel : (02) 741-4581, Fax : (02) 743-6385
E-mail : choibi@radcom.snu.ac.kr

*This study was supported by a grant (#HMP-95-G-1-1) of the 1997 Highly advanced National projects on the development of Biomedical Engineering and Technology.

INTRODUCTION

Early detection of hepatocellular carcinoma (HCC) is important, since the most effective treatment for HCC is surgical resection or local ablation therapy when the tumor is small. Fortunately, recent advances in liver imaging techniques have facilitated the detection of small HCCs (1).

HCC frequently occurs in association with liver cirrhosis, as chronic liver disease is one of the most important factors in carcinogenesis. In addition to small HCCs (less than 2 cm in diameter), recent reports of pathologic studies of resected specimens from cirrhotic liver describe associated small nodular lesions (i.e., regenerating nodule, adenomatous hyperplasia, and early HCC). In hepatocarcinogenesis of the cirrhotic liver, a regenerating nodule might be the first step in the development of HCC, going through phases of adenomatous hyperplasia and early HCC in a multistep fashion (1).

In this review, new nomenclature of small hepatocellular nodules, and detection and characterization of hepatic nodules in carcinogenesis with various imaging techniques will be described with focus on the pre-

malignant lesions and early stage of HCC. In addition, the efficacy of various imaging techniques for diagnosing them will be discussed.

HEPATOCARCINOGENESIS

General consideration

Recently, the increase in the number of resected liver specimens containing relatively small HCCs has given pathologists an opportunity to examine HCC lesions earlier in the course of the disease. Subsequently, Sakamoto et al. (2) proposed the stepwise development of HCC from regenerating nodules of liver cirrhosis through multiple steps in hepatocarcinogenesis. If chronic liver disease is the most important factor precipitating HCC, a regenerating nodule arising in the liver might be the first step in hepatocarcinogenesis, subsequently developing into a HCC through adenomatous hyperplasia, atypical adenomatous hyperplasia, early HCC in a multistep fashion (Fig. 1). The distinguishable criteria at each step are the size and cellularity of the atypical lesion - the size and

Fig. 1. Drawing shows stepwise development and growth of hepatocellular carcinoma (HCC). AH=adenomatous hyperplasia, AAH=atypical adenomatous hyperplasia, DN=dysplastic nodule, eHCC=early HCC. (Modified from reference 1).

cellularity of atypical lesions tend to increase in order from adenomatous hyperplasia to atypical adenomatous hyperplasia to early HCC. The distinctions between each step are not always clear, which suggests a continuous transition (1).

Regenerating nodules are composed of hepatocytes surrounded by fibrosis. They are formed by replication of hepatocytes that compress the surrounding stroma or collagen and thus distort the lobular architecture of the liver. In patients with hepatitis B cirrhosis, regenerating nodules are often large because several hepatic lobules are incorporated to form a large regenerative nodule, and septa are usually thin and the collagen is loose as compared with collagen in cases of alcoholic cirrhosis (3) (Fig. 2).

Adenomatous hyperplasia is defined as a nodular lesion significantly larger than other regenerating nodules in the cirrhotic liver and usually larger than 1.0 cm (Fig. 2). The lesion has no capsule but has portal area containing blood vessels and the bile duct (4) whereas advanced HCC can have capsule even though the tumor is small (Fig. 2). Histologically, the cell density is moderately increased in comparison with the surrounding tissue, however, no evident structural abnormalities are present. Due to the slight decrease of amount of cytoplasm, the nuclear/cytoplasmic ratio is slightly increased. Also, there is often heterogeneity of nuclear size. The cord structure often appears more prominent than that of the surrounding tissue (5, 6). Some areas of adenomatous hyperplasia contain atypical hepatocytes or obvious malignant foci. Therefore, this entity is divided into three histologic types: adenomatous hyperplasia without atypia (ordinary adenomatous hyperplasia), atypical adenomatous hyperplasia, and adenomatous hyperplasia with malignant foci. Atypical adenomatous hyperplasia is considered an intermediate stage between benign and malignant lesions.

Fig. 2. Gross pathology of hepatocellular nodules in liver cirrhosis. Photograph of the resected specimen of the liver shows two well circumscribed hepatocellular nodules (arrow and curved arrow) in macronodular cirrhotic liver. Regenerative nodules (short arrows) are small and scattered in the entire resected specimen. Dysplastic nodule (adenomatous hyperplasia; arrow) is significantly larger than regenerative nodules and shows reddish yellow cut surface. Small advanced hepatocellular carcinoma (curved arrow) is larger than the dysplastic nodule, and shows similar cut surface to that of dysplastic nodule.

Adenomatous hyperplasia with malignant foci is thought to be an early stage of HCC (Fig. 1). In these lesions, areas with different degrees of atypia appear in an area-in-area or nodule-in-nodule pattern. Microscopically, early HCC is well differentiated and shows structural atypia such as a thin trabecular pattern or acinus formation and increased cellularity with slight nuclear atypia; it differs from advanced HCC in that it has no pseudocapsule and shows no destruction of underlying liver structure (2, 7).

Early advanced HCC has been recently considered a transitional tumor between early HCC and advanced HCC. Japanese investigators describe that this nodule is advanced HCC within early HCC (8). Pathologically, it consists of a definite cancerous nodule of advanced HCC (Edmondson grade II or higher) that is large enough to be detected at gross examination, surrounded by a rim of early HCC (Edmondson grade I). On cut surface examination, the early component of early advanced HCC is relatively flat and red-yellow to yellow in color. The advanced component is usually but not always distinct as a discrete nodular lesion that often bulges out from the surface of the surrounding liver at gross examination (8).

An advanced HCC nodule within early advanced HCC is large enough to be detected at gross examination (7) and usually shows hypervascularity (9). In addition, recent histologic studies (10, 11) of specimens obtained surgically and by sonographically guided fine-needle biopsy have indicated that most HCCs at an early stage are well

differentiated. Kenmochi et al. (12) also suggested that as the tumor grows, foci of less differentiated malignant tissue arise in the well-differentiated HCC tissue.

Some small HCCs without a background of adenomatous hyperplasia have also been reported (12, 13), suggesting another pathway of hepatocarcinogenesis (i.e., de novo HCC). In the United States and other Western countries, HCC may arise de novo from a relatively normal liver without a background of hyperplastic nodules (14). However, in the Far East, HCC develops mainly by means of a multistep process in patients with chronic liver disease (1, 15, 16).

Terminology

Terminology of nodular hepatocellular lesions are still

confusing. Because pathogenetic and etiological concepts evolve, incorporation of these concepts increases the opportunity for obsolescence (17). The presumed premalignant nodular lesions in cirrhotic liver have a perplexing terminology in the literature, including adenomatous hyperplasia, macroregenerative nodules, adenomatoid hyperplasia, dysplastic nodules, and hepatocellular pseudotumors (17-19). To clarify the nomenclature, the new term "dysplastic nodule" has recently been introduced and replaces several previously used terms (17, 18). Dysplastic nodules are divided into low- and high-grade nodules. Low-grade dysplastic nodules have commonly been referred to as ordinary adenomatous hyperplasia or, occasionally, as "macroregenerative nodule type I". High-grade dysplastic nodules have commonly been referred to as atypical adenomatous hyperplasia or, occasionally, as

Table 1. Terminology for hepatocellular nodules

Suggested term	Available name	Synonym and related term
Monoacinar regenerative nodule	Micronodular regeneration	Miliary hepatocellular adenomatosis, nodular transformation, micronodular transformation, macronodular transformation, multiple nodular hyperplasia, noncirrhotic nodulation, multiple hepatocellular adenomatosis
Multiacinar regenerative nodule	Macronodular regeneration	Macroregenerative nodule, large regenerative nodule, macroregenerative nodule types I and II, partial nodular transformation, adenomatous hyperplasia, adenomatoid hyperplasia, cirrhotic pseudotumor
Lobar or segmental hyperplasia	Compensatory lobar hyperplasia	Atrophy-hypertrophy complex
Monoacinar cirrhotic nodule	Micronodular regeneration associated with cirrhosis	Micronodule
Multiacinar cirrhotic nodule	Macronodular regeneration associated with cirrhosis	Macronodule
Focal nodular hyperplasia	Nodular hyperplasia, focal	Focal cirrhosis, pseudo-cirrhosis, mixed hamartoma, hamartomatous cholangiohepatoma, solitary hyperplastic nodule, nodular transformation type 2, and mixed adenoma
Hepatocellular adenoma	Hepatocellular adenoma	Benign hepatoma, minimal deviation hepatoma, multiple adenomas, multiple hepatocellular adenomatosis, adenomatosis
Dysplastic focus	Focal hepatocellular dysplasia	Adenomatous regeneration, adenomatoid hyperplasia
Dysplastic nodule	Nodular regeneration with dysplasia	Adenomatous hyperplasia, borderline lesion, macroregenerative nodule, hyperplastic nodule, atypical macroregenerative nodule, regenerative nodule, nodular hyperplasia, adenomatoid hyperplasia, ordinary adenomatous hyperplasia, atypical adenomatous hyperplasia, adenomatous regeneration, normotrabeular hepatocellular carcinoma, early hepatocellular carcinoma, hepatocellular pseudotumor
Hepatocellular carcinoma	Hepatocellular carcinoma	Early hepatocellular carcinoma, hepatoma, malignant hepatoma, hepatocarcinoma

Modified from reference 17.

macroregenerative nodule type 2 (7-19). A dysplastic nodule may also contain a microscopic area of HCC, and it is then called a "dysplastic nodule with subfocus of HCC" that was previously referred to as early HCC (18).

Suggested terms from International Working Party instead of available name or synonym are listed in Table 1. International Working Party recommends to discontinue use of synonyms or related terms (17).

Terms may be modified from the basic vocabulary above. When insufficient criteria are present to arrive at a diagnosis, a term such as hepatocellular nodule of uncertain type or hepatocellular nodule of uncertain malignant potential may be used. Some observers may prefer to diagnose dysplastic nodules without applying a grade. These modifications may be especially appropriate when the entire lesion is not available for study (17).

IMAGING DIAGNOSIS OF NODULAR LESIONS IN HEPATOCARCINOGENESIS

Diagnostic imaging techniques

A variety of imaging modalities, including ultrasound (US), computed tomography (CT), magnetic resonance (MR), nuclear medicine, and angiography are currently used in evaluating patients with chronic liver disease and suspected HCC. Further technological advancement will undoubtedly have a major impact on liver nodule imaging. Increased speed of data acquisition and consequently shorter scan times in CT (spiral imaging) and MR (echo planar imaging) should show further improvement in resolution by further reducing motion artifacts. Development of new contrast materials for liver tumor imaging in US and MR may improve tumor detection by increasing the contrast between the tumor and the surrounding liver parenchyma (20).

Evaluation of the liver may be performed by multiple modalities. It is important to choose the diagnostic study appropriate for the patient's clinical situation. Also, it is important that the most efficacious techniques should be used to obtain the greatest information at the lowest cost (21).

Detection of hepatic nodules

Regenerative (regenerating) nodules

Liver cirrhosis is defined as progressive diffuse process of altered reconstruction of the lobular parenchyma with both extensive fibrosis and regenerative nodules involving the entire liver. Regenerative nodules in cirrhosis caused by viral hepatitis are 0.3-1.0 cm in diameter (3). Regenerative nodules are easily recognized on gross specimens.

On cut surfaces, the nodules bulge, reflecting the paucity of collagen within them.

With improvements in imaging techniques, regenerative nodules frequently are detected on sonograms and, sometimes, on CT scans. Recently, MR imaging has played an important role in showing regenerative nodules. An evaluation of the detection rate of imaging techniques for regenerative nodules is difficult because the nodules are usually numerous and compactly spaced.

Dysplastic nodule (adenomatous hyperplasia)

Screening procedures, including periodic US and CT evaluations and measurement of serum levels of alpha-feto-protein in patients with chronic liver disease, enable the detection of small HCCs. Noncancerous nodular lesions such as dysplastic nodule also are being detected more often (1, 2).

The prevalence and importance of dysplastic nodules were studied from Asian and non-Asian investigators. The prevalence of dysplastic nodules reported in American publications has ranged from 17% (22) to 25% (23). By comparison, the prevalence of dysplastic nodules in patients with cirrhosis reported in Japanese publications has ranged from 14% (nodules > 1 cm) (24) to 37% (nodules > 0.5 cm) (25). Therefore, the prevalence of dysplastic nodules does not appear to be significantly different in Asian and non-Asian population. It appears, however, that differences do exist between the two populations, not in the prevalence of dysplastic nodules but in the association of these lesions with malignant tumors. In Japan, dysplastic nodules are more commonly associated with HCC. Furuya et al. (24) reported that 32 (65%) of 49 dysplastic nodules were found in livers that also contained foci of HCC. By comparison, Ferrell et al. (22) reported that only six (14%) of 43 and Theise et al. (23) reported that only four (36%) of 11 dysplastic nodules were found in livers with foci of HCC (26).

Most dysplastic nodules without malignant foci are small, usually larger than 1.0 cm and less than 1.2 cm in diameter (1, 4, 27). On sonograms, particularly intra-operative sonograms, they are frequently found as a lesion associated with advanced HCC and usually appear as a hypoechoic mass. Typical dysplastic nodules usually are not detected with angiography and do not enhance on CT scans, even on CT arteriograms. Because these lesions are difficult to detect, the efficacy of imaging techniques for evaluation of these lesions has not been established. According to recent data (27), the overall sensitivity for detecting adenomatous hyperplasia was 23% with US, 4% with conventional CT, 0% with angiography, 25% with CT arteriography (CTA), 40% with CT arterial portography (CTAP), and 54% with intra-operative US.

Dysplastic nodule with subfocus of HCC (early HCC)

Dysplastic nodule with subfocus of HCC is defined as a nodular lesion that shows no substantial alteration of hepatic architecture and frequently contains a portal structure. The tumor usually occurs in patients with chronic liver disease, especially cirrhosis. The color of the cut surface of early HCC is mostly reddish yellow to yellow. Microscopically, cancer cells are very well differentiated, corresponding to grade I according to Edmondson's classification of HCC (6). Early HCC has an increased cell density with little atypia and frequent fatty changes (6, 7).

Dysplastic nodules with subfocus of HCC are also small, with mean diameters less than 1.7 cm (1, 8, 28-30). Therefore, detection is difficult, and the efficacy of imaging techniques for evaluation of these lesions has not been well established. Recent study indicated an overall sensitivity of 64% for US, 56-58% for CT, 31% for angiography, 50-70% for CTA, 66-71% for CTAP, and 88% for intraoperative US (22, 29, 30).

Early advanced HCC

The definition of early advanced HCC remains controversial. Although some Japanese investigators suggest that early advanced HCC is advanced HCC within early HCC, new nomenclature for this nodule has not been introduced by International Working Party (17). A recent Japanese study indicated an overall sensitivity of 81% for CT, 83% for MR, 100% for CTA, 86% for CTAP, and 63% for iodized-oil CT (8). Standard CT and MR imaging have essentially equivalent sensitivities for the detection of early advanced HCC. However, lesion conspicuity is generally better with CT. T1-weighted MR images seem to be superior to T2-weighted images in the detection of early advanced HCC, which is probably secondary to advantages in detecting the early component of early advanced HCC. The sensitivity of T1-weighted imaging is slightly greater than that of T2-weighted imaging (72% vs 61%) (8). The 100% sensitivities reported for CT arteriography are likely to be artificially elevated as a result of both the relatively small number of patients in these categories and an element of selection bias since standard CT and MR imaging are the initial diagnostic tests of choice and other imaging modalities are usually performed only after these two modalities show a suspicious lesion (8).

Imaging findings of hepatic nodules

Regenerative nodule

On sonograms and CT scans, the presence of regenerative nodules is frequently suggested by nodularity of the hepatic contour. When visualized directly, the nodules are seen as several hypoechoic masses on sonograms

Fig. 3. Sonographic characteristics of regenerative nodules. Intercoastal sonogram of the right lobe of the liver shows multiple, tiny, hypoechoic nodules (short arrows) scattered in the entire liver.

(Fig. 3) or as innumerable tiny masses of high or low attenuation on CT scans (Fig. 4). The multiple closely spaced nodules and their thin connective tissue borders produce a cobblestone appearance and are recognized because of their thin, slightly more echogenic borders, which correspond pathologically to fibrous and fatty connective tissue surrounding and separating the nodules (31). Regenerative nodules in liver cirrhosis are mostly detected in CTA and visualized as nonenhancing nodules surrounded by enhancing fibrous septa (Fig. 4). CTAP is insensitive in the detection of regenerative nodule. Visibility of the nodules depends on the degree of surrounding fibrous septa (32).

On MR images, some regenerative nodules are visualized as hypointense on T1- and T2-weighted images (Fig. 5), whereas small HCCs are seen as hyperintense (33, 34).

Fig. 4. CT characteristics of regenerative nodule. CT scan obtained during hepatic arteriography shows numerous, tiny hypoattenuating nodules (short arrows), less than 1 cm, compactly spaced, in the entire liver.

Fig. 5. MR characteristics of regenerative nodule. Spoiled gradient-echo T1-weighted MR image (130/5.0/70° flip angle) shows numerous, tiny nodules (short arrows) with low signal intensity in the liver. A large mass (arrow) with high signal intensity in the right liver is hepatocellular carcinoma.

Fig. 6. Dysplastic nodule in patient with liver cirrhosis. A. Intercostal sonogram of the right liver shows a hyperechoic nodule in segment 7 of the liver (arrow). Both arterial dominant (B) and portal dominant (C) CT scans of dual-phase spiral CT show a low attenuation lesion. D. Spin-echo T1-weighted MR image (600/30) shows a slightly hyperintense lesion (arrow) at the same site on sonogram and CT scans. E. Spin-echo T2-weighted MR image (2000/60) at the same site shows slightly hypointense lesion (arrow).

Dysplastic nodule

On sonograms, dysplastic nodules have a hyper- or hypoechoic pattern (Fig. 6A), and the findings are similar to those of regenerative nodules or small HCCs (35). On CT scans, the lesions show iso- or low attenuation (Fig. 6B, C). The lesions are not usually detected with CTAP, because typical dysplastic nodule, which has almost the same histologic features as regenerative nodules and which contains multiple portal tracts, shows almost the same volume of portal flow as does the surrounding cirrhotic liver (9). The usefulness of MR imaging was described by Matsui et al. (4). Dysplastic nodules without atypia are hyperintense on T1-weighted images (Fig. 6D) and hypointense on T2-weighted images (Fig. 6E), for unknown reasons. This combination of intensities on T1- and T2-weighted images is a finding specific to dysplastic nodule. The pathologic factors that constitute signal intensities in dysplastic nodules should be studied further (1).

Dysplastic nodules with subfocus of HCC (early HCC)

The term early is used to indicate that the lesion corresponds to the early stage of hepatocarcinogenesis and does not imply a good clinical prognosis after treatment. Early HCC is presumed to be an intermediate step between dysplastic nodule and early advanced HCC in the multistep progression of hepatocarcinogenesis (2, 30).

The precise diagnosis of early HCC is not always easy. Sonograms usually show a hypoechoic mass without evidence of a capsule or mosaic pattern (Fig. 7), closely resembling dysplastic nodule (9, 36).

In the recent study (29), the most common CT pattern of dysplastic nodule with subfocus of HCC was isoattenuation on unenhanced, early enhanced, and late enhanced CT scans (iso-iso-iso). These lesions were not detectable on CT scans because neither a low-attenuation ring on unenhanced CT scans nor a high-attenuation ring around the lesion on late enhanced CT scans was seen.

Fig. 7. Early hepatocellular carcinoma (HCC).

- A. Subcostal oblique sonogram of the right hepatic lobe shows an ovoid 2.0 cm hypoechoic mass (arrow) with central isoechoic portion (arrowhead). No tumor was detected at hepatic angiography (not shown). RK=right kidney.
- B. CT scan obtained after injection of iodized oil shows suspicious low-attenuation area (arrows) containing round, 1.0 cm area of retained iodized oil (arrowhead).
- C. Cross section of surgical specimen shows a mass (arrow) similar in configuration to the surrounding liver. No capsule is seen.
- D. Photomicrograph shows well-differentiated HCC (Edmondson grade I) (arrow) within adenomatous hyperplasia (A). This mass can be diagnosed as early HCC (H and E, original magnification $\times 10$).

Fig. 8. Drawing shows intranodular hemodynamic change during hepatocarcinogenesis in cirrhotic liver. Dotted area indicates variations of blood supply. RN=regenerative nodule, DN=dysplastic nodule, HCC=hepatocellular carcinoma (Modified from personal communication with Kudo M).

Early HCC is usually hypovascular. Matsui et al. (9) found that intranodular portal blood flow tends to decrease as the grade of malignancy increases (Fig. 8). Unlike dysplastic nodule, almost all HCCs of Edmondson grade 2 or greater had a definite decrease in the intranodular portal supply on CT scans obtained during arterial portography (Fig. 8). In intermediate lesions, such as early HCC, and well-differentiated (grade 1) HCC, the intranodular portal blood supply tended to decrease progressively as the grade of malignancy increased, whereas the intranodular hepatic arterial supply increased. Unlike early HCCs, dysplastic nodules are not visualized on CT scan obtained during arterial portography because of portal blood flow in the lesions (9). The relationship between the portal and arterial blood supplies in the hepatocytic lesions found in the cirrhotic liver was considered to be reciprocal at imaging (9) (Fig. 9A, B). Therefore, the combination of CTA and CTAP is more accu-

Fig. 9. Early hepatocellular carcinoma (HCC).

- CT scan obtained during hepatic arteriography shows a low attenuation nodule (arrow) due to poor hepatic arterial supply. Hepatic angiogram (not shown) showed no hypervascular mass in the liver.
- CT scan obtained during arterial portography shows no perfusion defect in the liver. The area of the nodule (arrow) shows increased attenuation.
- Spoiled gradient-echo T1-weighted MR image (170/4.2/9.0° flip angle) shows the nodule with high signal intensity (arrow).
- Fast spin-echo T2-weighted MR image (5000/104) shows the nodule with low signal intensity (arrow). On microscopic examination, the nodule turned out to be a dysplastic nodule with subfocus of HCC (early HCC).

rate than either alone in determining the nature of the nodular lesions associated with liver cirrhosis (1, 9).

On MR images, early HCC mainly has a hyper- or isointense pattern on T1-weighted images (Fig. 9C) and a hypo- or isointense pattern on T2-weighted images (Fig. 9D) (23, 37). Sometimes, early HCC has a unique MR appearance, consisting of a mostly low-intensity nodule with a small focus of intermediate or high intensity on T2-weighted images (4, 8, 38, 39). The relationship between progression of malignant disease and signal-intensity pattern for early stages of HCC has not been fully studied.

Early advanced HCC

Early advanced HCC consists of a definite cancerous nodule of HCC that is large enough to be detected at gross examination surrounded by early HCC, pathologically (8, 40, 41). Other terms used for early advanced HCC include HCC with early components (28), overt HCC with early components (1), advanced HCC in early HCC (41), nodule-in-nodule lesion (40), and adenomatous hyperplasia with malignant foci with macroscopic tumor nodules (28). The mean diameter of early advanced HCCs (2.0 cm) was substantially larger than that of early HCCs (1.4 cm) (40). As might be expected in this multistep model of hepatocarcinogenesis, the proportion of

early advanced HCCs to early HCCs increased with tumor diameter (42).

Recent study (8) described two types of imaging characteristics of early advanced HCC. A nodule-in-nodule appearance was identified in approximately one-third to one-half of cases. Signal behavior of early and advanced components of early advanced HCC followed the expected behaviors of isolated early HCC and isolated advanced HCC, respectively (8). The inner nodule represents the advanced component and the peripheral margin (general component) the early component (Fig. 10). The early component of early advanced HCC tended to be hypoattenuating or hypointense at early phase of enhanced CT (Fig. 10), CTA and T2-weighted MR imaging, and hyperintense at T1-weighted MR imaging. Conversely, the advanced component tended to be hyperattenuating or hyperintense at early phase of enhanced CT (Fig. 10), CTA and T2-weighted MR imaging, and hypointense at T1-weighted MR imaging (8).

If a nodule-in-nodule appearance was not seen on images, it was not possible to determine with certainty whether the general component of the lesion that was visualized at imaging represented the early component, the advanced component, or the entire lesion of early advanced HCC. For example, the visualized homogeneous lesion could correspond to the early component of the

Fig. 10. Early advanced hepatocellular carcinoma (HCC).

- A. CT scan in the arterial phase with spiral CT shows an exophytic mass (arrow) with two high-attenuating nodules (arrowheads) in segment 5 of the liver. The liver is contracted and nodular. Ascites is also seen.
- B. CT scan in the late phase shows the exophytic mass (arrow) with slight low-attenuation.
- C. CT scan during arterial portography shows two filling defects (arrowheads) in the exophytic mass (arrow), indicating partial defect of portal blood supply in the tumor. Therefore, the tumor is considered to be an early HCC associated with advanced small HCC, so called early advanced HCC.

Fig. 11. Advanced small hepatocellular carcinoma (HCC).

- A. CT scan in the arterial phase with spiral CT shows a highly enhancing mass (arrow) in segment 6 of the liver, indicating blood supply from the hepatic artery.
- B. CT scan in the late phase shows iso-attenuating mass (arrow) in segment 6 of the liver.
- C. CT scan during arterial portography shows a round filling defect (arrow) in the same area, indicating no portal blood supply. Therefore, the tumor is advanced HCC even though the tumor is small.

early advanced HCC that is directly adjacent to an undetected, isointense nodule of advanced HCC or vice versa (8).

On the other hand, advanced HCC shows high attenuation at early enhanced CT or CTA, and perfusion defect at CTAP (Fig. 11, 12) because advanced HCC is supplied by hepatic artery alone, not by portal vein. At MR imaging, advanced HCC shows hypo- or hyperintensity on T1-weighted images and hyperintensity on T2-weighted images (Fig. 12).

ROLE OF IMAGING TECHNIQUES IN PATIENT MANAGEMENT

Early detection of HCC is important because early treatment, either surgical resection or local ablation, of these tumors is the most effective. Therefore, screening and regular follow-up with imaging techniques have been introduced in patients at high risk for HCC (1).

The role of US and CT in the screening of HCCs is complementary. US has become a major screening technique in Asian populations because high sensitivity of real-time US for detection of these tumors has been established (43-47). Furthermore, the simplicity and flexibility of real-time US have made it a major tool for guiding diagnostic aspiration and therapeutic procedures

for HCC. CT is also an accurate, relatively noninvasive technique to evaluate HCC, and it is a complementary screening technique when clinical questions cannot be answered with US. With CT, not only can the extent of the HCC be defined more accurately, but the extra-hepatic spread of disease can be better defined (1, 48). When CT does not give sufficient informations, MR imaging is used to characterize them further.

Color flow Doppler imaging also is useful in the characterization of liver tumors. However, color Doppler imaging is not yet satisfactory for routine examination of the liver, where the blood flow is slow especially in deeply seated tumor (1). A newly developed power Doppler US, known variously as color Doppler energy (CDE) or US angiography, encodes the power of Doppler signal in color. The power of Doppler signal is related to the number of moving scatterers; red blood cells in the absence of contrast agents produce the recorded Doppler shift (49). Therefore, the advantages of power Doppler US are three to five times higher sensitivity to flow, no aliasing artifact and no angle dependency. Despite excitement generated by anecdotal reports, many have reservations about its clinical usefulness. However, what this technique does that has stimulated broad interest among leading sonologists is improving the sensitivity of color Doppler imaging. At this present time, power Doppler US may not be a major breakthrough, but it is a potentially useful adjunct to

Fig. 12. Typical example of hepatocarcinogenesis from a dysplastic nodule to an early hepatocellular carcinoma (HCC) and advanced HCC in a patient with liver cirrhosis.

- A. Conventional contrast-enhanced CT scan shows three masses (arrow, open arrow and curved arrow), and another suspicious mass (short arrow) in the right liver.
- B. T1-weighted MR image (550/15) shows two masses with high intensity (arrow and open arrow), and another mass with suspicious low intensity (curved arrow).
- C. T2-weighted MR image (2000/80) shows two masses with low intensity (arrow and open arrow), and another mass with high intensity (curved arrow). Therefore, the mass indicated by curved arrow is considered to be an advanced HCC.
- D. CT scan during arterial portography shows complete defect of portal flow in the mass indicated by curved arrow, partial defect (arrowhead) in the mass indicated by arrow, and no defect in the mass indicated by open arrow. Therefore, the mass indicated by curved arrow is consistent with advanced HCC; the mass indicated by arrow, early HCC; and the mass indicated by open arrow, dysplastic nodule. Another defect area (short arrow) of portal flow is also seen, indicating advanced HCC.
- E. CT scan after infusion of iodized oil shows dense complete retention of iodized oil in two masses (short arrow and curved arrow), indicating advanced HCC; partial retention (arrowhead) of iodized oil in one mass (arrow), indicating early HCC; and no retention of iodized oil in one mass (open arrow), indicating dysplastic nodule. These findings on iodized-oil CT scan correspond well to those on CT scan during arterial portography.

standard color Doppler imaging (50, 51).

If imaging findings suggest nodules are malignant, staging of the nodules by using CTAP, CT with iodized oil, or US angiography is necessary. At present, CTAP appears to be one of the most accurate approaches for detecting intrahepatic tumor and defining its extent (1,

52). CT with iodized oil is one of the most sensitive methods for detecting small hypervascular HCCs. US angiography is considered extremely sensitive for identifying the vascular pattern of the tumor even if the tumor is small. The selection of techniques for staging might be different because the decision as to which imaging

techniques are state-of the-art and the levels of familiarity with various techniques vary among institutions (1).

If the nodules are potentially resectable, intraoperative US is necessary for confirmation and for determination of the best operative method because small nodules may not be seen or palpated from the surface of the liver. Intraoperative US rarely limited by blind areas, because scanning during surgery is not disturbed by the ribs, lung, or bowel, and the distortion and weakening of the US beam caused by the abdominal wall can be avoided.

If the nodules are small and appear benign (such as regenerative nodules or dysplastic nodules), currently, follow-up serial scanning is the only practical method of choice. In such cases, final diagnosis based on histologic findings alone after percutaneous biopsy is sometimes difficult because entire pathologic specimens are needed for the histologic diagnosis.

If nodules are considered inoperable because screening procedures indicate multiplicity, vascular invasion, or extrahepatic metastasis, sonographically guided percutaneous biopsy is performed to allow a final diagnosis based on histologic findings in addition to the imaging findings for further non-surgical treatment (1).

CONCLUSION

Recent advances in various imaging techniques have facilitated the detection of small HCCs, with a marked improvement in the prognosis of these lesions. These improvements have led to an increase in the detection of other hepatic nodular lesions such as regenerative nodules, dysplastic nodule-low grade, dysplastic nodule-high grade, dysplastic nodule with subfocus of HCC (early HCC), and early advanced HCC in the cirrhotic liver. Because of the recent rapid evolution of knowledge regarding these small nodular lesions of the liver, the terminology used has been somewhat variable and confusing. Although the definitions of dysplastic nodule, early HCCs, and early advanced HCCs are still controversial, the concept of these borderline lesions is important to recognize.

Some of those lesions are malignant nodules; therefore, the distinction between benign and malignant nodules is important clinically. Recently, CTAP, CTA, and MR imaging have played important roles in differentiating these hepatic nodular lesions. However, most premalignant or borderline hepatic nodules including dysplastic nodules with or without subfocus of HCC are quite small and cannot be easily detected preoperatively, and they are, therefore, difficult to follow up. Data on their clinical course are lacking, and their biological behavior has not been analyzed in detail. Whether such lesions are pre-

lignant or already malignant can be determined when more knowledge of their biologic behavior has been accumulated.

Recent knowledge of the imaging findings of these hepatocellular nodules is mainly based on blood supply and partly based on histopathologic or histochemical findings. However, all features of the hepatocellular nodules in liver cirrhosis are not satisfactorily explained at the present time. Therefore, further study of these nodular lesions with imaging techniques is essential.

In addition, at this time, the clinical significance of the imaging diagnosis of these nodular lesions is uncertain. More research must be performed to ascertain whether any significant correlation exists between the different steps of HCC and the clinical outcome.

Acknowledgments

The author thank Yong Ho Auh, M.D., Jae Hoon Lim, M.D., and Ki Whang Kim, M.D. for reviewing manuscript, Myeong-Jin Kim, M.D. for preparing a case for Fig 9, and Yoon Kyung Choi for preparing manuscript.

REFERENCES

1. Choi BI, Takayasu K, Han MC. *Small hepatocellular carcinomas and associated nodular lesions of the liver: pathology, pathogenesis, and imaging findings.* *Am J Roentgenol* 1993; 160: 1177-87.
2. Sakamoto M, Hirohashi S, Shimosato Y. *Early stages of multi-step hepato-carcinogenesis: adenomatous hyperplasia and early hepatocellular carcinoma.* *Hum Pathol* 1991; 22: 172-8.
3. Kondo F, Wada K, Nagato Y, Nakajima T, Kondo Y, Hiroka N, Ebara M, Ohto M, Okuda K. *Biopsy diagnosis of well-differentiated hepatocellular carcinoma based on new morphologic criteria.* *Hepatology* 1989; 9: 751-5.
4. Matsui O, Kadota M, Kameyama T, Yoshikawa J, Arai K, Gabata T, Takashima T, Nakanuma Y, Terada T, Ida M. *Adenomatous hyperplastic nodules in the cirrhotic liver: differentiation from hepatocellular carcinoma with MR imaging.* *Radiology* 1989; 173: 123-6.
5. Kanehara Shupan. *The general rules for the clinical and pathological study of primary liver cancer.* *Liver Cancer Study Group of Japan* 1992.
6. Kojiro M. *Pathology.* In: Livraghi T, Makuuchi M, Buscarini L, eds. *Diagnosis and treatment of hepatocellular carcinoma.* London: Greenwich Medical Media, 1997: 37-50.
7. Kanai T, Hirohashi S, Upton MP, Noguchi M, Kishi K, Makuuchi M, Yamasaki S, Hasegawa H, Takayasu K, Moriyama N, Shimamoto Y. *Pathology of small hepatocellular carcinoma: a proposal for a new gross classification.* *Cancer* 1987; 60: 810-9.

8. Winter TC, Takayasu K, Muramatsu Y, Furukawa H, Wakao F, Koga H, Sakamoto M, Hirohashi S, Freeny PC. *Early advanced hepatocellular carcinoma: evaluation of CT and MR appearance with pathologic correlation. Radiology* 1994; 192: 379-86.
9. Matsui O, Kadota M, Kameyama T, Kameyama T, Yoshikawa J, Takashima T, Nakanuma Y, Unoura M, Kobayashi K, Izumi R, Ida M. *Benign and malignant nodules in cirrhotic livers: distinction based on blood supply. Radiology* 1991; 178: 493-7.
10. Kojiro M. *Pathology of the hepatocellular carcinoma (in Japanese). J Med Imaging* 1988; 8: 1258-65.
11. Edmondson HA, Peters RL. *Liver. In: Kissane JM ed. Anderson's pathology. St. Louis: Mosby, 1988: 1110-27.*
12. Kenmochi K, Sugihara S, Kojiro M. *Relationship of histologic grade of hepatocellular carcinoma (HCC) to tumor size and demonstration of tumor cells of multiple different grades in single small HCC. Liver* 1987; 7: 18-26.
13. Arakawa M, Sugihara S, Kenmochi K, Lai M, Wang T, Yu J, Yang P, Chuang C, Yang P, Lee C, Hsu H, How S. *Small mass lesions in cirrhosis: transition from benign adenomatous hyperplasia to hepatocellular carcinoma. J Gastroenterol Hepatol* 1986; 1: 3-14.
14. Freeny PC, Baron RL, Teefey SA. *Hepatocellular carcinoma: reduced frequency of typical findings with dynamic contrast-enhanced CT in a non-Asian population. Radiology* 1992; 182: 143-8.
15. Tsuda H, Hirohashi S, Shimozato Y, Terada M, Hasegawa H. *Clonal origin of atypical adenomatous hyperplasia of the liver and clonal identity with hepatocellular carcinoma. Gastroenterology* 1988; 95: 1664-6.
16. Takayama T, Makuuchi M, Hirohashi S, Sakamoto M, Okazaki N, Takayasu K, Kosuge T, Motoo Y, Yamazaki S, Hasegawa H. *Malignant transformation of adenomatous hyperplasia to hepatocellular carcinoma. Lancet* 1990; 336: 1150-3.
17. International working party. *Terminology of nodular hepatocellular lesions. Hepatology* 1995; 22: 983-93.
18. Wu TT, Boitnott J. *Dysplastic nodules: a new term for pre-malignant hepatic nodular lesions. Radiology* 1996; 201: 21-2.
19. Earls JP, Theise ND, Weinreb JC, DeCorato DR, Krinsky GA, Rofsky NM, Mizrahi H, Tepelman LW. *Dysplastic nodules and hepatocellular carcinoma: thin-section MR imaging of explanted cirrhotic livers with pathologic correlation. Radiology* 1996; 201: 207-14.
20. Kane RA. *Liver imaging update. Semin Ultrasound CT MR* 1992; 13: 311-2.
21. Choi BI. *Comparison of different imaging techniques. In: Livraghi T, Makuuchi M, Buscarini L, eds. Diagnosis and treatment of hepatocellular carcinoma. London: Greenwich Medical Media, 1997: 203-19.*
22. Ferrell L, Wright T, Lake J, Roberts J, Ascher N. *Incidence and diagnostic features of macrorregenerative nodules vs. small hepatocellular carcinoma in cirrhotic livers. Hepatology* 1992; 16: 1372-81.
23. Theise ND, Schwartz M, Miller C, Thung SN. *Macrorregenerative nodules and hepatocellular carcinoma in forty-four sequential adult liver explants with cirrhosis. Hepatology* 1992; 16: 949-55.
24. Furuya K, Nakamura M, Yamamoto Y, Toge K, Otsuka H. *Macrorregenerative nodule of the liver: a clinicopathologic study of 345 autopsy cases of chronic liver disease. Cancer* 1988; 62: 99-105.
25. Wada K, Konodo F, Kondo Y. *Large regenerative nodules and dysplastic nodules in cirrhotic livers: a histopathologic study. Hepatology* 1988; 8: 1684-8.
26. Nelson RC, Chezmar JL. *Pathology and imaging of hepatocellular neoplasms: are findings from Asian populations applicable to non-Asian groups? Am J Roentgenol* 1993; 160: 1188-90.
27. Takayasu K, Makuuchi M, Hirohashi S, Okazaki N, Muramatsu Y, Moriyama N, Takayama T, Hasegawa H. *Imaging of adenomatous hyperplastic lesions containing and not containing hepatocellular carcinoma in the liver [in Japanese]. Nippon Shokakibyo Gakkai Zasshi* 1989; 86: 2404-12.
28. Muramatsu Y, Nawano S, Takayasu K, Moriyama N, Yamada T, Yamasaki S, Hirohashi S. *Early hepatocellular carcinoma: MR imaging. Radiology* 1991; 181: 209-13.
29. Takayasu K, Furukawa, Wakao F, Muramatsu Y, Abe H, Terauchi T, Winter TC III, Sakamoto M, Hirohashi S. *CT diagnosis of early hepatocellular carcinoma: sensitivity, findings, and CT-pathologic correlation. Am J Roentgenol* 1995; 164: 885-90.
30. Takayasu K, Muramatsu Y, Furukawa H, Wakao F, Moriyama N, Takayama T, Yamaki S, Sakamoto M, Hirohashi S. *Early hepatocellular carcinoma: appearance at CT during arterial portography and CT arteriography with pathologic correlation. Radiology* 1995; 194: 101-5.
31. Freeman MP, Vick CW, Taylor KJW, Carithers RL, Brewer WH. *Regenerating nodules in cirrhosis: sonographic appearance with anatomic correlations. Am J Roentgenol* 1986; 146: 533-6.
32. Kim E, Lee W, Park CK, Do Y, Choo IW, Lim JH. *Regenerating nodules in liver cirrhosis: finding at CT arterial portography and CT arteriography with pathologic correlation. Radiology* 1997; 205: 714.
33. Itai Y, Ohnishi S, Ohtomo K, Kokubo T, Yoshida H, Yoshikawa K, Imawari M. *Regenerating nodules of liver cirrhosis: MR imaging. Radiology* 1987; 165: 419-23.
34. Ohtomo K, Itai Y, Ohtomo Y, Shiga J, Iio M. *Regenerating nodules of liver cirrhosis: MR imaging with pathologic correlation. Am J Roentgenol* 1990; 154: 505-7.
35. Tanaka S, Kitamura T, Fujita M, Kasugai H, Inoue A, Ishiguro S. *Small hepatocellular carcinoma: differentiation from adenomatous hyperplastic nodule with color Doppler flow imaging. Radiology* 1992; 182: 161-5.
36. Arakawa M, Kage M, Sugihara S, Nakashima T, Suenaga M, Okuda K. *Emergence of malignant lesions within an adenomatous hyperplastic nodule in a cirrhotic liver. Gastroenterology* 1986; 91: 198-208.
37. Yamashita Y, Fan ZM, Yamamoto H, Matsukawa T, Yoshimatsu

- S, Miyazaki T, Sumi H, Harada M, Takahashi M. *Spin-echo and dynamic gadolinium-enhanced FLASH MR imaging of hepatocellular carcinoma: correlation with histopathologic findings. J Magn Reson Imaging* 1994; 4: 83-90.
38. Mitchell DG, Rubin R, Siegelman ES, Burk DL Jr, Rifkin MD. *Hepatocellular carcinoma within siderotic regenerative nodules: appearance as a nodule within a nodule on MR images. Radiology* 1991; 178: 101-3.
  39. Sadek AG, Mitchell DG, Siegelman EV, Outwater EK, Matteucci T, Han HWL. *Early hepatocellular carcinoma that develops within macroregenerative nodules; growth rate depicted at serial MR imaging. Radiology* 1995; 195: 753-6.
  40. Rim K, Sakamoto M, Watanabe H, Hirohashi S, Ino Y. *Pathology and DNA cytophotometry of small hepatocellular carcinoma with a nodule-in-nodule appearance: evidence for stepwise progression of hepatocellular carcinoma. Jpn J Clin Oncol* 1992; 23: 26-33.
  41. Sakamoto M, Ino Y, Fujii T, Hirohashi S. *Phenotype change in tumor vessels associated with the progression of hepatocellular carcinoma. Jpn J Clin Oncol* 1993; 23: 98-104.
  42. Watanabe H, Hirohashi S, Sakamoto M, Ino Y, Fujii T. *New macroscopic subtype of small hepatocellular carcinoma-common type in early type-and histological consideration of the multistep progression of HCC [in Japanese]. Kanzo* 1990; 31: 1267-73.
  43. Sheu JC, Sung JL, Chen DS, Lai MY, How SW, Hsu HC, Lee CS. *Early detection of hepatocellular carcinoma by real-time ultrasonography: a prospective study. Cancer* 1985; 56: 660-6.
  44. Tanaka S, Kitamura T, Nakanishi K, Okuda S, Yamazaki H, Hiyama T, Fujimoto I. *Effectiveness of periodic checkup by ultrasonography for the early diagnosis of hepatocellular carcinoma. Cancer* 1990; 66: 2210-4.
  45. Sheu JC, Sung JL, Chen DS, Yu JY, Wang TH, Su CT, Tsang YM. *Ultrasonography of small hepatic tumors using high-resolution linear-array real-time instruments. Radiology* 1984; 150: 797-802.
  46. Tanaka S, Kitamura T, Nakanishi K, Okuda S, Kojima J, Fujimoto I. *Recent advances in ultrasonographic diagnosis of hepatocellular carcinoma. Cancer* 1989; 63: 1313-7.
  47. Choi BI, Kim CW, Han MC, Kim CY, Lee HS, Kim SJ, Kim YI. *Sonographic characteristics of small hepatocellular carcinoma. Gastrointest Radiol* 1989; 14: 255-61.
  48. Laberge JM, Laing FC, Federle MP, Jeffrey RB Jr, Lim RC. *Hepatocellular carcinoma: assessment of resectability by computed tomography and ultrasound. Radiology* 1984; 152: 485-90.
  49. Rubin JM, Bude RO, Carson PL, Bree RL, Adler RS. *Power Doppler US: a potentially useful alternative to mean frequency-based color Doppler US. Radiology* 1994; 190: 853-6.
  50. Choi BI, Kim TK, Han JK, Chung JW, Park JH, Han MC. *Power Versus Conventional Color Doppler Sonography: comparison in the depiction of vasculature in liver tumors. Radiology* 1996; 200: 55-8.
  51. Lencioni R, Pinto F, Armillotta N, Bartolozzi C. *Assessment of tumor vascularity in hepatocellular carcinoma: comparison of power Doppler US and color Doppler US. Radiology* 1996; 201: 353-8.
  52. Ferrucci JT. *Liver tumor imaging: current concepts. Radiol Clin North Am* 1994; 32: 39-54.