Review Article | Gastrointestinal Imaging

http://dx.doi.org/10.3348/kjr.2016.17.1.7
pISSN 1229-6929 · eISSN 2005-8330
Korean J Radiol 2016;17(1):7-24

Korean Journal of Radiology
KJR

Noninvasive Diagnosis of Hepatocellular Carcinoma: Elaboration on Korean Liver Cancer Study Group-National Cancer Center Korea Practice Guidelines Compared with Other Guidelines and Remaining Issues

Jeong Hee Yoon, MD[1, 2], Joong-Won Park, MD[3], Jeong Min Lee, MD[1, 2, 4]

[1]Department of Radiology, Seoul National University Hospital, Seoul 03080, Korea; [2]Department of Radiology, Seoul National University College of Medicine, Seoul 03080, Korea; [3]Center for Liver Cancer, National Cancer Center, Goyang 10408, Korea; [4]Institute of Radiation Medicine, Seoul National University Medical Research Center, Seoul 03080, Korea

Hepatocellular carcinoma (HCC) can be diagnosed based on characteristic findings of arterial-phase enhancement and portal/delayed "washout" in cirrhotic patients. Several countries and major academic societies have proposed varying specific diagnostic criteria for HCC, largely reflecting the variable HCC prevalence in different regions and ethnic groups, as well as different practice patterns. In 2014, a new version of Korean practice guidelines for management of HCC was released by the Korean Liver Cancer Study Group (KLCSG) and the National Cancer Center (NCC). According to the KLCSG-NCC Korea practice guidelines, if the typical hallmark of HCC (i.e., hypervascularity in the arterial phase with washout in the portal or 3 min-delayed phases) is identified in a nodule ≥ 1 cm in diameter on either dynamic CT, dynamic MRI, or MRI using hepatocyte-specific contrast agent in high-risk groups, a diagnosis of HCC is established. In addition, the KLCSG-NCC Korea practice guidelines provide criteria to diagnose HCC for subcentimeter hepatic nodules according to imaging findings and tumor marker, which has not been addressed in other guidelines such as Association for the Study of Liver Diseases and European Association for the Study of the Liver. In this review, we briefly review the new HCC diagnostic criteria endorsed by the 2014 KLCSG-NCC Korea practice guidelines, in comparison with other recent guidelines; we furthermore address several remaining issues in noninvasive diagnosis of HCC, including prerequisite of sonographic demonstration of nodules, discrepancy between transitional phase and delayed phase, and implementation of ancillary features for HCC diagnosis.

Index terms: *Hepatocellular carcinoma; Diagnosis; Criteria; Practice guideline*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men, the seventh in women worldwide (1), and the third most common cause of cancer-related death (2). In its advanced stage, median survival is < 1 year and 5-year survival is < 10% (3). Therefore, early diagnosis of HCC is critical as it can lead to early intervention with curative intent resulting in improved patients' prognosis. The staging of HCC relies heavily on imaging and appropriate management of a given specific stage of HCC depends on the accuracy of its imaging diagnosis (4), hence, there is a clear need for refined diagnostic criteria.

A unique feature of HCC is that it allows for a noninvasive diagnosis without histologic confirmation. During hepatocarcinogenesis, unpaired arterial blood flow increases and portal flow decreases as hepatocytes become dedifferentiated (5, 6). Owing to these hemodynamic changes, HCCs show a signature finding of arterial-phase enhancement followed by portal or delayed "washout" on contrast enhanced multi-detector computed tomography (MDCT) and/or magnetic resonance imaging (MRI) using extracellular contrast media (ECCM). Studies show that the

Received May 7, 2015; accepted after revision September 30, 2015.
Corresponding author: Jeong Min Lee, MD, Department of Radiology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
• Tel: (822) 2072-3154 • Fax: (822) 743-6385
• E-mail: jmlshy2000@gmail.com

noninvasive criteria of HCC shows nearly perfect specificity and positive predictive value of > 95% in nodules > 2 cm in cirrhosis (7, 8). Currently established guidelines by the Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver-European Organization for Research and Treatment of Cancer (EASL-EORTC), the Asian-Pacific Association for the Study of the Liver (APASL), Liver Imaging Reporting and Data System (LI-RADS), the Organ Procurement and Transplantation Network (OPTN) system, and the Japan Society of Hepatology (JSH) are commonly based on the characteristic hemodynamic changes of HCC (9-15). Therefore, all guidelines endorse multi-phasic CT and MRI with extracellular agents as first-line modalities (9-15).

However, several pathologic changes are known to occur during the development of HCCs in a cirrhotic liver, in addition to typical hemodynamic changes of HCC such as increased arterial flow and decreased portal flow (16). These include changes in cellularity, the transporters of hepatocytes, and a decrease in the number and function of Kupffer cells (17). Increased cellularity in progressed HCC is a distinct finding from cirrhotic nodules, and cumulative data suggests that diffusion weighted imaging (DWI) may improve the diagnostic performance for small HCCs (18, 19). In addition, there are ample data to suggest that hepatocyte-specific contrast media (gadoxetate disodium [gadoxetic acid or Gd-EOB-DTPA] and gadobenate dimeglumine) enable the visualization of another key feature of hepatocarcinogenesis *in vivo* i.e., alteration of hepatocyte function (16). Expression of organic anion transporting polypeptide 1B1/3 (OATP 1B1/3) assessed by hepatocyte-specific MR contrast agents that are taken up by normal hepatocytes via OATP 1B1/3, reduces with tumor progression (16, 20). Thus, hypointensity of cirrhotic nodules on the hepatobiliary phase of hepatocyte-specific contrast enhanced MRI suggests a lack of functioning hepatocytes in the tumor, which is shown earlier than hemodynamic changes in hepatocarcinogenesis (21, 22). Furthermore, recently introduced ultrasound contrast medium (Sonazoid, GE Healthcare, Oslo, Norway) is reportedly taken up by Kupffer cells, improving the contrast resolution between tumors and the background liver and providing a dynamic enhancement pattern (23). Such emerging findings require consideration in any current HCC diagnostic criteria, however, adopting these findings for the noninvasive diagnosis of HCCs remains controversial due to lack of specificity (20).

In 2003, Korea first established its own practice guidelines proposed by the Korean Liver Cancer Study Group (KLCSG) and the National Cancer Center (NCC). The newest version of the KLCSG-NCC Korea practice guidelines of 2014 includes modification of the noninvasive HCC diagnostic criteria (24, 25), incorporating utilization of hepatocyte-specific contrast-enhanced MRI and diagnosis of subcentimeter HCC. These guidelines are based on results of many recent studies that show that the potential of hepatobiliary contrast agents in detection of small HCCs (< 2 cm), and differentiating HCCs from benign cirrhotic nodules (17, 26-31). Similarly, the consensus guideline of JSH advocate MRI with gadoxetic acid as a first-line modality (13, 24).

In this review, we briefly review the new HCC diagnostic criteria endorsed by the 2014 KLCSG-NCC Korea practice guidelines followed by a comparison with the other aforementioned guidelines and address several remaining issues that remain to be solved in the noninvasive diagnosis of HCCs.

Consensus Statements in the 2014 KLCSG-NCC Korea Practice Guidelines

The diagnostic algorithm of the KLCSG-NCC Korea practice

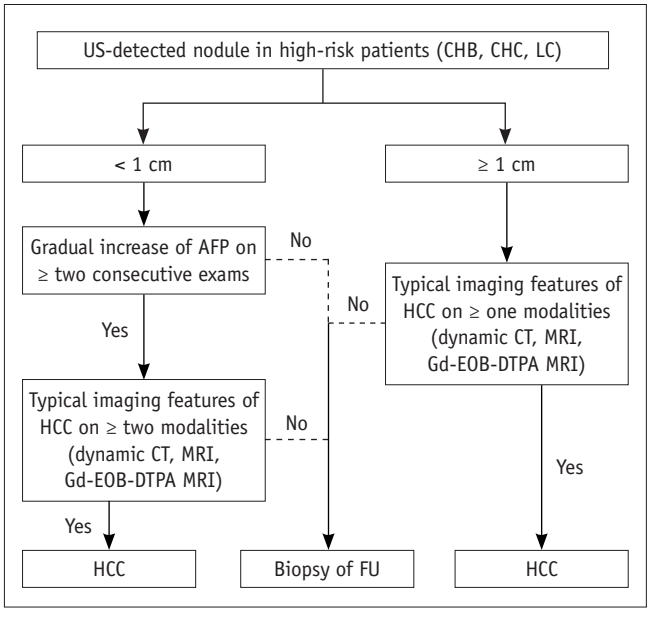

Fig. 1. Diagnostic algorithm for suspected hepatocellular carcinoma (HCC) with new Korean Liver Cancer Study Group-National Cancer Center Korea practice guideline. Typical imaging features of HCC include following: 1) arterial enhancement and 2) portal venous or delayed phase washout. AFP = alpha-fetoprotein, CHB = chronic hepatitis B, CHC = chronic hepatitis C, LC = liver cirrhosis, US = ultrasonography

Korean Journal of Radiology
KJR

guidelines is provided in Figure 1. The 2014 KLCSG-NCC Korea practice guidelines provide the following consensus statements (24, 25).

1) HCC is diagnosed on the basis of either pathology or clinical criteria in patients belonging in the high-risk group (chronic hepatitis B/C or cirrhosis) (A1).

2) When HCC is suspected during surveillance in the high-risk group, dynamic contrast-enhanced CT/MRI or MRI with liver-specific contrast agents should be performed for diagnosis (B1).

3) In the high-risk group, HCC can be diagnosed for nodules 1 cm in diameter if one or two of the above-mentioned imaging techniques show typical features of HCC (for the diagnosis of nodules 1–2 cm in diameter, two or more imaging modalities are required if a suboptimal imaging technique is used). Typical features of HCC include arterial phase enhancement with washout in the portal or delayed phase (B1).

4) Nodules < 1 cm in diameter can be diagnosed as HCC in the high-risk group when all of the following conditions are met: typical features of HCC in two or more of the above-mentioned imaging modalities and continuously rising serum alpha-fetoprotein levels with hepatitis activity under control (C1).

5) Pathological diagnosis should be considered when the clinical criteria are not met or typical features of HCC are not shown. Indeterminate nodules despite imaging workups or pathologic examination need to be followed-up with repeated imaging and serum tumor marker analysis (B1).

In the first statement, clinical criteria include imaging findings as well as tumor marker elevation in subcentimeter nodules (Fig. 1) (25). In the second statement, the 2014 KLCSG-NCC Korea practice guidelines do not include contrast-enhanced ultrasound for diagnosing HCC, due to its limited roles for HCC diagnosis and staging (32-34); consequently, more cumulative data are required for acceptance as a primary diagnostic tool (15, 25). Instead, the guidelines implement hepatocyte-specific contrast-enhanced MRI based on prior reports on its superior capability for liver lesion detection and characterization than CT (35, 36) and MRI using ECCM (37). In the third statement, optimal CT and MRI are specified in 2014 KLCSG-NCC Korea practice guideline (24, 25), and suboptimal imaging indicates imaging study that does not satisfy the specification. In nodules ≥ 1 cm, typical feature on single optimal study is sufficient for a diagnosis of HCC. However, atypical feature on single image study or typical feature on suboptimal image study may require additional imaging study according to the guidelines. Especially, for 1–2 cm nodules, the guidelines recommend that at least 2 imaging studies should show typical findings when the studies do not satisfy the required specification. In the fourth statement, continuous increases in serum alpha-fetoprotein refer to 1) serum alpha-fetoprotein above normal range; and 2) continuous increase in serum alpha-fetoprotein on follow-up test. However, the guidelines do not specify normal range of alpha-fetoprotein level, numbers of follow-ups, and follow-up interval, but provide clinicians room to apply the guidelines depending on clinical circumstances.

Comparison of the 2014 KLCSG-NCC Korea practice guidelines with AASLD and EASL-EORTC guidelines, as well as with LI-RADS, is summarized in Table 1. In the 2014 KLCSG-NCC Korea practice guidelines, “delayed phase” is used for 3-minute delayed phase after either ECCM or hepatobiliary contrast agents. However, late dynamic phase imaging or delayed phase of gadoxetic acid, which is usually obtained around 3 minutes after contrast administration, is not equal to the conventional equilibrium phase, as contrast uptake by hepatocytes may start around the end of portal venous phase with gadoxetic acid (38). Therefore, this unique time window between portal phase and hepatobiliary phase (10–20 minutes after contrast injection) of gadoxedate disodium-enhanced MRI is the transitional phase between the vascular and hepatobiliary phases, unlike gadobenate dimeglumine, which provides a pure equilibrium phase (38). The terminology for this time window is not yet well established and “delayed phase”, “late dynamic phase” or “transitional phase” are commonly used. Although “delayed phase” is used similar to ECCM agents in the 2014 KLCSG-NCC Korea practice guidelines, in this review, “transitional phase” is used instead of “delayed phase”.

Definition of the High-Risk Group for HCC

The population of patients who benefit most from a surveillance program are those who are at high risk of developing HCC (39). In the 2014 KLCSG-NCC Korea practice guidelines, high-risk patients are defined as patients with chronic hepatitis B, C, or cirrhosis of any cause, which is consistent with APASL guidelines (14). It is based on occurrence of HCC in patients with chronic hepatitis B before progression to cirrhosis (40). According to the EASL guidelines, cirrhosis is a criterion for inclusion in the high-

Table 1. Comparison of AASLD, EASL, KLCSG-NCC Korea Practice Guidelines, and LI-RADS

	AASLD	EASL	KLCSG-NCC Korea	LI-RADS
Target population	Patients at risk for HCC in surveillance program (CHB carriers,* LC of any cause)	LC of any cause	CHB, CHC, LC of any cause	All patients at risk for HCC
Targeted lesion	US detected nodule	US detected nodule	US detected nodule	All nodules
Imaging modality	CT, MRI using ECCM	CT, MRI using ECCM	CT, MRI using ECCM or hepatobiliary agents	CT, MRI using ECCM or hepatobiliary agents
Diagnostic hallmark	Nodule size ≥ 1 cm AP enhancement Washout on PVP, DP	Nodule size ≥ 1 cm AP enhancement Washout on PVP, DP	AP enhancement Washout on PVP, DP, or hypointensity on TP (Gd-EOB-DTPA MRI)	AP enhancement Washout on PVP, DP† Capsule appearance + threshold growth (LR-5g) + US visibility (LR-5us)
Ancillary findings	No	No	No	Yes - Up scoring (up to LR-4) - Down scoring
Number of required exam	One exam	≥ 2 cm: one exam 1–2 cm: two exams	≥ 2 cm: one exam 1–2 cm: two exams, if suboptimal study < 1 cm: two exams	One exam
Tumor marker (AFP)	N/A	N/A	Only for small nodules (< 1 cm)	N/A
Category	HCC Not HCC Indeterminate	HCC Not HCC Indeterminate	HCC Not HCC Indeterminate	Benign Probably benign Indeterminate Probably HCC Definitely HCC ± PVT Probably malignancy
Noninvasive diagnosis of subcentimeter HCC	No	No	Yes (tumor marker + imaging)	Yes (probably HCC)
Noninvasive diagnosis of hypovascular HCC	No	No	No	Yes (probably HCC)

*Chronic hepatitis B in Asian (> 40 years in men, > 50 years in women), chronic hepatitis B with family history of HCC, chronic hepatitis B in African and North American black, †Washout on PVP and/or DP in CT, MRI using ECCM, and MRI using gadobenate dimeglumine. Washout on PVP only in gadoxetic acid-enhanced MRI. AASLD = Association for the Study of Liver Diseases, AFP = alpha-fetoprotein, AP = arterial phase, CHB = chronic hepatitis B, CHC = chronic hepatitis C, DP = delayed phase, EASL = European Association for the Study of the Liver, ECCM = extracellular contrast media, exam = examination, HCC = hepatocellular carcinoma, KLCSG-NCC = Korean Liver Cancer Study Group-National Cancer Center, LC = liver cirrhosis, LI-RADS = Liver Imaging Reporting and Data System, N/A = not applicable, PVP = portal venous phase, TP = transitional phase, US = ultrasonography

risk group for HCCs; whereas, in the AASLD guidelines and LI-RADS, patients with chronic hepatitis B of a certain age and race, or with any cause of cirrhosis comprise the high-risk group (9, 10, 12). The difference between Eastern and Western guidelines may reflect the high prevalence of HCCs and hepatitis B or hepatitis C viral infections in Asia (24).

Cirrhosis by excessive alcohol consumption, vascular obstruction or severe portal hypertension increases incidence of HCC development, although it's annual incidence is reportedly lower than viral hepatitis (41-44). Furthermore, arterially enhancing nodules in these disease entities have often been confirmed as large regenerative nodules (45-47). Therefore, radiologists' caution is warranted when applying noninvasive HCC diagnostic criteria in patients with these diseases (Fig. 2). Finally, patients with history of HCC may have the greatest risk of tumor recurrence. Frequent follow-up may facilitate early detection after treatment, and strategy to improve sensitivity to diagnose HCC may be needed to provide additional opportunities to receive curative treatment. However, most guidelines including KLCSG-NCC Korea practice guidelines are established for initial diagnosis in patients without previous history, and

Korean Journal of Radiology
KJR

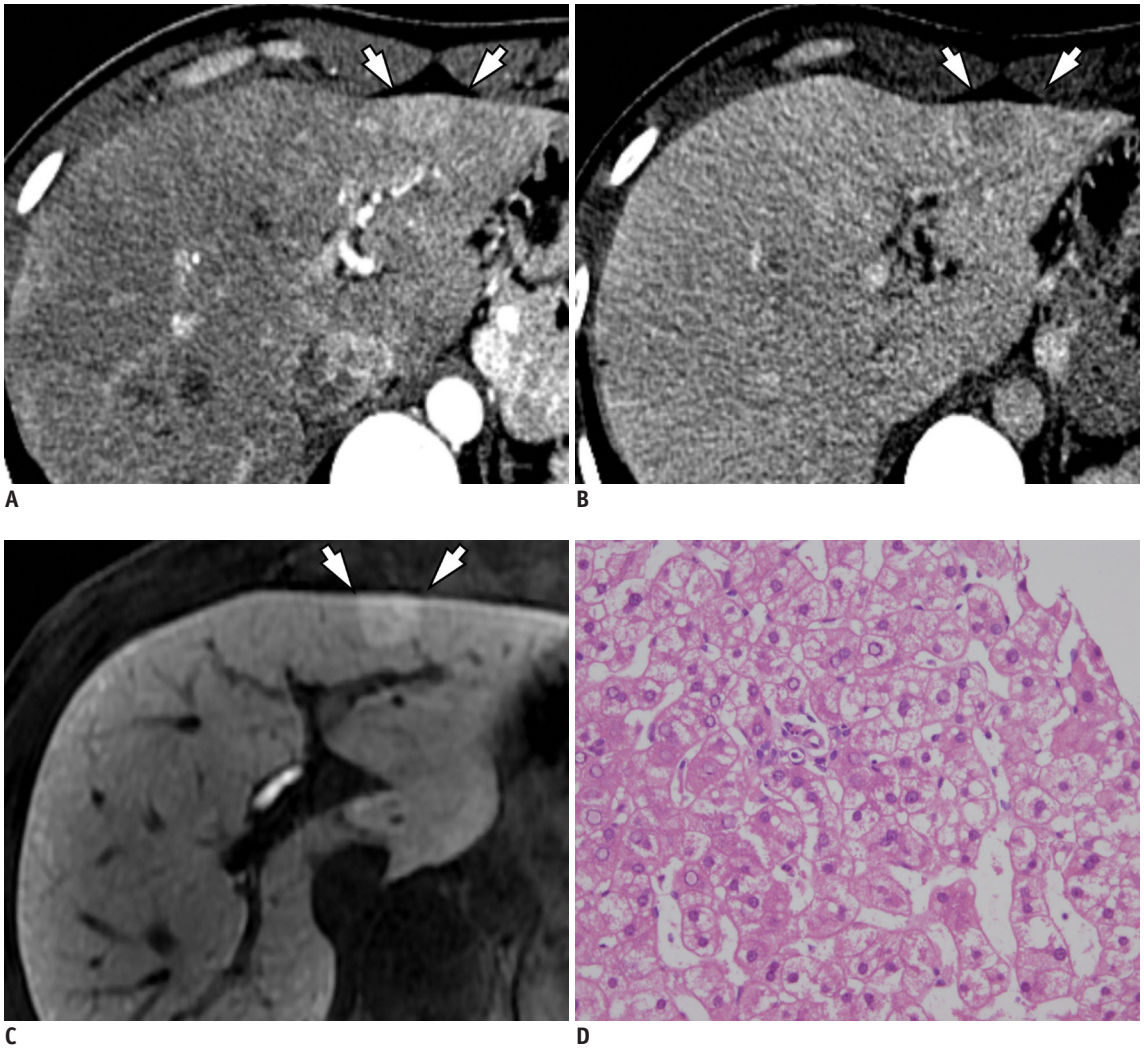

Fig. 2. CT and MR images in 24-year-old male patient without viral hepatitis but portal hypertension.
A, B. 2.2 cm mass is seen in S3 showing arterial "wash in" and portal "washout". **C.** Mass shows hyperintensity on hepatobiliary phase on gadoxetic acid-enhanced MRI. **D.** On repeated biopsy, nodule was diagnosed as focal nodular hyperplasia like nodule in background liver with periportal fibrosis.

do not state diagnostic criteria for recurrence. The risk stratification is necessary for establishing appropriate surveillance modality, follow-up interval after treatment and diagnostic strategy such as improving sensitivity or specificity, hence efforts are needed to clarify this issue in the next version of KLCSG-NCC Korea practice guidelines.

Detection of Nodules on Surveillance Ultrasound

According to the 2014 KLCSG-NCC Korea practice guidelines, nodules (≥ 1 cm) initially detected by surveillance ultrasound with arterial-phase enhancement and "washout" on the portal or delayed phase on CT or MRI, satisfy the diagnostic criteria for HCC. According to the literature, the presence of antecedent ultrasound visibility, which both raises the probability of HCC and also serves as an additional important imaging feature, raises the positive predictive value to nearly 100% (48-51). This ultrasound visibility on surveillance examinations for the noninvasive diagnosis of HCC is also suggested in the AASLD and EASL-EORTC guidelines. However, the reported sensitivity of surveillance ultrasound is in the range of 40% to 81% with a specificity of 80–100% (52), in which sensitivity is lower than CT or MRI (53-55) and specificity is lower than MRI using gadoxetic acid (54). Thus, although ultrasound has the advantage of being noninvasive, inexpensive, and without radiation, its diagnostic accuracy for HCC is limited among those with a more coarsened echo texture and in obese patients. Furthermore, the detection of subcentimeter

nodules in the cirrhotic liver can be quite challenging on ultrasound, even among examiners who are informed of tumor location (56, 57). As a result, dynamic CT or MRI are sometimes used as the adjunctive surveillance technique to ultrasound, depending on the clinicians' estimated risk for HCC (58). Likewise, the JSH recommends CT or MRI surveillance every 6–12 months in "super-high-risk patients" such as those with cirrhosis resulting from the hepatitis B or C virus and in patients in whom ultrasound is limited due to technical reasons (13, 48). Therefore, further study is warranted to determine whether ultrasound visibility is essentially required for the noninvasive diagnosis of HCC.

Implementation of Hepatocyte-Specific Contrast-Enhanced MRI

Appropriate Phase for Determining "Washout"

Hepatocyte-specific contrast enhanced MRI is increasingly performed owing to the growing evidence that it provides higher sensitivity for HCCs than MDCT or MRI using ECCM. This is mainly due to the higher contrast provided between the tumors and the background liver during hepatobiliary phase (59). The hepatobiliary phase is the temporal window during which hepatic parenchymal enhancement occurs as a result of hepatocyte uptake of contrast (38). Currently, the two hepatocyte-specific contrast media available in the market are gadoxetate disodium (Gd-EOB-DTPA, gadoxetic acid, Primovist or Eovist, Bayer Healthcare, Berlin, Germany) and gadobenate dimeglumine (Multihance, Bracco, Milan, Italy). The difference between the two is the percentage of hepatocyte uptake and the timing of the hepatobiliary phase. Approximately 50% of the administered dose of gadoxetic acid is taken up by hepatocytes and peak parenchymal enhancement is achieved in 20 minutes (60). In comparison, maximal parenchymal enhancement occurs 60–120 minutes after injection, as only 2–4% of gadobenate dimeglumine is taken up by hepatocytes (61). The liver parenchyma should be obviously brighter than the

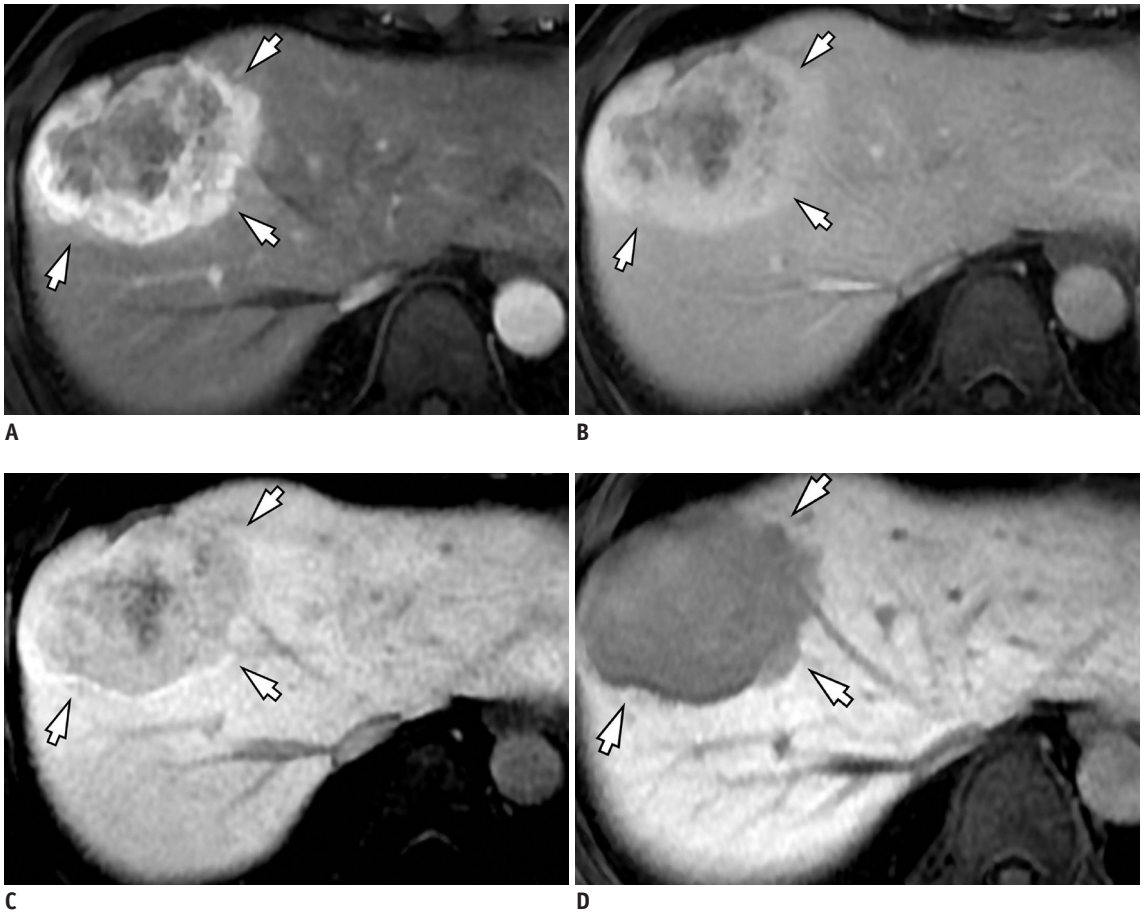

Fig. 3. Gadoxetic acid-enhanced MRI in 69-year-old man with chronic hepatitis C.
On arterial phase **(A)**, 1.2 cm enhancing nodule is seen in S8 (arrows), which is hyper-, hypo-, and hypointense on portal venous **(B)**, transitional **(C)**, and hepatobiliary **(D)** phases. Western guidelines are not applicable and it does not meet criteria of LR-5, but nodule is diagnosed with hepatocellular carcinoma according to Korean Liver Cancer Study Group-National Cancer Center and Japan Society of Hepatology guidelines.

Korean Journal of Radiology
KJR

portal vein or hepatic vein, and contrast should be seen in the bile duct on hepatobiliary phase (38). However, late dynamic phase imaging or delayed phase of gadoxetic acid, which is usually obtained around 3 minutes after contrast administration, is not equal to the conventional equilibrium phase, as contrast uptake by hepatocytes may start around the end of portal venous phase with gadoxetic acid (38), and refers to transitional phase in this review. Despite the great advantage of hepatobiliary phase for detection of malignancies, one possible pitfall of gadoxetic acid arises from its transitional phase, since hypointensity relative to the liver in the transitional phase may reflect hyperenhancement of the liver parenchyma rather than de-enhancement of a mass ("pseudo-washout"), thereby lowering the specificity for a HCC diagnosis (20). For this reason, AASLD, EASL-EORTC and OPTN guidelines, at present, consider only MDCT or MRI using ECCM as diagnostic modalities. Furthermore, although LI-RADS accepts gadoxetic acid-enhanced MRI, it recommends that "washout" should be evaluated only on the portal venous phase (38), whereas the KLCSG-NCC Korea practice guidelines permit the determination of "washout" on not only the portal phase but also on the transitional phase (3 minutes delayed scan). However, this concern over the loss of specificity is well founded (Figs. 3, 4). According to a recent study from Korea, sufficiently high specificity (97.9%) was achieved by admitting only "washout" on the portal venous phase of gadoxetic acid-enhanced MRI in nodules ≥ 1 cm (29). However, the specificity significantly dropped by permitting the determination of "washout" on the transitional phase (86.3%), although the sensitivity for the diagnosis of HCC also increased significantly (29). Indeed, approving the

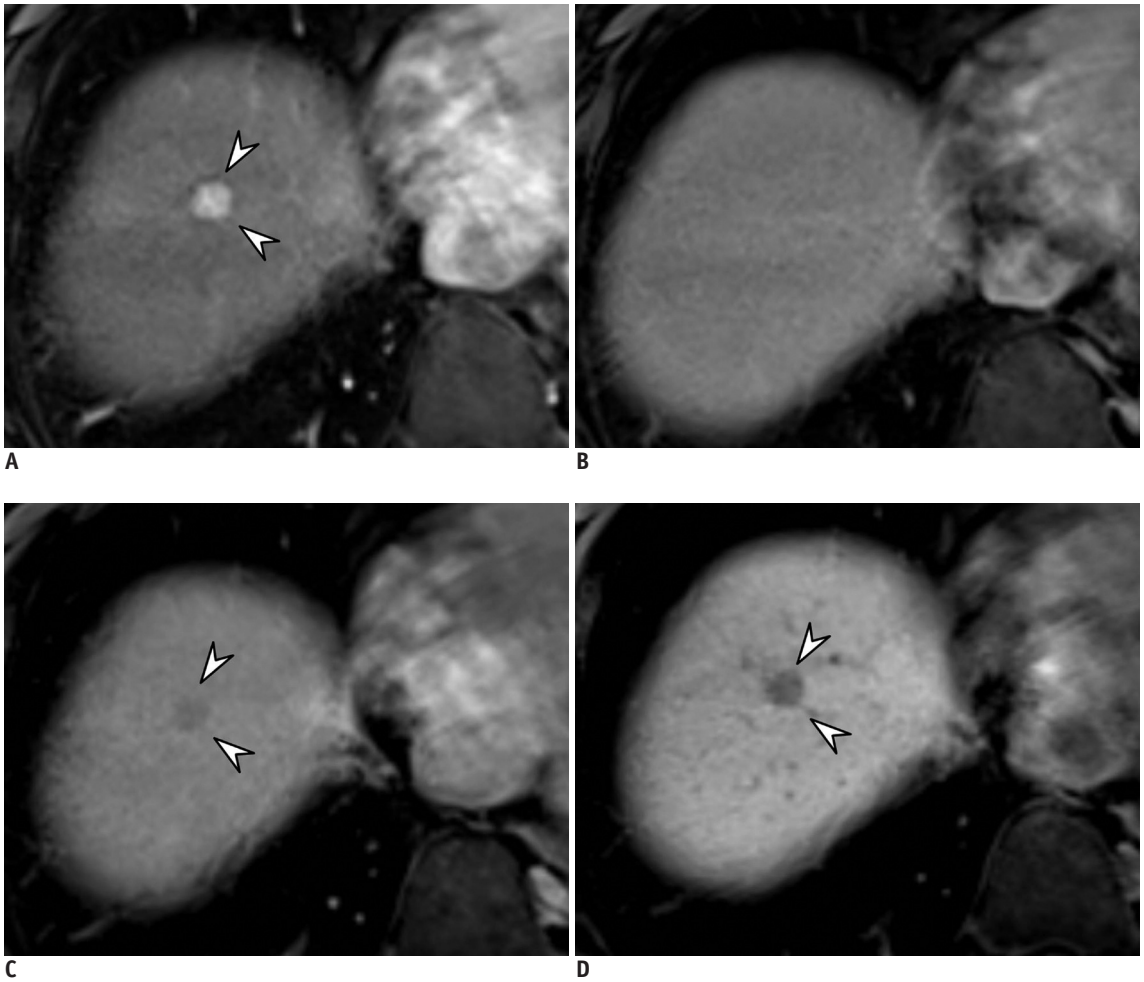

Fig. 4. Surgically confirmed cholangiocarcinoma in 49-year-old man.
On gadoxetic acid-enhanced MRI, there is approximately 7 cm arterially enhancing mass in S8 (**A**, arrowheads). Mass (arrowheads) shows isointensity on portal venous phase **(B)** and hypointensity on transitional **(C)** and hepatobiliary **(D)** phases, as compared with surrounding liver parenchyma. Mass can be diagnosed with hepatocellular carcinoma on basis of Korean Liver Cancer Study Group-National Cancer Center guideline, whereas it does not meet Liver Imaging Reporting and Data System recommendation that only accepts "portal washout".

alternative use of hypointensity on the hepatobiliary phase instead of "washout" actually lowered the specificity for the noninvasive diagnosis of HCC (48.4%), although this also showed the highest sensitivity (93.8%) (29). These results suggest that to maintain specificity, only portal venous phase "washout" should be used for a noninvasive HCC diagnosis. Furthermore, the diagnosis of HCCs is based on arterial-phase enhancement and solely washout on the hepatobiliary phase requires great caution by radiologists as it shows a specificity of < 50% (29). Nevertheless, methods to determine "washout" on hepatocyte-specific contrast media-enhanced MR imaging remains unclear, and may rather depend on results desired by radiologists and the clinicians, including high specificity or high sensitivity. In countries such as the United States, where the prevalence of HCC is not very high, and additional Model of End-Stage Liver Disease exception points equivalent to a 10% increase in mortality is allowed to patients with T2 stage HCC, this conservative definition of "washout" on only the portal venous phase would be reasonable. This is mainly because the overdiagnosis of HCCs may lead to unnecessary invasive treatments, unnecessary increase in the priority for liver transplantation allocations, or withdrawal of the chance for curative treatment in HCC patients. On the other hand, in Asian countries such as Korea, Japan, and China, which have the highest prevalence of HCCs globally, the diagnostic criteria for HCCs providing higher sensitivity with reasonably high specificity may be more appropriate, as early detection of HCCs may provide earlier adoption of potentially curative treatments such as radiofrequency ablation or surgical resection. Furthermore, low specificity for HCC diagnosis does not significantly alter the clinical management of liver transplantation in Korean practice, because liver transplantation is frequently used as a salvage operation after several attempts at interventional procedures or surgical resection; in addition, living donor transplantations are commonly performed and the presence of HCCs would not alter liver allocation priority. One may argue that false-positive diagnosis of HCC could lead to unnecessary invasive treatment. On the other hand, such high sensitivity may be helpful to avoid unnecessary surgery. A recent study shows that 4-year survival was superior in single nodular HCC on both CT and gadoxetic acid than single nodular HCC on CT only, after excluding patients with additionally detected definite or probable HCCs on gadoxetic acid MRI from surgery based on KLCSG-NCC Korea practice guideline and ancillary findings (62). The study demonstrated clinical value of diagnostic algorithm with high sensitivity in high-prevalence area, in terms of achieving "real curative resection" for the selected patients by avoiding futile surgery. Therefore, the alternative use of transitional or hepatobiliary phase hypointensity instead of "washout" on the portal venous phase would be quite appealing, especially if other ancillary findings of HCCs are carefully used to improve specificity.

Subdiagnostic Quality Arterial Phase Imaging on Gadoxetic Acid-Enhanced MRI

In phase I and II clinical trials, the recommended dose of gadoxetic acid is 0.025 mmol/kg (0.1 mL/kg) (60, 63), which is only half that compared to other ECCM agents (0.2 mL/kg) containing a quarter of the gadolinium concentration in ECCM (38). This raises the concern of a short arterial phase window, which may prevent development of proper late arterial phase. Furthermore, gadoxetic acid is frequently reported to cause acute transient dyspnea shortly after intravenous administration (64) with a reported range of incidence from 11–17%, which is significantly higher than the 1–2% reported with gadobenate dimeglumine (64, 65). Therefore, the arterial-phase enhancement of HCC can possibly be obscured. As a practical solution for this problem of gadoxetic acid-enhanced MRI, LI-RADS states that arterial-phase enhancement on recent CT scans may replace the inadequate arterial phase of MRI (38). The KLCSG-NCC Korea practice guidelines do not state such a substitution of arterial phase of recent CT or MRI scans using ECCM for suboptimal arterial phase of gadoxetic acid-enhanced MRI in patients with limited breathing-hold capacity or transient dyspnea. Furthermore, it is not clear whether the negative findings on arterial phase of recent CT or MRI with ECCM can also be applied. Therefore, further consensus is required concerning the substitution of other recent imaging modalities, criteria of 'recent' scan, and applicability of isovascular or hypovascular findings on the arterial phase of recent CTs or only tumoral hypervascularity on the arterial phase.

Nonhypervascular Hypointense Nodules: Noninvasive Diagnosis of Hypovascular HCC?

Nonhypervascular hypointense nodules detected on the hepatobiliary phase is another issue surrounding the use of hepatocyte-specific contrast-enhanced MRI. Although hypointense nodules are affected by hepatocarcinogenesis at the molecular level (21, 22), little is known about the

Korean Journal of Radiology
KJR

characteristics of these nodules due to lack of feasibility to biopsy of nonhypervascular hypointense nodules, owing to their multiplicity and small size. Furthermore, differentiation of dysplastic nodules from well-differentiated HCCs is challenging on biopsy. Recently, accumulating data shows histologic characters and clinical significance of these nodules. It was reported that a substantial proportion of nonhypervascular hypointense nodules (≥ 1 cm) or isovascular hypointense nodules (> 1 cm) are pathologically diagnosed as HCCs or high-grade dysplastic nodules (HGDNs) (Fig. 5) (27, 66). Moreover, approximately 10–30% of these nodules show arterial-phase hypervascularization on follow-up (Fig. 6) (26, 27, 67-70). The clinical impact of these nodules on patients' outcome is gaining attention. Patients with nonhypervascular hypointense nodules show shorter recurrence free survival after radiofrequency ablation (71), and lower overall survival rate after liver resection (72). Despite their clinical significance, currently LI-RADS is the only criteria that stratifies risk of nonhypervascular hypointense nodules by scoring LR-3 or -4, depending on ancillary findings (12). One of the reasons why these nodules are not stated in other guidelines might be the challenge to differentiate HCCs from HGDNs noninvasively. Although there have been attempts to differentiate HCCs from HGDNs in these nodules using ancillary findings such as mild to modest T2 hyperintensity and diffusion

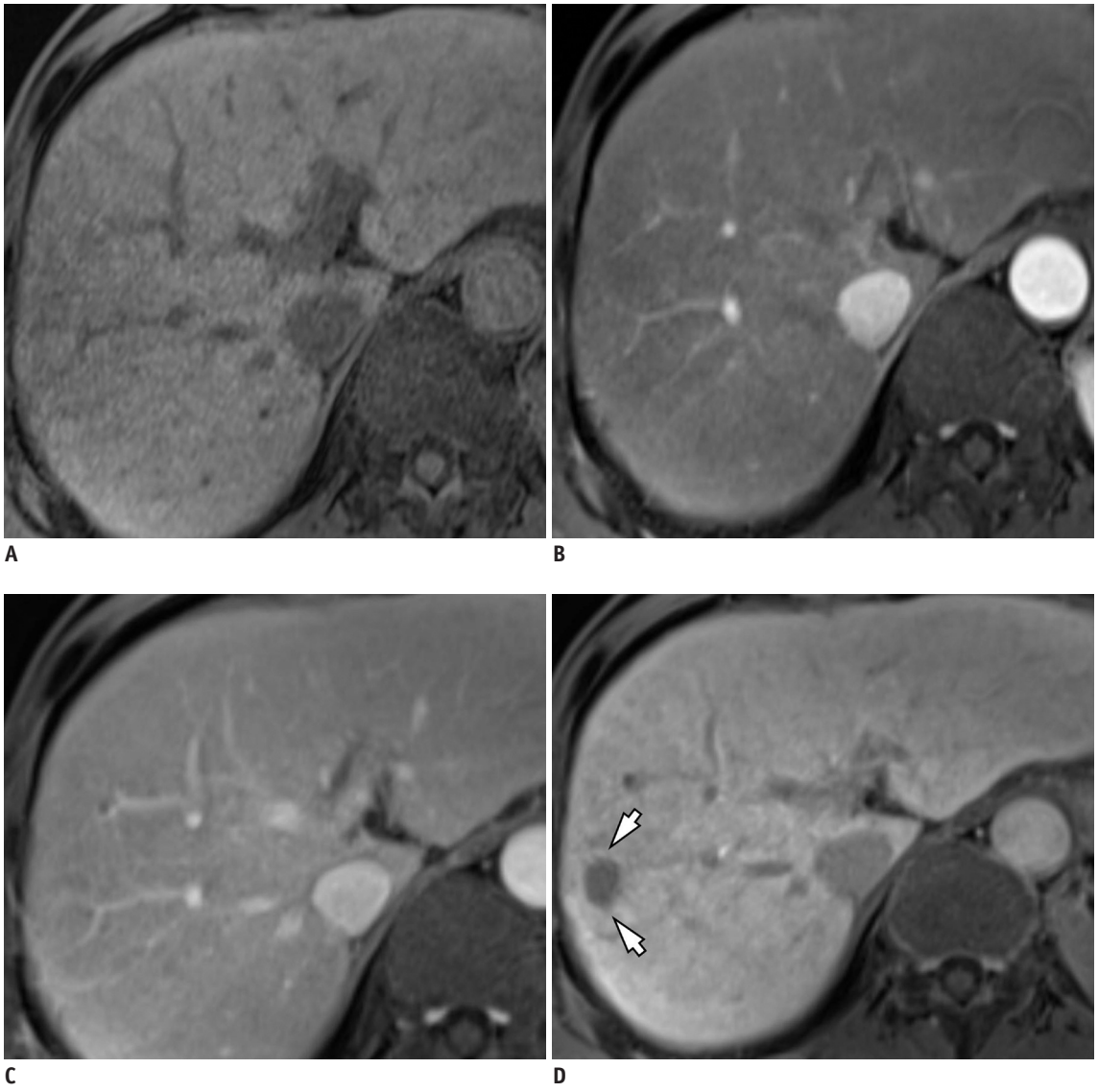

Fig. 5. Gadoxetic acid-enhanced MRI in 66-year-old man with chronic hepatitis B.
On precontrast T1-weighted **(A)**, arterial **(B)**, and portal venous phase **(C)** images, no focal lesion is shown in liver. On the hepatobiliary phase **(D)**, 1.2 cm defect is revealed in S7/8 (arrows). Nodule was not delineable on T2- or diffusion weighted images. After fusion biopsy, nodule was diagnosed as well-differentiated hepatocellular carcinoma.

restriction (27, 66, 73-75) or initial nodule size (> 1–1.5 cm in diameter) (28, 30, 68, 76), the results are controversial to date. Nonetheless, these nonhypervascular hypointense nodules should be addressed as potentially malignant, since a substantial number of the nodules are pathologically early HCCs, and they potentially progress to classic HCCs. However, implementation of the concept of nonhypervascular hypointense nodules may require critical revision of KLCSG-NCC Korea practice guidelines, because current guidelines provide only binary classification of either HCC or not. In addition, worse clinical outcome in patients with nonhypervascular hypointense nodules may also require additional modification of follow-up strategy including accelerated surveillance interval, selection of surveillance modalities, and further refined stratification of high-risk group. Thus, implementation of the concept and interpretation of these nodules followed by customized management plan is an important issue to be addressed in the next update of KLCSG-NCC Korea practice guidelines.

Increase Diagnostic Sensitivity of Noninvasive Diagnostic Criteria of HCC

Need for Implementation of Ancillary Findings: How and When

The approach based on hemodynamic alternations of HCC compared with the liver parenchyma may not be the best strategy in endemic areas, as it can potentially lead to the underdiagnosis of HCCs resulting from low sensitivity, thereby missing the chance for a timely treatment. According to previous studies using explanted livers as a standard of reference (31, 77), even the KLCSG-

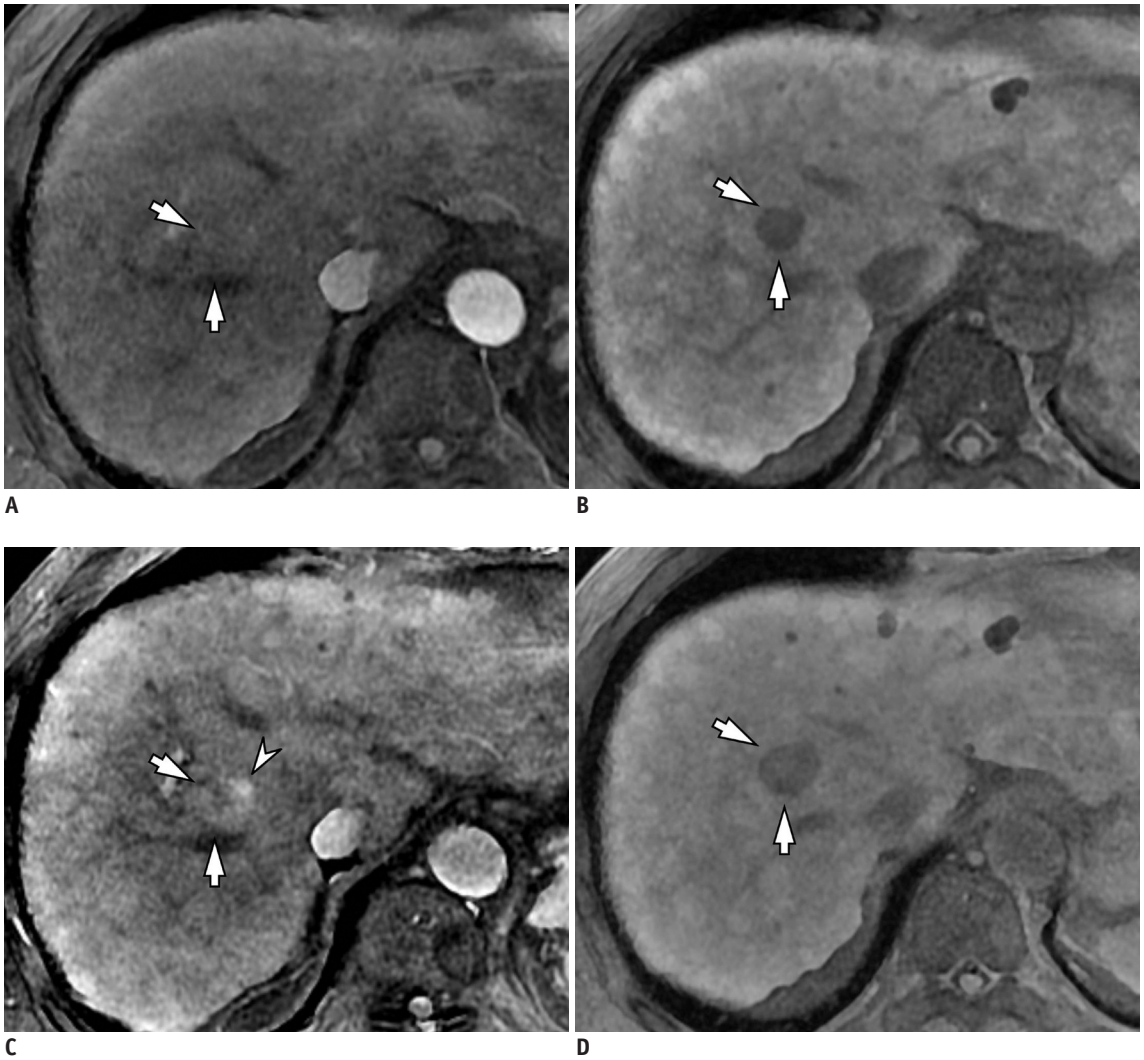

Fig. 6. Gadoxetic acid-enhanced MRI in 60-year-old man with chronic hepatitis B.
A, B. On initial MRI, 1.3 cm nonhypervascular hypointense nodule (arrows) is observed in S8. **C, D.** Nine months later, nodule showed interval development of arterial enhancement in nodule (arrowhead) with interval growth (2.2 cm, arrows) on follow-up MRI.

Korean Journal of Radiology
KJR

NCC Korea practice guideline approach (arterial-phase enhancement and portal venous and/or transitional phase washout at MR) show only 20.7–27.6% sensitivity using gadoxetic acid-enhanced MRI in 1–2 cm tumors, despite its 75–87.5% sensitivity in tumors ≥ 2 cm. Indeed, the low sensitivity of this noninvasive diagnostic criteria is more frequently observed in small HCCs, ranging between 1–2 cm in literature. Sangiovanni et al. (78) also report the sensitivity of contrast enhanced ultrasonography (US), MDCT, and MRI using ECCM for 1–2 cm HCCs as 26%, 44%, and 44%, respectively, with 100% specificity. This may be explained by lack of diagnostic hallmark in small HCCs (≤ 2 cm), resulting from incomplete neoangiogenesis. This low sensitivity may justify Asian guidelines such as APASL, JSH, and 2014 KLCSG-NCC Korea practice guidelines, which aim to increase sensitivity (13, 14, 24). It further re-emphasizes the issue of how to obtain improved sensitivity while maintaining specificity to achieve an accurate diagnosis and staging of HCCs.

In the recent literature, several strategies are suggested to improve diagnostic sensitivity i.e., hypointensity on hepatobiliary phase imaging, diffusion restriction on DWI (18, 79), presence of intralesional fat, and mild to modest hyperintensity on T2-weighted images (12, 80, 81). Previous studies show that hypointensity on the hepatobiliary phase can contribute to high sensitivity at hepatocyte-specific contrast enhanced MRI (59, 82) and that DWI also contributes to the improved sensitivity for HCCs (83, 84). The ancillary findings are clinically valuable particularly in nodules < 2 cm in diameter (18, 31). Although the 2014 KLCSG-NCC Korea practice guidelines describe ancillary findings as suggestive features of HCCs, the guidelines do not adopt these features as noninvasive diagnostic criteria, since they are not specific for HCC, and can be found in other hepatic malignancies such as cholangiocarcinoma, metastasis, or benign hemangioma. However, hypointensity on the hepatobiliary phase and diffusion restriction could improve the sensitivity for the diagnosis of HCC. Furthermore, according to another previous study (85), use of other common MR characteristics of HCC at such as peritumoral capsule, and intralesional fat, do not increase diagnostic accuracy of MRI, as compared with contrast enhancement patterns for the diagnosis of solitary nodules between 5–20 mm detected during surveillance in patients with cirrhosis. This leads radiologists to the dilemma of balancing sensitivity and specificity.

Among the several guidelines for the diagnosis of HCC, LI-RADS may provide a good example on how to deal with the aforementioned ancillary findings in the noninvasive diagnosis of HCCs (12). In LI-RADS, the diagnosis of "definitely HCC (LR-5)" is made on the basis of classical findings such as tumor size, arterial-phase enhancement, and 1 or 2 findings among "washout", "capsule appearance", and "threshold growth" (12). For the diagnosis of "probably HCC (LR-4)", morphologic findings such as fatty metamorphosis, and nodule in nodule architecture as well as the findings on T2-weighted imaging, DWI and hepatobiliary phase imaging, are considered as favoring malignancy. Hypointensity on the hepatobiliary phase is also considered as an ancillary finding for malignancy (12). In a recent prospective cohort study, which considered the diagnoses of "LR-5" and "LR-4" as definitive for HCC, sensitivity increased from 42.3% to 65.4%, without decreasing specificity (96.4%) in US detected small nodules (≤ 2 cm) (86). However, up-scoring and down-scoring using ancillary findings are one of the main causes of increased inter-observer variability in LI-RADS (87). Further refinement of the scoring system through standardization of up-scoring and down-scoring may be warranted to reduce inter-observer variability, especially in small nodules ranging between 1–2 cm. Furthermore, simply adopting ancillary findings in LI-RADS, in relation with major diagnostic criteria of HCC as well as frequent use of hepatocyte-specific contrast enhanced liver MRI requires caution. "Pseudo-washout" can be observed in tumor capsule appearance, which is 1 of the major criteria for diagnosing HCC. According to LI-RADS and OPTN guidelines, presence of tumor capsule appearance is the major criterion to diagnose HCC, where capsule appearance is defined as rim enhancement on delayed phase with or without arterial enhancement (12). However, because of "pseudo-washout", enhanced capsule appearance of tumor can be seen as hypointense rim on transitional phase, which shows enhancement on delayed phase at CT or MRI using ECCM (Fig. 7). Thus, the tumor fails to meet the criteria of OPTN and LI-RADS 5, because hypointense rim on transitional phase is not regarded as capsule appearance but discrete rim that is ancillary finding. Indeed, LI-RADS accepts capsule appearance on only vascular phases, to maintain consistency with OPTN guideline (12) for assessment of capsule appearance on transitional phase. Adoption and implementation of ancillary findings for noninvasive diagnosis for HCC should be discussed in the upcoming version of KLCSG-NCC Korea practice guidelines

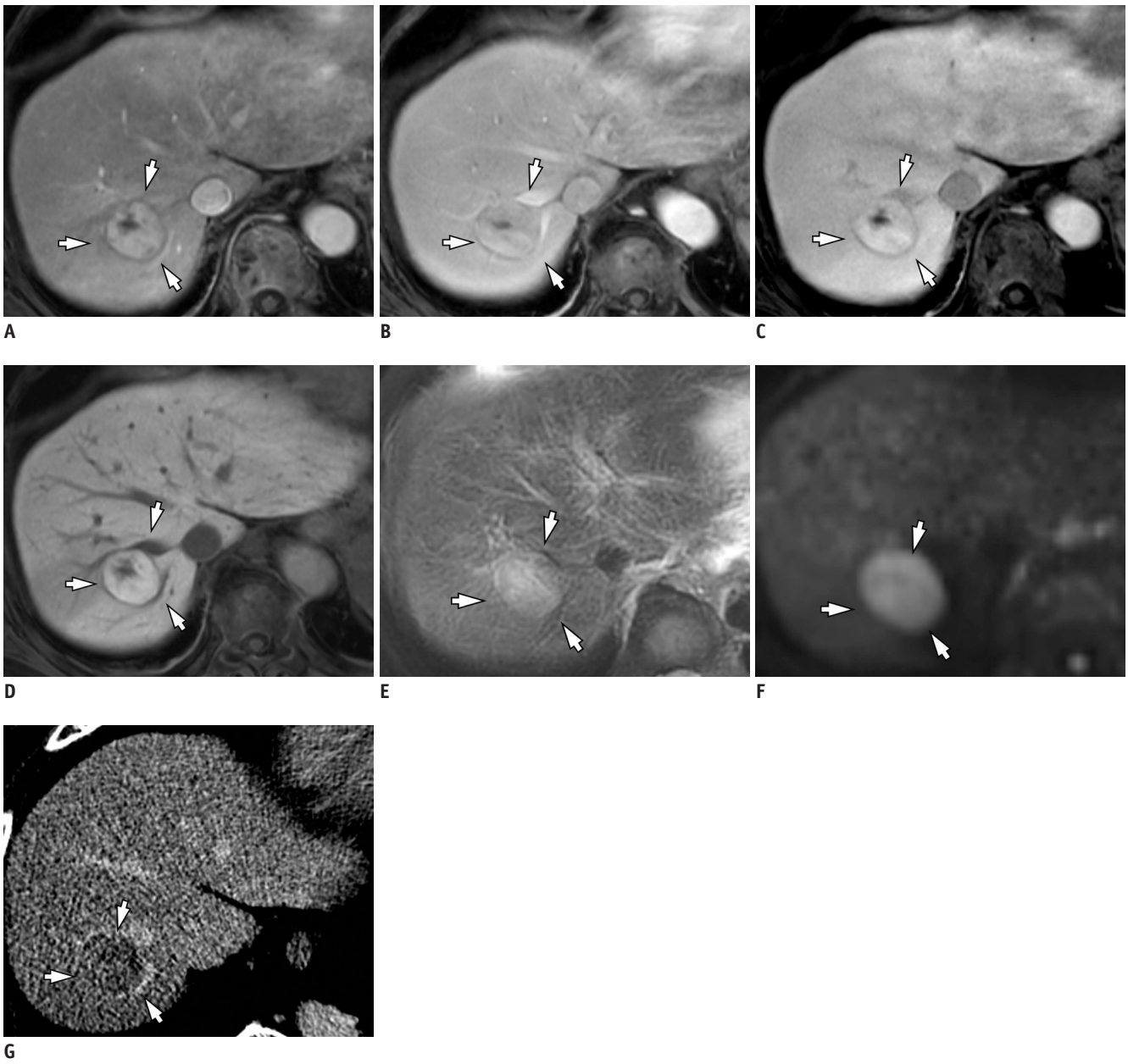

Fig. 7. Histologically confirmed hepatocellular carcinoma in 81-year-old man with chronic hepatitis B.
3.3 cm mass (arrows) is incidentally found in S7 showing "wash in" on arterial phase **(A)** without "washout" on portal venous phase **(B)**. On transitional **(C)** and hepatobiliary **(D)** phases of gadoxetic acid-enhanced MRI, mass remains as hyperintense. Although it shows discrete rim **(B-D)**, mild T2 high signal intensity **(E)**, diffusion restriction **(F)**, which is suggestive of malignancy, mass does not meet Association for Study of Liver Diseases, European Organization for Research and Treatment of Cancer, Korean Liver Cancer Study Group-National Cancer Center diagnostic criteria, and LR-5. On delayed phase CT scan **(G)**, tumor shows enhanced rim, which meets definition of "capsule" according to Liver Imaging Reporting and Data System and Organ Procurement and Transplantation Network, and hypointense rim on transitional phase of MR might be result of "pseudo-washout".

in conjunction with issue of nonhypervascular hypointense nodules.

Diagnosis of Small (< 1 cm) HCCs

According to the literature, the sensitivities of CT and MRI are closely related with tumor size. Owing to the low sensitivity of CT and MRI in diagnosing subcentimeter HCCs (59), noninvasive diagnostic criteria are not applicable to small (< 1 cm) nodules according to AASLD and EASL-EORTC guidelines (9, 10, 88). However, in clinical practice, an increasing number of subcentimeter cirrhotic nodules are found on hepatocyte-specific contrast-enhanced

Korean Journal of Radiology
KJR

MRI including DWI that are often confirmed as HCCs or high-grade dysplastic nodules (18, 66). Therefore, the first emerging question is the characterization of subcentimeter hypervascular nodules that show arterial-phase enhancement and "washout", diffusion restriction or hyperintensity on T2-weighted imaging and hypointensity on the hepatobiliary phase. In contrast to AASLD and EASL-EORTC guidelines, KLCSG-NCC Korea practice guidelines and LI-RADS include a category for these HCCs (< 1 cm). KLCSG-NCC Korea practice guidelines indicate that HCCs can be diagnosed by a combination of the typical hallmark features of HCCs in ≥ 2 imaging modalities and increased serum alpha-fetoprotein levels with a rising trend over time for liver nodules < 1 cm in patients with suppressed hepatitis activity (24). LI-RADS suggests that arterial-phase enhancing nodules (< 1 cm) showing one finding among "washout", "capsule", or "threshold growth" can be scored as LR-4, indicating "probably HCC" (12). Recent studies report that in subcentimeter (< 1 cm) hypervascular nodules showing typical imaging findings of HCC on gadoxetic acid-enhanced MRI and DWI, 89.9–100% of the nodules progress to overt HCCs (≥ 1 cm) within 12 months (89, 90), and all nodules (100%) > 5.5 mm turn to overt HCC within a year in patients with history of HCC, including a case of portal vein invasion (89). In addition, only initial nodule size is a significant risk factor for HCC progression (89). The cumulative rate of progression in these nodules is higher than those in nodules with atypical, nonhypervascular features (27, 75). To date, there are no studies regarding clinical outcome of subcentimeter HCCs between immediate treatment and imaging follow-up strategy after detection. However, given the high progression rate to typical HCCs (89.9–100%) (89, 90) and better prognosis of very early stage HCC than early stage HCC (91-93), diagnosis of subcentimeter HCC would be clinically beneficial by providing two different options including immediate treatment and intense follow-up. Further studies are warranted to establish more refined diagnostic criteria and to better stratify the degree of risk in these subcentimeter nodules.

Recommendation for Indeterminate Nodules: Biopsy for All vs. Follow-Up

According to the KLCSG-NCC Korea practice guidelines, either biopsy or follow-up could be used for nodules without the typical enhancement pattern of HCCs, i.e., arterial-phase enhancement and "washout" on contrast-enhanced CT or MRI. This is quite different from the AASLD (9) or EASL-EORTC guidelines (15), as biopsy is advocated for all indeterminate nodules on imaging work-up by contrast-enhanced scans. There are several rationales to implement follow-up strategy for indeterminate nodules in KLCSG-NCC Korea practice guidelines. First, neither the AASLD diagnostic algorithm nor the EASL-EORTC diagnostic algorithm would be appropriate to diagnose early HCCs, which frequently show atypical enhancement patterns. Second, biopsy of small (< 2 cm) nodules may not be technically possible in some patients, and may possess a risk of sampling bias or a serious diagnostic difficulty (23), as well as a potential risk of tract seeding (94). Third, the low prevalence of malignancies among the 1–2 cm indeterminate nodules (14–23%) (95) also justifies follow-up strategy. The study demonstrates that only arterial-phase hypervascularity and the presence of synchronous HCCs are significant predictors of malignancy (95). Therefore, applying these criteria may lead to substantial reduction of biopsy while it would detect the majority of HCCs. Fourth, no outcome study has shown that survival is prolonged by performing a biopsy for indeterminate nodules > 10 mm rather than following them closely for growth (48). Thus, this option of follow-up strategy is clinically feasible. However, there is no recommendation on prioritizing strategy for indeterminate nodules. The issue is also related to the need of risk stratification of atypical nodules in cirrhosis using ancillary findings, as discussed earlier in this review. Importantly, "threshold growth", which is included as a main diagnostic criterion in LI-RADS and the OPTN system introduced by the United Network for Organ Sharing (UNOS). OPTN-UNOS guidelines allow the diagnosis of arterial-phase hyperenhancing HCCs using threshold growth, defined as growth > 50% in ≤ 6 months (11). Currently, the KLCSG-NCC Korea practice guidelines incorporate follow-up imaging instead of biopsy for indeterminate nodules, but not the criterion of threshold growth on follow-up imaging. Threshold growth could possibly be used as a primary diagnostic criteria for HCC in future updates of KLCSG-NCC Korea practice guidelines.

Differential Diagnosis from Other Malignancies

According to recent reports, small intrahepatic cholangiocarcinomas (CC) in the cirrhotic liver may show atypical imaging features such as arterial-phase

hyperenhancement, mimicking those of HCCs (83, 84). Although a stable enhancement pattern without "washout" on MRI with ECCM is observed in all histologically confirmed intrahepatic CCs, according to a retrospective study (85), the differential diagnosis of small intrahepatic CCs in the cirrhotic liver from HCCs may be difficult solely through contrast-enhanced CT or MRI findings (20, 38, 96). Contrast-enhanced US is omitted from the diagnostic techniques since it may offer false positive HCC diagnosis in patients with CCs (9). Although the incidence of intrahepatic CCs in cirrhotic liver is regarded as low, chronic liver disease is also a risk factor for intrahepatic CCs (97). Repeated episodes of inflammation and regeneration in chronic liver disease result in various genetic and epigenetic changes to both parenchymal cells and hepatic stem cells, activating various signaling pathways due to the stromal microenvironment (96). Recent studies suggest that combined hepatocellular-cholangiocarcinomas (cHCC-CC) and some intrahepatic CCs originating from small ductules may arise from transformed hepatic stem cells, and would present a spectrum of imaging findings that are intermediate to HCCs and CCs (98). Identification of imaging features in differentiating HCCs from cHCC-CCs or CCs in the cirrhotic liver is clinically significant for appropriate patient management (99), hence, further refinement of the diagnostic criteria for small CCs in cirrhotic liver is warranted.

CONCLUSION

Several noninvasive diagnostic criteria endorsed by the new KLCSG-NCC Korea practice guidelines are consistent with AASLD and EASL-EORTC guidelines, but there is some variance. The new guidelines are more practical, in terms of implementing diagnostic criteria using hepatocyte-specific contrast enhanced MRI, and establishing criteria for subcentimeter sized HCCs. However, there are several remaining issues including diagnostic criteria using gadoxetic acid, report of nonhypervascular hypointense nodules, and the new concept of HCC spectrum, which introduces the possibility of CC-HCCs. These issues need to be addressed in the future update of the guideline on the basis of large scale data-driven evidence.

REFERENCES

1. El-Serag HB. Hepatocellular carcinoma. *N Engl J Med* 2011;365:1118-1127
2. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 2001;94:153-156
3. Trevisani F, Cantarini MC, Wands JR, Bernardi M. Recent advances in the natural history of hepatocellular carcinoma. *Carcinogenesis* 2008;29:1299-1305
4. Bruix J, Llovet JM. Major achievements in hepatocellular carcinoma. *Lancet* 2009;373:614-616
5. Coleman WB. Mechanisms of human hepatocarcinogenesis. *Curr Mol Med* 2003;3:573-588
6. Ueda K, Matsui O, Kawamori Y, Nakanuma Y, Kadoya M, Yoshikawa J, et al. Hypervascular hepatocellular carcinoma: evaluation of hemodynamics with dynamic CT during hepatic arteriography. *Radiology* 1998;206:161-166
7. Levy I, Greig PD, Gallinger S, Langer B, Sherman M. Resection of hepatocellular carcinoma without preoperative tumor biopsy. *Ann Surg* 2001;234:206-209
8. Torzilli G, Minagawa M, Takayama T, Inoue K, Hui AM, Kubota K, et al. Accurate preoperative evaluation of liver mass lesions without fine-needle biopsy. *Hepatology* 1999;30:889-893
9. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;53:1020-1022
10. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001;35:421-430
11. Wald C, Russo MW, Heimbach JK, Hussain HK, Pomfret EA, Bruix J. New OPTN/UNOS policy for liver transplant allocation: standardization of liver imaging, diagnosis, classification, and reporting of hepatocellular carcinoma. *Radiology* 2013;266:376-382
12. American College of Radiology. Liver imaging reporting and data system (LI-RADS). American College of Radiology. Web site. http://www.acr.org/Quality-Safety/Resources/LIRADS. Published May 25, 2014. Accessed August 1, 2015
13. Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, et al. JSH consensus-based clinical practice guidelines for the management of hepatocellular carcinoma: 2014 update by the Liver Cancer Study Group of Japan. *Liver Cancer* 2014;3:458-468
14. Omata M, Kanda T, Yu ML, Yokosuka O, Lim SG, Jafri W, et al. APASL consensus statements and management algorithms for hepatitis C virus infection. *Hepatol Int* 2012;6:409-435
15. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012;56:908-943
16. Choi JY, Lee JM, Sirlin CB. CT and MR imaging diagnosis and staging of hepatocellular carcinoma: part I. Development, growth, and spread: key pathologic and imaging aspects. *Radiology* 2014;272:635-654
17. Lee JM, Yoon JH, Kim KW. Diagnosis of hepatocellular carcinoma: newer radiological tools. *Semin Oncol* 2012;39:399-409

18. Park MJ, Kim YK, Lee MW, Lee WJ, Kim YS, Kim SH, et al. Small hepatocellular carcinomas: improved sensitivity by combining gadoxetic acid-enhanced and diffusion-weighted MR imaging patterns. *Radiology* 2012;264:761-770
19. Xu PJ, Yan FH, Wang JH, Lin J, Ji Y. Added value of breathhold diffusion-weighted MRI in detection of small hepatocellular carcinoma lesions compared with dynamic contrast-enhanced MRI alone using receiver operating characteristic curve analysis. *J Magn Reson Imaging* 2009;29:341-349
20. Choi JY, Lee JM, Sirlin CB. CT and MR imaging diagnosis and staging of hepatocellular carcinoma: part II. Extracellular agents, hepatobiliary agents, and ancillary imaging features. *Radiology* 2014;273:30-50
21. Kitao A, Matsui O, Yoneda N, Kozaka K, Shinmura R, Koda W, et al. The uptake transporter OATP8 expression decreases during multistep hepatocarcinogenesis: correlation with gadoxetic acid enhanced MR imaging. *Eur Radiol* 2011;21:2056-2066
22. Kogita S, Imai Y, Okada M, Kim T, Onishi H, Takamura M, et al. Gd-EOB-DTPA-enhanced magnetic resonance images of hepatocellular carcinoma: correlation with histological grading and portal blood flow. *Eur Radiol* 2010;20:2405-2413
23. Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y; Liver Cancer Study Group of Japan. Surveillance and diagnostic algorithm for hepatocellular carcinoma proposed by the Liver Cancer Study Group of Japan: 2014 update. *Oncology* 2014;87 Suppl 1:7-21
24. Lee JM, Park JW, Choi BI. 2014 KLCSG-NCC Korea Practice Guidelines for the management of hepatocellular carcinoma: HCC diagnostic algorithm. *Dig Dis* 2014;32:764-777
25. Korean Liver Cancer Study Group (KLCSG); National Cancer Center, Korea (NCC). 2014 Korean Liver Cancer Study Group-National Cancer Center Korea practice guideline for the management of hepatocellular carcinoma. *Korean J Radiol* 2015;16:465-522
26. Yamamoto A, Ito K, Tamada T, Higaki A, Kanki A, Sato T, et al. Newly developed hypervascular hepatocellular carcinoma during follow-up periods in patients with chronic liver disease: observation in serial gadoxetic acid-enhanced MRI. *AJR Am J Roentgenol* 2013;200:1254-1260
27. Yoon JH, Lee JM, Yang HK, Lee KB, Jang JJ, Han JK, et al. Non-hypervascular hypointense nodules ≥ 1 cm on the hepatobiliary phase of gadoxetic acid-enhanced magnetic resonance imaging in cirrhotic livers. *Dig Dis* 2014;32:678-689
28. Takayama Y, Nishie A, Nakayama T, Asayama Y, Ishigami K, Kakihara D, et al. Hypovascular hepatic nodule showing hypointensity in the hepatobiliary phase of gadoxetic acid-enhanced MRI in patients with chronic liver disease: prediction of malignant transformation. *Eur J Radiol* 2012;81:3072-3078
29. Joo I, Lee JM, Lee DH, Jeon JH, Han JK, Choi BI. Noninvasive diagnosis of hepatocellular carcinoma on gadoxetic acid-enhanced MRI: can hypointensity on the hepatobiliary phase be used as an alternative to washout? *Eur Radiol* 2015;25:2859-2868
30. Takechi M, Tsuda T, Yoshioka S, Murata S, Tanaka H, Hirooka M, et al. Risk of hypervascularization in small hypovascular hepatic nodules showing hypointense in the hepatobiliary phase of gadoxetic acid-enhanced MRI in patients with chronic liver disease. *Jpn J Radiol* 2012;30:743-751
31. Lee DH, Lee JM, Baek JH, Shin CI, Han JK, Choi BI. Diagnostic performance of gadoxetic acid-enhanced liver MR imaging in the detection of HCCs and allocation of transplant recipients on the basis of the Milan criteria and UNOS guidelines: correlation with histopathologic findings. *Radiology* 2015;274:149-160
32. Lee JM, Trevisani F, Vilgrain V, Wald C. Imaging diagnosis and staging of hepatocellular carcinoma. *Liver Transpl* 2011;17 Suppl 2:S34-S43
33. Rimola J, Forner A, Reig M, Vilana R, de Lope CR, Ayuso C, et al. Cholangiocarcinoma in cirrhosis: absence of contrast washout in delayed phases by magnetic resonance imaging avoids misdiagnosis of hepatocellular carcinoma. *Hepatology* 2009;50:791-798
34. Kim AY, Lee MW, Rhim H, Cha DI, Choi D, Kim YS, et al. Pretreatment evaluation with contrast-enhanced ultrasonography for percutaneous radiofrequency ablation of hepatocellular carcinomas with poor conspicuity on conventional ultrasonography. *Korean J Radiol* 2013;14:754-763
35. Kim SH, Kim SH, Lee J, Kim MJ, Jeon YH, Park Y, et al. Gadoxetic acid-enhanced MRI versus triple-phase MDCT for the preoperative detection of hepatocellular carcinoma. *AJR Am J Roentgenol* 2009;192:1675-1681
36. Sun HY, Lee JM, Shin CI, Lee DH, Moon SK, Kim KW, et al. Gadoxetic acid-enhanced magnetic resonance imaging for differentiating small hepatocellular carcinomas (< or =2 cm in diameter) from arterial enhancing pseudolesions: special emphasis on hepatobiliary phase imaging. *Invest Radiol* 2010;45:96-103
37. Park G, Kim YK, Kim CS, Yu HC, Hwang SB. Diagnostic efficacy of gadoxetic acid-enhanced MRI in the detection of hepatocellular carcinomas: comparison with gadopentetate dimeglumine. *Br J Radiol* 2010;83:1010-1016
38. Hope TA, Fowler KJ, Sirlin CB, Costa EA, Yee J, Yeh BM, et al. Hepatobiliary agents and their role in LI-RADS. *Abdom Imaging* 2015;40:613-625
39. Shoreibah MG, Bloomer JR, McGuire BM, Massoud OI. Surveillance for hepatocellular carcinoma: evidence, guidelines and utilization. *Am J Med Sci* 2014;347:415-419
40. Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan. *Lancet* 1981;2:1129-1133
41. Bagnardi V, Blangiardo M, La Vecchia C, Corrao G. A meta-analysis of alcohol drinking and cancer risk. *Br J Cancer* 2001;85:1700-1705
42. Bellentani S, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M, et al. Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. *Gut*

1997;41:845-850
43. Seitz HK, Stickel F. Molecular mechanisms of alcohol-mediated carcinogenesis. *Nat Rev Cancer* 2007;7:599-612
44. Vilgrain V, Rautou PE, Paradis V, Ronot M. Benign and malignant hepatocellular lesions in patients with vascular liver disease. *Clin Liver Dis (Hoboken)* 2014;3:122-125
45. Brancatelli G, Federle MP, Grazioli L, Golfieri R, Lencioni R. Benign regenerative nodules in Budd-Chiari syndrome and other vascular disorders of the liver: radiologic-pathologic and clinical correlation. *Radiographics* 2002;22:847-862
46. Choi JY, Lee HC, Yim JH, Shim JH, Lim YS, Shin YM, et al. Focal nodular hyperplasia or focal nodular hyperplasia-like lesions of the liver: a special emphasis on diagnosis. *J Gastroenterol Hepatol* 2011;26:1004-1009
47. Nakashima O, Kurogi M, Yamaguchi R, Miyaaki H, Fujimoto M, Yano H, et al. Unique hypervascular nodules in alcoholic liver cirrhosis: identical to focal nodular hyperplasia-like nodules? *J Hepatol* 2004;41:992-998
48. Mitchell DG, Bruix J, Sherman M, Sirlin CB. LI-RADS (Liver Imaging Reporting and Data System): summary, discussion, and consensus of the LI-RADS Management Working Group and future directions. *Hepatology* 2015;61:1056-1065
49. Sersté T, Barrau V, Ozenne V, Vullierme MP, Bedossa P, Farges O, et al. Accuracy and disagreement of computed tomography and magnetic resonance imaging for the diagnosis of small hepatocellular carcinoma and dysplastic nodules: role of biopsy. *Hepatology* 2012;55:800-806
50. Forner A, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology* 2008;47:97-104
51. Jang HJ, Kim TK, Khalili K, Yazdi L, Menezes R, Park SH, et al. Characterization of 1-to 2-cm liver nodules detected on hcc surveillance ultrasound according to the criteria of the American Association for the Study of Liver Disease: is quadriphasic CT necessary? *AJR Am J Roentgenol* 2013;201:314-321
52. Andersson KL, Salomon JA, Goldie SJ, Chung RT. Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2008;6:1418-1424
53. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, et al. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. *Aliment Pharmacol Ther* 2009;30:37-47
54. Kim S, Lim YS, Byun J, Won H, Lee S, Han S, et al. A prospective study to compare the diagnostic performance of gadoxetic acid-enhanced MRI and US for surveillance of HCC in high risk patients with liver cirrhosis. 21st Annual conference of European Congress of Radiology; 2015 March 4-8; Vienna
55. Yu NC, Chaudhari V, Raman SS, Lassman C, Tong MJ, Busuttil RW, et al. CT and MRI improve detection of hepatocellular carcinoma, compared with ultrasound alone, in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2011;9:161-167
56. Kim PN, Choi D, Rhim H, Rha SE, Hong HP, Lee J, et al. Planning ultrasound for percutaneous radiofrequency ablation to treat small (≤ 3 cm) hepatocellular carcinomas detected on computed tomography or magnetic resonance imaging: a multicenter prospective study to assess factors affecting ultrasound visibility. *J Vasc Interv Radiol* 2012;23:627-634
57. Rhim H, Lee MH, Kim YS, Choi D, Lee WJ, Lim HK. Planning sonography to assess the feasibility of percutaneous radiofrequency ablation of hepatocellular carcinomas. *AJR Am J Roentgenol* 2008;190:1324-1330
58. Sarkar M, Stewart S, Yu A, Chen MS, Nguyen TT, Khalili M. Hepatocellular carcinoma screening practices and impact on survival among hepatitis B-infected Asian Americans. *J Viral Hepat* 2012;19:594-600
59. Lee YJ, Lee JM, Lee JS, Lee HY, Park BH, Kim YH, et al. Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging-a systematic review and meta-analysis. *Radiology* 2015;275:97-109
60. Hamm B, Staks T, Mühler A, Bollow M, Taupitz M, Frenzel T, et al. Phase I clinical evaluation of Gd-EOB-DTPA as a hepatobiliary MR contrast agent: safety, pharmacokinetics, and MR imaging. *Radiology* 1995;195:785-792
61. Filippone A, Blakeborough A, Breuer J, Grazioli L, Gschwend S, Hammerstingl R, et al. Enhancement of liver parenchyma after injection of hepatocyte-specific MRI contrast media: a comparison of gadoxetic acid and gadobenate dimeglumine. *J Magn Reson Imaging* 2010;31:356-364
62. Kim HD, Lim YS, Han S, An J, Kim GA, Kim SY, et al. Evaluation of early-stage hepatocellular carcinoma by magnetic resonance imaging with gadoxetic acid detects additional lesions and increases overall survival. *Gastroenterology* 2015;148:1371-1382
63. Reimer P, Rummeny EJ, Shamsi K, Balzer T, Daldrup HE, Tombach B, et al. Phase II clinical evaluation of Gd-EOB-DTPA: dose, safety aspects, and pulse sequence. *Radiology* 1996;199:177-183
64. Davenport MS, Viglianti BL, Al-Hawary MM, Caoili EM, Kaza RK, Liu PS, et al. Comparison of acute transient dyspnea after intravenous administration of gadoxetate disodium and gadobenate dimeglumine: effect on arterial phase image quality. *Radiology* 2013;266:452-461
65. Pietryga JA, Burke LM, Marin D, Jaffe TA, Bashir MR. Respiratory motion artifact affecting hepatic arterial phase imaging with gadoxetate disodium: examination recovery with a multiple arterial phase acquisition. *Radiology* 2014;271:426-434
66. Golfieri R, Grazioli L, Orlando E, Dormi A, Lucidi V, Corcioni B, et al. Which is the best MRI marker of malignancy for atypical cirrhotic nodules: hypointensity in hepatobiliary phase alone or combined with other features? Classification after Gd-EOB-DTPA administration. *J Magn Reson Imaging* 2012;36:648-657
67. Akai H, Matsuda I, Kiryu S, Tajima T, Takao H, Watanabe Y, et al. Fate of hypointense lesions on Gd-EOB-DTPA-enhanced magnetic resonance imaging. *Eur J Radiol* 2012;81:2973-2977
68. Motosugi U. Hypovascular hypointense nodules on hepatocyte

phase gadoxetic acid-enhanced MR images: too early or too progressed to determine hypervascularity. *Radiology* 2013;267:317-318
69. Ichikawa S, Ichikawa T, Motosugi U, Sano K, Morisaka H, Enomoto N, et al. Presence of a hypovascular hepatic nodule showing hypointensity on hepatocyte-phase image is a risk factor for hypervascular hepatocellular carcinoma. *J Magn Reson Imaging* 2014;39:293-297
70. Kim YK, Lee WJ, Park MJ, Kim SH, Rhim H, Choi D. Hypovascular hypointense nodules on hepatobiliary phase gadoxetic acid-enhanced MR images in patients with cirrhosis: potential of DW imaging in predicting progression to hypervascular HCC. *Radiology* 2012;265:104-114
71. Lee DH, Lee JM, Lee JY, Kim SH, Kim JH, Yoon JH, et al. Non-hypervascular hepatobiliary phase hypointense nodules on gadoxetic acid-enhanced MRI: risk of HCC recurrence after radiofrequency ablation. *J Hepatol* 2015;62:1122-1130
72. Toyoda H, Kumada T, Tada T, Sone Y, Maeda A, Kaneoka Y. Non-hypervascular hypointense nodules on Gd-EOB-DTPA-enhanced MRI as a predictor of outcomes for early-stage HCC. *Hepatol Int* 2015;9:84-92
73. Hwang J, Kim YK, Jeong WK, Choi D, Rhim H, Lee WJ. Nonhypervascular Hypointense Nodules at Gadoxetic Acid-enhanced MR Imaging in Chronic Liver Disease: Diffusion-weighted Imaging for Characterization. *Radiology* 2015;276:137-146
74. Xu PJ, Yan FH, Wang JH, Shan Y, Ji Y, Chen CZ. Contribution of diffusion-weighted magnetic resonance imaging in the characterization of hepatocellular carcinomas and dysplastic nodules in cirrhotic liver. *J Comput Assist Tomogr* 2010;34:506-512
75. Hyodo T, Murakami T, Imai Y, Okada M, Hori M, Kagawa Y, et al. Hypovascular nodules in patients with chronic liver disease: risk factors for development of hypervascular hepatocellular carcinoma. *Radiology* 2013;266:480-490
76. Di Pietropaolo M, Briani C, Federici GF, Marignani M, Begini P, Delle Fave G, et al. Comparison of diffusion-weighted imaging and gadoxetic acid-enhanced MR images in the evaluation of hepatocellular carcinoma and hypovascular hepatocellular nodules. *Clin Imaging* 2015;39:468-475
77. Krinsky GA, Lee VS, Theise ND, Weinreb JC, Morgan GR, Diflo T, et al. Transplantation for hepatocellular carcinoma and cirrhosis: sensitivity of magnetic resonance imaging. *Liver Transpl* 2002;8:1156-1164
78. Sangiovanni A, Manini MA, Iavarone M, Romeo R, Forzenigo LV, Fraquelli M, et al. The diagnostic and economic impact of contrast imaging techniques in the diagnosis of small hepatocellular carcinoma in cirrhosis. *Gut* 2010;59:638-644
79. Taouli B, Koh DM. Diffusion-weighted MR imaging of the liver. *Radiology* 2010;254:47-66
80. Kadoya M, Matsui O, Takashima T, Nonomura A. Hepatocellular carcinoma: correlation of MR imaging and histopathologic findings. *Radiology* 1992;183:819-825
81. Matsui O, Kadoya M, Kameyama T, Yoshikawa J, Arai K, Gabata T, et al. Adenomatous hyperplastic nodules in the cirrhotic liver: differentiation from hepatocellular carcinoma with MR imaging. *Radiology* 1989;173:123-126
82. Bashir MR, Gupta RT, Davenport MS, Allen BC, Jaffe TA, Ho LM, et al. Hepatocellular carcinoma in a North American population: does hepatobiliary MR imaging with Gd-EOB-DTPA improve sensitivity and confidence for diagnosis? *J Magn Reson Imaging* 2013;37:398-406
83. Le Moigne F, Durieux M, Bancel B, Boublay N, Boussel L, Ducerf C, et al. Impact of diffusion-weighted MR imaging on the characterization of small hepatocellular carcinoma in the cirrhotic liver. *Magn Reson Imaging* 2012;30:656-665
84. Sandrasegaran K, Tahir B, Patel A, Ramaswamy R, Bertrand K, Akisik FM, et al. The usefulness of diffusion-weighted imaging in the characterization of liver lesions in patients with cirrhosis. *Clin Radiol* 2013;68:708-715
85. Rimola J, Forner A, Tremosini S, Reig M, Vilana R, Bianchi L, et al. Non-invasive diagnosis of hepatocellular carcinoma ≤ 2 cm in cirrhosis. Diagnostic accuracy assessing fat, capsule and signal intensity at dynamic MRI. *J Hepatol* 2012;56:1317-1323
86. Darnell A, Forner A, Rimola J, Reig M, García-Criado Á, Ayuso C, et al. Liver Imaging Reporting and Data System with MR Imaging: Evaluation in Nodules 20 mm or Smaller Detected in Cirrhosis at Screening US. *Radiology* 2015;275:698-707
87. Davenport MS, Khalatbari S, Liu PS, Maturen KE, Kaza RK, Wasnik AP, et al. Repeatability of diagnostic features and scoring systems for hepatocellular carcinoma by using MR imaging. *Radiology* 2014;272:132-142
88. Song do S, Bae SH. Changes of guidelines diagnosing hepatocellular carcinoma during the last ten-year period. *Clin Mol Hepatol* 2012;18:258-267
89. Song KD, Kim SH, Lim HK, Jung SH, Sohn I, Kim HS. Subcentimeter hypervascular nodule with typical imaging findings of hepatocellular carcinoma in patients with history of hepatocellular carcinoma: natural course on serial gadoxetic acid-enhanced MRI and diffusion-weighted imaging. *Eur Radiol* 2015;25:2789-2796
90. Jang KM, Kim SH, Kim YK, Choi D. Imaging features of subcentimeter hypointense nodules on gadoxetic acid-enhanced hepatobiliary phase MR imaging that progress to hypervascular hepatocellular carcinoma in patients with chronic liver disease. *Acta Radiol* 2015;56:526-535
91. Wang JH, Changchien CS, Hu TH, Lee CM, Kee KM, Lin CY, et al. The efficacy of treatment schedules according to Barcelona Clinic Liver Cancer staging for hepatocellular carcinoma - Survival analysis of 3892 patients. *Eur J Cancer* 2008;44:1000-1006
92. Tseng PL, Wang JH, Tung HD, Hung CH, Kee KM, Chen CH, et al. Optimal treatment increased survival of hepatocellular carcinoma patients detected with community-based screening. *J Gastroenterol Hepatol* 2010;25:1426-1434
93. Farinati F, Sergio A, Baldan A, Giacomin A, Di Nolfo MA, Del Poggio P, et al. Early and very early hepatocellular carcinoma: when and how much do staging and choice of treatment really matter? A multi-center study. *BMC Cancer* 2009;9:33

94. Silva MA, Hegab B, Hyde C, Guo B, Buckels JA, Mirza DF. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. *Gut* 2008;57:1592-1596
95. Khalili K, Kim TK, Jang HJ, Yazdi LK, Guindi M, Sherman M. Indeterminate 1-2-cm nodules found on hepatocellular carcinoma surveillance: biopsy for all, some, or none? *Hepatology* 2011;54:2048-2054
96. Joo I, Kim H, Lee JM. Cancer stem cells in primary liver cancers: pathological concepts and imaging findings. *Korean J Radiol* 2015;16:50-68
97. Lu Q, Xue LY, Wang WP, Huang BJ, Li CX. Dynamic enhancement pattern of intrahepatic cholangiocarcinoma on contrast-enhanced ultrasound: the correlation with cirrhosis and tumor size. *Abdom Imaging* 2015;40:1558-1566
98. Fowler KJ, Sheybani A, Parker RA 3rd, Doherty S, M Brunt E, Chapman WC, et al. Combined hepatocellular and cholangiocarcinoma (biphenotypic) tumors: imaging features and diagnostic accuracy of contrast-enhanced CT and MRI. *AJR Am J Roentgenol* 2013;201:332-339
99. Ji J, Wang XW. Clinical implications of cancer stem cell biology in hepatocellular carcinoma. *Semin Oncol* 2012;39:461-472