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Consensus Statement

Novel Imaging Diagnosis for Hepatocellular Carcinoma: Consensus from the 5th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2014)

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Key Words
Consensus · Diagnostic imaging · Hepatocellular carcinoma

Abstract
Current novel imaging techniques in the diagnosis of hepatocellular carcinoma (HCC), with the latest evidence in this field, was discussed at the Asia-Pacific Primary Liver Cancer Expert (APPLE) meeting held in Taipei, Taiwan, in July 2014. Based on their expertise in a specific area of research, the novel imaging group comprised 12 participants from Japan, South Korea,

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Taiwan, and China and it included 10 abdominal radiologists, one hepatologist, and one pathologist. The expert participants discussed topics related to HCC imaging that were divided into four categories: (i) detection method, (ii) diagnostic method, (iii) evaluation method, and (iv) functional method. Consensus was reached on 10 statements; specific comments on each statement were provided to explain the rationale for the voting results and to suggest future research directions.

Introduction

Although computed tomography (CT) and magnetic resonance imaging (MRI) are recommended by clinical practice guidelines for the diagnosis of hepatocellular carcinoma (HCC), there are many debates regarding the standardized imaging diagnosis of HCC. For example, the American Association for the Study of Liver Diseases (AASLD) [1] defines a typical HCC as a tumor size of more than 1 cm in diameter, with arterial hypervascularity and washout in the venous or delayed phase, that is visible in four-phase multi-detector CT (MDCT) or dynamic MRI, in patients with chronic hepatitis B infection or cirrhosis. However, a second dynamic contrast-enhanced (DCE) imaging modality is required only if the first imaging modality is not diagnostic. The definition by the Asian-Pacific Association for the Study of the Liver (APASL) [2] of a typical HCC on imaging is similar to that in the AASLD guidelines, except that the lesion size does not have to be more than 1 cm in diameter. In contrast to the AASLD guidelines, the APASL guidelines suggest using contrast-enhanced (perfluorobutane microbubbles) ultrasound (US) or superparamagnetic iron oxide (SPIO)-enhanced MRI for a hypervascular lesion that does not have washout in the portal or delayed venous phase. The rationale is that HCCs generally have a low Kupffer cell density, whereas benign hypervascular lesions and pseudolesions tend to have normal or elevated Kupffer cell densities. Recently, a hepatocyte-specific MR contrast agent, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), has been found to be useful in the early detection of small HCCs [3] and has been used as a part of HCC diagnostic algorithms in Japanese hepatology practice [4]. As new scientific information concerning the imaging diagnosis of HCC has become available, a consensus conference was convened to review and integrate the most updated information in this field.

Method

Current novel imaging in the diagnosis of HCC, with the latest evidence in this field, was discussed at the APPLE meeting held in Taipei, Taiwan, on July 11–13, 2014 [5]. Based on their expertise in a specific area of research, the novel imaging group comprised 12 participants from Japan, South Korea, Taiwan, and China and it included 10 abdominal radiologists, one hepatologist, and one pathologist. The expert participants discussed topics related to HCC imaging that were divided into 4 categories: (i) detection method, (ii) diagnostic method, (iii) evaluation method, and (iv) functional method. Based on the experience and opinions of the expert participants, the consensus statements were refined after the discussions and were voted on by using an electronic voting system; the available options were "agree" and "disagree." The evidence level of each statement on the related topic was labeled, and a specific comment was provided for each statement only when >80% agreement was achieved by the committee members. The level of evidence and the recommendation of each statement were based on the Oxford Centre for Evidence-based Medicine (table 1).

This manuscript summarizes the consensus of the forum attendees. The consensus statements are presented throughout the manuscript with the supporting evidence, and the percentage of participants

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Table 1. Oxford Centre for Evidence-based Medicine – Levels of evidence and recommendation

Level of evidence	
1A	Systematic review (SR) of Randomized controlled trial (RCT)
1B	Individual RCT
1C	All-or-none
2A	SR of cohort studies
2B	Individual cohort study
2C	"Outcomes" Research; Ecological studies
3A	SR of case-control studies
3B	Individual Case-Control Study
4	Case-series
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
Recommendations	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

From Centre for Evidence-Based Medicine in Oxford in the UK. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

who agreed with each statement is also reported. Specific comments on each statement are provided to explain the rationale for the voting results and to suggest future research directions. These consensus statements provide the latest information on HCC diagnosis and could be useful for radiologists or clinicians in their daily clinical practice.

Consensus Statements

1. Detection Methods (Algorithms) in a Case after US and Tumor Marker Screening
Statement 1: Gd-EOB-DTPA-MRI is useful for detecting small (<2 cm diameter) hepatic tumors in patients with cirrhosis.

Level of agreement: 100%; Level of evidence: IA; Grade of recommendation: A

Comment: We may require more evidence to prove that Gd-EOB-DTPA-MRI is more effective than extracellular contrast medium (ECCM)-MRI in detecting small hypervascular HCCs.

Recently, two meta-analyses have shown that Gd-EOB-DTPA-MRI has a high diagnostic accuracy in the detection of HCC. Liu et al. [6] showed that the pooled sensitivity, specificity, and area under curve (AUC) values were 0.91, 0.93, and 0.98, respectively, in patients with cirrhosis; the AUC was 0.99 for ≤20 mm diameter HCCs. In addition, Junqiang et al. [7] showed that the pooled sensitivity, specificity, and AUC values were 0.92, 0.95, and 0.98, respectively, it demonstrating high sensitivity in the detection of lesions >10 mm in diameter. For HCCs ≤10 mm in diameter, the diagnostic performance of Gd-EOB-DTPA-MRI detection remains low, with a mean sensitivity of 46.0% and a mean positive predictive value of 48.3%; however, the diagnostic performance can be improved by adding hypointensity on hepatobiliary phase images as a washout [8].

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For hypervascular HCCs, Gd-EOB-DTPA-MRI showed higher performance than that of dynamic MDCT [9–11], even in patients with cirrhosis [12], precontrast MRI [13], and MRI with SPIO [14]. For hypovascular early HCCs, Gd-EOB-DTPA-MRI is the most sensitive of all currently available imaging modalities [15–18]. During multistep hepatocarcinogenesis, the immunohistochemical expression of OATP8 significantly decreases, resulting in the decrease of the enhancement ratio of Gd-EOB-DTPA-MRI [15]. Although current evidence suggests that Gd-EOB-DTPA-MRI may be the most sensitive technique for the detection of small HCCs, confirmatory studies are necessary to prove that Gd-EOB-DTPA-MRI is more effective than ECCM-MRI in detecting small hypervascular HCCs, especially in patients with advanced cirrhosis.

Statement 2: Gd-EOB-DTPA-MRI can replace the role of CT during hepatic arteriography (CTHA) and CT during arterial portography (CTAP) in the diagnosis of HCC.

Level of agreement: 100%; Level of evidence: IB; Grade of recommendation: A

Comment: CTHA and CTAP through conventional MDCT are occasionally useful for detecting and diagnosing hypervascular small HCCs (diameter ≤1 cm).

Image quality of CT-like images of C-arm CT should be further improved.

Invasive procedures such as CTAP and CTHA are commonly used in some countries to diagnose HCC, and several recent studies have compared their diagnostic performance with that of Gd-EOB-DTPA-MRI.

Sabo et al. [16] compared the diagnostic performance of Gd-EOB-DTPA-MRI, CTAP, and CTHA in 108 resected small hepatic lesions (diameter ≤2 cm) in 64 patients, including dysplastic nodules (DN) (n=12), advanced HCCs (n=66), or early HCCs (n=30). The diagnostic performance of Gd-EOB-DTPA-MRI (area under the receiver operating characteristic [AUROC], 0.98 and 0.99) was significantly higher than that of CTHA-CTAP (AUROC, 0.85 and 0.86) because of its significantly higher sensitivity ($p<0.001$).

Another study [19] found that Gd-EOB-DTPA-MRI including a gradient dual-echo sequence and diffusion-weighted imaging (DWI) has a significantly higher sensitivity than CTAP/CTHA, and thus is recommended for the pre-therapeutic evaluation of patients with HCC. The difference in the specificity, positive predictive values, and negative predictive values of the two modalities was non-significant.

A recent study [20] found that the diagnostic accuracy of Gd-EOB-DTPA-MRI was greater than that of C-arm CT (0.890 vs. 0.681, respectively; $p<0.001$). However, in small HCCs (diameter ≤1 cm), C-arm CT showed a higher sensitivity (90.9% vs. 70.5%, respectively; $p=0.023$) and a lower positive predictive value than that of MRI (40.8% vs. 57.4%, $p=0.073$).

2. Diagnostic Methods

Statement 3: Contrast-enhanced US (CEUS) is useful for characterizing small (diameter <2 cm) hepatic tumors in patients with cirrhosis.

Level of agreement: 100%; Level of evidence: IA; Grade of recommendation: A

Comment: CEUS is useful for evaluating intranodular vascularity. Sonazoid® can also evaluate the Kupffer function of nodules. These findings are highly useful for the characterization of hepatic lesions.

There was a high level of agreement with this statement. CEUS utilizes microbubbles that are confined to the intravascular space as opposed to contrast agents in CT and MRI that are rapidly cleared from the blood pool into the extracellular space. Currently, CEUS is not recommended as a diagnostic test in the guidelines of either the AASLD or the European Association for the Study of the Liver and the European Organisation for Research and Treatment of Cancer, because it may provide false-positive results in patients with cholangiocarcinoma [21]. However, recent prospective studies have demonstrated a relatively high

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specificity (91%–100%) of CEUS for the diagnosis of small HCCs (diameter <2 cm) in patients with cirrhosis [22–24].

Several multicenter studies have also demonstrated the accuracy of CEUS in the characterization of hepatic lesions. A multicenter prospective study (Soutien aux Techniques Innovantes et Coûteuses, STIC) was conducted at 15 centers in France. The study found diagnostic performance levels similar to those reported for CT and MRI, with a concordance rate of 84.5%, sensitivity >80% and specificity >90% for all types of lesions [25]. Another multicenter study (German Society of Ultrasound in Medicine and Biology, DEGUM), performed at 14 centers in Germany demonstrated that the diagnostic accuracy of CEUS was 80.6% for focal liver lesions ≤10 mm in diameter and 84.9% for lesions 10–20 mm in diameter [26]. A recent study in Romania demonstrated that the accuracy of CEUS for the differentiation between malignant and benign liver lesions was similar in tumors with a diameter of ≤2 cm and those with a diameter of >2 cm; this study is in concordance with the studies conducted in Germany (DEGUM) and France (STIC) [27]. In the DEGUM study, CEUS was similar to MRI for the differentiation and specification of newly discovered liver tumors, for the differentiation of benign and malignant lesions, and for the characterization of metastases and HCCs [28]. In addition, economic analyses also indicated that CEUS was a cost-effective replacement for contrast-enhanced MRI [29].

Sonazoid® can evaluate Kupffer function of a nodule for characterization of the lesion. Ohama et al. compared Sonazoid®-enhanced US (SEUS) with Gd-EOB-DTPA-enhanced MRI in 73 histologically proven HCCs (33 hypovascular well-differentiated HCCs and 40 progressed HCCs) and 9 DNs. They found that the uptake of Sonazoid® starts decreasing later than that of Gd-EOB-DTPA. Although signal reductions on the post-vascular phase of SEUS or the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI suggest HCC, the hypoechoic appearance in the post-vascular phase of SEUS is more likely found in progressed HCCs (95%), compared to well-differentiated HCCs (9%) and DNs (0%) [30].

Statement 4: Follow-up is the most appropriate strategy for a hypovascular nodular lesion <10 mm in diameter that is hypointense in the hepatobiliary phase of Gd-EOB-DTPA MRI.

Level of agreement: 82%; Level of evidence: IIIB; Grade of recommendation: B

Comment: Using US to detect a nodule <10 mm in diameter and performing a biopsy on it are difficult. Therefore, precise follow-up is necessary [31–34].

Generally, most patients with hypovascular hypointense nodules are followed-up before the nodules appear to be hypervascular in hepatic arterial images or with other typical HCC features. Therefore, it is critical to clarify the fate of such nodules during the follow-up period and to identify high-risk nodules.

A common risk factor for developing hypervascularity in these studies was the lesion size, especially when the lesions were >10 mm in diameter [35, 36]. Previous studies have shown that the hypovascular hypointense nodules develop into hypervascular HCCs at 1-year cumulative progression rates of 15.5% [37] and 14.9% [38] for average tumor sizes of 8.4 mm and 9.3 mm, respectively, but this increased to 43.5% [39] for an average tumor size of 14 mm. In addition, the imaging and clinical features for early progression of hypovascular hypointense nodules to hypervascular HCCs include hyperintensity at DWI [32, 38], hyperintensity in T2-weighted images, and a treatment history for HCC [34, 38].

In another study with precise imaging-pathological correlation, almost all hypovascular, early-stage hepatocellular nodules showing hypointensity in hepatobiliary phase images were an early HCC and rarely a dysplastic nodule [16]. Because these nodules tend to appear hypervascular during the relatively short follow-up, most of them might be treated as early HCCs. However, for hepatic nodules <1 cm in diameter, because of the difficulty in obtaining a biopsy, it is recommended that they are closely followed up using US every 3–4 months until they grow to 1 cm or show imaging features of early progression to hypervascular HCC [4, 23].

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3. Evaluation Methods

Statement 5: CEUS is useful for evaluating intrahepatic treatment response after radiofrequency ablation (RFA) and transarterial chemoembolization (TACE).

Level of agreement: 100%; Level of evidence: IIB; Grade of recommendation: B

Comment: CEUS is useful to evaluate intranodular vascularity; therefore, it can evaluate not only tumor size but also tumor viability [40–43].

In addition to tumor characterization, CEUS is also helpful for response evaluation after locoregional treatment. Lu et al. [44] used CEUS with SonoVue® to assess the tumor vascularity of HCCs after RFA or microwave ablation treatment in 118 patients, and compared the results with those obtained using contrast-enhanced CT/MR. One month after treatment, no enhancement was seen in 110 patients (93.2%) both on CEUS and contrast-enhanced CT/MR. Concordance between CEUS and contrast-enhanced CT/MR in the presence of residual vascularization was obtained in four patients (true positive). The specificity and accuracy of CEUS in detecting tumor vascularity were 98.2% and 96.6%, respectively. Lu et al. concluded that real-time CEUS provided results comparable with those obtained using contrast-enhanced CT/MR for the assessment of response to thermal ablation after 1 month [44].

Inoue et al. [38] used CEUS with Sonazoid® to evaluate the treatment response of HCC after RFA, finding that the assessment of CEUS for a complete or incomplete ablated response was comparable with that of dynamic CT. Therefore, CEUS can be used to assess the efficacy of RFA for HCC, with the potential to reduce the number of CT scans required for confirmation.

For patients with hypervascular HCC after TACE, Takizawa et al. [43] found that the detection rate for residual HCC lesions by using CEUS 1-day after TACE (95.7%, 45/47) was significantly higher than that using 1-month contrast-enhanced CT (78.7%, 37/47) (p<0.05) [43]. CEUS can evaluate both tumor size and vascularity after treatment, both of which are crucial imaging features for determining residual tumors after RFA or TACE.

Statement 6: Contrast-enhanced MRI with an extracellular contrast agent is the most accurate imaging tool for the therapeutic response assessment of HCC after TACE.

Level of agreement: 82%; Level of evidence: IIB; Grade of recommendation: B

Comment: Contrast-enhanced MRI with an extracellular contrast agent can detect hypervascular viable regions in multiple tumors simultaneously without an artifact of lipiodol accumulation [45].

TACE typically results in the liquefaction necrosis of a HCC, and follow-up imaging frequently shows no enhancement within the tumor when adequately embolized. If lipiodol is used in combination with TACE, follow-up imaging by using MRI may be the preferred modality because the extremely radiodense lipiodol may interfere with the CT evaluation of marginal enhancement in residual or recurrent tumors [46]. If subtraction techniques of unenhanced and contrast-enhanced images are not available, the side-by-side assessment of unenhanced and contrast-enhanced images is the standard technique for detecting viable tumors [47].

Kloeckner et al. [48] compared MDCT with ECCM-MRI for the European Association for the Study of the Liver (EASL) criteria response evaluation of 115 HCCs in 20 patients after TACE. In the lipiodol-based TACE protocol, MDCT underestimated residual viable tumors compared with MRI because of the lipiodol artifacts (23.2% vs. 47.7% after the first TACE, 11.9% vs. 31.2% after the second TACE, and 11.4% vs. 23.7% after the third TACE; all p values <0.001). In the drug-eluting bead-based lipiodol-free TACE protocol, MRI and CT showed similar residual tumors and ratings of treatment results (46.4% vs. 41.2%, 31.9 vs. 26.8%, and 26.0% vs. 25.6%; all p>0.05). Therefore, MRI is mandatory for reliable decision-making during follow-up after applying lipiodol-based TACE protocols [48].

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Thus far, no study has compared the differences between ECCM-MRI and Gd-EOB-DTPA-MRI in the response evaluation of HCC after TACE. Although many clinical studies have proved that Gd-EOB-DTPA is valuable for the early detection of small HCCs, further investigation is necessary to confirm its value in the evaluation of treatment response after TACE.

Statement 7: DWI helps assessing tumor response after HCC treatment with systemic therapy.

Level of agreement: 88%; Level of evidence: IIB; Grade of recommendation: B

Comment: An apparent diffusion coefficient (ADC) measured using DWI is affected by tumor cellularity [49–52].

DWI offers insight into the molecular water composition and the degree of tumor viability at the cellular level. Viable tumors are highly cellular and have intact cell membranes, thus restricting the motion of water molecules, which result in hyperintensity on DWI and reduction in the ADC [53]. After treatment, changes in the ADC are inversely correlated with changes in cellularity. In a tumor with necrosis or apoptosis, an increase in the ADC suggests a decrease in the cellular size or number. By contrast, a decrease in the ADC indicates an increase in the total cellular size or number, because of tumor progression, fibrosis, or edema. Because molecular and cellular changes in response to injury precede volumetric changes, changes in diffusion MRI have been considered as an early surrogate for later pathologic or radiologic end points [54].

Several studies have demonstrated that changes in the ADC precede or can be observed in the absence of radiographic response for either primary or metastatic cancer confined to the liver, such as hepatic metastasis after systemic chemotherapy [55], HCC after TACE [56], or targeted radiation therapy by using yttrium-90 microspheres [57, 58]. For example, Kamel et al. [53] found that DWI can quantify tumor necrosis after chemoembolization to a greater degree than gadolinium-enhanced MRI. In addition, Vandecaveye et al. [49] found that the ADC ratio 1 month after TACE was an independent predictor of progression-free survival (PFS), which showed stronger association with tumor response than did Response Evaluation Criteria In Solid Tumors (RECIST), EASL criteria, or modified RECIST.

In a prospective study that assessed treatment response by using volumetric functional MRI metrics in patients with HCC treated with a combination of doxorubicin-eluting bead-TACE and sorafenib, the volumetric ADC increased significantly (1.32×10^3 mm^2/sec to 1.60×10^3 mm^2/sec, p<0.001) 3–4 weeks posttreatment, whereas the median tumor size by using RECIST remained unchanged [59]. Another recent study used DWI to assess the HCC response after concurrent chemoradiotherapy (CCRT) and found that patients with a higher ADC had significantly longer PFS than those with a lower ADC [51]. The ADC of HCC acquired before CCRT was valuable in the prediction of the clinical outcome of HCC treated with CCRT.

Statement 8: Perfusion MRI or CT helps assessing tumor response after HCC treatment with systemic or local therapies.

Level of agreement: 100%; Level of evidence: IIB; Grade of recommendation: B

Comment: Perfusion MRI or CT can quantitatively evaluate intratumoral vascularity [51].

Perfusion MRI and CT are functional imaging techniques that provide quantitative information about liver hemodynamics and tumor-related angiogenesis through the acquisition of serial images after the administration of a bolus of contrast agent [60, 61]. Combined with a pharmacokinetic model, perfusion MRI or CT imaging enables the generation of highly reproducible parametric maps of quantitative parameters in HCCs, which may prove to be accurate and early biomarkers of tumor response to systemic or local therapies [52, 62]. In the setting of clinical trials, perfusion imaging may identify clinically relevant pharmacokinetics and the efficacy of novel anti-angiogenesis drugs as early as two weeks after treatment.

In perfusion imaging, the parameter K^{trans} represents a combination of perfusion and permeability within a tumor, and it has been used to estimate tumor angiogenesis in many clini-

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cal trials [61]. In a previous study [63] that used perfusion MRI to evaluate locally advanced HCCs receiving sunitinib and cytotoxic therapy, a high pretreatment K^{trans} identified patients with HCCs who did not develop progressive disease. A decrease in K^{trans} by ≥40% after 14 days of treatment was correlated with longer PFS and overall survival (OS). In addition, the percentage of K^{trans} change after treatment is an independent predictor of tumor response, PFS, and OS [63].

Previous reports have suggested that CT perfusion parameters can be used for quantifying tumor vascularity and angiogenesis in HCC [62, 64], as biomarkers to monitor the response to RFA or TACE [65], and to monitor antiangiogenic therapy [66, 67]. In another study in which locally advanced HCCs received bevacizumab and cytotoxic therapy, a high pretreatment K^{trans} by perfusion CT indicated that those patients had a RECIST response (by tumor size) [68]. However, the main drawbacks of perfusion CT include increased radiation and lower resolution, which may be improved by using recent low-dose CT technology. In addition, the CT perfusion parameters obtained using different software versions were not exchangeable [64]; therefore, further validation studies are necessary to prove its efficacy in treatment response assessment.

4. Functional Methods

Statement 9: Gd-EOB-DTPA-MRI can be used to evaluate hepatic function and has the complementary role of the indocyanine green (ICG) test in preoperative HCC patients.

Level of agreement: 100%; Level of evidence: IIB; Grade of recommendation: B

Comment: Enhancement of Gd-EOB-DTPA is affected by hepatocyte function and is related to the ICG test. Gd-EOB-DTPA-MRI has the potential to evaluate segmental liver function [69–74].

ICG clearance has been used to evaluate preoperative liver functional reserve. The uptakes of ICG and Gd-EOB-DTPA into functional hepatocytes are dependent on the same transport mechanisms that are mediated by the organic anion transporters OATP1B1/B3 [75]. Therefore, many studies have tried to evaluate hepatic function by hepatic or biliary enhancement after the administration of Gd-EOB-DTPA and to correlate hepatic function by using an ICG test (ICG retention at 15 minutes (R15)) [76]. For example, Utsunomiya et al. [77] found that the correlation coefficient of ICG-R15 and the relative enhancement of the liver was 0.67 (p<0.001). Other studies have used Gd-EOB-DTPA-enhanced MR relaxometry [73] and DCE-MRI techniques [61] to assess hepatic function, and both have shown promising results. Although methods based on the direct measurement of hepatic parenchymal signals are simple, they are easily affected by sampling errors and technical factors. MR relaxometry and DCE-MRI require dedicated software and lack uniformity in analysis methods. Therefore, additional technical developments and validation studies are necessary to address these concerns.

The degree of hepatic parenchymal enhancement after Gd-EOB-DTPA can facilitate quantifying liver function and estimating prognosis after hepatic surgery. Cho et al. [72] observed an inverse relationship between liver enhancement and the probability of liver failure after major liver resection, based on the International Study Group of Liver Surgery (ISGLS) grading system. Wibmer et al. [78] found that the relative liver enhancement (RLE) 20 minutes after contrast injection was directly related to the probability of 1-year retransplantation-free survival. They also found that RLE was inversely related to the probability of liver failure after major liver resection according to the 50–50 (p=0.02) and ISGLS (p<0.001) criteria. In addition, in the evaluation of the risk of posthepatectomy liver failure, RLE seems to be superior to the ICG test. Thus, Gd-EOB-DTPA-MRI may be a helpful noninvasive prognostic biomarker and may play a complementary role in the ICG test for preoperative patients.

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Statement 10: Gd-EOB-DTPA MRI can be used to stage liver fibrosis, but further validation studies are necessary.

Level of agreement: 100%; Level of evidence: IIB; Grade of recommendation: B

Comment: Enhancement of Gd-EOB-DTPA is affected by the amount of fibrosis and the hepatic pathological architecture due to cirrhosis.

However, further studies are necessary to confirm the optimal cutoff of each fibrous stage [79–82].

Many studies have shown that RLE after Gd-EOB-DTPA injection is significantly lower in patients with chronic liver disease, particularly in those with fibrosis and cirrhosis compared with normal individuals. The decreased RLE is a reflection of hepatocyte malfunction caused by the accumulation of liver fibrosis and increased necroinflammatory activity [83]. Feier et al. [79] found that RLE values were correlated strongly with the stage of liver fibrosis ($r=-0.65$, $p<0.0001$) and moderately correlated with grades of necroinflammatory activity ($r=-0.41$, $p=0.002$), but such assessment could be confounded in the setting of abnormal aspartate aminotransferase, gamma glutamyl transpeptidase, and alkaline phosphatase levels. In addition, Motosugi et al. [84] found that corrected liver-enhancement ratio had a greater AUC in the prediction of mild fibrosis ($\geq$F1) than the aspartate aminotransferase-to-platelet ratio index.

Liver fibrosis causes hepatic hemodynamic changes and functional damage simultaneously; hence, the perfusion changes or decreased RLE after Gd-EOB-DTPA administration may be used to diagnose and distinguish between stages of liver fibrosis. For example, Chen et al. [80, 85] found that multiple Gd-EOB-DTPA-enhanced perfusion parameters can be measured to evaluate the severity of liver fibrosis. The most accurate predictors for mild fibrosis versus no fibrosis were hepatic arterial blood flow (AUROC: 0.701) and the contrast enhancement index of the liver at 10 minutes (AUROC: 0.797). Although recent evidence is promising for the staging of fibrosis with Gd-EOB-DTPA, further studies are required to confirm the optimal cutoff of each fibrous stage.

Conclusions

In this consensus meeting, the strong evidence of CEUS for the characterization of hepatic lesion and response evaluation after locoregional treatments were emphasized. Besides, MRI with Gd-EOB-DTPA may be used for many purposes, including small HCC detection, hepatic functional evaluation, staging of liver fibrosis, and preoperative staging to replace the role of CTHA/CTAP. The follow-up criteria for undetermined hepatic nodules were also specified. In addition, the usefulness of DWI and perfusion MRI/CT for the response evaluation in post-treatment HCC patients were widely accepted. Although further validation studies are necessary in some statements, this consensus report may serve as the foundation for future clinical studies in Asia-Pacific areas for the imaging diagnosis of HCC.

Disclosure Statement

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