Efficacy of Fusion Imaging Combining Sonography and Hepatobiliary Phase MRI With Gd-EOB-DTPA to Detect Small Hepatocellular Carcinoma

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OBJECTIVE. We evaluated the efficacy of fusion imaging that fuses conventional sonography images with hepatobiliary phase contrast-enhanced MR images obtained with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) as the reference image for the detection of hepatocellular carcinomas (HCCs).

Liver Cirrhosis

- Differential diagnosis of FLL
- Low US accuracy detection
  - Small HCC nodules
- Gd-EOB-DTPA
  - New nodules in HBP
    - Hypointense
- Imaging modality combination

Aims

- Problems
  - Diagnosis of small HCC (<3cm)
  - 2 imaging modalities (wash-in/wash-out)
  - Findings on HBP of EOB-DTPA
- Goals
  - Merit of fusion imaging
    - EOB + gray-scale US
    - Gray-scale US only
    - CEUS (perflubutane)

Patients

- Chronic liver disease
- Suspicion nodules
  - CEUS
  - Gd-EOB-DTPA enhanced MRI
  - Fusion imaging
    - US+HBP EOB DTPA
  - 50 patients/98 nodules
    - 23 nodules >2cm
    - 45 nodules 1-2cm

Nodules

- 30 nodules not assigned as HCC
- 4 excluded
- 26 biopsy
  - 19 WD HCC
  - 6 dysplastic
  - 1 regenerative
- 87 HCCs enrolled
- Mean nodule size: 1,7cm (1-3cm)

Diagnostic Flowchart

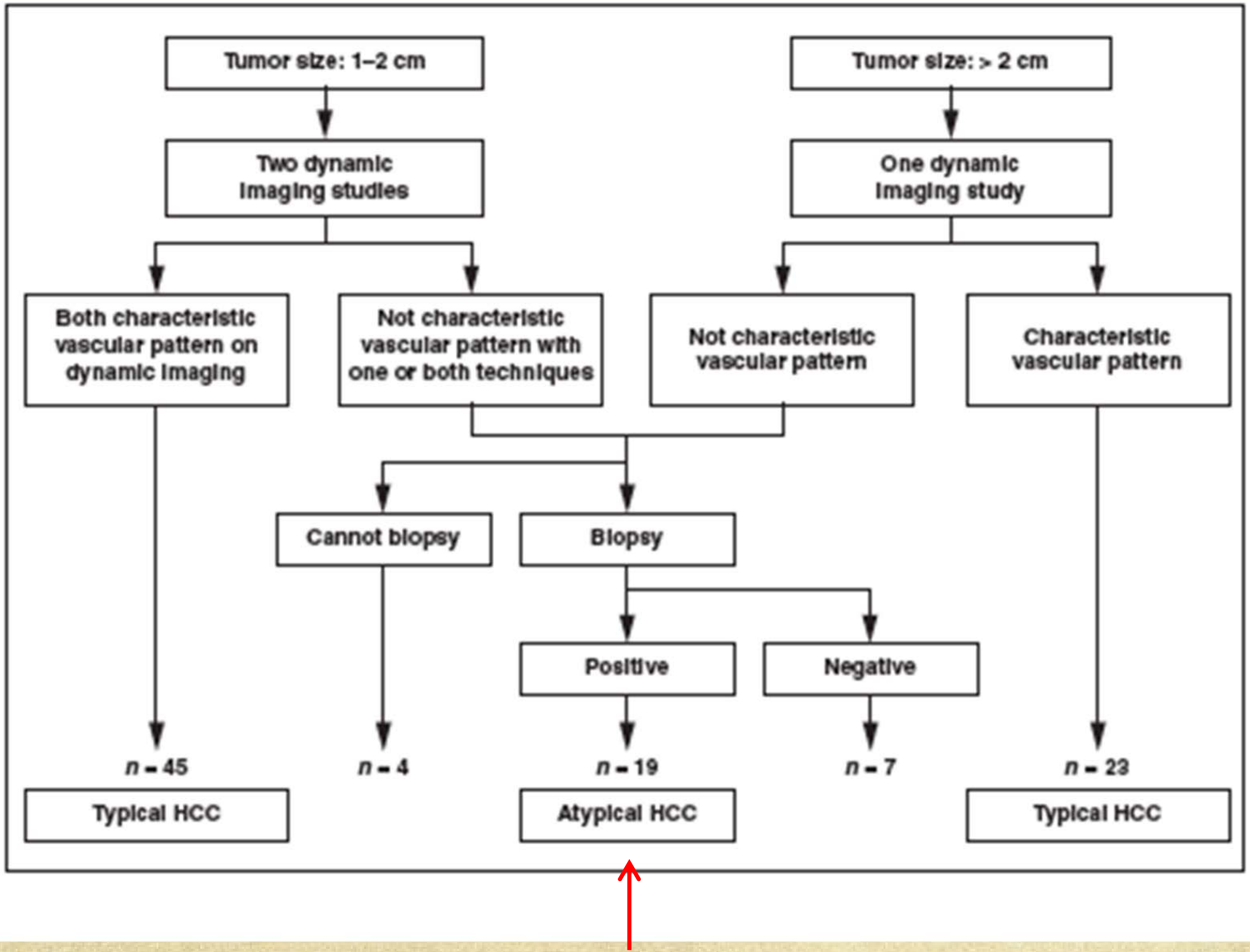

Fig. 1—Diagnosis of hepatocellular carcinoma (HCC). HCCs were diagnosed according to this flowchart. Finally, 98 nodules were detected using hepatobiliary phase gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid contrast-enhanced MRI, and 87 nodules were diagnosed as HCC. "Dynamic imaging" means contrast-enhanced CT or contrast-enhanced sonography with perflubutane (Sonazoid, Daiichi Sankyo). "Characteristic vascular pattern" means arterial hypervascularization and venous washout.

Fusion Imaging

Fig. 2—Photograph shows fusion imaging system (Logiq E9, GE Healthcare) used for this study. It is composed of position-sensing unit mounted on ultrasound unit (Logiq E9), magnetic field transmitter (**A**), and two sensors connected to transducer bracket (**B**). Display of ultrasound unit (**C**) shows fusion imaging combining conventional sonography and hepatobiliary phase of contrast-enhanced MRI with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid. Used with permission of GE Healthcare

Fusion imaging (2)

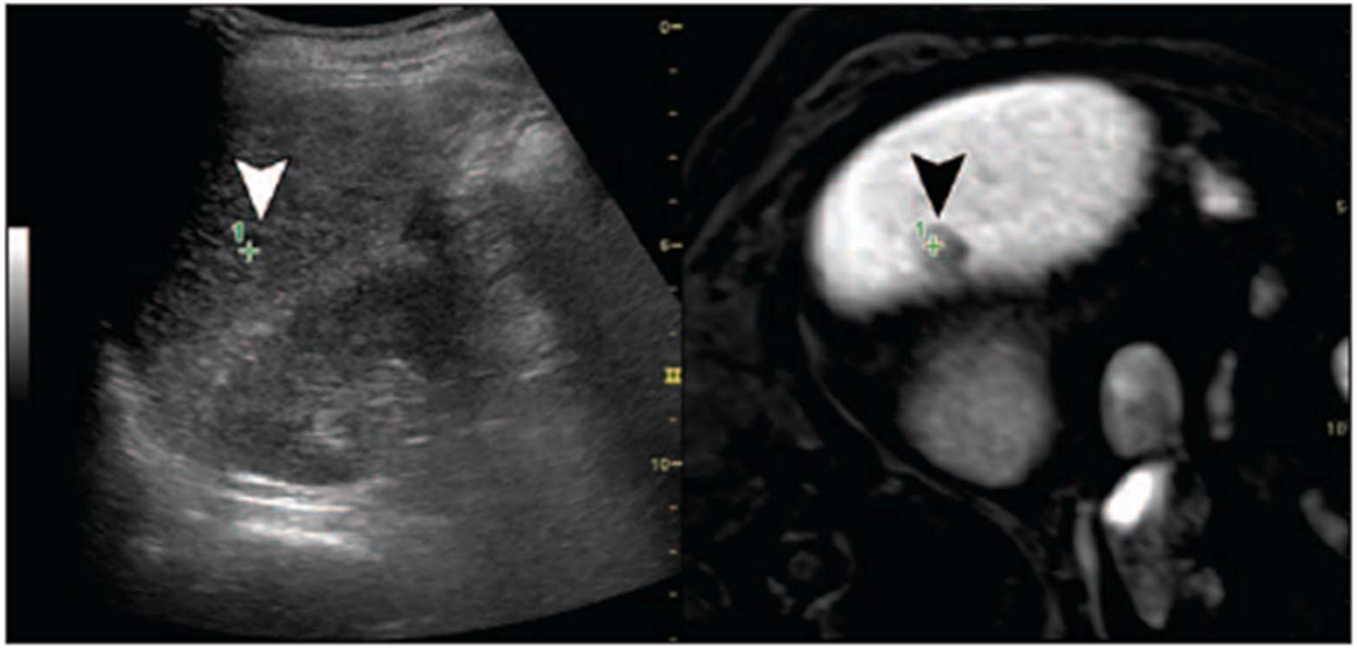

Fig. 3—71-year-old man with hepatocellular carcinoma (HCC) lesion (maximum diameter, 11 mm) in segment VI. Fusion image combining conventional sonography (left) and hepatobiliary phase of contrast-enhanced MRI with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) (right) was marked using global positioning system (GPS). Real-time motion images of fused images were displayed on workstation monitor. Hepatobiliary phase Gd-EOB-DTPA–enhanced MR image shows hypointense area in segment VI (*black arrowhead*). Because lesion was not detected using conventional sonography imaging alone, we used GPS tool to detect lesion. After registration of conventional sonography image and hepatobiliary phase Gd-EOB-DTPA–enhanced MR image, we set GPS mark (green cross) at location of lesion that was visualized as low-intensity area on hepatobiliary phase Gd-EOB-DTPA–enhanced MR image. This mark simultaneously appears as small green cross graphic on hepatobiliary phase Gd-EOB-DTPA–enhanced MR image and conventional sonography image. Using fusion imaging in combination with GPS green cross graphic as reference standard enabled small HCC lesion to be detected as hypoechoic area (*white arrowhead*) on conventional sonography.

SOR

- Multimodality including CT/CEUS/MRI
- Typical HCC
  - Characteristic vascular pattern
  - Nodule 1-3cm
- Atypical
  - Nodule >2cm
    - Absence of wash-in/wash-out
    - Histological diagnosis

Results

TABLE 1: Detection Rates of Conventional Sonography and Fusion Imaging for Hepatocellular Carcinoma (HCC) Lesions

HCC Lesions	Conventional Sonography	Fusion Imaging[a]
Detected, % (No. / Total No.) of lesions	76 (66/87)	98 (85/87)
Not detected, % (No. / Total No.) of lesions	24 (21/87)	2 (2/87)
p^b	< 0.01	< 0.01

Note—We considered 16-MDCT, contrast-enhanced sonography, and histology to be the gold standard for the diagnosis of HCCs.
[a]Combining conventional sonography and hepatobiliary phase contrast-enhanced MRI with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid as the reference image.
[b]According to McNemar tests comparing HCC detection rates of fusion imaging and conventional sonography.

TABLE 2: Detection Rates of Contrast-Enhanced Sonography and Fusion Imaging for Hepatocellular Carcinoma (HCC) Lesions

HCC Lesions ($n = 87$)	Contrast-Enhanced Sonography[a]	Fusion Imaging[b]
Lesions detected, % (No. / Total No.)	83 (72/87)	98 (85/87)
Lesions not detected, % (No. / Total No.) of lesions	17 (15/87)	2 (2/87)
p^c	< 0.01	< 0.01

Note—We considered 16-MDCT, contrast-enhanced sonography, and histology to be the gold standard for the diagnosis of HCCs.
[a]Perflubutane (Sonazoid, Daiichi Sankyo).
[b]Combining conventional sonography and hepatobiliary phase contrast-enhanced MRI with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid as the reference image.
[c]According to McNemar tests comparing HCC detection rates of fusion imaging and contrast-enhanced sonography with Sonazoid.

Results (2)

TABLE 3: Detection Rate of Each Sonography Modality by Type of Hepatocellular Carcinoma (HCC)

Type of HCC	Fusion Imaging,[a] % (No. of Lesions Detected / Total No. of Lesions)	Conventional Sonography		Contrast-Enhanced Sonography[b]	
		% (No. of Lesions Detected / Total No. of Lesions)	p^c	% (No. of Lesions Detected / Total No. of Lesions)	p^d
Typical HCC[e]	99 (67/68)	82 (56/68)	< 0.01	99 (67/68)	NS
Atypical HCC[f]	95 (18/19)	53 (10/19)	< 0.01	26 (5/19)	< 0.01

TABLE 4: Detection Rate of Hepatocellular Carcinoma (HCC) Lesions Using Each Sonography Imaging Modality According to Tumor Size

HCC Tumor Size	Fusion Imaging,[a] % (No. of Lesions Detected / Total No. of Lesions)	Conventional Sonography		Contrast-Enhanced Sonography[b]	
		% (No. of Lesions Detected / Total No. of Lesions)	p^c	% (No. of Lesions Detected / Total No. of Lesions)	p^d
> 20 mm	100 (26/26)	100 (26/26)	NS	89 (23/26)	NS
10 to ≤ 20 mm	97 (59/61)	66 (40/61)	< 0.01	80 (49/61)	< 0.01

Note—We considered 16-MDCT, contrast-enhanced sonography, and histology to be the gold standard for the diagnosis of HCCs. NS = not statistically significant.
[a]Combining conventional sonography and the hepatobiliary phase of contrast-enhanced MRI with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid as the reference image.
[b]Perflubutane (Sonazoid, Daiichi Sankyo).
[c]According to McNemar tests comparing HCC detection rates of fusion imaging and conventional sonography.
[d]According to McNemar tests comparing HCC detection rates of fusion imaging and contrast-enhanced sonography.

Cases

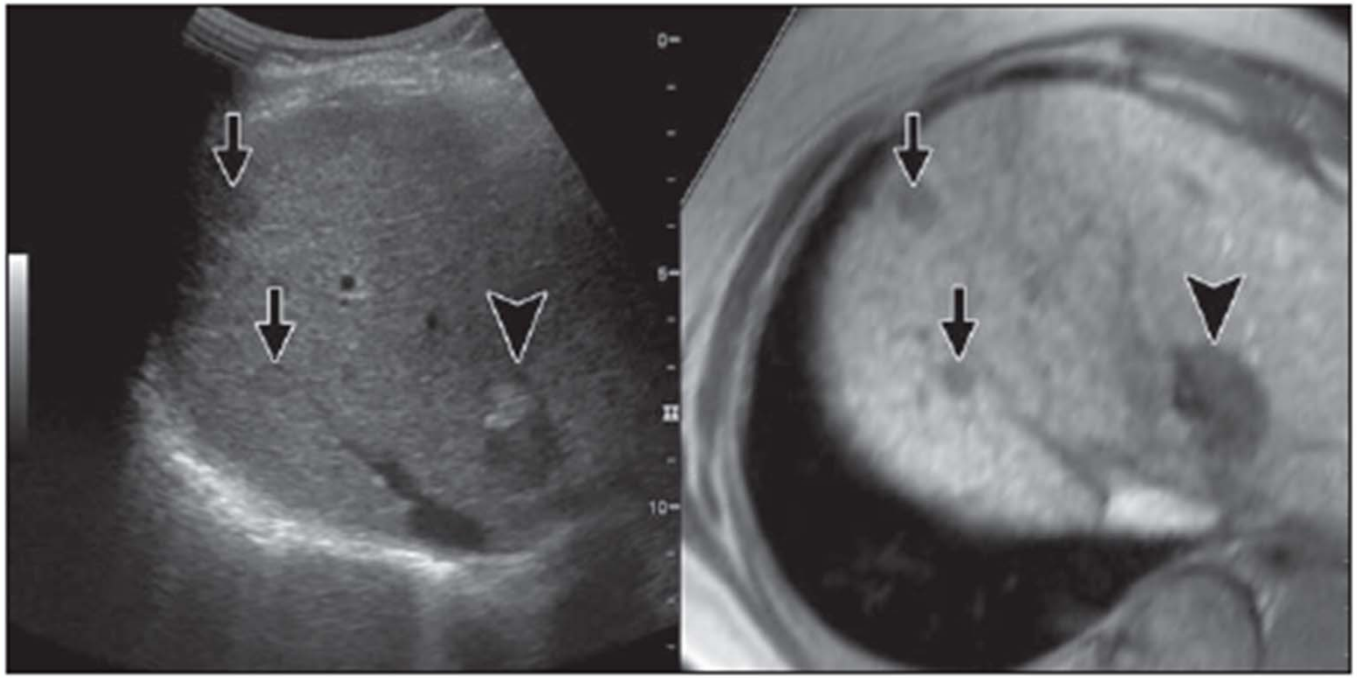

Fig. 4—78-year-old woman with hepatocellular carcinoma (HCC) lesions (maximum diameters, 24, 12, and 10 mm) in segments IV and VIII. Fusion image combining conventional sonography (left) and hepatobiliary phase of contrast-enhanced MRI with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) (right) shows that HCC lesion (*arrowheads*) located in segment IV is easily recognized as hypoechoic and partially hyperechoic lesion on conventional sonography and as hypointense area on hepatobiliary phase Gd-EOB-DTPA–enhanced MRI. However, two small HCC lesions (*arrows*, left image) located in segment VIII cannot be clearly detected using conventional sonography alone. Hepatobiliary phase Gd-EOB-DTPA–enhanced MR image shows hypointense areas in segment VIII (*arrow*, right image). Using hepatobiliary phase of contrast-enhanced MRI with Gd-EOB-DTPA as reference standard for fusion images enabled conventional sonography to detect these small HCC lesions easily.

Cases (2)

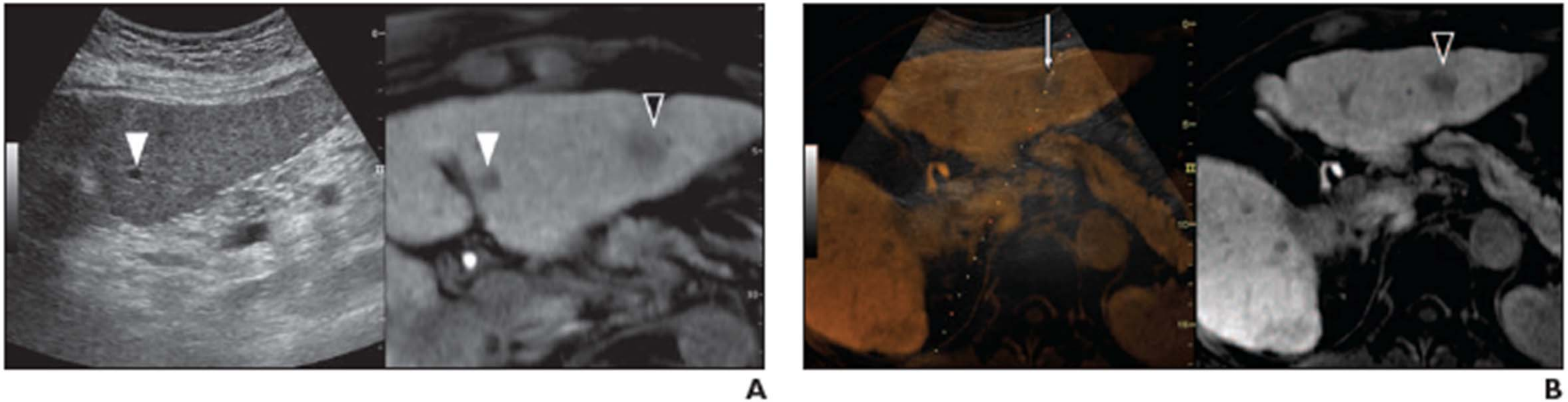

Fig. 6—82-year-old man with hepatocellular carcinoma (HCC) lesion (maximum diameter, 15 mm) in lateral segment.
A, Fusion image combining conventional sonography (*left*) and hepatobiliary phase of contrast-enhanced MRI with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) (*right*). Hepatobiliary phase Gd-EOB-DTPA–enhanced MR image shows two hypointense areas in lateral lobe of liver. Using fusion image, conventional sonography shows part of portal vein corresponding to one small hypointense area (*white arrowheads*) on hepatobiliary phase Gd-EOB-DTPA–enhanced MR image. Even using fusion image, conventional sonography could not detect lesion corresponding to remaining hypointense area (*black arrowhead*) on hepatobiliary phase Gd-EOB-DTPA–enhanced MR image. This lesion was isoechoic on conventional sonography images.
B, Lesion (*arrowhead*) that was not recognized on fusion image because of its isoechogenicity on conventional sonography image was diagnosed using percutaneous tumor biopsy by overlaying hepatobiliary phase Gd-EOB-DTPA–enhanced MR image on conventional sonography image. Arrow indicates tip of biopsy needle. Pathologic examination showed well-differentiated HCC.

Conclusions

- Fusion imaging (+CT/MRI) detects more HCC nodules
- Allows US/GPS guided biopsy of unseen nodules
  - Information integration
    - Dynamic CT/MR data
    - HBP EOB-DTPA
  - Added value
    - Atypical HCC
    - Smaller liver nodules

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OBJECTIVE. We evaluated the efficacy of fusion imaging that fuses conventional sonography images with hepatobiliary phase contrast-enhanced MR images obtained with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) as the reference image for the detection of hepatocellular carcinomas (HCCs).

SUBJECTS AND METHODS. Eighty-seven HCCs with a maximum diameter of between 1 and 3 cm at the time of diagnosis were enrolled in this prospective study. We compared the detection rates of HCCs using three sonography modalities: conventional sonography, late phase of contrast-enhanced sonography with Sonazoid, and fusion imaging combining conventional sonography and the hepatobiliary phase of contrast-enhanced MRI with Gd-EOB-DTPA as the reference image. The comparisons were made using the McNemar test.

RESULTS. The detection rate of HCCs using fusion imaging (98%, 85/87) was significantly higher than the detection rates using conventional sonography (76%, 66/87) and contrast-enhanced sonography (83%, 72/87) ($p < 0.01$, for both). For small HCCs (maximum diameter, 1–2 cm), the detection rate using fusion imaging (97%, 59/61) was also significantly higher than those using conventional sonography (66%, 40/61) and contrast-enhanced sonography (80%, 49/61) ($p < 0.01$, for both). The detection rate for atypical HCCs was also significantly higher using fusion imaging (95%, 18/19) than using conventional sonography (53%, 10/19) and contrast-enhanced sonography (26%, 5/19) ($p < 0.01$, for both).

CONCLUSION. Fusion imaging combining conventional sonography and the hepatobiliary phase of contrast-enhanced MRI with Gd-EOB-DTPA is more sensitive than conventional sonography or contrast-enhanced sonography for detecting HCCs, especially small or atypical HCCs.

Keywords: cirrhosis, contrast-enhanced MRI with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), contrast media, fusion imaging, hepatocellular carcinoma, liver disease, magnetic navigation, sonography

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In patients with advanced cirrhosis, conventional sonography detects many hypo- or hyperechoic areas in the liver parenchyma [1, 2], making the targeting of small hepatocellular carcinoma (HCC) lesions difficult [3]. When such cases are evaluated using sonography, the detection of hepatic lesions depends heavily on the operator's skill [4]. If these small HCC lesions can be precisely detected using sonography, they can be ablated safely and easily. Small HCC lesions are more likely than large lesions to be completely ablated, thereby improving patient survival [5].

Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA, Primovist, Bayer Schering Pharma) is a new liver-specific contrast agent used for MRI that accumulates in normal hepatocytes during the hepatobiliary phase [6–8]. HCC lesions do not take up substantial amounts of Gd-EOB-DTPA, enabling the detection of lesions as hypointense nodules in the hepatobiliary phase of contrast-enhanced MRI with Gd-EOB-DTPA [9–13]. Compared with contrast-enhanced CT, hepatobiliary phase Gd-EOB-DTPA–enhanced MRI seems to be especially beneficial for the detection of HCC lesions in a cirrhotic liver background [13, 14].

Furthermore, to detect HCC lesions, a combination of modalities using different imaging techniques is recommended to increase the sensitivity and specificity of diagnosis. To achieve this combination of different imaging modalities, we used fusion imaging, which can fuse sonography images with multiplanar reconstructed CT or MR images on a single screen in real time using a Logiq E9 unit (GE Healthcare). A new ultrasound transducer together with a navigation system and dynamic positioning system (Volume Navigation System, referred to