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Added Value of Contrast-Enhanced Ultrasound on Biopsies of Focal Hepatic Lesions Invisible on Fusion Imaging Guidance

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Objective: To assess whether contrast-enhanced ultrasonography (CEUS) with Sonazoid can improve the lesion conspicuity and feasibility of percutaneous biopsies for focal hepatic lesions invisible on fusion imaging of real-time ultrasonography (US) with computed tomography/magnetic resonance images, and evaluate its impact on clinical decision making.
Materials and Methods: The Institutional Review Board approved this retrospective study. Between June 2013 and January 2015, 711 US-guided percutaneous biopsies were performed for focal hepatic lesions. Biopsies were performed using CEUS for guidance if lesions were invisible on fusion imaging. We retrospectively evaluated the number of target lesions initially invisible on fusion imaging that became visible after applying CEUS, using a 4-point scale. Technical success rates of biopsies were evaluated based on histopathological results. In addition, the occurrence of changes in clinical decision making was assessed.
Results: Among 711 patients, 16 patients (2.3%) were included in the study. The median size of target lesions was 1.1 cm (range, 0.5–1.9 cm) in pre-procedural imaging. After CEUS, 15 of 16 (93.8%) focal hepatic lesions were visualized. The conspicuity score was significantly increased after adding CEUS, as compared to that on fusion imaging ($p < 0.001$). The technical success rate of biopsy was 87.6% (14/16). After biopsy, there were changes in clinical decision making for 11 of 16 patients (68.8%).
Conclusion: The addition of CEUS could improve the conspicuity of focal hepatic lesions invisible on fusion imaging. This dual guidance using CEUS and fusion imaging may affect patient management via changes in clinical decision-making.
Keywords: *Liver; Biopsy; Contrast-enhanced ultrasonography; Fusion imaging; Sonazoid*

INTRODUCTION

Technical advances in computed tomography (CT) and magnetic resonance (MR) imaging have resulted in more frequent detection of small indeterminate focal hepatic lesions (1-3). Correct diagnosis of these lesions using biopsy is of paramount importance in patients with primary cancer, because misdiagnosis as a malignant lesion can potentially deprive the patient of the opportunity for curative treatment, whereas misdiagnosis as a benign lesion can lead to unnecessary invasive surgery (4).

Ultrasonography (US) is generally the preferred imaging modality for guidance of biopsy of focal hepatic lesions due to its several advantages including real-time capability, absence of radiation hazard, easy accessibility, and low cost (5, 6). However, not all focal hepatic lesions can be localized with conventional B-mode US. According to some previous studies (7, 8), the US detection rates of

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hepatic metastasis from gastrointestinal malignancy and hepatocellular carcinoma (HCC) were 55% and 33–84%, respectively. Accordingly, both fusion imaging and contrast-enhanced US (CEUS) have been used to augment US-guided interventional procedures (9, 10). Although these two techniques are of great help in guiding percutaneous biopsy or radiofrequency ablation (RFA), they are not always perfect. For example, the detection rate of HCC < 2 cm in diameter on fusion imaging was 86.7% (11), and mistargeting of index tumor can occur during RFA despite the use of fusion imaging (12). To overcome these problems, CEUS and fusion imaging can be used simultaneously for guidance of RFA of HCCs (13-15).

Currently, second-generation US contrast agents such as SonoVue (sulphur hexafluoride microbubbles, Bracco, Milano, Italy) and Sonazoid (gaseous perflubutane, GE Healthcare, Oslo, Norway), which can stabilize microbubbles by replacing air with a more inert and slowly diffusing gas, are widely used in clinical practice (16). Among various US contrast agents, Sonazoid has the advantage of offering a unique post-vascular phase, also called the Kupffer phase (17). Therefore, malignant tumors with few or no Kupffer cells appear as contrast defects, as compared with the relatively well-enhancing surrounding liver in the post-vascular phase (18). In addition, unlike the vascular phase, the post-vascular phase offers a longer temporal window sufficient for guidance of interventional procedures (10).

Contrast-euhanced US with Sonsazoid as well as fusion imaging have limitations in localizing small focal hepatic lesions during percutaneous biopsy (10, 19); hence, the diagnostic yield from biopsy would be enhanced if they were to be used simultaneously. However, the integrated approach of fusion imaging and CEUS in percutaneous biopsies for focal hepatic lesions invisible on fusion imaging of real-time US with CT/MR images remains unclear. Additionally, the clinical role of pathologic confirmation in patients with these invisible hepatic focal lesions as well as fusion imaging has not been evaluated. Therefore, we assessed whether the combined use of fusion imaging and CEUS with Sonazoid could improve the lesion conspicuity and technical feasibility of percutaneous biopsy for focal hepatic lesions invisible on fusion imaging, and evaluated its impact on clinical decision-making.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the Institutional Review Board of Samsung Medical Center, which waived the need for patient informed consent. Between June 2013 and January 2015, a total of 915 consecutive patients (538 men and 377 women; mean age, 60.6 years; range, 21–91 years) underwent percutaneous liver biopsy in radiology department, Sungkyunkwan University School of Medicine, Seoul, Korea. Of these, 204 patients were excluded because hepatic parenchyma biopsies were performed for the following reasons: evaluation for cause of acute liver failure (n = 11), evaluation of chronic liver disease including cirrhosis (n = 110), or evaluation of rejection for transplanted liver (n = 83). Among the remaining 711 patients who underwent biopsy for focal hepatic lesions, 16 patients who underwent percutaneous biopsy under CEUS with fusion imaging guidance were ultimately included in our study. All lesions included were totally invisible on fusion imaging via conventional B-mode US with CT/MR images at the time of procedure. Therefore, CEUS using Sonazoid was added to fusion imaging for lesion localization. The detailed selection process of our study was presented in Figure 1.

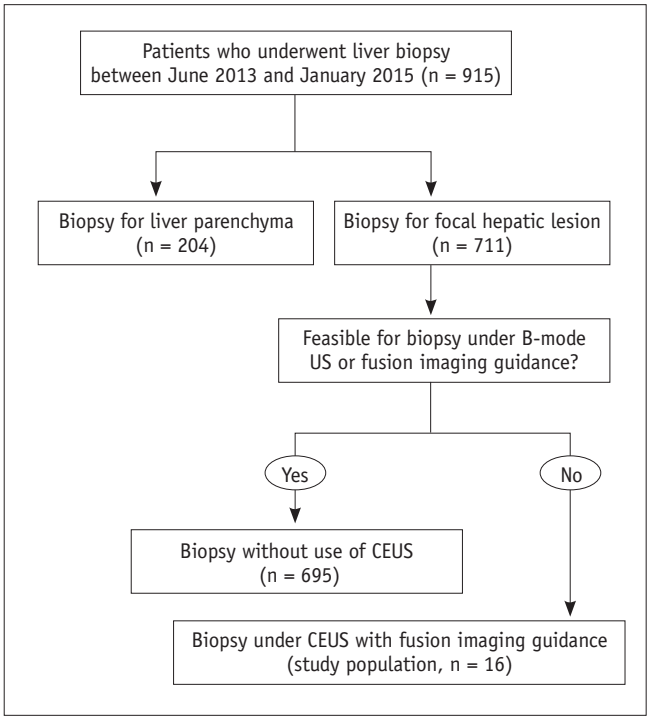

Fig. 1. Flow diagram for our study. CEUS = contrast-enhanced ultrasonography, US = ultrasonography

Biopsy Protocol

We performed US-guided biopsy for suspected malignant lesion or indeterminate focal hepatic lesion on CT/MR images when histological confirmation was clinically required to establish further treatment plans. In general, our institutional protocol of percutaneous liver biopsy for focal hepatic lesion is as follows (19): 1) in patients with multiple lesions with similar imaging characteristics on CT or MR, the most appropriate lesion is selected as a target lesion according to lesion conspicuity and target accessibility (20); 2) the biopsy procedure is performed under conventional B-mode US guidance index for lesions that are well-delineated by conventional B-mode US; 3) biopsy is performed under fusion imaging guidance of real-time US with CT/MR images for lesions that are insufficiently conspicuous on B-mode US; 4) for lesions that are totally invisible even on fusion imaging, CEUS using Sonazoid is added and post-vascular phase imaging (Kupffer phase imaging) is used for guidance of biopsy (21). However, CEUS is not performed if the lesion is deeply located, i.e., > 12 cm below the skin surface, especially in patients with fatty liver, in accordance with current guidelines for CEUS (22); and 5) for lesions that are invisible even after applying CEUS, biopsy is performed at the predicted location of the target lesion after correlating perilesional anatomic landmarks between real-time US and fused CT/MR images, if possible. We selectively employed CEUS for target lesions invisible even on fusion imaging, because it is a rather time-consuming examination involving a 10 minute wait after the contrast injection to see the Kupffer phase. In addition, it requires additional cost for contrast media.

CEUS with Image Fusion

Either a LOGIQ E9 (GE healthcare, Milwaukee, WI, USA) or RS80A (Samsung Medison, Seoul, Korea) US system was used for biopsy procedures. Prior to CEUS, image fusion between B-mode US and CT/MR images was performed using either Volume Navigation (GE Healthcare) or S-Fusion (Samsung Medison). At the time of image fusion, we preferred MR images, especially those obtained at the hepatobiliary phase, over MR or CT images in other phases, since both the target lesion and landmark vessels were clearly visible in most cases (23). After image fusion, real-time US images and the fused CT or MR images were displayed on the US monitor side-by-side, and the operators attempted to localize the target lesion on real-time US image of fusion imaging after correlating perilesional anatomic landmarks.

If the target lesion was invisible on fusion imaging, CEUS was performed with a 1–5 or 1–7 MHz convex probe. The acoustic power was set at the default setting of a mechanical index level of 0.20–0.24 with contrast harmonic imaging. The focus point was located in the posterior margin of the liver, 9–12 cm from the body surface. Sonazoid was administered at a dose of 0.015 mL/kg by manual bolus injection, followed by a 10 mL normal saline flush via a peripheral venous line. CEUS was performed with fusion imaging (one side of screen: contrast mode; the other side: fused CT/MR images), rather than with conventional B-mode US (13).

Biopsy Procedures

All biopsy procedures were performed percutaneously at the post-vascular phase (10 minutes after contrast administration) by 1 of 3 board-certified abdominal radiologists with 11, 5, and 4 years of clinical experience of biopsy procedures, respectively. Each radiologist had experience of at least 300 cases of percutaneous liver biopsy before the start of this study. Before the procedure, local anesthesia was performed along the expected needle path using 2% lidocaine hydrochloride (Huons, Hwaseong, Korea) between the skin and hepatic capsule. Biopsy was performed using an 18-gauge automated side-cutting biopsy needle (Acecut; TSK Laboratory, Tochigi, Japan) with free-hand technique. We completed the procedure after confirming needle penetration through the target lesion on US image and visual inspection of the tissue core. Repeated sampling was performed, if needed.

Outcome Analysis

The radiologists who performed the biopsy and another investigator reviewed the US images obtained before and after contrast administration via a picture archiving and communication system (Centricity; GE Healthcare, Chicago, IL, USA). They retrospectively graded lesion conspicuity with consensus, using the following 4-point scoring system on the post-vascular phase: score 0, invisible; score 1, the echogenicity of target lesion was nearly iso-echoic to the surrounding liver and < 50% of the lesion had a well-defined margin; score 2, slightly different from that of surrounding liver and > 50% of the lesion had a well-defined margin; and score 3, the echogenicity of the target lesion was distinctly different from that of the surrounding liver, and > 90% of the lesion was visible (13). In addition, we reviewed reports on interpretations of the target lesions

Table 1. Baseline Characteristics of 16 Patients and Their Lesions

ID	Age	Sex	Underlying Disease	Reason for Liver Biopsy	Location (Segment)	Size (cm)	Conspicuity Score on CEUS	Number of Needle Passes	Final Pathology	Change of Plan
1	56	M	Pancreatic cancer	Suspicious hepatic metastasis	S8	0.5	3	2	Cavernous hemangioma	Y
2	77	M	(-)	Indeterminate lesion	S7	0.8	3	2	Non-specific inflammation	Y
3	66	M	Colon and lung cancer	Suspicious tumor recurrence	S5	1.5	3	2	Metastasis	Y
4	64	M	HCC	Suspicious CCC	S8	1.9	3	1	HCC	Y
5	55	M	Cecal cancer	Suspicious hepatic metastasis	S4	1.0	3	3	Eosinophilic abscess	Y
6	64	M	HCC	Suspicious another HCC in other hepatic lobe	S6	1.1	3	2	Eosinophilic abscess	Y
7	43	F	HCC	Suspicious tumor recurrence	S6	0.7	3	4	HCC	N
8	68	F	Pancreatic cancer	Suspicious hepatic metastasis	S4	1.1	2	2	Biliary micro-hamartoma	Y
9	61	F	Breast cancer	Suspicious tumor recurrence	S5	0.6	3	1	Metastasis	Y
10	32	F	Sickle cell anemia	Indeterminate lesion	S5	0.9	1	2	Non-specific inflammation	Y
11	48	M	Alcoholic liver cirrhosis	Suspicious benign lesion	S8	0.5	0	2	Non-specific inflammation	N
12	64	M	Pancreatic cancer	Suspicious hepatic metastasis	S6	1.5	3	2	Metastasis	Y
13	55	F	Breast cancer	Suspicious hepatic metastasis	S8	1.2	3	2	Non-specific inflammation	Y
14	77	F	Pancreatic cancer	Indeterminate lesion	S5	0.5	3	3	Metastasis	N
15	54	M	Ampulla of Vater cancer	Suspicious tumor recurrence	S5	1.8	1	2	No pathologic alteration or tumor*	(-)
16	41	M	Viral liver cirrhosis	Suspicious HCC	S2	1.2	1	2	No pathologic alteration or tumor*	(-)

*Indicates technical failure of biopsy procedure even after adding CEUS to fusion imaging. Location of focal hepatic lesion is based on Couinaud classification system. Tumor recurrence is defined as appearance of new metastatic lesion in liver on follow-up imaging in patients who were previously considered to have no tumor in intra- and extrahepatic areas, and on clinical examination at final visit. Change of plan indicates modification of therapeutic plan in consequence of biopsy results. CCC = cholangiocarcinoma, CEUS = contrast-enhanced ultrasonography, HCC = hepatocellular carcinoma

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on pre-procedural imaging studies. Subcapsular location was defined as an index lesion located within 0.1 cm of the liver capsule (24). The shortest distance from the skin to the closest portion of the target lesion was also measured using a picture archiving and communication system (Centricity; GE Healthcare).

Final diagnosis was based on specific findings of neoplasia on histopathological examination of the specimen by a pathologist specializing in the liver. If the pathologic examination revealed benign non-neoplastic conditions, the patients were followed up with imaging studies and laboratory examinations, and the final diagnosis was made based on biopsy results as well as follow-up clinical and radiologic findings. If specific histopathological diagnosis could not be made using the biopsy specimen, it was regarded as a technical failure of biopsy. When biopsy could not be attempted even after applying CEUS, it was also considered as technical failure of biopsy procedure. Changes in clinical decision-making were categorized as follows: 1) change of treatment option between curative and palliative treatment, 2) change in extent of hepatic resection relative to the therapeutic plan prior to biopsy or, 3) change of chemotherapeutic agent.

Statistical Analysis

Descriptive statistics were presented as median with range according to normality for the continuous variable, and with frequency (percentage) for the categorical variable. To compare lesion conspicuity before and after use of CEUS, a Wilcoxon signed rank test was used. All statistical analyses were performed using the SPSS software package (SPSS Statistics, version 18.0; SPSS Inc., Chicago, IL, USA). A p value of < 0.05 was considered statistically significant.

RESULTS

Patient and Lesion Characteristics

The baseline characteristics of the 16 patients were summarized in Table 1. They underwent 13 MR images and 3 CT images for pre-procedural work-up. Twelve patients had a current or past history of cancer. The interpretations of the lesions on pre-procedural imaging studies were as follows: suspicious malignant lesion (n = 12), indeterminate lesion (n = 3), and probably benign lesion (n = 1). The median size of target lesions was 1.1 cm (range, 0.5–1.9 cm) on CT/MR images. Eight lesions (50%) were located in the subcapsular portion of liver. The median depth of the target lesions indicating the shortest distance from the skin to the closest portion of the target lesion was 4.9 cm (range, 1.8–9.2 cm). Median time interval from the date of imaging study to that of biopsy was 5 days (range, 1–9 days).

Lesion Conspicuity

Before administration of the contrast agent, the conspicuity scores of target lesions were graded as 0 for all lesions. The median injected amount of Sonazoid was 0.9 mL (range, 0.7–1.2 mL). The conspicuity score in 15 (93.8%) of 16 lesions increased on CEUS (score 3, n = 11; score 2, n = 1; score 1, n = 3; and score 0, n = 1). The increase in conspicuity scores of these lesions was statistically significant (p < 0.001) (Table 1, Fig. 2). One lesion (0.5 cm) suspected as a small abscess on pre-procedural MR images was invisible even after CEUS.

Technical Success of Biopsy

Biopsy was performed on all 16 patients without complications. A biopsy of the one lesion invisible after CEUS was also taken, based on adjacent landmark hepatic vessels on fusion imaging. The technical success rate of biopsy procedures was 87.6% (14/16). The histopathological results from the biopsy specimens were as follows: malignant neoplasm (n = 6), benign neoplasm (n = 2), benign non-neoplastic inflammatory lesion (n = 6), and no pathologic alteration (n=2) (Figs. 3, 4). In the benign non-neoplastic inflammatory lesions, 4 disappeared and 2 showed decrease in size on follow-up imaging studies

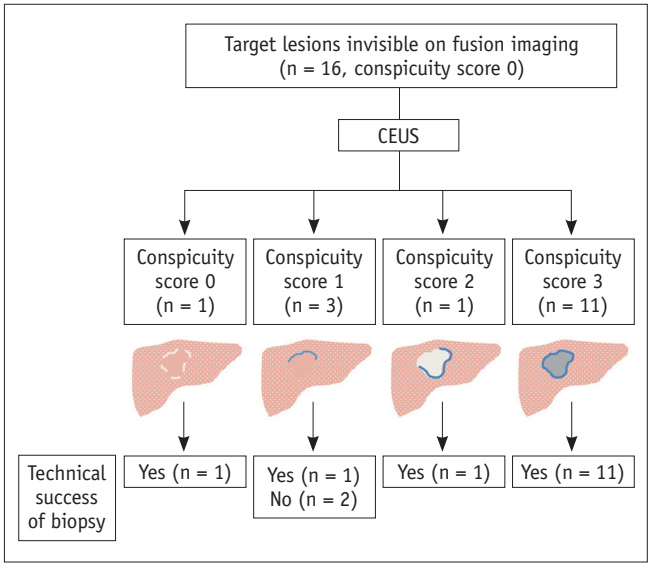

Fig. 2. Lesion conspicuity and technical success of biopsy. CEUS = contrast-enhanced ultrasonography

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(median, 9 months; range, 1–17 months). Two lesions with no pathologic alteration in the biopsy specimen were regarded as technical failures of biopsy. Both lesions were challenging cases with poor conspicuity (grade 1) even after CEUS: one lesion (1.2 cm) was located in the deep portion of segment II, and the other lesion (1.8 cm) was located in the superficial portion of segment V.

Change in Clinical Decision-Making

Among 16 patients who underwent biopsy under CEUS and fusion imaging guidance, changes in treatment plan in 11 (68.8%) patients were as follows: change of therapeutic plan for curative or palliative treatment or observation with imaging follow-up (n = 7); change in extent of hepatic resection (n = 2); and change of chemotherapeutic agents due to confirmation of tumor recurrence or metastasis in liver (n = 2). These changes in clinical decision making in 11 patients were summarized in Table 2.

DISCUSSION

Our results showed that the additional use of CEUS with Sonazoid could enhance lesion conspicuity and thereby aid in performing accurate percutaneous biopsy for focal hepatic lesions invisible on fusion imaging of real-time US with CT/MR images. Most invisible lesions on fusion imaging became visible after adding CEUS and, consequently, the biopsy results influenced further therapeutic plans in most patients.

Either fusion imaging or CEUS can be used for target

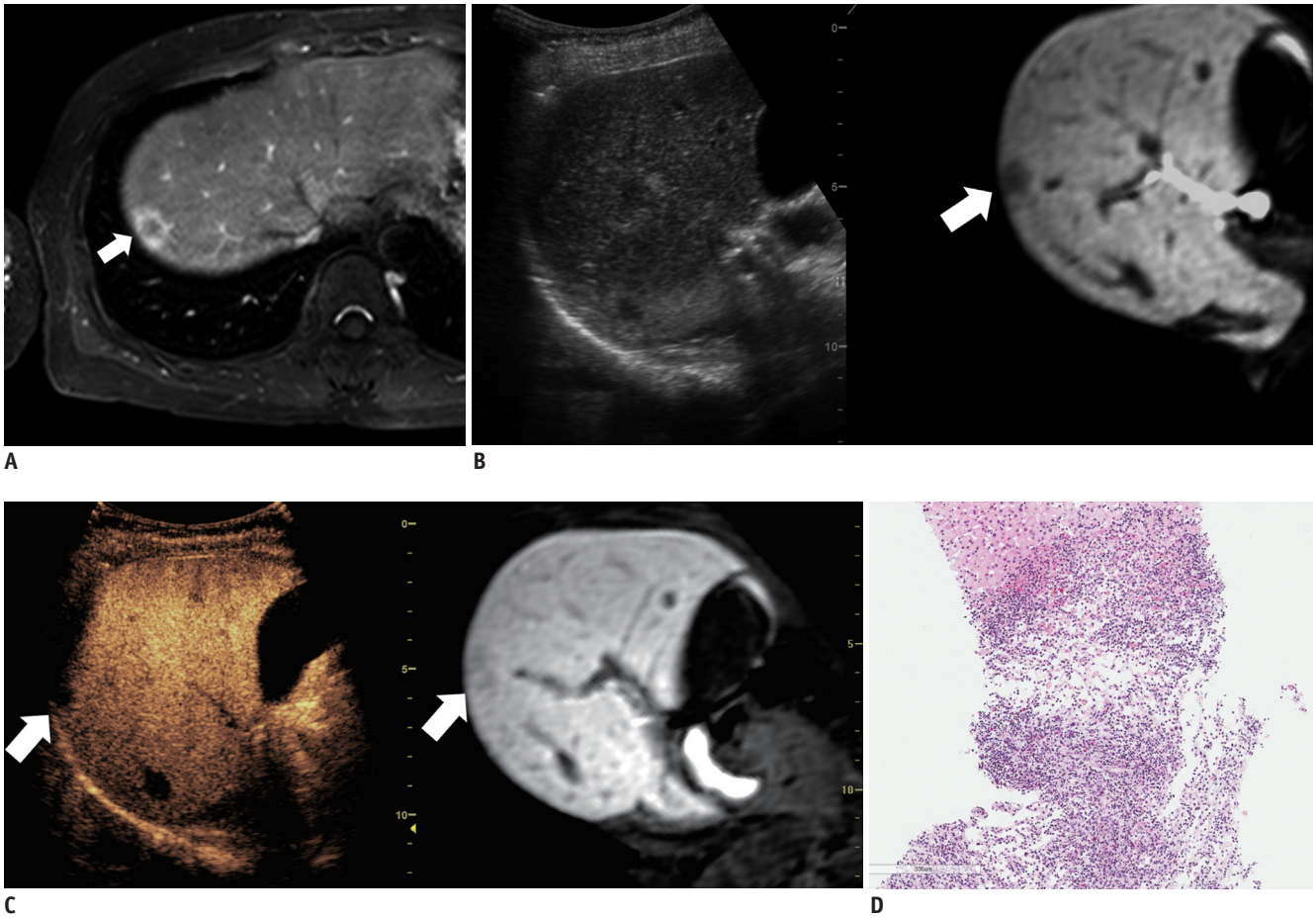

Fig. 3. CEUS with fusion imaging-guided biopsy for suspected malignant hepatic lesion.
A. Gadoxetic acid-enhanced MR image obtained during arterial phase shows 1.2-cm ill-defined peripheral rim-like enhancing lesion (arrow) in segment VIII in patient with breast cancer. Lesion was suspected as hepatic metastasis based on MR imaging findings including hypointensity on T1-weighted images and apparent diffusion coefficient map (not shown). **B.** On fusion imaging, focal lesion is not identified on real-time US at corresponding site on fused MR images (arrow). **C.** In post-vascular phase after use of Sonazoid, hypoechoic lesion (arrows) is visualized in subcapsular portion of liver at corresponding site on fused MR images. **D.** Magnification view of liver biopsy specimen shows infiltration of mixed inflammatory cells with loose fibrosis representing non-specific inflammation (hematoxylin-eosin stain). Patient underwent curative resection of breast cancer instead of palliative chemotherapy. CEUS = contrast-enhanced ultrasonography, MR = magnetic resonance, US = ultrasonography

lesion with poor sonographic conspicuity during percutaneous biopsy or RFA. A previous study (19) suggested percutaneous biopsy based on perilesional anatomic landmarks for focal hepatic lesions invisible even on fusion imaging. However, if the target lesion invisible on fusion imaging is located in the periphery of the liver and is thus at a distance from large landmark vessels, fusion imaging-guided biopsy may be inaccurate because the peripheral portion of the liver is likely to be affected by registration error due to liver deformation or displacement by the patient's breathing motion or heartbeat (5). Similarly, a recent study investigating mistargeting after fusion imaging-guided percutaneous RFA of HCCs (12) reported that peripheral location of the target lesion a common cause of mistargeting by RFA even after fusion imaging guidance.

In such situations, CEUS can serve as an additional guidance method for focal hepatic lesions with poor conspicuity (21, 25). In our study, CEUS was performed with fusion imaging and not with B-mode US, because fusion imaging allowed us to estimate the location of the target lesion before injecting the contrast agent (13). Consequently, careful evaluation of the target lesion throughout the vascular and post-vascular phases was possible. As expected, most of the lesions initially invisible on fusion imaging became visible after adding CEUS, and

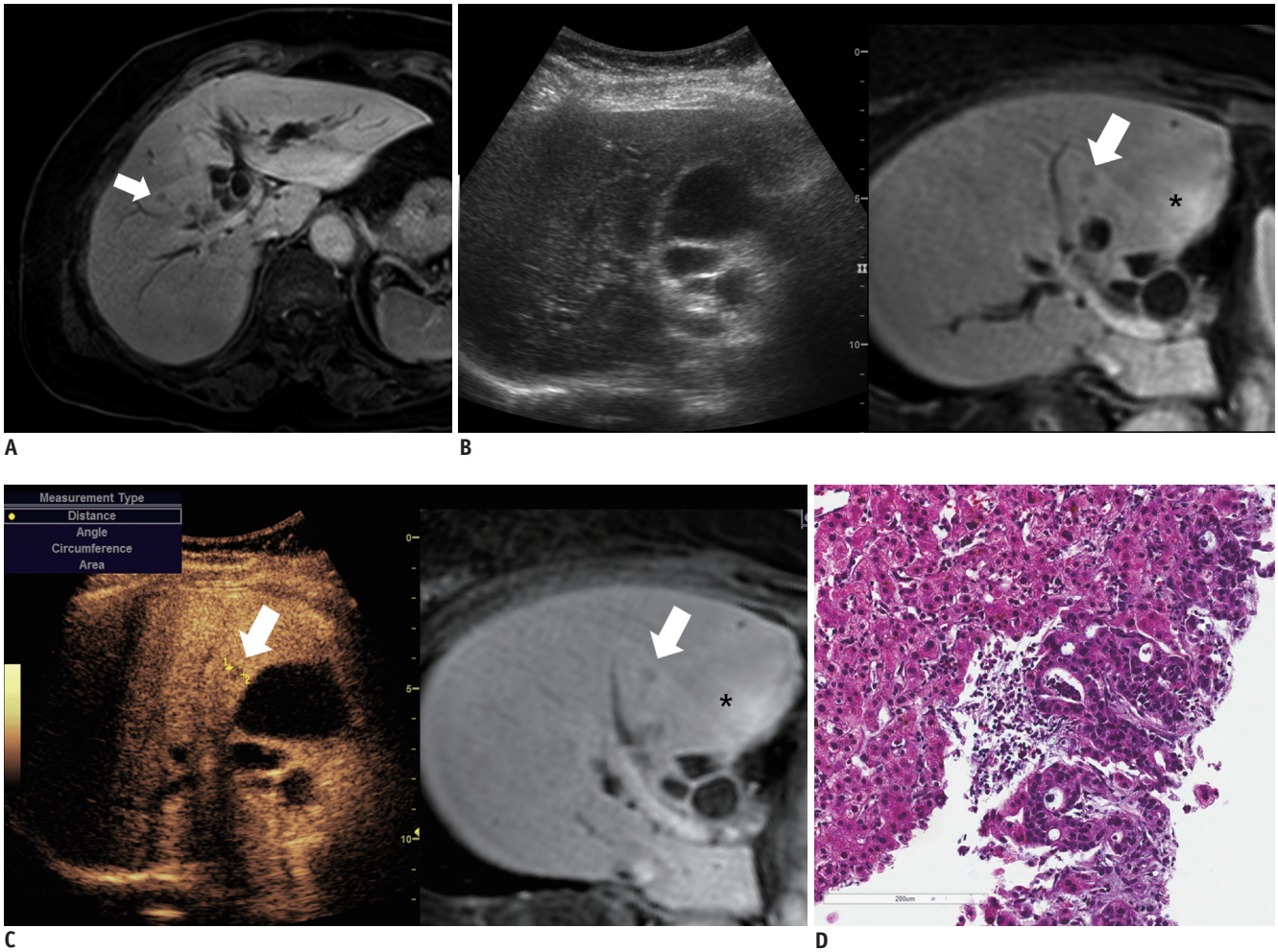

Fig. 4. CEUS and fusion imaging-guided biopsy for indeterminate focal hepatic lesion.
A. Gadoxetic acid-enhanced MR image obtained during hepatobiliary phase shows 0.5-cm small nodular lesion (arrow) in segment V in patient with resectable pancreatic cancer. Lesion is considered as indeterminate since it shows no peripheral enhancement in early dynamic phase and is not delineated on apparent diffusion coefficient map in MR images (not-shown). **B.** On fusion imaging, indeterminate lesion (arrow) detected on MR images could not be localized on B-mode US. Asterisk indicates gallbladder. **C.** After CEUS, tiny low echoic lesion (arrows) is visualized adjacent to gallbladder (asterisk). **D.** Histology features of few atypical glandular structures with nuclear atypia confirmed adenocarcinoma with moderate differentiation from pancreatic cancer. Patient underwent palliative chemotherapy instead of pylorus-preserving pancreaticoduodenectomy for pancreatic cancer. CEUS = contrast-enhanced ultrasonography, US = ultrasonography

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Table 2. Changes in Clinical Decision Making after Biopsy under Guidance of CEUS and Fusion Imaging in 11 Patients

ID	Underlying Disease	Therapeutic Plan before Biopsy Based on Images	Biopsy Results	Therapeutic Plan after Histologic Confirmation Using Biopsy
1	Pancreatic cancer	Palliative chemotherapy due to hepatic metastasis	Cavernous hemangioma	Curative resection for pancreatic cancer
2	(-)	Surgical resection if lesion is increased in follow-up images	Inflammation	Imaging follow-up
3	Colon and lung cancer	Use of chemotherapy for possible metastasis from lung cancer	Metastasis	Choice of chemotherapy agent for metastasis from colon cancer
4	HCC	Suspected intrahepatic mass forming CCC	HCC	TACE for HCC instead of chemotherapy for CCC
5	Cecal cancer	Surgical resection for hepatic metastasis	Inflammation	Imaging follow-up
6	HCC	Right hemihepatectomy for HCC	Inflammation	Bisegmentectomy for HCC
8	Pancreatic cancer	Palliative chemotherapy due to hepatic metastasis	Biliary micro-hamartoma	Curative resection for pancreatic cancer
9	Breast cancer	Sustain current chemotherapy regimen	Metastasis	Change of chemotherapy agent for disease progression
10	Sickle cell anemia	Laparoscopic excisional biopsy	Inflammation	Imaging follow-up
13	Breast cancer	Palliative chemotherapy due to hepatic metastasis	Inflammation	Curative resection for breast cancer
14	Pancreatic cancer	Curative resection for pancreatic cancer with imaging follow-up	Metastasis	Palliative chemotherapy due to hepatic metastasis

Patient identification number is identical to Table 1. CCC = cholangiocarcinoma, CEUS = contrast-enhanced ultrasonography, HCC = hepatocellular carcinoma, TACE = transcatheter arterial chemoembolization

pathological confirmation by biopsy was feasible in most of the target lesions in our study.

However, there were 2 cases of technical failure after biopsy in our study even combined use of fusion imaging and CEUS. Although these lesions were localized after CEUS, the lesion conspicuity was inadequate and scored as 1 in both cases. In addition, one target lesion was invisible even after employing CEUS. This may be explained by the very small (0.5 cm) lesion size and possibility of functioning Kupffer cells, which makes it difficult to visualize in the post-vascular phase. In addition, the lesion was favored as benign on pre-procedural MR images with gadoxetic acid-enhancement since it showed iso- to subtle low signal intensity in the hepatobiliary phase consistent with the presence of intra-lesion functioning hepatocytes as well as Kupffer cells (26, 27).

In a previous large series of biopsy studies (28), the rate of misdiagnosis of focal hepatic lesions based on imaging findings was > 10% in cancer patients. Hence, pathological confirmation by biopsy can still play a vital role in the proper management of some cancer patients. It also prevents unnecessary imaging follow-up for indeterminate focal hepatic lesions, thereby reducing patients' anxiety (25, 29). In our study, of the 12 patients with suspected malignant hepatic lesions in the imaging studies, 5 patients (41.7%) were confirmed with benign or inflammatory lesions by dual guidance percutaneous biopsy, which led to curative resection or routine follow-up instead of unnecessary palliative chemotherapy or invasive surgery.

Our study had several limitations. First, the selection bias related to its retrospective design. Only patients who underwent percutaneous biopsy were included in our study, however there may have been patients who did not undergo percutaneous biopsy for various reasons including difficult location for biopsy, such as blind spot or unfavorable location. Therefore, the patients analyzed may not represent the overall population requiring percutaneous biopsy resulting in possible overestimation of the technical success rate of biopsy. However, in our series, all the patients who underwent Sonazoid-enhanced US for localizing focal hepatic lesions invisible on fusion imaging, also underwent biopsy. Second, although we used a large retrospective cohort, the final study population was relatively small. Fusion imaging is very useful for localizing focal hepatic lesions with poor sonographic conspicuity, hence, the small sample size was inevitable in a single institutional study. Third, this was a single arm study with no control

group. Since percutaneous biopsy for invisible lesions can be attempted under fusion imaging guidance based on perilesional anatomic landmarks (19) or CEUS guidance, each group could have been used as a control group. However, the diagnostic yield by each technique alone may not be sufficiently high for lesions with no perilesional anatomic landmarks. In addition, interpretation of negative biopsy results is difficult when performing these biopsy techniques, due to occurrence of true benign lesions similar to normal hepatocytes, or false negatives by mistargeting. Hence, a direct comparison study between these techniques and fusion imaging plus CEUS guidance was problematic ethically. Despite these limitations, our findings suggest the usefulness of this cutting-edge biopsy technique for patients with invisible focal hepatic lesion on fusion imaging and its clinical implications.

In summary, the additional use of CEUS with Sonazoid improves the conspicuity of focal hepatic lesions invisible on fusion imaging of real-time US with CT/MR images. It could enable otherwise infeasible percutaneous biopsy of target lesions invisible on fusion imaging, and may affect patient management through consequent changes in clinical decision-making.

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