Real-time Contrast-Enhanced Sonographically Guided Biopsy or Radiofrequency Ablation of Focal Liver Lesions Using Perflurobutane Microbubbles (Sonazoid)

Value of Kupffer-Phase Imaging

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Objectives—To evaluate the utility of Kupffer-phase imaging by real-time contrast-enhanced sonography using the perflurobutane microbubble contrast agent Sonazoid (GE Healthcare, Oslo, Norway) in guiding biopsy or radiofrequency (RF) ablation of focal liver lesions.

Methods—A total of 75 patients (mean age, 59.7 years) who were referred for percutaneous biopsy (n = 42) or RF ablation (n = 33) were included in the study. Grayscale sonography and contrast-enhanced sonography using Sonazoid were performed in all patients before the procedure. The conspicuity of each targeted liver lesion on grayscale sonography, vascular-phase contrast-enhanced sonography, and Kupffer-phase contrast-enhanced sonography was graded using a 5-point scale. Lesion detection rates were calculated, and the conspicuity of the lesions among the imaging modalities was compared. The technical success of the procedures was also assessed.

Results—The procedures were conducted in 66 patients (biopsy in 41 and RF ablation in 25) under real-time guidance by Kupffer-phase contrast-enhanced sonography. Lesion detection rates were 77.3% (58 of 75), 84.0% (63 of 75), and 92.0% (69 of 75) on grayscale sonography, vascular-phase contrast-enhanced sonography, and Kupffer-phase contrast-enhanced sonography, respectively, and were significantly different among the 3 modalities ($P = .034$). Overall, lesion conspicuity was significantly increased on vascular-phase and Kupffer-phase contrast-enhanced sonography compared to grayscale sonography ($P < .001$). Technical success rates for the procedures were 95.2% (40 of 42) for biopsy and 69.7% (23 of 33) for RF ablation.

Conclusions—Kupffer-phase imaging by contrast-enhanced sonography using Sonazoid increases the conspicuity of the liver lesions compared to grayscale sonography, and it is useful for real-time guidance of percutaneous biopsy or RF ablation of focal liver lesions.

Key Words—contrast-enhanced sonography; focal liver lesion; gastrointestinal ultrasound; grayscale sonography; Kupffer phase; percutaneous biopsy; radiofrequency ablation; Sonazoid

Received April 29, 2014, from the Department of Radiology, Konkuk University School of Medicine, Seoul, Korea. Revision requested May 29, 2014. Revised manuscript accepted for publication June 25, 2014.

This study was supported by Konkuk University.

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Abbreviations

CT, computed tomography; MRI, magnetic resonance imaging; RF, radiofrequency

doi:10.7863/ultra.34.3.411

Sonography is the most preferred imaging modality for guiding biopsy of focal liver lesions or for guiding radiofrequency (RF) ablation of hepatic malignancy.[1] It is superior to other modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) in terms of imaging capability. However, although real-time confident visualization of the target lesion is mandatory for performing sonographically guided procedures, the target lesion is often not sufficiently visualized on grayscale sonography for various reasons.[1] According to prior reports on the performance of grayscale sonography in terms of hepatic focal lesion detection, per-patient sensitivity rates were 55% for detection of hepatic metastasis from cancers of the gastrointestinal tract[2] and 33% to 84% for detection of hepatocellular carcinoma.[3]

As an alternative to grayscale sonography, the use of contrast-enhanced sonography has led to improved visualization of hepatic focal lesions that were not clearly depicted on grayscale sonography, and it has also contributed to lesion characterization.[4,5] A prospective study regarding contrast-enhanced sonography using sulfur hexafluoride microbubbles (SonoVue; Bracco SpA, Milan, Italy) for guiding biopsy reported that real-time contrast-enhanced sonographically guided biopsy is a feasible and useful technique for detecting lesions that are not clearly localized on grayscale sonography.[1] However, the utility of contrast-enhanced sonography during the vascular phase is limited because of its narrow time window for hepatic enhancement, especially when conducting ablation procedures.[6]

Sonazoid (GE Healthcare, Oslo, Norway) is a second-generation ultrasound contrast agent that consists of a lipid-stabilized suspension of perflurobutane gas microbubbles within a hard shell of phosphatidyl-serine (2–3 μm in diameter).[7] These microbubbles provide stable nonlinear oscillations in low-power acoustic fields and produce echoes at the second harmonic frequency of the transmitted pulse, which are used for contrast-enhanced harmonic imaging.[8] Along with the ability of real-time vascular-phase imaging, Sonazoid microbubbles are taken up by Kupffer cells in the reticuloendothelial system of the liver, which enables parenchyma-specific liver imaging.[7,8] This Kupffer-phase imaging is generally performed 10 minutes after intravenous contrast media administration, at which time the normal hepatic parenchyma is enhanced.[9] Therefore, malignant lesions containing few or no Kupffer cells are clearly shown as contrast defects in this phase.[10] In addition, since Sonazoid microbubbles continue to resonate with moderate ultrasound pressure without collapse, Kupffer-phase imaging is stable for more than several hours, which facilitates whole-liver scanning.[11] Many previous studies have reported the utility of contrast-enhanced sonography using Sonazoid for detection of hepatic metastasis[8,12–14] and for detection and diagnosis of hepatocellular carcinoma[9,11,15,16] as well as the usefulness of intraoperative contrast-enhanced sonography in patients with hepatocellular carcinoma or metastasis from colorectal cancer.[17–19] However, there are only a few reports on the usefulness of contrast-enhanced sonography using Sonazoid in guiding a procedure such as biopsy or RF ablation of liver lesions.[6,20–22] Therefore, the purpose of this study was to evaluate the utility of contrast-enhanced sonography using Sonazoid in guiding biopsy of focal hepatic lesions or RF ablation of malignant focal liver lesions.

Materials and Methods

Patient Population

This study was approved by the Institutional Review Board of our institution. Written informed consent was obtained from all of the patients participating in the study. Between January 2013 and March 2014, a total of 75 consecutive patients who were referred for biopsy of focal hepatic lesions (n = 42) or RF ablation of malignant hepatic focal lesions (n = 33) were included in the study. There were 52 male and 23 female patients, and their ages ranged from 28 to 90 years (mean ± SD, 59.7 ± 12.6 years) years. All of the patients underwent cross-sectional imaging such as contrast-enhanced CT or MRI. The indication for percutaneous biopsy was to diagnose or rule out hepatic metastasis from a known malignancy in the other organs (n = 23) or to diagnose or rule out malignancy in an indeterminate focal liver lesion (n = 19). As for 19 indeterminate lesions, they were inconclusive on CT only (n = 3) or both CT and MRI (n = 16). The reasons for biopsy of these lesions were differentiation of hepatocellular carcinoma versus cholangiocarcinoma (n = 5), hepatocellular adenoma versus atypical focal nodular hyperplasia (n = 4), hepatocellular carcinoma versus another hypervascular tumor such as hepatocellular adenoma or a neuroendocrine tumor (n = 3), metastasis versus cholangiocarcinoma (n = 3), cholangiocarcinoma versus a benign lesion (n = 3), and hepatocellular carcinoma versus a dysplastic nodule (n = 1).

Radiofrequency ablation was requested for hepatocellular carcinoma (n = 21) or metastasis from colorectal cancer (n = 12), either in a percutaneous manner (n = 26) or intraoperatively (n = 7). Eleven of 21 patients (52.4%) with hepatocellular carcinoma who were referred for RF ablation had already undergone transarterial chemoembolization for the same lesions, which were treated incompletely. A flow chart of the study profile based on the recommended standards for reporting diagnostic accuracy is presented in Figure 1.

Grayscale Sonography

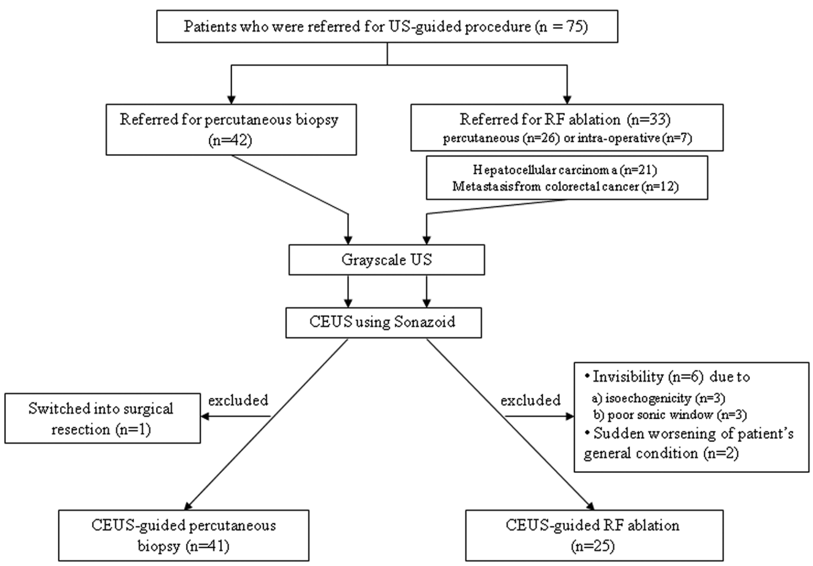
All preprocedural grayscale sonographic, contrast-enhanced sonographic, biopsy, and RF ablation procedures were performed by a board-certified abdominal radiologist who had 8 years of experience in abdominal sonography and had performed more than 300 sonographically guided biopsies of focal liver lesions, 90 diagnostic contrast-enhanced sonographic examinations, and 50 real-time contrast-enhanced sonographically guided interventions. For grayscale sonography, patients fasted for at least 8 hours. An 18-gauge intravenous catheter was inserted into a forearm vein. The radiologist scanned the liver in the standard B-mode using a 2–5-MHz curvilinear transducer (iU22; Philips Healthcare, Bothell, WA) for the percutaneous procedures and both 2–5- and 5–8-MHz curvilinear transducers for the intraoperative procedures. If a patient had 2 or more potential target lesions for biopsy based on the cross-sectional images, the radiologist selected the most appropriate lesion as the procedure target, considering the lesion visibility and technical feasibility of the procedure.[1]

At the time of the sonographic examination, the performing radiologist, who was aware of the patient's clinical and radiologic information, graded the conspicuity of the target lesion on the basis of the visibility of the lesion compared to adjacent liver parenchyma using a 5-point confidence scale, with 1 indicating not visualized and 5 indicating well visualized.[24] The lesion was scored as 3 when it was localized but more than half of the lesion was not clearly demarcated (very poorly defined). When the lesion was scored as 1 or 2, the major presumed reason for invisibility of the lesion was recorded.

Contrast-Enhanced Sonography

Contrast-enhanced sonography was performed with the same ultrasound system as for grayscale sonography. One vial (16 μg) of Sonazoid was reconstituted with 2 mL of sterile water for injection, and the solution at a dose of 0.015 mL/kg body weight was injected as a bolus via the forearm catheter, immediately followed by a 10-mL normal saline flush. Imaging was performed with a 2–5-MHz transducer in a split-screen mode, which displays the contrast-enhanced sonogram on the left and the reference B-mode sonogram on the right simultaneously on a single monitor. The acoustic power for contrast-enhanced sonography was set at the default setting with a mechanical index of 0.21. The focus was set below the lesion of interest to minimize microbubble disruption. Scanning of the liver was started simultaneously with injection of the contrast agent, and the target lesion was searched. After the vascular-phase imaging, which lasted approximately 3 minutes, scanning of the liver with Kupffer-phase imaging was performed 5 to 10 minutes after contrast agent injection when no contrast enhancement was visualized in the hepatic vasculature. Similar to grayscale sonography, conspicuity of the target lesion was graded on the 5-point confidence scale for the vascular-phase and Kupffer-phase images separately. When the

Figure 1. Flowchart of the study profile based on recommended standards for reporting diagnostic accuracy.[23] CEUS indicates contrast-enhanced sonography; and US, sonography.



lesion was scored as 1 or 2, the major presumed reason for invisibility of the lesion was recorded. When the lesion was visible, its location, diameter, and depth were determined by the imaging modality in which the lesion was most conspicuous. When the lesion was not visualized on grayscale or contrast-enhanced sonography, its location, diameter, and depth were measured from previous CT or MRI.[1]

Percutaneous Biopsy

If the target lesion was not identified on grayscale sonography or Kupffer-phase contrast-enhanced sonography, biopsy was not performed. Biopsy procedures were performed under the guidance of Kupffer-phase contrast-enhanced sonography. An 18-gauge automated side-cutting biopsy gun (Acecut; TSK Laboratory, Tochigi, Japan) was used in a freehand technique. The number of samples ranged from 2 to 5, based on the performing radiologist's decision.

Radiofrequency Ablation

Percutaneous RF ablation was performed for the lesions localized on Kupffer-phase contrast-enhanced sonography. At our institution, since pre–RF ablation planning sonography, including contrast-enhanced sonography, is usually performed in the morning and RF ablation is performed in the afternoon, enhancement of the liver parenchymal becomes weaker during this interval. Therefore, for guiding the RF ablation procedures, the previously injected microbubbles were destroyed by imaging the liver in a high–mechanical index flash mode for several minutes, and then contrast-enhanced sonography was repeated after a second injection of the same contrast agent dose. Percutaneous RF ablation was performed under conscious sedation with intravenous midazolam (2 mg) and fentanyl (40 μg) and local anesthesia using lidocaine (1%); intraoperative RF ablation was performed under general anesthesia. Lesions were treated with a 17- or 15-gauge internally cooled electrode with an adjustable active tip (VIVA RF electrode; STARmed, Goyang, Korea). The length of the active tip applied, ablation time, and number of overlapping ablations were decided by the operator according to the size, depth, location, and previous transarterial chemoembolization of the targeted lesion.

Analysis of Technical Success

For percutaneous biopsy, a case was considered technically successful if the pathologic findings of the specimen indicated malignancy. For pathologically benign lesions, a case was regarded as technically successful when the pathologic results were in accordance with the presumed diagnosis made by the preprocedural cross-sectional imaging and when the target lesions decreased in size at the minimum 1-month follow up imaging. A case was considered a technical failure when the biopsy procedure was not completed for any reason or the pathologic results failed to specifically indicate the final diagnosis.

For RF ablation, technical success was assessed on the basis of immediate (percutaneous) or 1-week (intraoperative) post-RF ablation CT with contrast enhancement. Immediate CT was performed usually within 2 hours after contrast-enhanced sonography. When CT showed a nonenhancing area covering the entire target tumor, it was defined as a technical success. When a residual tumor was noted on immediate post-RF ablation CT, the case was regarded as a technical failure, and a second RF ablation session was performed during the same hospitalization. The presence of any complications related to the procedure or the use of the contrast agent was evaluated and recorded for at least 3 days after the procedure.

Statistical Analysis

Detection rates for the target lesions were calculated for grayscale sonography, vascular-phase contrast-enhanced sonography, and Kupffer-phase contrast-enhanced sonography. Comparisons of detection rates among the groups and pair-wise comparisons were performed with the Fisher exact test. For comparisons of lesion conspicuity on grayscale sonography, vascular-phase contrast-enhanced sonography, and Kupffer-phase contrast-enhanced sonography, repeated measures analysis of variance was used, and post hoc analysis with a Bonferroni correction was used for pair-wise comparisons . $P < .05$ was considered statistically significant. Results of the statistical analysis were obtained with commercially available software (MedCalc version 10.1.0.0; MedCalc Software, Mariakerke, Belgium).

Results

Lesion Characteristics

The mean diameter of the target lesions ± SD was 3.0 ± 2.5 cm. The mean diameter of the potential lesions for biopsy was 4.1 ± 2.9 cm, and that of the potential lesions for RF ablation was 1.5 ± 0.6 cm. The mean depth of the target lesions (distance from the skin surface to the closest portion of the lesion) was 4.1 ± 2.0 cm. For the lesions that were not visualized on grayscale sonography (conspicuity score of 1 or 2), the mean lesion diameter measured on the cross-sectional image was 1.7 ± 1.1 cm, and the mean lesion depth was 4.6 ± 2.1 cm. Lesion characteristics are summarized in Table 1.

Lesion Detection

On grayscale sonography, the target lesion was not visualized (conspicuity score of 1 or 2) in 17 of 75 patients (22.7%), very poorly defined (conspicuity score of 3) in 25 (33.3%), and visible (conspicuity score of 4 or 5) in 33 (44.0%). The major presumed reasons for invisibility (score of 1 or 2) was isoechogenicity (n = 15), followed by poor sonic penetration due to a deep-seated lesion (n = 1) and a location near the dome of the liver (n = 1).

On vascular-phase contrast-enhanced sonography, the target lesion was not visualized in 12 of 75 patients (16.0%), very poorly defined (conspicuity score of 3) in 9 (12.0%), and visible in 54 (72.0%). The major presumed reason for invisibility of the lesion (conspicuity score of 1 or 2) was isoechogenicity (n = 6), followed by failed localization (n = 4), inadequate penetration to visualize a deep-seated lesion (n = 1), and a liver dome lesion (n = 1).

On Kupffer-phase contrast-enhanced sonography, the target lesion was not visualized in 6 of 75 patients (8.0%), very poorly defined (conspicuity score of 3) in 7 (9.3%), and visible in 62 (82.7%). The major presumed reason for invisibility of the lesion was isoechogenicity (n = 4), followed by inadequate penetration to visualize a deep-seated lesion (n=1) and a location near the dome of the liver (n = 1).

Of the 17 lesions that were not visualized on grayscale sonography, 9 and 11 were visible on vascular-phase and Kupffer-phase contrast-enhanced sonography, respectively. Of the 12 lesions that were not visualized on vascular-phase contrast-enhanced sonography, 4 and 6 were visible on grayscale sonography and Kupffer-phase contrast-enhanced sonography. Meanwhile, none of the 6 lesions that were not visualized on Kupffer-phase contrast-enhanced sonography were visible on grayscale sonography or vascular-phase contrast-enhanced sonography.

Overall lesion detection rates were 77.3% (58 of 75), 84.0% (63 of 75), and 92.0% (69 of 75) on grayscale sonography, vascular-phase contrast-enhanced sonography, and Kupffer-phase contrast-enhanced sonography, respectively. The detection rates were significantly different among the 3 modalities (Table 2).

Lesion Conspicuity

Overall lesion conspicuity scores were 3.29 ± 1.25, 3.97 ± 1.41, and 4.36 ± 1.18 on grayscale sonography, vascular-phase contrast-enhanced sonography, and Kupffer-phase contrast-enhanced sonography, respectively. Lesion conspicuity was significantly different among the 3 groups and was significantly better on Kupffer-phase contrast-enhanced sonography than on the grayscale sonography or vascular-phase contrast-enhanced sonography, and lesion conspicuity on vascular-phase contrast-enhanced sonography was better than on the grayscale sonography (Table 3).

With respect to potential lesions for biopsy, conspicuity was significantly better on vascular-phase (4.43 ± 0.83) and Kupffer-phase (4.60 ± 0.66) contrast-enhanced sonography than on grayscale sonography (3.67 ± 1.00; Table 3). However, Kupffer-phase contrast-enhanced sonography was not significantly superior to vascular-phase contrast-enhanced sonography. With respect to potential lesions for RF ablation, lesion conspicuity was significantly improved on vascular-phase (3.39 ± 1.77) and Kupffer-phase (4.06 ± 1.58) contrast-enhanced sonography compared to grayscale sonography (2.81 ± 1.38), and lesion conspicuity on Kupffer-phase contrast-enhanced sonography was also better than on the vascular-phase contrast-enhanced sonography (Table 3).

Table 1. Lesion Characteristics (n = 75)

Characteristic	Value
Location, n	
Segment 1	1
Segment 2	1
Segment 3	3
Segment 4	13
Segment 5	24
Segment 6	8
Segment 7	6
Segment 8	19
Diameter, cm	
Range	0.5–10.0
Mean ± SD	3.0 ± 2.5
Depth, cm	
Range	2–9.1
Mean ± SD	4.1 ± 2.0

Table 2. Comparison of Lesion Detection (n = 75)

Modality	Yes, n	No, n	*P*[a]
All			.034[b]
Grayscale sonography	58	17	.409[c]
Vascular-phase contrast-enhanced sonography	63	12	.208[d]
Kupffer-phase of contrast-enhanced sonography	69	6	.022[e]

[a]Fisher exact test.
[b]Comparison of all modalities.
[c]Comparison between grayscale sonography and vascular-phase contrast-enhanced sonography.
[d]Comparison between vascular-phase and Kupffer-phase contrast-enhanced sonography.
[e]Comparison between Kupffer-phase contrast-enhanced sonography and grayscale sonography.

As for the lesions that were not visualized on grayscale sonography (conspicuity score of 1 or 2; n = 17), the mean lesion conspicuity scores were 1.47 ± 0.51, 2.65 ± 1.73, and 3.47 ± 1.91 on grayscale sonography, vascular-phase contrast-enhanced sonography, and Kupffer-phase contrast-enhanced sonography, respectively. Lesion conspicuity was significantly improved after contrast enhancement (Table 4). Six (35.3%) and 11 (64.7%) of the 17 lesions were well shown (conspicuity score of 4 or 5) on vascular-phase and the Kupffer-phase contrast-enhanced sonography (Table 4 and Figure 2). When the lesions that were not visualized or very poorly defined (conspicuity score of 1, 2, or 3; n = 42) were considered, lesion conspicuity was significantly improved on vascular-phase or Kupffer-phase contrast-enhanced sonography compared to grayscale sonography (Table 4 and Figure 3).

Technical Success of Biopsy

Of the 42 patients who were referred for percutaneous biopsy, 1 did not undergo biopsy because it was thought that it would be better to surgically resect the lesion rather than performing a biopsy due to a high suspicion of malignancy after contrast-enhanced sonography, in consensus with the referring clinician and the operating radiologist. The final pathologic diagnosis of that lesion, which was obtained from surgery, was hepatocellular carcinoma. Pathologic results for the biopsy specimens from the remaining 41 patients are summarized in Table 5. Confirmative diagnoses were established in 37 patients. Pathologic results for the remaining 4 lesions were lymphocyte infiltration in patients with esophageal cancer (n = 1), fibrosis in postoperative surveillance of distal common bile duct cancer (n = 1), cholangitis (n = 1), and a sinusoidal lymphocyte (n=1). For these 4 patients, follow-up cross-sectional imaging revealed resolution of the target lesions (n = 3) and lesion progression suggesting metastasis (n = 1). Therefore, the technical success rate of percutaneous biopsy was 95.2% (40 of 42).

Technical Success of RF Ablation

Of the 33 patients who were referred for RF ablation, 8 did not undergo the ablation procedure because of invisibility of the lesion on grayscale and contrast-enhanced sonography due to isoechogenicity (n = 3), a deep-seated lesion (n = 1), a liver dome lesion (n = 1), invisibility due to high-grade obesity and poor sonic penetration (n = 1), and sudden worsening of the patient's underlying general

Table 3. Comparison of Lesion Conspicuity

Lesions	Conspicuity	*P*[a]
All (n = 75)		<.0001[b]
Grayscale sonography	3.29 ± 1.25	<.0001[c]
Vascular-phase contrast-enhanced sonography	3.97 ± 1.41	.004[d]
Kupffer-phase contrast-enhanced sonography	4.36 ± 1.18	<.0001[e]
Biopsy candidates (n = 42)		<.0001[b]
Grayscale sonography	3.67 ± 1.00	.001[c]
Vascular-phase contrast-enhanced sonography	4.43 ± 0.83	.592[d]
Kupffer-phase contrast-enhanced sonography	4.60 ± 0.66	<.0001[e]
RF ablation candidates (n = 33)		<.0001[b]
Grayscale sonography	2.81 ± 1.38	.038[c]
Vascular-phase contrast-enhanced sonography	3.39 ± 1.77	.006[d]
Kupffer-phase contrast-enhanced sonography	4.06 ± 1.58	<.0001[e]

Data are presented as mean ± SD.
[a]Repeated measures analysis of variance and Bonferroni-corrected pairwise comparison.
[b]Comparison among all modalities.
[c]Comparison between grayscale sonography and vascular-phase contrast-enhanced sonography.
[d]Comparison between vascular-phase and Kupffer-phase contrast-enhanced sonography.
[e]Comparison between Kupffer-phase contrast-enhanced sonography and grayscale sonography.

Table 4. Comparison of Conspicuity of Lesions That Were Not Visualized or Very Poorly Defined on Grayscale Sonography

Lesions	Conspicuity	*P*[a]
Not visualized (n = 17)		.0001[b]
Grayscale sonography	1.47 ± 0.51	.016[c]
Vascular-phase contrast-enhanced sonography	2.65 ± 1.73	.103[d]
Kupffer-phase contrast-enhanced sonography	3.47 ± 1.91	.0003[e]
Not visualized or very poorly defined (n = 42)		<.0001[b]
Grayscale sonography	2.38 ± 0.83	<.0001[c]
Vascular-phase contrast-enhanced sonography	3.43 ± 1.58	.003[d]
Kupffer-phase contrast-enhanced sonography	4.05 ± 1.43	<.0001[e]

Data are presented as mean ± SD.
[a]Repeated measures analysis of variance and Bonferroni-corrected pairwise comparison.
[b]Comparison among all modalities.
[c]Comparison between grayscale sonography and vascular-phase contrast-enhanced sonography.
[d]Comparison between vascular-phase and Kupffer-phase contrast-enhanced sonography.
[e]Comparison between Kupffer-phase contrast-enhanced sonography and grayscale sonography.

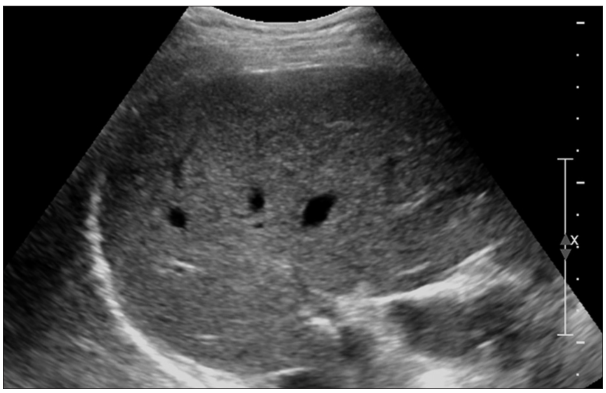
condition (bleeding tendency [n = 1] and bradycardia [n = 1]). Radiofrequency ablation was performed in the remaining 25 patients. On CT performed immediately after RF ablation, there were 2 cases of insufficient treatment due to mistargeting of the lesion (n = 1) and the presence of a residual viable tumor (n = 1). Therefore, the technical success rate of RF ablation was 69.7% (23 of 33).

Complications

There were no major procedure-related complications requiring additional treatment or hospitalization. A minor complication was pain at the needle or RF electrode entry site, which was self-limiting. Also, there were no complications related to the use of the ultrasound contrast agent.

A

B



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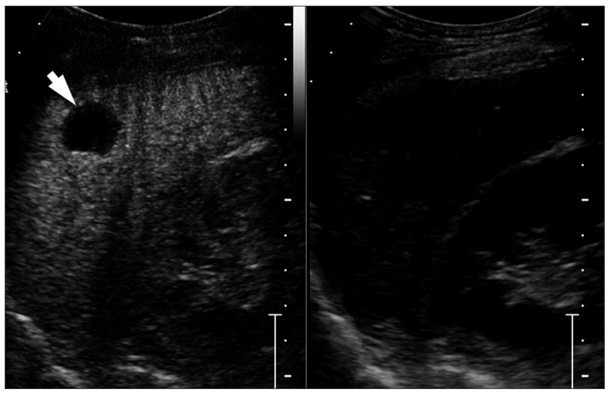

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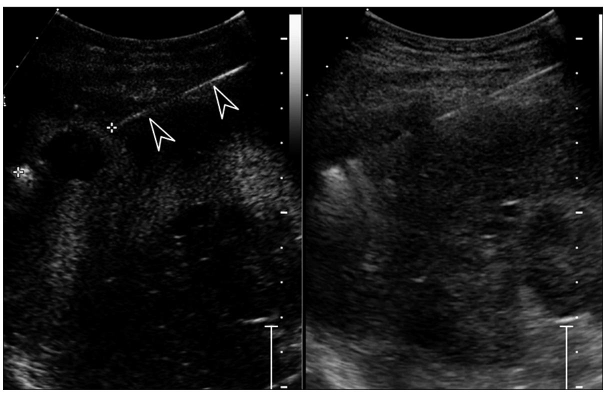


E

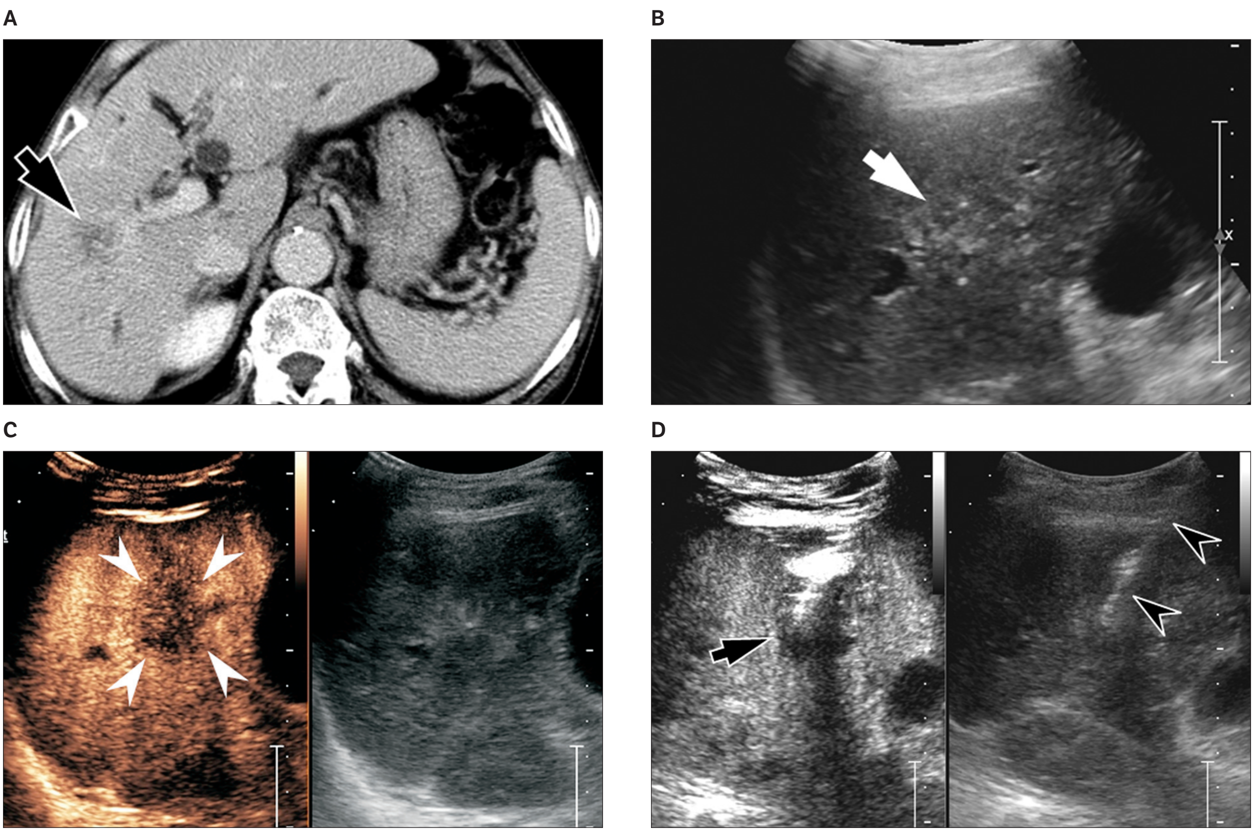
Figure 2. Hepatic metastasis from colon cancer in a 49-year-old man. **A**, Axial contrast-enhanced CT showing a low-density nodule in segment 6 of the liver (arrow). **B**, Grayscale sonogram in the transverse plane, which did not localize the target lesion (conspicuity score of 1). **C**, Split-screen sonogram in the same plane clearly showing a 1.6-cm hypoechoic nodule during the Kupffer phase (left, arrow; conspicuity score of 5). **D**, Radiofrequency electrode passing through the center of the nodule under contrast-enhanced sonographic guidance (arrowheads). **E**, Enhanced CT obtained immediately after RF ablation showing that the metastatic lesion was completely ablated (arrow).

Discussion

Our results demonstrated that the conspicuity of target lesions in the liver on sonography was significantly increased after contrast enhancement using Sonazoid. The mean lesion conspicuity scores were 3.29, 3.97, and 4.36 on grayscale sonography, vascular-phase contrast-enhanced sonography, and Kupffer-phase contrast-enhanced sonography, respectively. Improved lesion conspicuity was achieved on both vascular-phase and Kupffer-phase contrast-enhanced sonography, with statistical significance. In addition, 35.3% and 64.7%, of the lesions that were not shown on grayscale sonography were confidently visualized on vascular-phase and Kupffer-phase contrast-enhanced sonography, respectively.

A couple of requirements need to be met for the use of sonography in guidance of procedures such as biopsy and local ablation therapy. First, confident visualization and clear demarcation of the target lesion are necessary.[1,25] Biopsy of a lesion with poor conspicuity has the risk of mistargeting or obtaining a sample volume that is too small for making a pathologic diagnosis, which leads to repeated biopsies of an invasive nature and additional costs.[25] In addition, during a local ablation procedure, precise insertion of the RF electrode through the center of the target lesion is necessary for achieving a complete ablation as well as for minimizing additional unnecessary overlapping ablation sessions. In our study, of the 22 candidate lesions for RF ablation that were not visualized or very poorly defined (conspicuity score 1, 2, or 3) on grayscale sonography, 13 (59.1%) were well visualized on Kupffer-phase contrast-

Figure 3. Intrahepatic cholangiocarcinoma in a 74-year-old woman. **A**, Axial contrast-enhanced CT showing a poorly defined low-density lesion in segment 5 of the liver (arrow). **B**, Grayscale sonogram in the transverse plane showing a very indistinct hyperechoic area, presumed to be the target lesion (arrow; conspicuity score of 3). **C**, Split-screen contrast-enhanced sonogram in the same plane showing a hypoechoic lesion with increased conspicuity on the Kupffer-phase image (left, arrow; conspicuity score of 5). **D**, Biopsy was performed under real-time Kupffer-phase contrast-enhanced sonographic guidance. The biopsy needle (right, arrowheads) on the grayscale sonogram passes through the center of the target lesion (left, arrow).



enhanced sonography, and 12 were successfully treated (1 lacked an appropriate route for electrode insertion). Second, continuous visualization of the target lesion for sonographically guided targeting should be ensured. This factor is especially true when the target lesion is located deeply or in the dome portion and its visualization is dependent on the patients' respiration. Even though the overall lesion conspicuity was significantly better on vascular-phase contrast-enhanced sonography than on the grayscale sonography in our study, the utility of vascular-phase imaging was limited because of its short duration for satisfactory guidance of the procedure. Skills and experience are required for vascular-phase contrast-enhanced sonography to visualize enhancing hepatic lesions and to insert the biopsy needle or RF electrode via the most safe and appropriate route.[6] In our study, among the lesions that were not visualized on grayscale sonography, 4 were not localized on vascular-phase contrast-enhanced sonography because the vascular phase had passed during the course of lesion localization. On the other hand, Kupffer-phase contrast-enhanced sonography lasted for at least 30 minutes and therefore provided sufficient time for the operating radiologist to select the proper approach and precisely target the index lesions. Therefore, according to our study results, Kupffer-phase contrast-enhanced sonography using Sonazoid is beneficial not only in terms of lesion conspicuity but also in terms of long-lasting visibility of the lesion in guiding the procedure. Certainly, it might be technically feasible to perform the procedure for lesions that are not visualized or very poorly defined on grayscale sonography only in a sterotactic manner based on an anatomic landmark judged from previous cross-sectional images. However, this process is possible only for very highly experienced operators, and even in those cases, the risk of mistargeting or insufficient tissue sampling still exists.[1]

In our study, 11 hepatocellular carcinoma lesions were referred for complementary RF ablation after transarterial chemoembolization due to incomplete retention of iodized oil within the tumors. The mean lesion conspicuity was poor (2.59 ± 1.14) on grayscale sonography, and 9 of 11 lesions (81.8%) were not visualized or very poorly defined. According to a previous report on grayscale sonography of hepatocellular carcinoma after transarterial chemoembolization, lesion conspicuity was maximized immediately after chemoembolization and decreased thereafter, and increased conspicuity was observed only in the compact iodized oil uptake group.[24] Because the interval between transarterial chemoembolization and planning sonography, including contrast-enhanced sonography, was 1 to 3 days, and iodized oil uptake was not compact in the target lesions of our study, poor lesion conspicuity on grayscale sonography was expected. However, Kupffer-phase contrast-enhanced sonography allowed for clear depiction of the target lesion and successful treatment in 64.6% (5 of 9). Although fluoroscopy is also useful in guiding RF ablation of hepatocellular carcinoma nodules after transarterial chemoembolization, due to the radiopacity created by iodized oil retention, its utility is limited in small lesions and poor radiopacity caused by noncompact iodized oil retention. Ensuring lesion conspicuity on sonography is also necessary even with good visibility on fluoroscopy to avoid injury to the hepatic vessels or adjacent organs along the course of the electrode passage. For further differentiation between the viable tumor portion and the avascular tumor portion indicated by iodized oil retention, application of the defect reinjection method introduced by Minami et al[6] may be helpful.

Among the 17 lesions that were not visible on grayscale sonography, 6 (35.3%) were not visible after contrast enhancement on vascular-phase or Kupffer-phase imaging. The presumed reason for the invisibility of the lesions on contrast-enhanced sonography was isoechogenicity in 4 patients and attenuated echogenicity due to a deep-seated lesion (segment 7) in 1 patient. As a result, the procedure was not performed for the 4 lesions, and 1 lesion was falsely targeted. The pathologic types of the

Table 5. Final Pathologic Diagnoses From Biopsy (n = 41)

Final Diagnosis	n
Malignancy	
Primary hepatic malignancy	
Hepatocellular carcinoma	6
Cholangiocarcinoma	6
Metastasis	
Pancreatic cancer	7
Lung cancer	2
Colon cancer	2
Gallbladder cancer	1
Breast cancer	1
Adrenal cancer	1
Urothelial cancer	1
Prostate cancer	1
Benign	
Benign neoplasm	
Focal nodular hyperplasia	3
Hepatic adenoma	1
Non-neoplastic lesion	
Lymphocyte infiltration	3
Abscess	2
Focal fat infiltration	2
Fibrosis	1
Cholangitis	1

4 lesions that were not visualized due to isoechogenicity were hepatocellular carcinoma on underlying cirrhotic liver (n = 3) and metastasis from colon cancer (n = 1), which were referred for RF ablation. According to a previous report investigating contrast-enhanced sonography using Sonazoid for diagnosis of hepatocellular carcinoma, most well-differentiated hepatocellular carcinomas were isoechoic on Kupffer-phase imaging, whereas moderately or poorly differentiated hepatocellular carcinomas showed low echogenicity because most well-differentiated hepatocellular carcinomas contained Kupffer cells that were similar in number to the adjacent hepatic parenchyma.[16] Although we did not obtain pathologic diagnoses for those 3 hepatocellular carcinoma lesions, isoechogenicity on Kupffer-phase contrast-enhanced sonography suggests the possibility of well-differentiated hepatocellular carcinoma.

Our study had several limitations. First, the patient population was somewhat heterogeneous, including candidates for both biopsy and RF ablation. The pathologic types of the target tumors for RF ablation included both hepatocellular carcinoma and metastasis from colorectal cancer, and the mode of approach was either percutaneous or intraoperative. Hepatocellular carcinoma included post–transarterial chemoembolization tumors, which can present alterations in the vascularization on contrast-enhanced sonography. However, in terms of improved lesion conspicuity on Kupffer-phase contrast-enhanced sonography for the purpose of guiding the procedure, the results were consistent irrespective of the differences in the patient population. Second, the lesion conspicuity scoring on grayscale and contrast-enhanced sonography was performed by a single radiologist, which may have been affected by subjectivity and bias.

In conclusion, Kupffer-phase imaging by contrast-enhanced sonography using Sonazoid significantly improves the conspicuity of focal liver lesions compared to grayscale sonography; therefore, it is useful for real-time guidance of percutaneous biopsy or RF ablation of focal liver lesions.

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