The Role of Late-Phase Pulse Inversion Harmonic Imaging in the Detection of Occult Hepatic Metastases

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Objective. The purpose of this study was to investigate the efficacy of late-phase pulse inversion harmonic imaging (PIHI) in detecting occult metastases and to compare the results with helical computed tomography (CT) in a group of patients whose fundamental liver sonographic results were normal. ***Methods.*** Thirty-two patients (21 women and 11 men; age range, 20–87 years) with a known primary malignancy were enrolled in the study. The patients were evaluated with conventional sonography, unenhanced PIHI, and PIHI 3 minutes after the injection of Levovist (SH U 508A; Schering AG, Berlin, Germany). All patients also underwent triphasic helical CT within 1 week after sonography. In 1 patient, mangafodipir-enhanced magnetic resonance imaging was performed as part of the clinical workup. ***Results.*** After Levovist injection, in 4 (12.5%) of 32 patients, at least 1 hypoechoic lesion was detected by PIHI; multiple lesions were shown in 1 patient. The mean diameter of newly detected lesions was 12 mm. Triphasic helical CT also showed all of the lesions that were detected by PIHI. The diagnoses were confirmed by biopsy and CT findings in 2 patients and by the typical CT and magnetic resonance imaging findings in 1 patient. For the fourth patient, the diagnosis was confirmed by follow-up and CT. ***Conclusions***. Late-phase PIHI is comparable to helical CT for detecting occult hepatic metastases, but it protects patients from the potentially hazardous effects of radiation and iodinated contrast agents. Further series involving a larger number of patients are needed to determine its place in the evaluation of cancer staging and treatment planning. ***Key words:*** contrast agent; harmonic imaging; occult hepatic metastases; pulse inversion; sonography.

Abbreviations
CT, computed tomography; MI, mechanical index; Mn-DPDP, mangafodipir; MRI, magnetic resonance imaging; PIHI, pulse inversion harmonic imaging

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The liver is one of the most commonly involved organs in metastatic disease. The accurate detection of metastatic disease at the time of diagnosis or during the course of treatment is crucial for planning surgical, interventional, and medical therapy.

Different imaging modalities are available for the detection of liver metastases, including sonography, computed tomography (CT), magnetic resonance imaging (MRI), and scintigraphy. Sonography is convenient, quick, and inexpensive and therefore is a widely used imaging modality in the detection of liver metastases. Despite its routine clinical use, it also has several potential drawbacks that diminish its sensitivity and accuracy in assessing hepatic metastases compared with dual-phase CT and MRI.[1] Its operator dependency and the lower sensi-

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tivity of detection of either small (the sensitivity for detecting lesions <1 cm is only 20%) or isoechoic lesions may be counted among its disadvantages.[2] A technique that could increase the lesion-to-liver contrast difference would therefore be of great value in increasing the sensitivity of sonography.

In the past few years, the use of microbubble contrast agents and the development of contrast-specific techniques have greatly improved the ability of sonography to detect liver metastases.[3–8] These techniques generate images based on the nonlinear and transient acoustic effects of microbubble contrast agents. They offer high sensitivity to microbubble movement or destruction. Pulse inversion harmonic imaging (PIHI), also called wideband harmonic imaging, is a contrast-specific imaging technique. It works by sending 2 sets of pulses that are out of phase with each other and summing the returning echoes. The linear signals from 2 pulses cancel each other, and only nonlinear harmonic signals, especially those from microbubbles, are visualized.[9]

Levovist (SH U 508A; Schering AG, Berlin, Germany) is a galactose-based contrast agent composed of microparticles in which microbubbles of air have been trapped. The microbubbles are stabilized by palmitic acid for the passage of particles through the pulmonary capillaries. After intravenous injection, it produces systemic enhancement of Doppler signals for 3 to 5 minutes.[10] In addition to its vascular phase, Levovist also has a late hepatosplenic-specific parenchymal phase after blood pool clearance.[11] In this phase, the microbubbles are stationary in liver and spleen parenchyma, probably pooled in sinusoids or phagocytosed by the reticuloendothelial system. Because microbubbles are stationary in this phase, they cannot be detected with conventional gray scale or Doppler sonography. Contrast-specific techniques such as the pulse inversion mode or stimulated acoustic emission, as discussed above, must be used.[3] On PIHI, hepatic malignancies are seen as defects surrounded by intensely enhanced parenchyma during the late phase of contrast enhancement with Levovist.[9]

The aim of this study was to investigate the efficacy of late-phase pulse inversion sonography in detecting occult liver metastases that were not visible during routine sonographic examination and to compare the results with helical CT findings.

Materials and Methods

During a 4-month period in 2002, 32 patients (21 women and 11 men; age range, 20–87 years; mean age, 51 years) were enrolled in this study. These patients had known primary malignancies that were diagnosed during the previous year and had no liver metastases on routine transabdominal sonography. The histopathologic diagnoses of primary malignancies were as follows: carcinoma of the breast (n = 11), adenocarcinoma of the colon (n = 7), adenocarcinoma of the stomach (n = 2), ovarian carcinoma (n = 2), cervix carcinoma (n = 3), small cell carcinoma of the lung (n = 1), bladder carcinoma (n = 1), renal cell carcinoma (n = 1), testicular yolk sac tumor (n = 1), malignant stromal tumor (n = 1), epitheloid sarcoma (n = 1), and Klatskin tumor (n = 1). Children, pregnant women, and patients with renal insufficiency or galactosemia were excluded from the study. Ethics Committee approval and informed consent of each patient were obtained.

All patients were evaluated with both conventional B-mode sonography and PIHI. Pulse inversion harmonic imaging was performed before and after intravenous administration of Levovist. The patients also underwent contrast-enhanced triphasic helical CT examinations within 1 to 7 days after sonographic imaging. In 1 patient, MRI examination with mangafodipir (Mn-DPDP) was also performed as a part of clinical workup.

All sonographic examinations were done by the same radiologist (C.Y.), who had 10 years' experience in sonography, using an HDI 5000 scanner (Philips Medical Systems, Bothell, WA) with a 2- to 5-MHz broadband convex array transducer. First, the liver was scanned by fundamental B-mode sonography. With no lesions detected on conventional sonography, the patients were then examined with PIHI before Levovist administration. The standard scanning parameters for PIHI were selected (mechanical index [MI], 1.2–1.3; persistence, off; line density, low; and frame rate, low), and then the whole liver was scanned from right to left sagittally or from superior to inferior transversely depending on the location of the lesion before the administration of the contrast agent. A single focus was used, and the focal zone was kept at the deep third of the image. The contrast agent (Levovist) was prepared by shaking for 10 seconds after the addition of 11 mL of saline. After a delay of 2 minutes, all patients received a 4-g bolus injection of Levovist through an 18-gauge

peripheral intravenous cannula; immediately afterward, the cannula was flushed with 10 mL of saline. Three minutes after the bolus injection of Levovist, PIHI was again performed with the same parameters. Scanning parameters were kept constant in all examinations. Sweeps were stored as cine loops for later evaluation. The digitally stored movie files were reviewed with dedicated software (HDI-Lab; Philips Medical Systems).

In all cases, triphasic helical CT examinations were performed with a HiSpeed Advantage CT/I system (GE Healthcare, Milwaukee, WI). The imaging parameters were set as follows: collimation, 5 to 7 mm; interval, 7 mm; pitch, 1; and power settings, 170 mA and 120 kV. Contrast-enhanced CT scans were acquired 20 seconds (arterial phase), 60 seconds (portal phase), and 5 minutes (parenchymal phase) after bolus injection of 130 to 150 mL of nonionic iodinated contrast material (iopamidol at a concentration of 300 mg/mL or iohexol at 300 mg/mL) at a rate of 4 mL/s.

In 1 patient, MRI was also performed with a 1-T Signa Horizon System (GE Healthcare) with a body coil. After unenhanced T1- and T2-weighted spin echo sequences in axial and coronal planes, Teslascan (Mn-DPDP; Amersham Health, Oslo, Norway) at a concentration of 0.01 mmol/mL was administered to the patient at a dose of 0.5 mL/kg through a peripheral cannula at a rate of 2 to 3 mL/min. Twenty minutes after the injection of the contrast agent, gradient-recalled echo T1-weighted sequences in the axial and coronal planes were obtained.

The sonographic images were reviewed by 2 experienced radiologists (S.G. and H.Ö.) who were blinded to the patients' data. These observers were asked to note the presence of any lesions that were not seen on fundamental sonography or precontrast PIHI but became apparent on PIHI after Levovist administration. Helical CT and, in 1 patient, MRI findings were noted separately by 2 other radiologists (M.A. and H.Ç.) who were blinded to the sonographic findings and clinical history of the patients. The number and location of detected lesions were noted by each reviewer according to the Couinaud system.[12]

Results

No unexpected adverse effect was observed after administration of Levovist and nonionic iodinated contrast material. Scanning time per patient was 8 to 15 minutes.

After Levovist administration, a strong and transient enhancement was observed in the liver parenchyma in all cases. In all 32 patients, no metastatic lesions were detected on fundamental sonography and PIHI before Levovist injection. In 4 patients (12.5%), late-phase PIHI after Levovist administration revealed lesions that were not apparent on unenhanced scans (Table 1). These lesions appeared hypoechoic in comparison with enhanced normal liver parenchyma. The primary malignancies of these 4 patients were carcinomas of the stomach, lung, colon, and ovary. In the patient with colon carcinoma, 2 lesions, 12 and 14 mm in diameter and located in segments 5 and 8, respectively, were depicted (Figure 1). The patient with gastric carcinoma had 1 metastatic lesion, 14 mm in diameter, located in segment 2 (Figure 2). In the patient with ovarian carcinoma, 1 lesion, 10 mm in diameter, was shown in segment 2. Numerous lesions located in every segment of the liver were detected in the patient with lung carcinoma (Figure 3). All of these lesions detected only on late-phase PIHI after Levovist injection were subsequently confirmed on triphasic helical CT examination. The lesions appeared hypodense surrounded by enhanced normal liver parenchyma on CT. Because of the equivocal findings on CT examination in the patient with ovarian carcinoma, an MRI examination that led to confirmation of the diagnosis was also performed.

Among the 4 patients with lesions detected only on late-phase PIHI after Levovist administration, biopsies were done to confirm the diagnosis in 2 patients with colon and lung carcinoma. The final diagnosis was made on the basis of follow-up and characteristic CT findings in the patient with gastric carcinoma. In the patient with ovarian carcinoma, the final diagnosis was determined by typical CT and MRI findings (Table 1).

Table 1. Characteristics of the Lesions Visualized Only on PIHI

Case	Primary Malignancy	Final Diagnosis	No. of Lesions	Lesion Diameter, mm
1	Lung carcinoma	Biopsy	>10	27 (largest diameter)
2	Gastric carcinoma	Follow-up CT	1	14
3	Colon carcinoma	Biopsy	2	14, 12
4	Ovarian carcinoma	CT, MRI	1	10

Figure 1. Metastatic colon carcinoma in a 45-year-old woman. Postcontrast PIHI (**A**) reveals a hypoechoic lesion (arrow) against enhancing hepatic parenchyma in segment 5. Although not obvious, retrospective evaluation of precontrast PIHI (**B**) shows a questionable isoechoic lesion at the same location (arrow). On postcontrast helical CT (**C**), the lesion is hypodense (arrow).

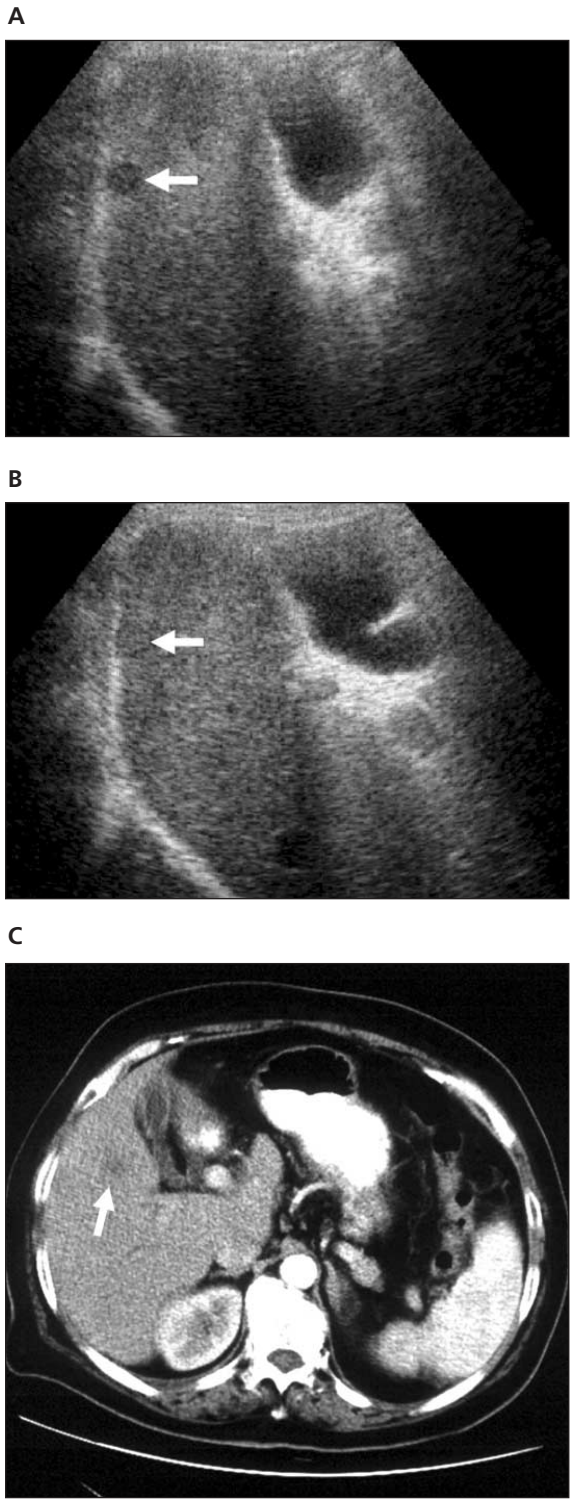


Figure 2. Metastatic gastric carcinoma in a 54-year-old man. A lesion (arrow) in segment 2 that is not apparent on precontrast PIHI (**A**) is shown on postcontrast PIHI (**B**). The lesion enhances intensively (arrow) on postcontrast helical CT (**C**), consistent with hypervascular metastasis.

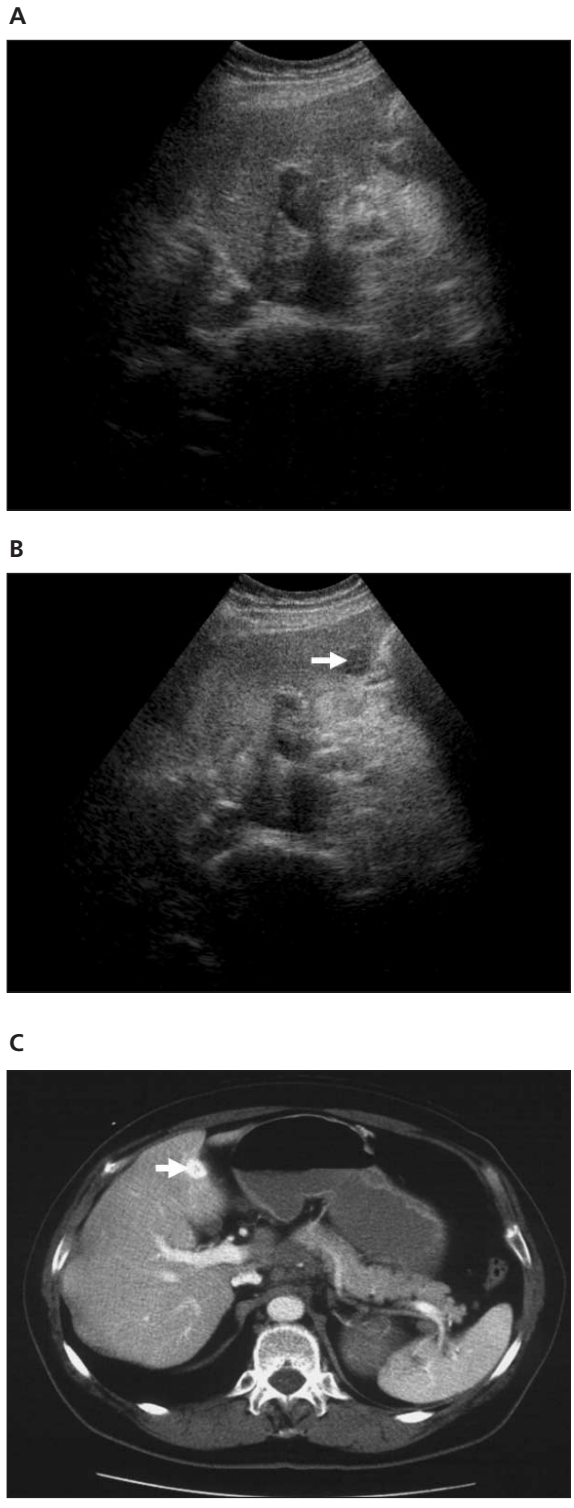
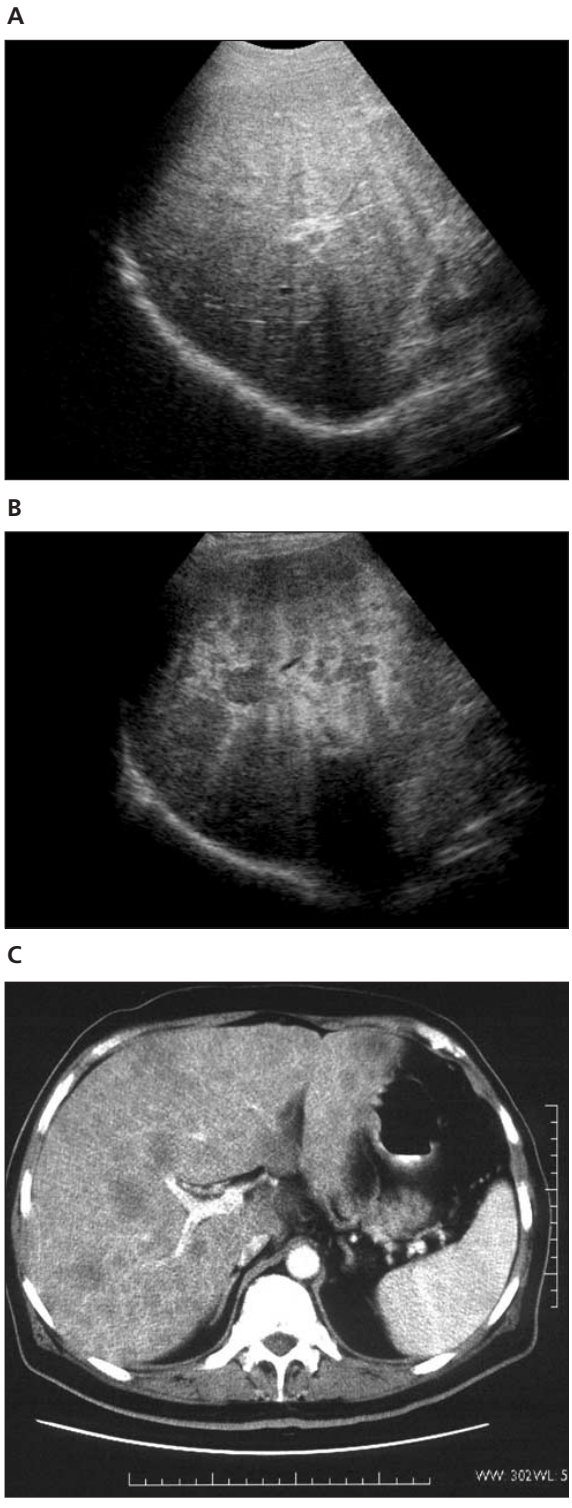


Figure 3. Metastatic lung carcinoma in a 45-year-old man. Precontrast PIHI (**A**) shows heterogeneous hepatic parenchyma. Postcontrast PIHI (**B**) shows multiple metastases confirmed by postcontrast helical CT (**C**).



The results of our study showed that the sensitivity and specificity of the late-phase PIHI after Levovist administration were 100%, the same as those of triphasic helical CT examination.

Discussion

Early diagnosis of metastatic disease is crucially important in liver imaging. Pulse inversion harmonic imaging, a recently introduced sonographic technique, has been shown to improve the depiction of liver metastases, and PIHI coupled with the administration of a sonographic contrast agent improves the quality of the examination. Contrast-enhanced PIHI is particularly useful in detecting small and isoechoic metastases.

Levovist is a sonographic contrast agent that may be used effectively to increase the sensitivity and specificity of sonographic examinations. Homogeneous parenchymal uptake of Levovist in the liver-specific late phase is a useful indicator of benign hepatic lesions. Primary liver malignancies and liver metastases show little or no late-phase uptake of contrast material because of the absence of normal sinusoids or reticuloendothelial cells in malignancies. Thus liver malignancies appear as hypoechoic lesions surrounded by normal liver parenchyma, which becomes more echogenic as a result of the accumulation of contrast agent microbubbles.

In our institution, sonography is generally the first imaging modality used for the detection of possible metastatic liver lesions in patients with known malignancies; CT and MRI are reserved for patients for whom conventional sonography is equivocal. Our study depicted improved lesion detection with Levovist in late-phase PIHI in 4 patients (12.5%) in whom lesions were not apparent on the precontrast imaging. This finding is notable given the importance of accurate staging of patients with malignant disorders for selection of appropriate treatment strategies. Previous studies have also revealed improved conspicuity of lesions with contrast-enhanced PIHI compared with conventional sonography in patients with malignancies[3–8]; however, those examinations were performed in patients with known or suspected liver metastasis. Unique to our study was the detection of lesions that were undetectable on routine conventional abdominal sonography. These results underscore the accuracy of late-phase PIHI with contrast for accurate patient evaluation and treatment planning.

We also investigated the ability of late-phase PIHI to detect liver metastases in comparison with helical CT. Except for 1 patient in whom spiral CT findings were equivocal, spiral CT depicted all of the lesions in the 4 patients with documented metastasis on late-phase PIHI. In the patient with equivocal CT findings, the lesion was located at the most superior part of segment 2, and liver-specific contrast-enhanced (Mn-DPDP) MRI with multiplanar sections confirmed the presence of the lesion revealed by late-phase PIHI. Although we could not confirm, in previous reports it has been noted that in some cases, late-phase PIHI detected more lesions than spiral CT.[3,6,7,13] Esteban et al[6] reported a higher sensitivity of postcontrast PIHI over a CT examination for the detection of liver metastases. If this finding is confirmed in larger trials, PIHI may influence or perhaps change imaging protocols for tumor staging. Harvey et al[3] stated that PIHI may also be of value in segmental liver resection by helping detection of occult neoplastic disease, thus directing the surgical intervention site.

Findings in previous studies documented that both subjective and objective conspicuities of liver malignancies are increased in late-phase PIHI compared with fundamental sonography.[3,6,7,13] Similarly, in our study we reported new lesions on late-phase PIHI in 4 patients (12.5%). In 3 of them, new lesions detected with PIHI were barely seen on a retrospective evaluation of fundamental sonography. These data could be interpreted to indicate that late-phase PIHI increases lesion conspicuity compared with fundamental sonography. When the size of the lesions was analyzed, late-phase PIHI was able to detect smaller lesions in comparison with both fundamental sonography and spiral CT, as reported previously.[3,5–7,13] Yücel et al[13] documented that lesions as small as 3 mm could be detected with late-phase PIHI. In our study, with the exclusion of the patient with multiple metastases, the mean size of the lesions revealed on late-phase PIHI was 12 mm, not different from that of spiral CT (Table 1). This might be explained by our relatively small number of patients (4 of 32) with lesions detected with late-phase PIHI. Although the number of patients in our study was adequate to show that lesion conspicuity is increased with the use of late-phase PIHI, larger series are needed to show whether late-phase PIHI is a sensitive technique for detecting subcentimetric liver metastases.

Despite being a promising technique, late-phase PIHI has some technical disadvantages. The transient nature of late-phase enhancement with Levovist is a limitation of this technique. The high MI used in the late phase of Levovist allows only 1 or 2 sweeps because of the high rate of bubble destruction. In addition to its transience, enhancement on PIHI is limited by the depth and focal zone. The maximum contrast effect is seen at the focal zone. Deeply (>12 cm below the skin surface) or superficially located lesions may decrease the sensitivity of the examination and may cause the radiologist to miss the lesion in a single sweep.

Levovist shows the highest microbubble detectability only at a high MI of the ultrasound beam, which also destroys microbubbles in the examined area. With the current high-MI technique, a part of the liver can be visualized in only 1 or 2 sweeps because of rapid bubble depletion. This problem may be solved by the use of other sonographic contrast agents, such as second-generation fluorocarbon agents, which have more stabilized microbubbles of sulfur hexafluoride gas. After intravenous injection, these microbubbles stay in circulation for a long time and produce nonlinear (harmonic) signals even at very low MI values (<0.1).[14] Similar to dynamic CT examinations with iodine contrast media, it becomes possible to perform sonographic dynamic examinations at a low MI with the use of second-generation fluorocarbon agents, such as for the characterization of focal liver lesions. Because of their ability to provide a reliable assessment of vascularity, contrast-specific sonographic techniques and second-generation sonographic contrast agents, such as the sulfur hexafluoride contrast agent BR1 (SonoVue; Bracco SpA, Milan, Italy), seem to have the potential to become valuable tools in screening for liver metastases.[15]

For the lesions seen only in late-phase PIHI, sonographic biopsies are difficult because the contrast effect of Levovist is brief. The small size of the lesions also makes it difficult to perform biopsies. Although the examiners assigned the lesions to their Couinaud segments, comparison of longitudinal sonographic images with axial CT scans may be a potential source of error. In our study, biopsies could be performed in 2 of the patients because of the size and accessibility of their lesions.

In conclusion, late-phase PIHI seems comparable to helical CT in the detection of occult hepatic metastases, but it protects patients from the potentially hazardous effects of radiation and iodinated contrast agents. Further series involving a larger number of patients are needed to determine its place in the evaluation of accurate cancer staging and treatment planning.

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