Characterization of Hyperechoic Focal Liver Lesions

Quantitative Evaluation With Pulse Inversion Harmonic Imaging in the Late Phase of Levovist

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Objective. The aim of this study was to evaluate hyperechoic focal liver lesions with pulse inversion harmonic imaging in the late phase of SH U 508A (Levovist; Schering AG, Berlin, Germany) and to determine whether quantitative evaluation improves the characterization of the lesions. ***Methods.*** Twenty-six patients with hyperechoic liver lesions were enrolled in this study. Pulse inversion harmonic imaging was performed before and after administration of Levovist. Scan data were digitally stored, and each lesion was analyzed with a personal computer–based quantification package. All lesions were confirmed by histologic or triphasic spiral computed tomographic examinations. The intensity was measured in decibels in regions of interest drawn within the lesion and surrounding liver parenchyma. The lesion-liver ratios were than calculated. After contrast agent administration, a ratio equal to or greater than 1 was presumed benign, whereas a ratio of less than 1 was considered malignant. ***Results.*** Nine malignant (7 metastases, 1 hepatocellular carcinoma, and 1 cholangiocarcinoma) and 17 benign (14 hemangioma, 1 focal nodular hyperplasia, 1 focal fatty change, and 1 inflammatory pseudotumor) hyperechoic lesions were quantitatively evaluated. All malignant (n = 9) and 2 benign lesions (1 hemangioma and 1 inflammatory pseudotumor) had ratios of less than 1. In 15 of 17 benign lesions, the ratios were equal to or greater than 1. The intensity ratios calculated for benign and malignant lesions showed a statistically significant difference ($P < .05$). ***Conclusions.*** Pulse inversion harmonic imaging with quantitative evaluation facilitates the differential diagnosis of hyperechoic focal liver lesions. A lesion-liver ratio equal to or greater than 1 predicts a benign nature, assuming that malignant lesions show a ratio of less than 1. ***Key words:*** contrast media; hyperechoic liver tumors; pulse inversion harmonic imaging; ultrasonography.

Abbreviations
CT, computed tomographic; FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma; PIHI, pulse inversion harmonic imaging; ROI, region of interest

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Ultrasonography is generally the first imaging modality of choice for the primary evaluation of focal liver lesions; however, the B-mode ultrasonographic features of benign and malignant lesions are often not clear-cut and generally overlap.[1] Early detection and characterization of focal liver lesions will improve the success rate of surgical resection, percutaneous ablation therapy, or chemotherapy.

The ultrasonographic contrast agent SH U 508A (Levovist, Schering AG, Berlin, Germany) is a suspension of galactose-based microbubbles and contains 99.9% D-galactose and 0.1% palmitic acid. It provides reproducible concentrations of stabilized air containing bubbles that are small enough to pass the pulmonary capillary bed. As a result, blood echogenicity in the arte-

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rial system is increased by 10 to 20 dB.[2] Levovist also accumulates in normal liver and spleen tissue at a late parenchymal-specific phase.[3–5]

Pulse inversion harmonic imaging (PIHI) or phase inversion harmonic imaging is used to detect contrast effects in the late parenchymal-specific phase. This technique uses 2 separated pulses that are phase shifted by 180° for 1 image frame. Linear signals from 2 pulses will cancel each other, and the image will be produced by nonlinear echoes. Pulse inversion harmonic imaging produces a considerable B-mode enhancement of the liver parenchyma in the late phase of Levovist with an excellent spatial and temporal resolution.[4]

The aim of this study was to evaluate hyperechoic focal liver lesions with PIHI in the late phase of Levovist and to determine whether quantitative evaluation improves the characterization of the lesions.

Materials and Methods

During a 3-month period, 26 patients (14 male and 12 female; age range, 40–73 years; mean age, 53 years) with hyperechoic liver lesions were enrolled in this study. Ethics Committee approval and informed consent of each patient were obtained. Fourteen of the patients had histopathologically proven extrahepatic malignancies; the diagnoses were carcinoma of the breast (n = 3), adenocarcinoma of the colon (n = 3), ovarian carcinoma (n = 1), adenocarcinoma of the lung (n = 1), large-cell neuroendocrine carcinoma of the lung (n = 1), epidermoid carcinoma of the lung (n = 1), sarcoma of the lung (n = 1), neuroendocrine carcinoma of the pancreas (n = 1), malignant mesenchymal tumor of the intestine (n = 1), and adenocarcinoma of the anal canal (n = 1). Four patients were undergoing follow-up for probable liver hemangioma, and in 8 patients, the lesions were detected during routine abdominal ultrasonography.

All patients were evaluated with both conventional B-mode ultrasonography and PIHI. Pulse inversion harmonic imaging was performed before and after intravenous administration of Levovist. The patients also underwent contrast-enhanced triphasic helical computed tomographic (CT) examinations within 1 to 7 days after ultrasonographic imaging.

All ultrasonographic examinations were done by the same radiologist (H.Ö.) 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 ultrasonography. The segmental site of each lesion was noted in accordance with the Couinaud classification.[6] The standard scanning parameters for PIHI were selected (mechanical index, 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 because of the location of the lesion before the contrast agent administration. 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, and 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 scan data were analyzed with a personal computer–based quantification package (HDILab; 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, 7 to 10 mm; interval, 10 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 1.5-mL/kg nonionic iodinated contrast material (300-mg/mL iopamidol or 300-mg/mL iohexol) at a rate of 3 mL/s.

The ultrasonographic images were reviewed by 2 experienced radiologists (H.C. and C.Y.) who were blinded to the patients' data. The evaluated parameters were the number of visible lesions, the presence of rim enhancement, and the diameter of the lesions. Helical CT findings were separately noted by 2 other radiologists (M.A. and S.G.) who were blinded to the ultrasonographic findings.

Nine malignant (7 metastases, 1 hepatocellular carcinoma [HCC], and 1 peripheral cholangiocarcinoma) and 17 benign (14 hemangioma, 1 focal nodular hyperplasia [FNH], 1 focal fatty

change, and 1 inflammatory pseudotumor) hyperechoic lesions were quantitatively evaluated. Regions of interest (ROIs) of the same size were placed inside the lesion and at the surrounding ultrasonographically normal liver parenchyma free of hepatic vessels, and ultrasonographic artifacts both in the precontrast and postcontrast images and quantitative measurements were recorded. Because the amount of bubble destruction and therefore echogenicity depends on focalization of the ultrasound beam, ROIs inside the lesion and at the neighboring liver parenchyma were placed at the same depth. Measurements were done from the central portion of the lesions, and the lesions having smaller diameters were almost nearly contained in the ROI. All calculations of signal intensity values were performed with the use of the logarithmic scale (decibels) for matching intensity differences perceivable by the human eye as different gray levels. In all cases, the relative intensity of the lesion to the liver parenchyma intensity (lesion-liver ratio) and the difference between the signal intensity measured in the lesion and the liver parenchyma (lesion-minus-liver intensity), representing precontrast and postcontrast examinations, were calculated. After contrast agent administration, a lesion-liver ratio equal to or greater than 1 was presumed benign, whereas a ratio of less than 1 was considered an indicator of malignancy.

After the radiologic examinations, biopsies were performed in 8 patients (4 with metastases, 1 with cholangiocarcinoma, 1 with HCC, 1 with an inflammatory pseudotumor, and 1 with hemangioma with atypical imaging features) on the basis of imaging characteristics of the lesions. In 17 patients, the final diagnosis was made on the basis of characteristic CT findings, and in 1 patient, the diagnosis was made on the basis of characteristic CT findings supported by color Doppler examination. In 5 of these 18 patients, the 6- to 12-month follow-up ultrasonographic and CT examinations revealed no evidence of changes in lesion size and appearance. The lesions in patients without any known primary malignancy having typical ultrasonographic and tomographic features of benign lesions were presumed to be benign lesions, and those having atypical ultrasonographic and tomographic features were referred for biopsy. In 3 patients with metastasis, the final diagnosis was reached on the basis of the typical imaging and clinical findings of the patients with previously diagnosed primary malignancies and known widespread multiorgan metastasis. The final diagnosis of FNH was made on the basis of characteristic CT findings supported by color Doppler examination. Thirteen of 14 cases of hemangioma were diagnosed on the basis of typical ultrasonographic and tomographic findings. In 5 of these 13 patients with hemangioma, who had primary extrahepatic malignancy, the 6- to 12-month follow-up ultrasonographic and CT examinations revealed no evidence of changes in lesion size and appearance.

Statistical analysis was done by the Mann-Whitney and Wilcoxon tests. $P = .05$ was considered significant.

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.

Triphasic helical CT examinations revealed single or multiple focal hepatic lesions in all 26 patients. One lesion was observed in 14 patients; 2 to 4 were observed in 7 patients; and more than 4 were observed in 5 patients. For each patient, a marker lesion was chosen for subjective and objective assessment. The lesions for biopsy were chosen for the final analysis (n = 8). In the remaining patients, the observer chose a marker lesion that was seen without difficulty on fundamental and precontrast PIHI to ensure that the contrast enhancement of the lesion could be evaluated. The diameter of the marker lesions varied between 1 and 6.5 cm (mean, 2.5 cm; SD, 1.48 cm) and were chosen among the ones that were within 12 cm of the skin surface.

Conventional ultrasonography and precontrast PIHI showed the same number of lesions shown by helical CT examinations. In 2 patients with metastasis, postcontrast PIHI revealed more lesions than the other mentioned imaging modalities. In 4 patients with benign lesions (1 FNH and 3 hemangioma), postcontrast PIHI missed these lesions because they became isoechoic to the liver parenchyma subjectively and objectively.

On fundamental and precontrast PIHI, all lesions were hyperechoic and had a lesion-liver ratio of greater than 1. On precontrast PIHI, the mean lesion-minus-liver intensity was 6.19 dB (SD, 3.28 dB).

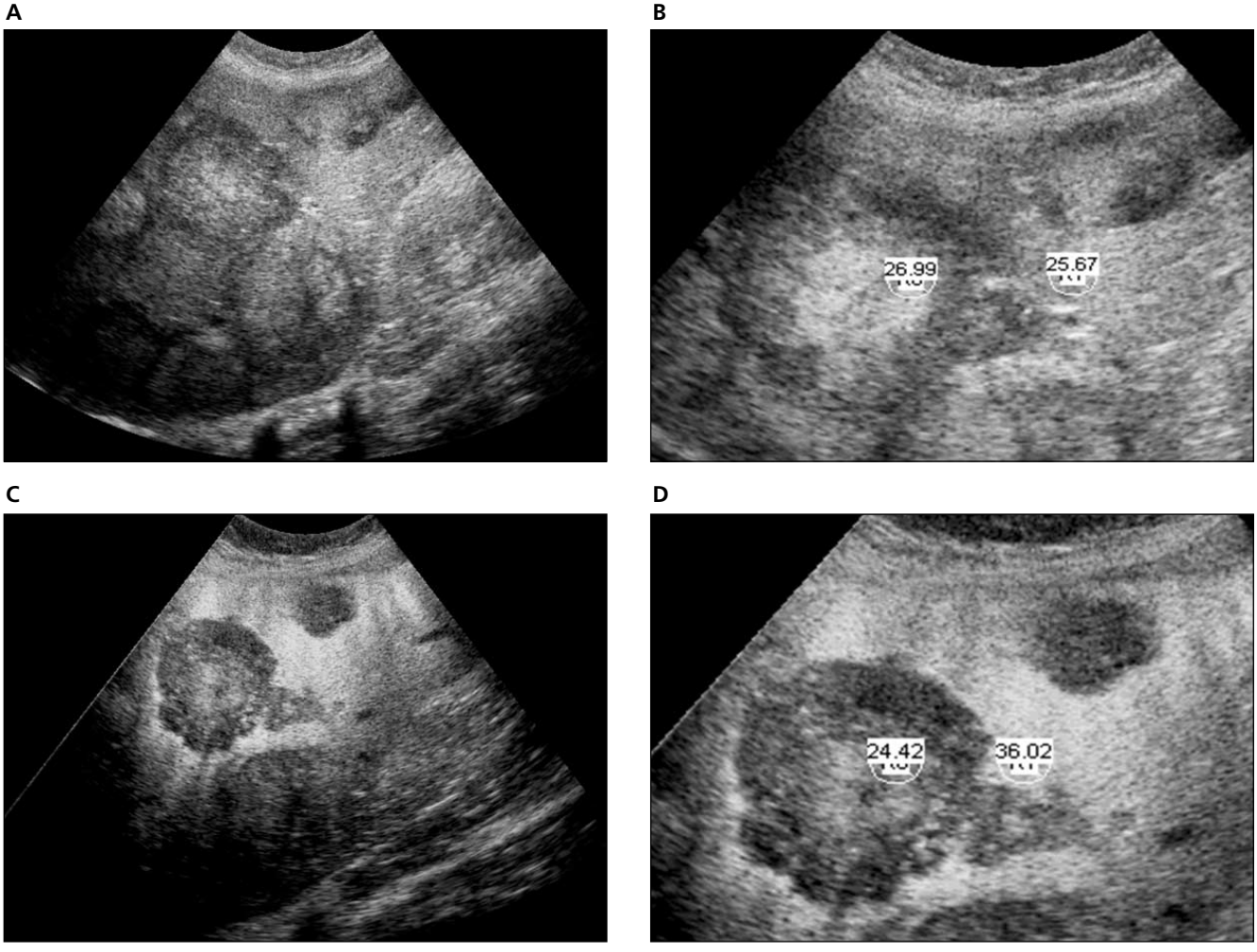
Strong and transient enhancement was observed subjectively in all cases after Levovist administration. The mean liver parenchyma intensities before and after contrast agent administration were 19.69 dB (SD, 7.10 dB) and 29.35 dB (SD, 7.39 dB), respectively. The mean value of increase in the liver echogenicity at the level of the marker lesions was 9.65 dB (SD, 8.74 dB).

On postcontrast PIHI, the lesions were hyperechoic in 11, isoechoic in 4, and hypoechoic in 11 (2 benign and 9 malignant) patients relative to the liver parenchyma. In malignant and benign lesions on postcontrast PIHI, the mean lesion-minus-liver intensities were –10.11 dB (SD, 5.10 dB) and 2.58 dB (SD, 4.40 dB), respectively.

In 2 (22%) of the 9 malignant marker lesions, a hyperechoic rim was observed on postcontrast PIHI (Figure 1). The first was metastasis of the adenocarcinoma of the lung, and the second was a case of peripheral cholangiocarcinoma. Seven malignant and all 17 benign lesions did not show any apparent rim enhancement.

All malignant (n = 9) and 2 benign (1 hemangioma and 1 inflammatory pseudotumor) lesions had lesion-liver ratios of less than 1 (Figure 2). Four benign marker lesions had a lesion-liver ratio of 1, and 11 benign lesions had lesion-liver ratios of greater than 1 (Figure 3). When a lesion-liver ratio of less than 1 was used as the predictor of malignancy, our results were highly sensitive and specific: 100%, and 88%, respectively. The lesion-liver ratios for benign

Figure 1. Multiple metastases from adenocarcinoma of the lung in a 46-year-old woman. Objective assessment of conspicuity was performed by measuring the intensity of the lesion and the parenchyma on precontrast and postcontrast PIHI. **A** and **B**, Precontrast PIHI with ROIs drawn in the lesion (intensity, 26 dB) and the adjacent parenchyma (intensity, 25 dB). The lesion-liver ratio is 1.04. **C** and **D**, Postcontrast PIHI with ROIs drawn in the lesion (intensity, 24 dB) and the adjacent parenchyma (intensity, 36 dB). The lesion-liver ratio is 0.67. An echogenic halo is shown around the metastatic lesion.



and malignant lesions showed a statistically significant difference ($P < .05$). Precontrast and postcontrast liver and lesion intensities, lesion-liver ratios, and final diagnoses of the focal liver lesions are shown in Table 1.

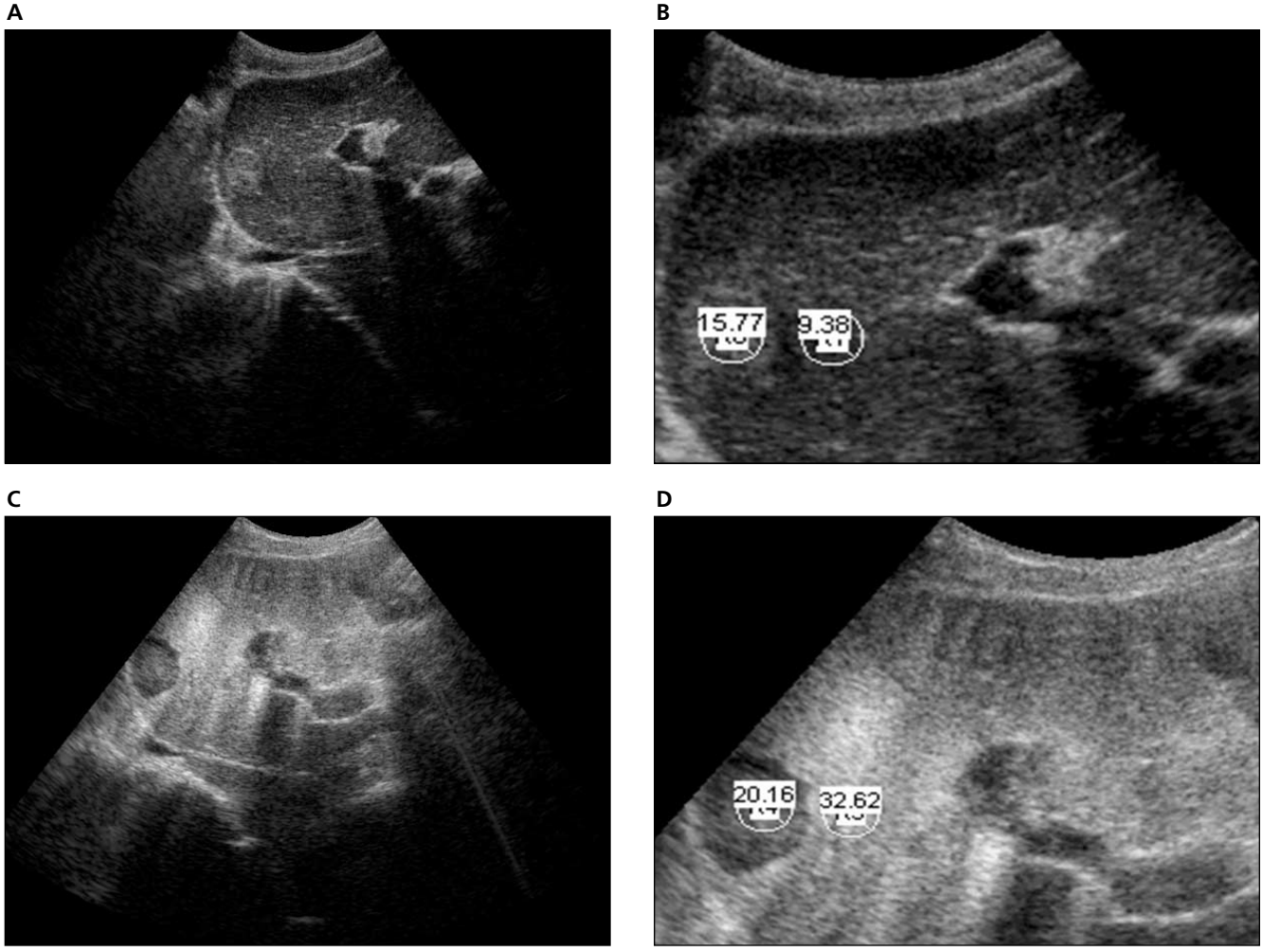
Additional lesions that were not seen on precontrast PIHI were detected on contrast-enhanced PIHI in 2 patients with metastasis. In contrast, 3 hemangiomas and 1 FNH that could be seen easily on precontrast PIHI were undetectable on postcontrast PIHI (Figure 4). No additional lesions were detected during contrast-enhanced PIHI in patients with benign lesions.

There was a statistically significant difference between the lesion-liver ratios before and after contrast agent administration among benign and malignant lesions ($P < .05$).

Discussion

Correct characterization and avoidance of the imaging pitfalls of focal liver lesions are major tasks of radiologists in daily clinical practice and are crucially important for the success of the patient treatment. Color Doppler ultrasonography is a major supplemental technique to B-mode imaging in selected patients and may allow characterization of some radiologically indeterminate liver lesions (ie, HCC and FNH). Unfortunately, there is a considerable overlap between color Doppler findings of benign and malignant lesions, and different sensitivity and specificity values have been reported.[7–10] The echogenic patterns of liver lesions differ widely and are practically nonspecific for accurate lesion characterization.

Figure 2. Metastatic large-cell lung cancer in a 50-year-old man. **A** and **B**, Precontrast PIHI showing hyperechoic metastasis. The lesion-liver ratio is 1.67. **C** and **D**, Contrast-enhanced PIHI showing the metastases with relative reversal of echogenicity in comparison with the adjacent liver. The lesion-liver ratio is 0.63.



Hemangioma, focal fatty infiltration, adenoma, HCC, FNH, lipoma, and metastasis may be seen as hyperechoic lesions during ultrasonographic examinations. Metastases from renal cell carcinoma, carcinoid, choriocarcinoma, and islet cell carcinoma are hypervascular lesions and tend to be hyperechoic.[1]

Levovist may be used effectively to increase the sensitivity and specificity of ultrasonographic examinations. Homogeneous parenchymal uptake of Levovist in the liver-specific late phase is a useful indicator of benign focal hepatic lesions. The exact mechanism of Levovist-specific uptake in the parenchyma of the liver is unknown, but it may accumulate in the reticuloendothelial cells or may be entrapped in the liver sinusoids. The fundamental mechanism seems to be comparable with that of liver-specific magnetic resonance contrast agents with an affinity for the reticuloendothelial cells.[5]

In this study, we tried to characterize hyperechoic focal liver lesions in the late phase of Levovist to differentiate benign and malignant lesions. We used a lesion-liver ratio of less than 1 as a predictor of malignancy, with sensitivity and specificity values of 100%, and 88%, respectively.

With the marked increase of the intensity in the normal liver parenchyma, without contrast agent uptake in the lesion itself we observed the reversal of the echogenicity of the malignant lesions. All malignant liver lesions were hypoechoic compared with the normal liver parenchyma and had lesion-liver ratios of less than 1 on postcontrast PIHI. Harvey et al[11] reported that the initially

Figure 3. Hemangioma in a 44-year-old woman. **A** and **B**, Precontrast PIHI showing a hyperechoic lesion in the right lobe of the liver. **C** and **D**, Postcontrast PIHI showing a lesion-liver ratio of 1.23, indicating a benign nature.

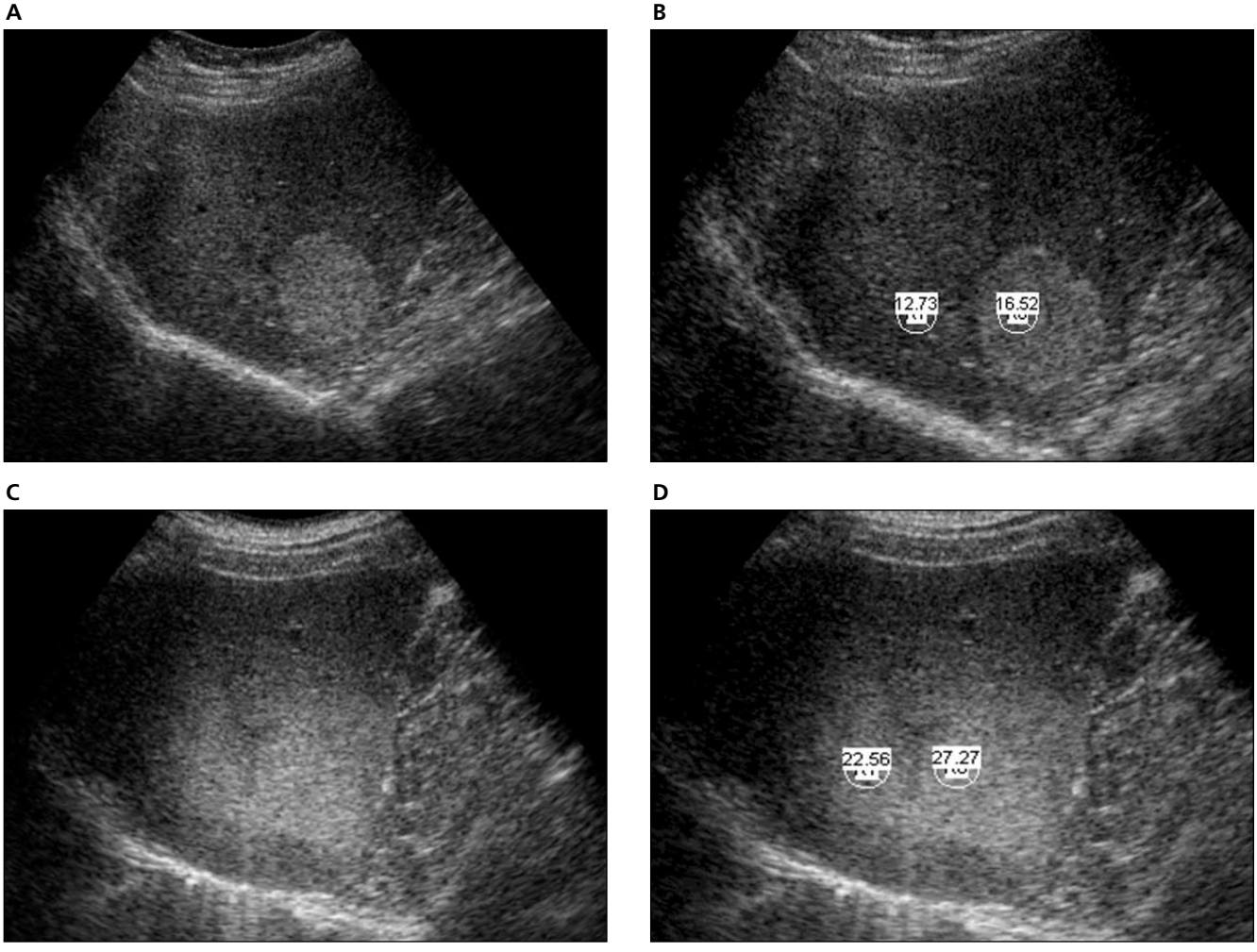
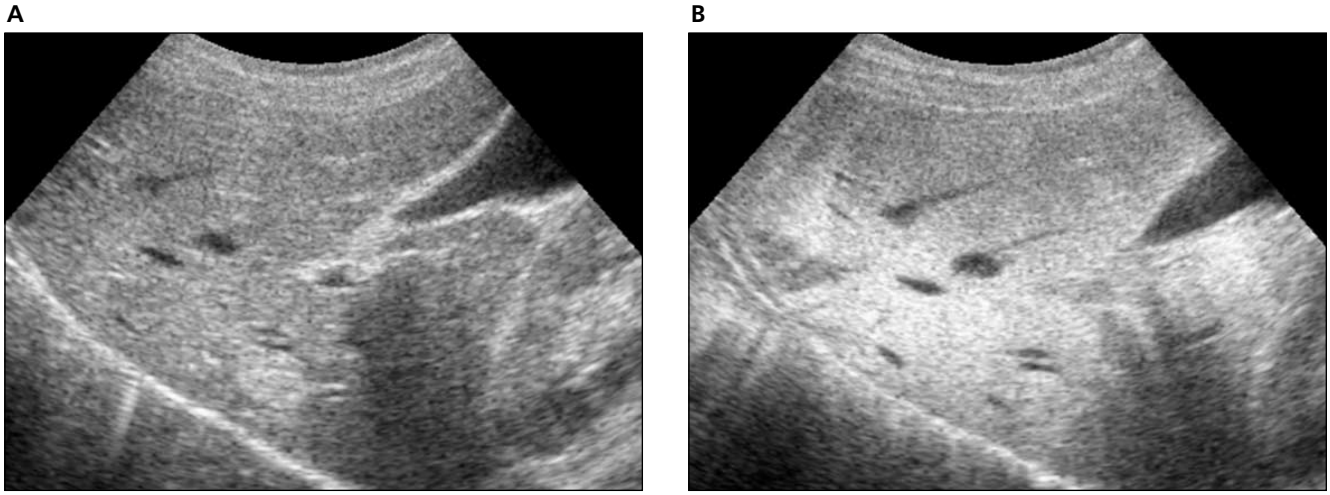


Table 1. Precontrast and Postcontrast Liver and Lesion Intensities, Lesion-Liver Ratios, and Final Diagnoses of the Focal Liver Lesions

Patient	Precontrast Liver Intensity, dB	Precontrast Lesion Intensity, dB	Postcontrast Liver Intensity, dB	Postcontrast Lesion Intensity, dB	Precontrast Lesion-Liver Ratio	Postcontrast Lesion-Liver Ratio	Final Diagnosis
1	25	26	36	24	1.04	0.67	Metastasis
2	9	15	32	20	1.67	0.62	Metastasis
3	14	19	20	22	1.36	1.1	Hemangioma
4	13	22	14	27	1.69	1.92	Focal fatty change
5	15	23	36	16	1.53	0.44	Cholangiocarcinoma
6	12	16	22	27	1.33	1.22	Hemangioma
7	24	32	26	26	1.33	1.0	Hemangioma
8	28	34	34	36	1.21	1.05	Hemangioma
9	17	30	25	31	1.76	1.24	Hemangioma
10	22	29	29	26	1.31	0.89	Metastasis
11	29	36	26	30	1.24	1.15	Hemangioma
12	7	15	16	17	2.14	1.06	Hemangioma
13	21	26	34	20	1.23	0.56	Metastasis
14	15	19	45	35	1.26	0.77	Metastasis
15	18	31	40	40	1.72	1.0	Hemangioma
16	21	21	26	21	1.0	0.8	Inflammatory pseudotumor
17	24	26	34	26	1.08	0.76	HCC
18	18	26	25	27	1.44	1.08	Hemangioma
19	24	30	25	32	1.25	1.28	Hemangioma
20	8	19	31	28	2.37	0.9	Hemangioma
21	14	16	33	33	1.14	1.0	FNH
22	29	36	34	35	1.24	1.02	Hemangioma
23	33	37	29	23	1.12	0.79	Metastasis
24	22	28	35	29	1.27	0.82	Metastasis
25	20	28	20	29	1.4	1.45	Hemangioma
26	30	33	36	36	1.1	1.0	Hemangioma

Figure 4. Hemangioma in a 56-year-old man. **A**, Precontrast PIHI showing a hyperechoic lesion in the right lobe of the liver (segment VI). **B**, Postcontrast PIHI showing that the lesion has the same echogenicity as the surrounding normal liver parenchyma.



hyperechoic malignant lesions became relatively hypoechoic in comparison with the normal liver in the late phase. Yücel et al[12] reported that the echogenicity of both metastases and HCCs decreased relative to that of the liver parenchyma on late-phase scans. von Herbay et al[5] pointed out that none of the histologically proven malignant liver lesions showed homogenous Levovist uptake in the late phase.[5]

Fifteen of the 17 benign lesions were isoechoic or hyperechoic when compared with the normal liver parenchyma and had lesion-liver ratios equal to or greater than 1. In our study, the absence of Levovist uptake in the late phase was found in 2 patients with liver hemangiomas and in the patient with an inflammatory pseudotumor.

Bertolotto et al[13] obtained ultrasonographic images 30 seconds and 2 and 4 minutes after contrast agent injection in 10 patients with small hemangiomas and observed that 2 of them were hypoechoic on the 2-minute scans and became isoechoic or hyperechoic on the 4-minute scans. Eight of 10 small hemangiomas were isoechoic to liver parenchyma on the 2-minute scan in that study.[13] von Herbay et al[5] observed absence of Levovist uptake in 3 of 8 patients with liver hemangiomas and heterogenous enhancement in 5 of the 8 large hemangiomas. This finding of the absence of Levovist uptake is possibly due to the vascular architecture of hemangiomas. Hemangiomas are free of liver tissue and reticuloendothelial cells but contain veins of a very small caliber surrounded by endothelial cells, which could be the explanation for the substantial prolongation of the blood pool phase. The period necessary for complete isoattenuation of the hemangiomas differs widely among individual lesions on CT scans. Central areas without enhancement may be seen, particularly in large hemangiomas, because of sluggish flow in central vascular spaces, tissue fibrosis, thrombosis, or hemorrhage.[14] We did not observed inhomogeneous enhancement of the hemangiomas in our study.

One of our patients had a pathologically proven inflammatory pseudotumor (myofibroblastic tumor), which is a rare benign condition characterized by a mass of localized proliferation of fibroblasts and infiltration of mononuclear inflammatory cells. The absence of liver tissue and reticuloendothelial cells may possibly explain the nonenhancement of the lesion after Levovist injection.[15] Dietrich et al[16] reported a similar case that did not show contrast enhancement in the portal venous and liver-specific late phase of Levovist.[16]

In our study, contrast-enhanced PIHI detected additional lesions that could not be seen on precontrast PIHI, fundamental ultrasonography, and helical CT scans in 2 patients with metastasis. Several studies reported improved sensitivity of contrast-enhanced PIHI in the detection of the liver metastasis.[4,11,12,17] Three hemangiomas and 1 FNH that could easily be seen on precontrast PIHI were undetectable on postcontrast PIHI. No additional lesions were observed during contrast-enhanced PIHI in patients with benign lesions. To our knowledge, no hyperechoic malignant lesion showing contrast enhancement on postcontrast PIHI has been reported.

A hyperechoic halo was observed in 22% of the malignant lesions (1 metastasis and 1 cholangiocarcinoma), but none was observed in benign lesions. The exact pathophysiologic mechanism of this phenomenon is not known, but the enhancement may be secondary to an immunologic response, with a possibly increased number of Kupffer cells, or an accumulation of blood vessels at the interface between normal tissue and the lesion itself. A hyperechoic halo was observed in 53% of malignant lesions in a study by Yücel et al[12] and in 70% in a study of metastatic lesions by Bertolotto et al.[13]

The transient nature of late-phase enhancement with Levovist is a limitation of this technique. The high mechanical index used in the late phase of Levovist allows only 1 or 2 sweeps because of the high rate of bubble destruction. The enhancement is focal zone dependent, so maximal contrast enhancement is seen in this site. 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. In patients with presumed hemangioma, the diagnosis was presumably based purely on imaging criteria. This is a limitation of our study, but confirmation by typical triphasic helical CT findings might be adequate for the limited goal of this study.

In conclusion, PIHI with quantitative evaluation, is a useful tool for narrowing the list of differential diagnoses and may improve diagnostic accuracy. Our results revealed that the lesion-liver ratio may be a relevant indicator in the characterization of the liver lesions, with values greater than 1 predicting a benign nature and those less than 1 predicting malignancy.

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