Malignant focal liver lesions at contrast-enhanced ultrasonography and magnetic resonance with hepatospecific contrast agent

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Abstract

The aim of this study was to compare the diagnostic accuracy of the late phase of CEUS and the hepatobiliary phase of CE-MR with Gd-BOPTA in the characterization of focal liver lesions in terms of benignity and malignancy. A total of 147 solid focal liver lesions (38 focal nodular hyperplasias, 1 area of focal steatosis, 3 regenerative nodules, 8 adenomas, 11 cholangiocarcinomas, 36 hepatocellular carcinomas and 49 metastases) were retrospectively evaluated in a multicentre study, both with CEUS, using sulphur hexafluoride microbubbles (SonoVue, Bracco, Milan, Italy) and CE-MR, performed with Gd-BOPTA (Multihance, Bracco, Milan, Italy). All lesions thought to be malignant were cytohistologically proven, while all lesions thought to be benign were followed up. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values and accuracy were calculated for the late phase of CEUS and the hepatobiliary phase of CE-MRI, respectively, and in combination. Analysis of data revealed 42 benign and 105 malignant focal liver lesions. We postulated that all hypoechoic/hypointense lesions on the two phases were malignant. The diagnostic errors were 13/147 (8.8%) by CEUS and 12/147 (8.2%) by CE-MR. Sensitivity, specificity, PPV, NPV and accuracy of the late phase of CEUS were 90%, 93%, 97%, 80% and 91%, 93%, 97%, 81% and 92% for the hepatobiliary phase of CE-MRI, respectively. If we considered both techniques, the misdiagnosis diminished to 3/147 (2%) and sensitivity, specificity, PPV, NPV and accuracy were 98%, 98%, 99%, 95% and 98%. The combination of the late phase of CEUS and the hepatobiliary phase of CE-MR in the characterization of solid focal liver lesions in terms of benignity and malignancy is more accurate than the two techniques used separately.

Keywords: Focal liver lesion, contrast enhanced ultrasonography, magnetic resonance imaging, hepatospecific contrast agent

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Introduction

Solid focal liver lesions (FLL) frequently represent a diagnostic problem.¹ In recent years, several studies have evaluated the diagnostic accuracy of contrast-enhanced ultrasonography (CEUS) and contrast-enhanced magnetic resonance (CE-MR).^{2–4} It has already been proven that the late phase of contrast medium examinations may improve the detection and characterization of focal liver lesions.^{5–12} Guidelines recommend the use of CEUS in the characterization of FLL detected and indeterminate with conventional ultrasonography (US).^{9,10} The late phase plays a pivotal role for the differential diagnosis of benignity vs. malignancy.

MRI is a powerful imaging method for FLL detection and characterization, especially when using liver specific

contrast media, as reported in the literature.^{4,7,8,13,14} Microbubble contrast agents used for US differ from hepatocyte-specific contrast agents used in MR in their purely intravascular distribution, without any interstitial phase. This explains the substantial concordance with MR imaging on arterial phase imaging and the relative discordance of enhancement patterns in the delayed phases of imaging.^{15–18}

Some articles report a diagnostic accuracy between 85% and 95% in the distinction of benignity and malignancy for the late phase of CEUS,^{5,19} compared to the 80–85% diagnostic accuracy of dynamic imaging, with a significant increase in diagnostic confidence compared with baseline US.^{15,20} Furthermore, other studies show that the

hepatobiliary phase of CE-MRI allows better detection and characterization of solid focal liver lesions, particularly of metastases, compared to pre-contrast and dynamic imaging, because of the markedly improved lesion-to-liver contrast in the absence of perfusion changes.^{4,16}

The aim of this study was to retrospectively compare the diagnostic accuracy of CEUS and CE-MR, using a hepatospecific contrast agent, in the characterization of focal liver lesions in terms of benignancy and malignancy.

Materials and methods

Study population

To evaluate the capability of CEUS and CE-MRI in the characterization of malignant focal liver lesions, consecutive solid focal liver lesions undetermined at US imaging and studied with CEUS and CE-MR imaging were retrospectively evaluated. Research ethics board approval for chart review was obtained for this multicentre study. All patients signed an informed consent form before each examination. We evaluated only patients where both examinations had been performed in the same institution within two weeks. Patients with cystic lesions or lesions characterized by a dynamic pattern typical for angiomatous vascular structures were excluded. The final diagnosis of lesions identified as malignant at imaging was obtained by core-needle biopsy, while all lesions thought to be benign were followed up within 6–12 months.

Imaging techniques

For the contrast enhanced ultrasound (CEUS), a contrast agent containing sulphur hexafluoride in the form of microbubbles (SonoVue, Bracco, Milan, Italy) was used and injected intravenously via an antecubital vein (dose of 2.4 mL) using a 20-gauge cannula as a rapid bolus, followed by a 5 mL saline flush. Harmonic microbubble-specific imaging with low acoustic US pressure (2–4 MHz transducer; mechanical index < 0.2; frame rate 12–13 Hz) was performed using Sequoia (Acuson-Siemens, Erlangen, Germany) and Aplio (Toshiba, Otawara, Japan) US scanners. All CEUS examinations were recorded on VHS/video-tape or magneto-optical disk systems. A standard dynamic study was performed. It went through the arterial phase (about 15–25 seconds after contrast injection), the portal/venous phase (about 40–60 seconds after contrast injection) and the late phase (about 120 seconds after contrast injection). We considered only the last phase.

All MR examinations were performed on a 1.5-T Magnetom Symphony scanner (Siemens), with high-performance gradients and a phased array body coil. A standard liver protocol was performed, which included an unenhanced spoiled gradient echo T1-weighted sequence in and out of phase (repetition time 75 ms, echo time 2.4 ms, inversion time 4.8 ms and flip angle 70°), a turbo spin-echo T2-weighted sequence (repetition time 1800 ms, echo time 84 ms and echo train length 15), a turbo inversion recovery T2-weighted sequence (repetition time 5000 ms, echo time 103 ms, inversion time 145 ms and echo train length 33), axial breath hold sequence and a half Fourier acquisition

T2-weighted (repetition time 1000 ms, echo time 82 ms, echo train length 144) 'free-breathing' fat-saturated sequence. The protocol also included a dynamic study, performed after the administration of dimeglumine-gadobenate (Gd-BOPTA, Multihance, Bracco, Milan, Italy) with a three-dimensional fat-saturated gradient-echo T1-weighted volume interpolated breath hold examination ('VIBE', repetition time 4.5 ms, echo time 1.7 ms, flip angle 10°), which was repeated 1–2 hours after Gd-BOPTA administration. Similarly, for the MR imaging, we only considered the last (hepatobiliary) phase.

All biopsies were performed under US guidance using a 20-, 19- or 18-gauge Menghini-type needle, with either automatic (Biomol, Hospital Service, Rome, Italy) or manual aspiration (Surecut, Hospital Service, Rome, Italy).

Analysis

Based on the enhancement patterns following contrast and on histopathology, we postulated that all lesions that appeared hypoechoic/hypointense on the late phase of CEUS or hepatobiliary phase of MRI respectively were malignant. In patients with more than one lesion with the same features, i.e. metastases, only the largest lesion was evaluated. We classed the adenomas as malignant lesions, due to the necessity of their surgical removal because of the risk of hemorrhage or malignant degeneration.²¹

Considering only the late phase of CEUS and the hepatobiliary phase of MRI, focal liver masses were classified as hypoechoic/hypointense, iso-echoic/iso-intense or hyper-echoic/hyper-intense relative to the rest of the liver parenchyma.

Statistics

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated for the late CEUS and hepatobiliary MRI phases respectively and in combination.

Results

The study population consisted of 147 patients (93 men and 54 women) with a mean age of 59.4 years (age range: 17–75 years). Each patient had one or more focal liver lesions. In cases with more than one focal lesion, we evaluated only the largest lesion; mean lesion diameter was 5.8 cm (range: 0.4–10 cm).

Liver lesions comprised 38 focal nodular hyperplasias (FNHs), 1 area of focal steatosis, 3 regenerative nodules, 8 adenomas (one with focal degeneration), 11 cholangiocarcinomas (CCCs), 36 hepatocellular carcinomas (HCCs – one of these well differentiated and one fibrolamellar variant) and 49 metastases.

Analysis of late phase of CEUS data revealed 98 hypoechoic, 46 isoechoic and 3 hyperechoic lesions, while on the MR hepatobiliary phase the intensity was lower than, equal to or greater than that of the adjacent liver parenchyma, respectively, in 99, 39 and 4 cases and five lesions presented central pooling with peripheral wash-out.

Thus, the complete radiological analysis of data showed that there were 42 benign lesions, 39/42 (93%) of which were hyper-echoic or iso-echoic on the late phase of CEUS. Three of the 42 (7%) masses were hypoechoic on late phase of CEUS and therefore thought to be malignant, but histology revealed these to be FNHs. Also on the hepatobiliary phase of MRI, 39/42 (93%) were hyper-intense/iso-intense and 3/42 (7%) were hypointense and so misdiagnosed; 1/42 (2.3%) was a FNH, 1/42 (2.3%) an area of focal steatosis and 1/42 (2.3%) a regenerative nodule. Only 1/42 (2.3%) diagnosis was mistaken by both techniques and the core-biopsy revealed it was a FNH.

The histo-pathological analysis of data showed that there were 105 malignant masses, 95/105 (90%) of which were hypoechoic on the late phase of CEUS. Ten of the 105 lesions (10%) were hyper-echoic/iso-echoic and so erroneously thought to be benign; actually, three of them were adenomas (Figure 1) and seven were HCCs, respectively. Based on the hepatobiliary phase of MR, 96/105 (91%) were hypointense and so correctly diagnosed as malignant. Four of the 105 lesions (4%) were hyper-intense/iso-intense and 5/105 (5%) showed central pooling with peripheral wash out and were wrongly defined as benign masses.

The first four lesions were HCCs, and in the second group there were three metastases (Figure 2) and two CCCs. Only 2/105 (2%) HCCs were misdiagnosed by both CEUS and CE-MRI; one was isoechoic on the late phase and hyperintense at the hepatobiliary phase and the other one was iso-hypoechoic/intense at both phases (Table 1).

Evaluating all 147 focal liver lesions, our study showed that diagnostic errors were made in 13/147 (8.8%) by means of CEUS (Figures 1 and 2) and 12/147 (8.2%) by means of CE-MR (Figure 2), respectively. Considering both techniques combined, the rate of misdiagnosis decreased to 3/147 (2%).

Thus, the sensitivity calculated as the ratio of true positive to the total number of malignant focal liver masses was 90% for CEUS and 91% for CE-MRI, while the specificity, defined as the ratio of true negative to the total number of benign lesions, was 93% for both techniques. The PPV, calculated as the ratio between true positive and the sum of true and false positives, was 97% for both 95/98 masses and 96/99 masses, respectively. The NPV, derived from the ratio between true negative and the sum of true and false negatives, was 80% for CEUS and 81% for CE-MR. So, the diagnostic accuracy, defined as the ratio between true positive

Figure 1 Adenoma. (a) The basic US showed a focal iso-hypoechoic, well-demarcated lesion (caliper) in the left lobe of liver. (b,c) After the administration of contrast media, the lesion was slightly hyperechoic (arrow) in the late phase of CEUS and so erroneously diagnosed to be benign, but was hypointense (arrow) at the hepatobiliary phase of CE-MR (diagnostic error with CEUS)

Figure 2 Metastasis. (a) The late CEUS showed a focal, markedly hypoechoic lesion in the left lobe of liver (arrow), correctly diagnosed as malignancy. (b) After the administration of Gd-BOPTA, it was hypointense (arrow) on the venous phase and (c) showed a central pooling becoming hyperintense (arrow) at the hepatobiliary phase of CE-MR (diagnostic error with CE-MR)

Table 1 Contrast-enhanced ultrasound and magnetic resonance in the late and hepatobiliary phases of 147 focal liver lesions

Final diagnosis	n	Late phase		Hepatobiliary phase		
		Hypo	Iso-Hyper	Hypo	Iso-Hyper	Central pooling
Benignancy	42	3	39	3	39	–
FNHs	38	3	35	1	37	–
Area of focal steatosis	1	–	1	1	–	–
Regenerative nodule	3	–	3	1	2	–
Malignancy	105	95	10	96	4	5
Adenomas	8	5	3	8	–	–
CCC	11	11	–	9	–	2
HCC	36	29	7	32	4	–
Metastases	49	49	–	46	–	3
		98	49	99	43	5

plus true negative and the total number of the lesions, was 91% for CEUS and 92% for CE-MR. The sensitivity, specificity, PPV, NPV and accuracy of the association between CEUS and CE-MR were 98%, 98%, 99%, 95% and 98%, respectively (Table 2).

Discussion

The detection and characterization of solid focal liver lesions frequently represent a diagnostic challenge. The results obtained by ultrasonography and magnetic

Table 2 Statistical data about the late phase of CEUS and the hepatobiliary phase of MR, respectively, and together

	Late phase (%)	Hepatobiliary phase (%)	Late and hepatobiliary phases (%)
Sensitivity	90	91	98
Specificity	93	93	98
PPV	97	97	99
NPV	80	81	95
Accuracy	91	92	98

resonance are significantly improved by the administration of contrast agents.^{4,22,23} Ultrasound contrast agent sulphur-hexafluoride filled microbubbles (SonoVue, Bracco, Milan, Italy) only distributes intravascularly without any passage into the interstitial space so, in the delayed phase, microbubbles only fill the sinusoids. According to some studies,¹⁹ the only phase useful for hepatic lesion characterization with CEUS is the late/sinusoidal phase, because it allows evaluation of the entire liver parenchyma. CEUS contrast agent clearly demonstrates the washout phenomenon, whereas CT and MRI may show prolonged enhancement due to contrast leakage into the tumour interstitium.^{24,25} MRI is used mainly in indeterminate cases, such as when US and/or CT are not fully definitive in terms of the number and location of liver lesions or when the differential diagnosis of selected liver lesions may affect subsequent patient treatment.¹⁶

Different contrast materials, with different biological properties, are used in different clinical settings in MR liver imaging. Contrast materials with an interstitial distribution phase are not well suited for liver lesion detection because they alter both the normal liver parenchyma and the lesion equally. With these agents, the lesion-to-liver contrast is high only in the non-equilibrium perfusion phases, so that only the fast dynamic component is of any benefit.¹⁶ Another possible way of MRI contrast distribution is the hepatobiliary pathway. Gadobenate dimeglumine (Gd-BOPTA, Multihance, Bracco) is a gadolinium chelate that combines the properties of a conventional extracellular fluid gadolinium agent with those of an agent targeted specifically to the liver.^{18,26,27} The contrast-effective chelate of gadobenate dimeglumine is Gd-BOPTA, which has the capacity for weak and transient interaction with serum albumin,^{28,29} which markedly increases the r1 and r2 relaxivities of gadobenate dimeglumine relative to conventional gadolinium agents, permitting similar contrast enhancement to be obtained with lower doses.³⁰ Furthermore, around 96% of the injected dose of gadobenate dimeglumine is excreted renally via glomerular filtration, while the remaining 3–5% is taken up by functioning hepatocytes and eliminated via the hepatobiliary pathway.^{18,26,27} This property allows a marked and long-lasting increase in signal intensity of normal liver parenchyma, beginning around 40 minutes after contrast medium administration.^{8,16,18,26,27,31,32} As a contrast agent for liver imaging, gadobenate dimeglumine

therefore behaves analogously to conventional extracellular gadolinium agents during the initial dynamic phase of contrast enhancement and as a liver-specific agent during the delayed hepatobiliary phase. Thus, the conventional approach to lesion detection and characterization based on the differential distribution of contrast agent during the initial dynamic phase can be augmented by an additional functional approach in which lesion detection and characterization is based on the ability of lesions to take up and excrete Gd-BOPTA.^{4,13,27,33–37} Studies have shown that delayed hepatobiliary phase imaging can improve not only the detection of focal liver lesions but also the characterization of detected lesions, particularly lesions that demonstrate atypical enhancement patterns on dynamic imaging.^{4,13,27,33–37}

In the light of these considerations, lesions with liver-like structures (sinusoidal network and hepatocytes), classified as benign, are usually iso-echoic/hyper-echoic in the late CEUS and iso-intense/hyper-intense in the hepatobiliary phase.^{4,38}

Distribution and retention of the contrast microbubbles in the sinusoidal network without passage into the interstitium make the CEUS sinusoidal phase fundamental in distinguishing benign from malignant lesions (diagnosis of malignancy based on the presence of a clear hypoechoic defect in the sinusoidal phase was possible in about 96% of malignant focal liver lesions in a reported series).¹⁹ During the late phase, lesions with liver-like (FNH, adenoma) or angiomatous (hemangiomas) vascular structure appear isoechoic or hyperechoic because of the retention of microbubbles similar to or greater than that in adjacent liver parenchyma.^{17,19,39–47}

Conversely, in those lesions with neoangiogenic vascular structure (HCC, CCC and metastases), there is not a similar degree of retention of microbubbles compared to the liver parenchyma. Therefore, malignant liver lesions typically appear as a clear hypoechoic defect inside the liver parenchyma, which is homogeneously enhanced during the late/sinusoidal CEUS phase.^{3,17,19,39,48}

The sinusoidal phase of CEUS presents some limitations when evaluating the cirrhotic liver. Firstly, a minority of HCCs tend to maintain the original sinusoidal architecture, particularly in well-differentiated forms.⁴⁹ These vessels, which have an endothelial layer, are similar to those of normal liver and thus tend to accumulate microbubbles in the late phase of CEUS and do not show the typical washout of malignant lesions, as reported in literature.⁵⁰ Also, the focus of HCC is not always detectable as a clear defect due to fibrosis of adjacent parenchyma associated with a sinusoidal capillarization and with a loss of endothelial fenestrations and development of baseline membranes.⁵¹ This may prevent the accumulation of microbubbles in the cirrhotic liver with a consequent decrease in hyperechogenicity and decreased conspicuity of lesions in the sinusoidal phase.²³

Thus, in our study 39/42 (93%) benign lesions were correctly detected and characterized both by the late phase of CEUS (35 FNHs, one area of focal steatosis and three regenerative nodules) and the hepatobiliary phase of CE-MR (37 FNHs and two regenerative nodules). A small number of

benign lesions appeared hypoechoic/hypointense on the delayed phases, as reported in other series.^{19,52} In our series, three FNHs were erroneously diagnosed (falsely positive) by late CEUS. The immunohistopathological analysis demonstrated the presence of few anomalous sinusoidal vessels with a large number of vascular structures without cytologic atypia, for example in the non-classic FNH type. One of these atypical FNHs was misdiagnosed also by CE-MR. The focal area of steatosis was hypointense in the hepatobiliary phase, so resembling malignancy, because the sequence performed was a 'VIBE', a fat-saturated gradient-echo T1-weighted sequence, while in the late contrast-enhanced ultrasound it was hyperechoic, according to the normal echogenicity of fat. The further case that proved to be a false positive at the hepatobiliary phase of MRI was a large regenerative nodule (4 cm in diameter) that appeared normally hyperechoic on the delayed phase of CEUS. At CE-MRI, it showed a peripheral hypointensity because of functional failure of the hepatocytes due to the atrophic and congested perilesional area.

Lesions with altered or absent sinusoids and/or hepatocytes, thus considered malignant, are usually hypoechoic/hypointense in the late phases of CEUS and CE-MRI.^{19,52} In our study, 95/105 (90%) malignant masses were correctly detected and characterized by the late phase of CEUS (5 adenomas, 11 CCCs, 29 HCCs and 49 metastatic lesions from pancreatic, gastric and colo-rectal cancers) and 96/105 (91%) by the hepatobiliary phase of CE-MR (8 adenomas, 9 CCCs, 32 HCCs and 46 metastases from pancreatic, gastric and colo-rectal cancers).

Not all malignant focal liver masses appear hypoechoic/intense in the delayed phases.^{38,53} In our series, three adenomas were misdiagnosed (false negative cases) because they were iso-hyperechoic in the late phase. Histo-pathological analysis of these cases revealed dilated vessels, large amounts of fat and the arterio-venous shunts. These mistakes were mostly made on hepatocellular carcinomas, which arise in cirrhotic liver, characterized by architectural parenchymal distortion, with fibrosis and late 'capillarization', with loss of endothelial fenestrations and development of basement membranes.⁵⁴ Thus, seven out of 36 HCCs were erroneously interpreted as benign lesions (false negatives) by the late phase of CEUS because they were isoechoic. Immunohistochemical studies also reported that well-differentiated forms usually maintain the original parenchymal architecture.^{13,55} For the same reasons, four HCCs appeared iso-hyperintense in the hepatobiliary phase of MRI. This reflects the preservation of sufficient hepatocytic activity.⁵⁶ The other misdiagnoses observed at the delayed phase of CE-MRI were 2/9 CCCs and 3/46 metastases (all from colo-rectal cancer), which showed central pooling with peripheral wash out, due to the retention of the contrast in the central fibrous tissue.^{52,57} In contrast, these lesions were hypoechoic in the late phase of CEUS and so correctly diagnosed by this technique.

In our study, we demonstrated that considering the late phase of CEUS and the hepatobiliary phase of CE-MRI independently, the probability of a diagnostic error in terms of benignancy and malignancy is about 7% (3/42) for the truly benign focal liver lesions, and 10% (10/105)

and 9% (9/105), respectively, for the truly malignant focal liver masses. However, if we considered both techniques together, the rate of misdiagnosis decreased to 2.3% (1/42) and to 2% (2/105) for benign and malignant lesions respectively, with the three misdiagnosed cases represented by an atypical FNH and two well-differentiated HCCs.

Conclusion

Imaging diagnosis of malignant focal liver lesions is accurate. In our study, diagnostic accuracy for the late phase of CEUS is about 91% and about 92% for the hepatobiliary late phase of CE-MR. Diagnostic accuracy was improved to around 98% by combining the two imaging methods.

Abbreviations

CEUS	= Contrast-enhanced ultrasonography
MR/MRI	= Magnetic resonance imaging
PPV	= Positive predictive value
NPV	= Negative predictive value
CE-MR	= Contrast-enhanced magnetic resonance
US	= Ultrasonography
FNH	= Focal nodular hyperplasia
CCC	= Cholangiocarcinoma
HCC	= Hepatocellular carcinoma

DECLARATIONS

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REFERENCES

- Harvey CJ, Albrecht T. Ultrasound of focal liver lesions. *Eur Radiol* 2001;**11**:1578-93
- Wilson SR, Kim TK, Jang HJ, et al. Enhancement patterns of focal liver masses: discordance between contrast-enhanced sonography and contrast-enhanced CT and MRI. *AJR* 2007;**189**:W7-12
- Tanaka S, Ioka T, Oshikawa O, et al. Dynamic sonography of hepatic tumors. *AJR* 2001;**177**:799-805
- Kim YK, Lee JM, Kim CS. Gadobenate dimeglumine-enhanced liver MR imaging: value of dynamic and delayed imaging for the characterization and detection of focal liver lesions. *Eur Radiol* 2004;**14**:5-13
- Nicolau C, Vilana R, Catala V, et al. Importance of evaluating all vascular phases on contrast-enhanced sonography in the differentiation of benign from malignant focal liver lesions. *AJR* 2006;**186**:158-67
- Nicolau C, Bru C. Focal liver lesions: evaluation with contrast-enhanced ultrasonography. *Abdominal Imag* 2004;**29**:348-59
- Morana G, Grazioli L, Schneider G, et al. Hypervascular hepatic lesions: dynamic and late enhancement pattern with Gd-BOPTA. *Acad Radiol* 2002;**9**:S476-9
- Pirovano G, Vanzulli A, Marti-Bonmati L, et al. Evaluation of the accuracy of gadobenate dimeglumine-enhanced MR imaging in the detection and characterization of focal liver lesions. *AJR* 2000;**175**:1111-20

9. Claudon M, Cosgrove D, Albrecht T, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) – update 2008. *Ultraschall in der Medizin* 2008;**29**:28–44
10. Claudon M, Dietrich CF, Choi B, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) in the liver – update 2012: A WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. *Ultrasound Med Biol* 2013;**39**:187–210
11. Quaia E, D'Onofrio M, Palumbo A, et al. Comparison of contrast-enhanced ultrasonography versus baseline ultrasound and contrast-enhanced computed tomography in metastatic disease of the liver: diagnostic performance and confidence. *Eur Radiol* 2006;**16**:1599–609
12. Strobel D, Seitz K, Blank W, et al. Contrast-enhanced ultrasound for the characterization of focal liver lesions—diagnostic accuracy in clinical practice (DEGUM multicenter trial). *Ultraschall in der Medizin* 2008;**29**:499–505
13. Grazioli L, Morana G, Caudana R, et al. Hepatocellular carcinoma: correlation between gadobenate dimeglumine-enhanced MRI and pathologic findings. *Invest Radiol* 2000;**35**:25–34
14. Seale MK, Catalano OA, Saini S, et al. Hepatobiliary-specific MR contrast agents: role in imaging the liver and biliary tree. *Radiographics* 2009;**29**:1725–48
15. Burns PN, Wilson SR. Focal liver masses: enhancement patterns on contrast-enhanced images—concordance of US scans with CT scans and MR images. *Radiology* 2007;**242**:162–74
16. Petersein J, Spinazzi A, Giovagnoni A, et al. Focal liver lesions: evaluation of the efficacy of gadobenate dimeglumine in MR imaging – a multicenter phase III clinical study. *Radiology* 2000;**215**:727–36
17. Quaia E, Calliada F, Bertolotto M, et al. Characterization of focal liver lesions with contrast-specific US modes and a sulfur hexafluoride-filled microbubble contrast agent: diagnostic performance and confidence. *Radiology* 2004;**232**:420–30
18. Spinazzi A, Lorusso V, Pirovano G, et al. Multihance clinical pharmacology: biodistribution and MR enhancement of the liver. *Acad Radiol* 1998;**5**:S86–9
19. D'Onofrio M, Rozzanigo U, Masinielli BM, et al. Hypoechoic focal liver lesions: characterization with contrast enhanced ultrasonography. *JCU* 2005;**33**:164–72
20. Hohmann J, Albrecht T, Hoffmann CW, et al. Ultrasonographic detection of focal liver lesions: increased sensitivity and specificity with microbubble contrast agents. *Eur J Radiol* 2003;**46**:147–59
21. Grazioli L, Federle MP, Brancatelli G, et al. Hepatic adenomas: imaging and pathologic findings. *Radiographics* 2001;**21**:877–92
22. Solbiati L, Tonolini M, Cova L, et al. The role of contrast-enhanced ultrasound in the detection of focal liver lesions. *Eur Radiol* 2001;**11**:E15–26
23. Leen E. The role of contrast-enhanced ultrasound in the characterisation of focal liver lesions. *Eur Radiol* 2001;**11**:E27–34
24. Isozaki T, Numata K, Kiba T, et al. Differential diagnosis of hepatic tumors by using contrast enhancement patterns at US. *Radiology* 2003;**229**:798–805
25. Jang HJ, Yu H, Kim TK. Contrast-enhanced ultrasound in the detection and characterization of liver tumors. *Cancer Imag* 2009;**9**:96–103
26. Kirchin MA, Pirovano GP, Spinazzi A. Gadobenate dimeglumine (Gd-BOPTA). An overview. *Invest Radiol* 1998;**33**:798–809
27. Spinazzi A, Lorusso V, Pirovano G, et al. Safety, tolerance, biodistribution, and MR imaging enhancement of the liver with gadobenate dimeglumine: results of clinical pharmacologic and pilot imaging studies in nonpatient and patient volunteers. *Acad Radiol* 1999;**6**:282–91
28. Cavagna FM, Maggioni F, Castelli PM, et al. Gadolinium chelates with weak binding to serum proteins. A new class of high-efficiency, general purpose contrast agents for magnetic resonance imaging. *Invest Radiol* 1997;**32**:780–96
29. Giesel FL, von Tengg-Kobligh H, Wilkinson ID, et al. Influence of human serum albumin on longitudinal and transverse relaxation rates (r_1 and r_2) of magnetic resonance contrast agents. *Invest Radiol* 2002;**41**:222–8
30. Schneider G, Maas R, Schultze Kool L, et al. Low-dose gadobenate dimeglumine versus standard dose gadopentetate dimeglumine for contrast-enhanced magnetic resonance imaging of the liver: an intra-individual crossover comparison. *Invest Radiol* 2003;**38**:85–94
31. Kuwatsuru R, Kadoya M, Ohtomo K, et al. Comparison of gadobenate dimeglumine with gadopentetate dimeglumine for magnetic resonance imaging of liver tumors. *Invest Radiol* 2001;**36**:632–41
32. Caudana R, Morana G, Pirovano GP, et al. Focal malignant hepatic lesions: MR imaging enhanced with gadolinium benzyloxypionic-tetra-acetate (BOPTA)—preliminary results of phase II clinical application. *Radiology* 1996;**199**:513–20
33. Grazioli L, Morana G, Federle MP, et al. Focal nodular hyperplasia: morphologic and functional information from MR imaging with gadobenate dimeglumine. *Radiol* 2001;**221**:731–9
34. Grazioli L, Morana G, Kirchin MA, et al. MRI of focal nodular hyperplasia (FNH) with gadobenate dimeglumine (Gd-BOPTA) and SPIO (ferumoxides): an intra-individual comparison. *JMRI* 2003;**17**:593–602
35. Kim YK, Kim CS, Lee YH, et al. Comparison of superparamagnetic iron oxide-enhanced and gadobenate dimeglumine-enhanced dynamic MRI for detection of small hepatocellular carcinomas. *AJR* 2004;**182**:1217–23
36. Kim YK, Lee JM, Kim CS, et al. Detection of liver metastases: gadobenate dimeglumine-enhanced three-dimensional dynamic phases and one-hour delayed phase MR imaging versus superparamagnetic iron oxide-enhanced MR imaging. *Eur Radiol* 2005;**15**:220–8
37. Grazioli L, Morana G, Kirchin MA, et al. Accurate differentiation of focal nodular hyperplasia from hepatic adenoma at gadobenate dimeglumine-enhanced MR imaging: prospective study. *Radiology* 2005;**236**:166–77
38. D'Onofrio M, Martone E, Faccioli N, et al. Focal liver lesions: sinusoidal phase of CEUS. *Abdominal Imag* 2006;**31**:529–36
39. Bryant TH, Blomley MJ, Albrecht T, et al. Improved characterization of liver lesions with liver-phase uptake of liver-specific microbubbles: prospective multicenter study. *Radiology* 2004;**232**:799–809
40. Nicolau C, Catala V, Vilana R, et al. Evaluation of hepatocellular carcinoma using SonoVue, a second generation ultrasound contrast agent: correlation with cellular differentiation. *Eur Radiol* 2004;**14**:1092–9
41. Giorgio A, Ferraioli G, Tarantino L, et al. Contrast-enhanced sonographic appearance of hepatocellular carcinoma in patients with cirrhosis: comparison with contrast-enhanced helical CT appearance. *AJR* 2004;**183**:1319–26
42. Quaia E, D'Onofrio M, Cabassa P, et al. Diagnostic value of hepatocellular nodule vascularity after microbubble injection for characterizing malignancy in patients with cirrhosis. *AJR* 2007;**189**:1474–83
43. Dai Y, Chen MH, Yin SS, et al. Focal liver lesions: can SonoVue-enhanced ultrasound be used to differentiate malignant from benign lesions? *Invest Radiol* 2007;**42**:596–603
44. Luo W, Numata K, Kondo M, et al. Sonazoid-enhanced ultrasonography for evaluation of the enhancement patterns of focal liver tumors in the late phase by intermittent imaging with a high mechanical index. *J Ultrasound Med* 2009;**28**:439–48
45. Lin MX, Xu HX, Lu MD, et al. Diagnostic performance of contrast-enhanced ultrasound for complex cystic focal liver lesions: blinded reader study. *Eur Radiol* 2009;**19**:358–69
46. Chen LD, Xu HX, Xie XY, et al. Intrahepatic cholangiocarcinoma and hepatocellular carcinoma: differential diagnosis with contrast-enhanced ultrasound. *Eur Radiol* 2010;**20**:743–53
47. Bartolotta TV, Taibbi A, Matranga D, et al. Hepatic focal nodular hyperplasia: contrast-enhanced ultrasound findings with emphasis on lesion size, depth and liver echogenicity. *Eur Radiol* 2010;**20**:2248–56
48. Kim TK, Han JK, Kim AY, et al. Limitations of characterization of hepatic hemangiomas using a sonographic contrast agent (Levovist) and power Doppler ultrasonography. *J Ultrasound Med* 1999;**18**:737–43
49. Sun HC, Tang ZY, Li XM, et al. Microvessel density of hepatocellular carcinoma: its relationship with prognosis. *J Cancer Res Clin Oncol* 1999;**125**:419–26
50. Quaia E, Forgacs B, Calderan L, et al. Characterization of focal hepatic lesions in cirrhotic patients by Pulse Inversion Harmonic Imaging US contrast specific technique with Levovist. *La Radiologia medica* 2002;**104**:285–94
51. Efremidis SC, Hytioglou P. The multistep process of hepatocarcinogenesis in cirrhosis with imaging correlation. *Eur Radiol* 2002;**12**:753–64

52. Gabata T, Matsui O, Kadoya M, et al. Delayed MR imaging of the liver: correlation of delayed enhancement of hepatic tumors and pathologic appearance. *Abdominal Imag* 1998;**23**:309-13
53. Gehl HB, Bourne M, Grazioli L, et al. Off-site evaluation of liver lesion detection by Gd-BOPTA-enhanced MR imaging. *Eur Radiol* 2001;**11**:187-92
54. Albrecht T, Blomley MJ, Cosgrove DO, et al. Non-invasive diagnosis of hepatic cirrhosis by transit-time analysis of an ultrasound contrast agent. *Lancet* 1999;**353**:1579-83
55. D'Onofrio M, Rozzanigo U, Caffarri S, et al. Contrast-enhanced US of hepatocellular carcinoma. *La Radiologia Medica* 2004;**107**:293-303
56. Manfredi R, Maresca G, Baron RL, et al. Delayed MR imaging of hepatocellular carcinoma enhanced by gadobenate dimeglumine (Gd-BOPTA). *JMRI* 1999;**9**:704-10
57. Albrecht T, Hoffmann CW, Schmitz SA, et al. Phase-inversion sonography during the liver-specific late phase of contrast enhancement: improved detection of liver metastases. *AJR* 2001;**176**:1191-8