

Alexander Huppertz, MD
 Thomas Balzer, MD
 Anthony Blakeborough, MD
 Josy Breuer, MD
 Andrea Giovagnoni, MD
 Gertraud Heinz-Peer, MD
 Michael Laniado, MD
 Riccardo M. Manfredi, MD
 Didier G. Mathieu, MD
 Dieter Mueller, MD
 Peter Reimer, MD
 Philip J. Robinson, MD
 Michael Strotzer, MD
 Matthias Taupitz, MD
 Thomas J. Vogl, MD
 For the European EOB
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¹ From the Institute of Clinical Radiology, Klinikum Grosshadern, University of Munich, Germany (A.H.) and Department of Clinical Development Diagnostics, Schering, Muellerstrasse 178, D-13342 Berlin, Germany (A.H., T.B., J.B.). The complete list of authors and their affiliations is at the end of this article. Received March 15, 2002; revision requested May 29; final revision received May 6, 2003; accepted June 16. Address correspondence to A.H. (e-mail: alexander.huppertz@schering.de).

Author contributions:

Guarantors of integrity of entire study, T.B., A.H. The complete list of author contributions appears at the end of this article.

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Improved Detection of Focal Liver Lesions at MR Imaging: Multicenter Comparison of Gadoteric Acid-enhanced MR Images with Intraoperative Findings¹

PURPOSE: To evaluate the safety and efficacy of gadoteric acid disodium-enhanced magnetic resonance (MR) imaging for the detection of focal liver lesions, with results of histopathologic examination and/or intraoperative ultrasonography used as a standard of reference.

MATERIALS AND METHODS: One hundred sixty-nine patients who were known to have or suspected of having focal liver lesions and were scheduled for liver surgery were included in this study. Results in 131 patients could be included in the efficacy analysis. MR imaging was performed before and immediately and 20 minutes after bolus injection of 0.025 mmol/kg of the liver-specific hepatobiliary contrast agent gadoteric acid. T1-weighted gradient-echo (with and without fat saturation and including dynamic data sets) and T2-weighted fast spin-echo/turbo spin-echo sequences were performed. All images were evaluated on site and by three independent and blinded off-site reviewers. Lesion matching based on the standard-of-reference results was performed. Differences in lesion detection with precontrast and with postcontrast MR images were assessed with the two-sided Wilcoxon signed rank test.

RESULTS: Gadoteric acid was well tolerated. In the on-site review, the number of patients in whom all lesions were correctly matched increased from 89 of 129 patients at precontrast MR imaging to 103 of 129 patients at postcontrast MR imaging. In the off-site evaluation, the number of patients in whom all lesions were correctly matched and the corresponding sensitivity values increased from 72 (55.8%), 68 (52.7%), and 66 (51.2%) with the precontrast images to 88 (68.2%), 69 (53.5%), and 76 (58.9%) with the postcontrast images for readers 1, 2, and 3, respectively. Two of the three blinded readers showed a statistically significant difference in lesion detection between precontrast and postcontrast MR imaging ($P < .001$ and $P = .008$). A large number of additionally correctly detected and localized lesions were smaller than 1 cm.

CONCLUSION: MR imaging with gadoteric acid is safe and improves lesion detection and localization.

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Liver malignancies, including primary liver cancers (1) and metastases, are among the most common tumors in the world. Accurate detection of these tumors is of utmost clinical importance before resection, laser coagulation, or radiofrequency ablation is performed as a potential curative treatment. Palliative interventions such as chemoembolization also require exact lesion localization. The quality of lesion detection is mainly determined by sensitivity and specificity. High sensitivity is necessary for accurate lesion

detection to ensure correct staging, while high specificity prevents tumors from being falsely rated as inoperable and patients with inoperable tumors from being scheduled for surgical procedures.

Relatively noninvasive modalities used to image the liver include ultrasonography (US), computed tomography (CT), and magnetic resonance (MR) imaging; more invasive modalities include CT during arterial portography, angiography, and intraoperative US. Among the noninvasive techniques, MR imaging with an extracellular contrast medium such as gadopentetate dimeglumine or a liver-specific contrast agent has been shown to have higher sensitivity and specificity for lesion detection and characterization than spiral CT (2–5). Liver-specific contrast media already approved and in use include superparamagnetic iron oxide particles, which target the Kupffer cells, and mangafodipir trisodium and gadobenate dimeglumine, which are taken up by hepatocytes (6–8).

The majority of published clinical studies have involved assessment of the accuracy of lesion detection by counting lesions. However, the decision as to whether a patient should undergo surgery and the planning of any surgery require that the number of lesions and the location and nature of each lesion are determined with the highest possible accuracy. Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (gadoteric acid disodium, Primovist; Schering, Berlin, Germany) is an alternative hepatobiliary contrast agent that can be administered as a bolus injection. It is characterized by a higher biliary excretion fraction in humans than is gadobenate dimeglumine (9). Given the unique properties of this contrast agent, the purpose of our study was to evaluate the safety and efficacy of gadoteric acid–enhanced MR imaging for the detection of focal liver lesions, with results of histopathologic examination and/or intraoperative US used as a standard of reference.

MATERIALS AND METHODS

The study was designed as a prospective, open-label, within-patient comparison of the diagnostic performance of nonenhanced and gadoteric acid–enhanced MR imaging in terms of liver lesion detection and localization. Investigators from 14 European centers in six different countries took part in the study and constituted the European EOB Study Group. The study was reviewed and approved by

a central ethics committee and the local ethics committee at each study center. Each patient gave written informed consent.

Patients

Of the 169 patients enrolled, seven were later classified as having dropped out according to the study protocol. Ultimately, results in 162 patients who received the contrast material being tested were valid for safety analysis and were evaluated in the blinded reading. Results in 26 of these 162 patients were excluded from the efficacy analysis because a valid standard of reference for the whole liver was lacking in these cases. There had been major protocol deviations (eg, T1-weighted gradient-echo imaging was not performed 20 minutes after contrast agent injection, or the administered contrast agent dose was $\pm 10\%$ of the required dose) in the examinations of five of the remaining 136 patients; hence, data in these patients were excluded from all per-protocol-set analyses. Thus, the data from the remaining 131 patients (78 men, 53 women; mean age, 58 years; age range, 21–82 years; mean weight, 73 kg; weight range, 41–130 kg) were able to be evaluated for efficacy and were included.

At the time of a patient's inclusion in the study, all diagnostic procedures performed within 4 months prior to the study were recorded. The most common previous procedures were US (144 of 162 patients), followed by spiral CT (138 of 162 patients) and laboratory testing (eg, for tumor markers; 118 of 162 patients). MR imaging with an extracellular contrast medium had been performed in 63 of 162 patients, and biopsy results were available for 53 of 162 patients. Most procedures had been performed within 2 months before a patient entered the study.

Patients at least 18 years of age who were known to have or suspected of having focal liver lesions and who had been referred for both pre- and postcontrast MR imaging of the liver for preoperative work-up were included in the study. The following patients were excluded from the study: those who had received gadoteric acid or any other investigational product within 30 days before study entry, those who had received another contrast material within 24 hours before or after administration of the study agent, those who had received any liver-specific contrast agent within 2 weeks before administration of gadoteric acid, pregnant or nursing women, patients whose con-

dition was clinically unstable or who were scheduled for biopsy or liver surgery within 24 hours after administration of the study agent, and patients with a history of anaphylactoid or anaphylactic reaction to any medication or contrast medium.

In addition, each patient was required to undergo a standard-of-reference examination (either histopathologic examination or intraoperative US), and, thus, only patients scheduled for surgery were included in the study. The resected pathologic specimen was to be sectioned in the same orientation (transverse) in which the MR images were obtained and with a slice thickness that was the same as the section thickness of the MR images (ie, 5–8 mm). Intraoperative US was required to be performed for the evaluation of nonresected segments of the liver. If pathologic examination and/or a complete intraoperative US examination was not performed in an individual case (eg, if a benign lesion was not resected and was not confirmed as benign with intraoperative US), follow-up with CT, MR imaging, or US was performed up to 3 months after the MR imaging study.

Contrast Agent

Gadoxetic acid is a liver-specific hepatobiliary MR imaging contrast agent (10,11) consisting of $C_{23}H_{28}GdN_3Na_2O_{11}$ molecules with a molecular weight of 725.71 Da. Specific properties of gadoteric acid, such as its uptake by the anionic transporter protein in liver cells, have been described previously (12). Gadoteric acid exhibits a T1 relaxivity of $4.9 \text{ L} \cdot \text{mmol}^{-1} \cdot \text{sec}^{-1}$ in water at 0.47 T. This is similar to the T1 relaxivity of gadopentetate dimeglumine ($3.7 \text{ L} \cdot \text{mmol}^{-1} \cdot \text{sec}^{-1}$) in the same conditions. In human plasma the T1 relaxivity of gadoteric acid ($8.2 \text{ L} \cdot \text{mmol}^{-1} \cdot \text{sec}^{-1}$) is higher than that of gadopentetate dimeglumine ($5.0 \text{ L} \cdot \text{mmol}^{-1} \cdot \text{sec}^{-1}$). This may be explained by the higher degree of protein binding of gadoteric acid ($10.7\% \pm 3.4$ [SD]) compared with that of gadopentetate dimeglumine ($1.6\% \pm 4.2$). At 37°C , gadoteric acid has an osmolality of 0.89 osm per kilogram of water and a viscosity of 1.22 mPa. Biodistribution studies in humans revealed that gadoteric acid has a dose-independent renal elimination of 41.6%–51.2%, a biliary elimination of 43.1%–53.2%, and an extrahepatic recirculation of approximately 4% (9).

All patients received a 0.025 mmol -per-kilogram-of-body-weight dose of a

0.25 mol/L solution of gadoxetic acid (volume range, 4.1–13.0 mL). The contrast material was administered as a bolus at a speed of about 2 mL/sec through an intravenous line placed in the cubital vein. The line was flushed with 30 mL of 0.9% saline. Patients were observed for adverse events for 24 hours. All untoward medical occurrences, including local reactions at the injection site, were registered, independently of their potential relationship to the study agent. One clinical investigator in each center classified any adverse event, according to the definitions in the study protocol, as having no relationship or an unlikely, possible, probable, or definite relationship to the contrast agent. The coding of adverse events was performed centrally at Schering by using the Hoechst Adverse Reaction Terminology System. Vital signs (eg, blood pressure, heart rate) were monitored. Clinical laboratory tests (hematologic, coagulation, and clinical chemistry tests, as well as urinalysis) were performed, and their results were evaluated for clinically important changes in all patients.

MR Imaging

All imaging centers had high-field-strength (1.0–1.5-T) MR imaging systems and used phased-array coils that covered the entire liver. Before contrast material administration, patients were imaged with a T2-weighted fast spin-echo/turbo spin-echo breath-hold sequence (repetition time msec/echo time msec, $\geq 3,000/90$ – 120 ; matrix, 192 – 256×256 ; section thickness, 5–8 mm; intersection gap, 0–2 mm) and T1-weighted gradient-echo sequences with and without chemically selective fat suppression (100 – $200/4$ – 8 ; flip angle, 70° – 80° ; matrix, 160 – 192×256 ; section thickness, 5–8 mm; intersection gap, 0–2 mm). Immediately after contrast material administration, dynamic imaging in five sets, with 30 seconds between each set, was performed by using the T1-weighted gradient-echo sequence without fat suppression. Twenty minutes after contrast agent injection, the T1-weighted sequence with fat suppression and the T2-weighted fast spin-echo/turbo spin-echo breath-hold sequence were repeated.

Image Evaluation

Image evaluation was performed as an on-site assessment by one clinical investigator in each center and separately as an off-site assessment by three experi-

enced and independent abdominal radiologists (M.L., D.G.M., P.J.R.) who were not involved in the clinical investigation. These readers were fully blinded to any patient-related information and as to whether a given MR image had been acquired after the administration of contrast material. The readers were informed that the suspicion or knowledge of focal liver lesions was one of the inclusion criteria for the study. This off-site image reading was performed at a core laboratory for digital image management at Bio-Imaging Technologies in Philadelphia, Pa.

Image evaluation by the clinical investigators (ie, the on-site evaluation) included separate assessments of the precontrast T1- and T2-weighted images and of the postcontrast dynamic T1-weighted images and the T1- and T2-weighted images obtained 20 minutes after contrast material injection (ie, in the delayed hepatocyte phase).

The blinded off-site evaluation of the MR images consisted of three parts. Part Ia consisted of the presentation, in a randomized order, of either the precontrast or the postcontrast T1-weighted images only. Part Ib consisted of a randomized presentation of either all precontrast images (ie, the T1- and the T2-weighted precontrast images) or all postcontrast images (ie, the T1-weighted dynamic images and the T1- and T2-weighted images obtained 20 minutes after contrast material injection). In part II (which was performed at least 3 weeks after completion of part I), all precontrast and postcontrast images were displayed and evaluated together. This combined evaluation was intended to reflect clinical practice. Each of the three independent and blinded radiologists assessed all images of all patients in each part of the reading.

The efficacy parameters evaluated included the number of lesions and the size, location, and extension within liver segments of each individual lesion.

As a secondary variable, the performance of gadoxetic acid-enhanced MR imaging for the classification and characterization of focal liver lesions was evaluated both in the clinical on-site evaluation and in the off-site evaluation. Lesion classification consisted of differentiation between benign, malignant, or nonassessable lesions, whereas lesion characterization consisted of defining the specific lesion type. The following focal liver lesions were included in the differentiation process: hepatocellular carcinoma, cholangiocellular carcinoma, metastasis, and focal lymphoma, which were consid-

ered malignant lesions; and adenoma, focal nodular hyperplasia, hemangioma, abscess, focal liver fibrosis or fatty infiltration, regenerative nodule, hydatid cyst, liver cyst, and focus of normal liver tissue in fatty liver, which were considered benign lesions.

Correlation to Standard-of-Reference Results with Lesion Mapping and Lesion Tracking

It was ensured that individual lesions were correctly identified and compared throughout the study by using a method for lesion tracking and matching. For each image assessment, the investigator and the blinded readers completed liver maps by drawing each individual liver lesion on a map according to the Couinaud system of liver anatomy (13). This was to be performed as accurately as possible (relative to lesion size and location) on the liver maps. Each lesion was allocated a number in each assessment—at this stage, the lesion numbers were not consistent between assessments. Similar maps were completed for the intraoperative US and histopathologic findings, as well as the findings at any follow-up examination. The surgeon did not record individual lesions on the map but instead marked the areas of the liver that were resected.

To track the lesions between assessments, an independent radiologist (A.B.) not participating in either the clinical study or the blinded reading compared the standard-of-reference maps with the maps generated after precontrast and postcontrast MR imaging. It was then possible to allocate a new number to each lesion that was consistent across all the assessments.

Statistical Analysis

The primary objective of this study was to calculate sensitivity in lesion detection and correct localization on a per-patient basis. Thus, the alternative hypothesis tested in this study was that the probability of a positive difference between the per-patient sensitivity of a first (eg, precontrast MR imaging) and a second test procedure (eg, postcontrast MR imaging) differed from the probability of a negative difference (ie, the distribution of the difference was not symmetric around zero). For each patient, the sensitivity for detected lesions was calculated as the relative frequency of lesions correctly detected with the procedure versus the frequency of lesions detected with the

standard-of-reference examination. The comparison of the two test procedures—that is, precontrast MR imaging and postcontrast MR imaging—was then based on differences between the per-patient sensitivities for the two test procedures in the individual patient (ie, paired differences). A two-sided Wilcoxon signed rank test, in which the clustered nature of the data was taken into account (14–16), was used for hypothesis testing for various comparisons, with $P < .05$ considered to indicate a statistically significant difference.

The comparison of combined unenhanced and gadoxetic acid-enhanced MR imaging versus unenhanced MR imaging alone (ie, combined vs precontrast imaging) was selected as the primary analysis. Comparisons of postcontrast MR imaging versus precontrast MR imaging and gadoxetic acid-enhanced T1-weighted MR imaging versus precontrast T1-weighted MR imaging were performed as part of a secondary analysis of this primary end point (Fig 1). To investigate the homogeneity of the results, subgroup analyses for sex and for age (ie, patients < 45 years of age, patients between 45 and 65 years of age, and patients 65 years of age or older) were performed.

In addition to the patient-based approach, a lesion-based analysis that included all lesions verified at the standard-of-reference examinations and matched to the lesions detected at the imaging examinations was performed.

Because the majority of therapeutic options in the treatment of focal liver lesions require information on a segmental level, an evaluation on this level was performed by assessing the involvement of liver segments by focal liver lesions. Sensitivity and specificity for “segment affected or not affected by lesion” were estimated in the usual way: sensitivity as $N_{TPS}/(N_{TPS} + N_{FNS})$ and specificity as $N_{TNS}/(N_{TNS} + N_{FPS})$, where N_{TPS} is the number of truly positive segments, N_{FNS} is the number of falsely negative segments, N_{TNS} is the number of truly negative segments, and N_{FPS} is the number of falsely positive segments.

As secondary efficacy variables, lesion classification and characterization at gadoxetic acid-enhanced MR imaging were evaluated and compared with the results of the standard-of-reference procedure. In the on-site evaluation, postcontrast MR imaging was evaluated versus precontrast MR imaging, and in the off-site

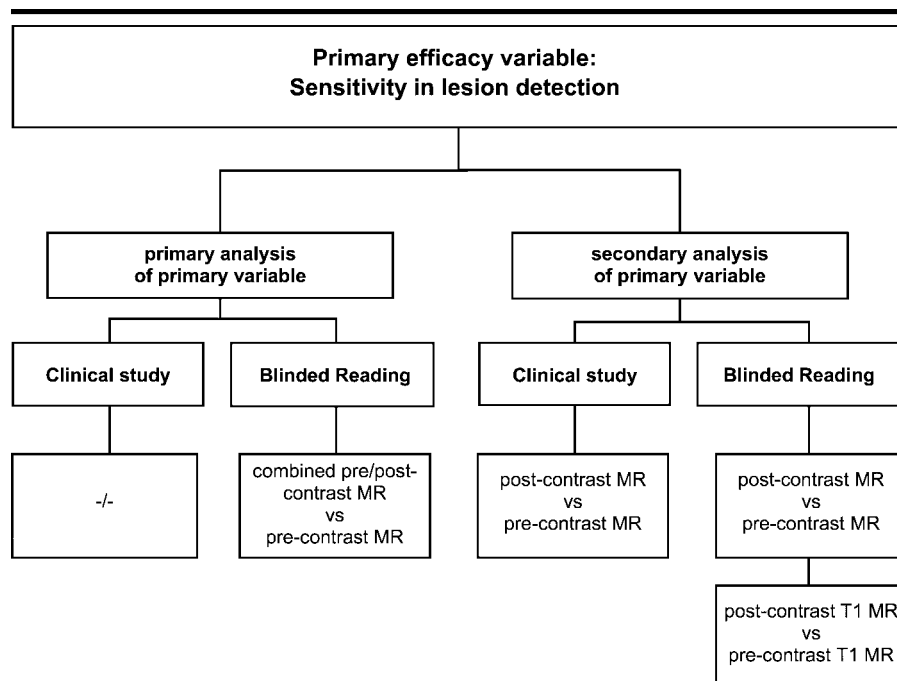


Figure 1. Flowchart depicts the study design. The primary efficacy variable was sensitivity in lesion detection. Different levels of evaluation of this primary efficacy variable were performed. The primary analysis was evaluation of combined precontrast and postcontrast MR imaging versus precontrast MR imaging in the blinded reading. In secondary analyses, postcontrast MR imaging was compared with precontrast MR imaging both in the clinical study and in the blinded reading, and postcontrast T1-weighted MR imaging was compared with precontrast T1-weighted MR imaging in the blinded reading. -/- = not applicable.

evaluation, combined precontrast and postcontrast MR imaging was evaluated versus precontrast MR imaging.

RESULTS

Safety

The contrast medium was well tolerated by the patients. There were no clinically relevant changes in hemodynamic or laboratory parameters. No death or any adverse event leading to the discontinuation of a patient's participation in the study was reported. Of the 162 patients who received the gadoxetic acid injection, a total of 11 (6.8%) reported 21 adverse events. These adverse events were assessed as follows: one (injection site pain) was considered to be definitely related, five (nausea, vasodilatation, taste perversion, akathisia, paresthesia) were considered to be probably related, seven were considered to be possibly related, one was considered unlikely to be related, and seven were considered to be not related to the contrast agent. The most frequently reported adverse events that were definitely, possibly, or probably related to the contrast agent were nausea, vasodilatation, headache, taste per-

ception, and injection site pain (as classified with the Hoechst Adverse Reaction Terminology System terms).

Efficacy

A total of 302 lesions in 131 patients (mean number of lesions per patient, 2.31; range of lesions per patient, 0–8) were verified at the standard-of-reference examinations (ie, histopathologic examination and/or intraoperative US and/or follow-up imaging). Histopathologic specimens were available for 112 patients; these revealed 205 lesions. In 129 patients, intraoperative US of the entire liver or the entirety of the nonresected liver segments was performed. In two patients, the entire liver could not be assessed with intraoperative US, and a follow-up examination with MR imaging and/or CT was performed.

At the standard-of-reference examinations, 215 of the lesions were classified as malignant and 80 were classified as benign. Seven lesions could not be assessed. The majority of the malignant lesions (172 lesions in 96 patients) were metastases (the primary malignancy was gastric or colorectal cancer in 81 patients, breast

Sensitivity and *P* Values for Lesion Characterization in Clinical Study and Blinded Reading

Study	Per-Patient Sensitivity with Postcontrast MR Imaging (%)*	<i>P</i> Value for Postcontrast vs Precontrast MR Imaging Sensitivity Values	Per-Patient Sensitivity with Combined MR Imaging (%)*	<i>P</i> Value for Combined vs Precontrast MR Imaging Sensitivity Values
Clinical Blinded reading	86 (25/29)	<.001		
Reader 1	71 (32/45)	.063	74 (29/39)	.041
Reader 2	68 (27/40)	.004	78 (36/46)	.001
Reader 3	80 (41/51)	<.001	60 (27/45)	.480

* Data in parentheses are those used to calculate the sensitivity values.

cancer in five, unknown in three, pancreatic cancer in two, and other cancers in five). The remaining malignant lesions were hepatocellular carcinoma ($n = 31$) or cholangiocellular carcinoma ($n = 12$). The benign lesions included 41 liver cysts, 18 hemangiomas, seven focal nodular hyperplasias, and 14 other lesions (eg, adenomas, hydatid cysts, abscesses).

Of 131 patients whose results could be included in the efficacy analysis, two were found to have no lesions at the standard-of-reference examination. The patient-based analyses in both the on-site and the off-site evaluations were therefore based on results in 129 patients.

Patient-based Evaluation of On-Site Data

In the patient-based evaluation of correct lesion detection and localization on site, results of precontrast MR imaging were identical to those of the standard-of-reference examination in 89 patients (69.0%). With postcontrast MR images (ie, the dynamic MR images and the images obtained 20 minutes after contrast agent injection in the delayed hepatocyte phase), results matched those of the standard-of-reference examination in 103 patients (79.8%). Overall, in 21 of the 129 patients, postcontrast MR imaging results differed from precontrast MR imaging results. In 19 of these patients (90%), the findings at gadoteric acid-enhanced MR imaging proved to be correct, resulting in a highly significant difference between postcontrast and precontrast MR imaging in correct detection and localization of lesions ($P < .001$). The number of patients with falsely positive results increased from 39 at precontrast MR imaging to 43 at postcontrast MR imaging.

Lesion-by-Lesion Analysis of On-Site Data

When a lesion-based analysis of correct lesion detection and localization was performed (for the 302 lesions verified at the standard-of-reference examination), the percentages of correctly matched lesions were observed to have changed from 80.8% at precontrast MR imaging to 87.4% at postcontrast MR imaging: At precontrast MR imaging, 244 lesions (214 lesions ≥ 1 cm and 30 lesions < 1 cm) were correctly matched, whereas 264 lesions (222 lesions ≥ 1 cm and 42 lesions < 1 cm) were correctly matched at postcontrast MR imaging.

Evaluation of Lesion Classification and Characterization at On-Site Reading

Injection of gadoteric acid also improved the number of patients in whom all lesions were correctly detected, localized, and classified (from 75 [58.1%] to 91 [70.5%] of 129 patients) and in whom all lesions were correctly detected, localized, and characterized (from 66 [51.2%] to 81 [62.8%] of 129 patients). The per-patient sensitivity for classification ($P < .001$) and that for characterization ($P < .001$) (Table) were significantly higher with postcontrast MR imaging than with precontrast MR imaging.

Patient-based Evaluation of Off-Site Data

In the patient-based evaluation of the assessments of all three readers, we found that the readers correctly matched all lesions in more patients with the gadoteric acid-enhanced MR images (Fig 2). The numbers of the 129 patients in whom lesions were correctly matched increased from 72 (55.8%), 68 (52.7%), and 66

(51.2%) with precontrast MR images to 88 (68.2%), 69 (53.5%), and 76 (58.9%) with postcontrast MR images for readers 1, 2, and 3, respectively. When precontrast and postcontrast MR images were presented together, the results for all three readers improved versus their results with the precontrast MR images presented alone, although the results were slightly lower for two of the three readers (ie, reader 1 matched all lesions correctly for 85 [65.9%] patients, while reader 2 matched all lesions correctly for 72 [55.8%] patients and reader 3 matched all lesions correctly for 70 [54.3%] patients) (Fig 3).

Overall, for 30 (reader 1), 29 (reader 2), and 37 (reader 3) of the 129 patients, postcontrast MR imaging results differed from those at precontrast MR imaging. In 26 (87%), 19 (66%), and 27 (73%) of these patients, the findings at gadoteric acid-enhanced MR imaging were correct. For readers 1 and 3, this constituted a statistically significant difference ($P < .001$ for reader 1, $P = .008$ for reader 3) in favor of gadoteric acid-enhanced MR imaging. When combined precontrast and postcontrast MR images were compared with precontrast images alone, the difference was significant for one reader ($P = .006$ for reader 1 vs $P = .101$ and $P = .059$ for readers 2 and 3, respectively).

To evaluate the effect of gadoteric acid at T1-weighted MR imaging alone, the precontrast T1-weighted MR images were compared with the postcontrast T1-weighted MR images. The results of all three readers demonstrate the superiority of gadoteric acid-enhanced MR imaging: With postcontrast T1-weighted MR images, reader 1 correctly matched all lesions in 83 (64.3%) of the 129 patients, reader 2 correctly matched all lesions in 70 (54.3%) patients, and reader 3 correctly matched all lesions in 68 (52.7%) patients. However, with unenhanced T1-weighted MR images, reader 1 correctly matched all lesions in 69 (53.5%) patients, reader 2 correctly matched all lesions in 64 (49.6%) patients, and reader 3 correctly matched all lesions in 61 (47.3%) patients. This increase in accuracy with gadoteric acid-enhanced MR images was statistically significant for two of the three readers ($P = .007$ and $P = .024$ for readers 1 and 3, respectively, vs $P = .060$ for reader 2).

The numbers of 131 patients for whom the readers recorded at least one falsely positive lesion at precontrast MR imaging were 55 (42.0%), 25 (19.1%), and 25 (19.1%) for readers 1, 2, and 3, respectively. These numbers increased for all



Figure 2. Transverse MR images obtained at 1.5 T in a 59-year-old man suspected of having multiple liver metastases from a primary colon carcinoma. (a) Nonenhanced half-Fourier single-shot turbo spin-echo image (4.4/64; flip angle, 140°) shows a cyst (arrow) in the ventral part of segment V. (b) Nonenhanced T1-weighted gradient-echo fat-suppressed breath-hold image (124/4.8; flip angle, 75°) confirms the presence of the lesion, but no additional lesions are clearly delineated at this level. (c) Image obtained 20 minutes after administration of 0.025 mmol/kg of gadoxetic acid with the same parameters used to obtain **b** shows additional lesions that do not demonstrate uptake of the liver-specific contrast agent. On the basis of findings in this image, a lesion (straight arrow) in the lateral part of segment V/segment VI and a subcapsular lesion (curved arrow) in segment VI were suspected. Note the biliary enhancement in the common hepatic duct (arrowhead) caused by the hepatobiliary excretion of the contrast agent. Results of histopathologic examination confirmed a 7-mm-diameter metastasis in segment V/segment VI and a 16-mm-diameter metastasis in segment VI.

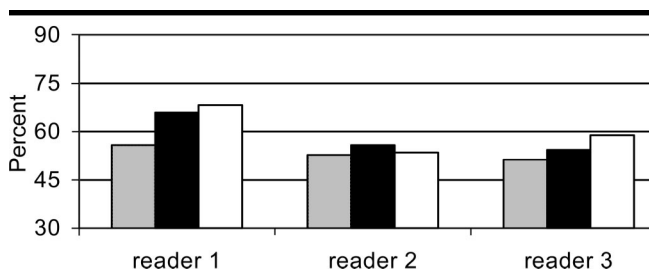


Figure 3. Graph shows the percentage of 129 patients in whom all lesions were correctly matched for each MR image set. All three readers had higher values with postcontrast MR images. For readers 1 and 3, the results were higher when postcontrast MR images were presented alone. Gray bars = precontrast MR images alone, black bars = pre- and postcontrast MR images together, and white bars = postcontrast MR images alone.

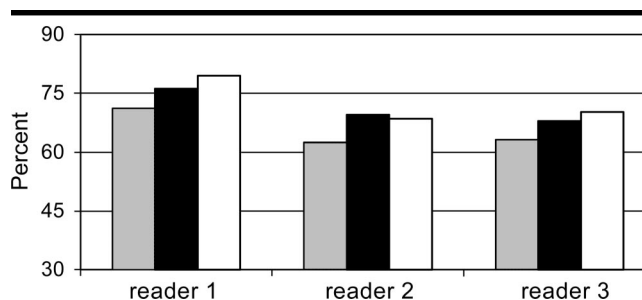


Figure 4. Graph shows the percentage of 302 lesions that were correctly detected and localized (according to standard-of-reference results) with each MR image set. For the three readers, increases in the percentage of correctly detected and localized lesions were observed that ranged from 3.3% to 8.3% with postcontrast versus precontrast MR images and from 4.3% to 5.0% with combined versus precontrast MR images. Gray bars = precontrast MR images alone, black bars = pre- and postcontrast MR images together, and white bars = postcontrast MR images alone.

three readers at postcontrast MR imaging (to 64 [48.9%], 36 [27.5%], and 40 [30.5%] for readers 1, 2, and 3, respectively).

Lesion-by-Lesion Analysis of Off-Site Data

When a lesion-based analysis of the off-site data was performed (for the 302 lesions verified at the standard-of-reference examination), the numbers of correctly matched lesions were 215 (71.2%), 197 (65.2%), and 191 (63.2%) with the precontrast MR images and 240 (79.5%), 207 (68.5%), and 212 (70.2%) with the postcontrast MR images for readers 1, 2, and 3, respectively. As in the patient-based evaluation, two of the three blinded readers had a slightly lower percentage when precontrast and postcon-

trast MR images were presented together: Readers 1, 2, and 3, respectively, correctly matched 230 (76.2%), 210 (69.5%), and 205 (67.9%) lesions (Fig 4).

As in the clinical portion of the study, in this portion of the study, more small lesions were detected on postcontrast than on precontrast MR images (Fig 5): The 215, 197, and 191 lesions, respectively, that were correctly matched by readers 1, 2, and 3 with the precontrast MR images represented 193, 183, and 177 lesions 1 cm or larger and 22, 14, and 14 lesions smaller than 1 cm, whereas the 240, 207, and 212 lesions, respectively, that were correctly matched by readers 1, 2, and 3 with the postcontrast MR images represented 205, 190, and 189 lesions 1

cm or larger and 35, 17, and 23 lesions smaller than 1 cm.

Segment-Level Evaluation of Off-Site Data

A total of 1,029 liver segments were identified at the standard-of-reference examinations. With the precontrast MR images, reader 1 had 268 true-positive results, 564 true-negative results, 111 false-positive results, and 86 false-negative results, while reader 2 had 264 true-positive results, 572 true-negative results, 103 false-positive results, and 90 false-negative results and reader 3 had 235 true-positive results, 601 true-negative results, 74 false-positive results, and 119

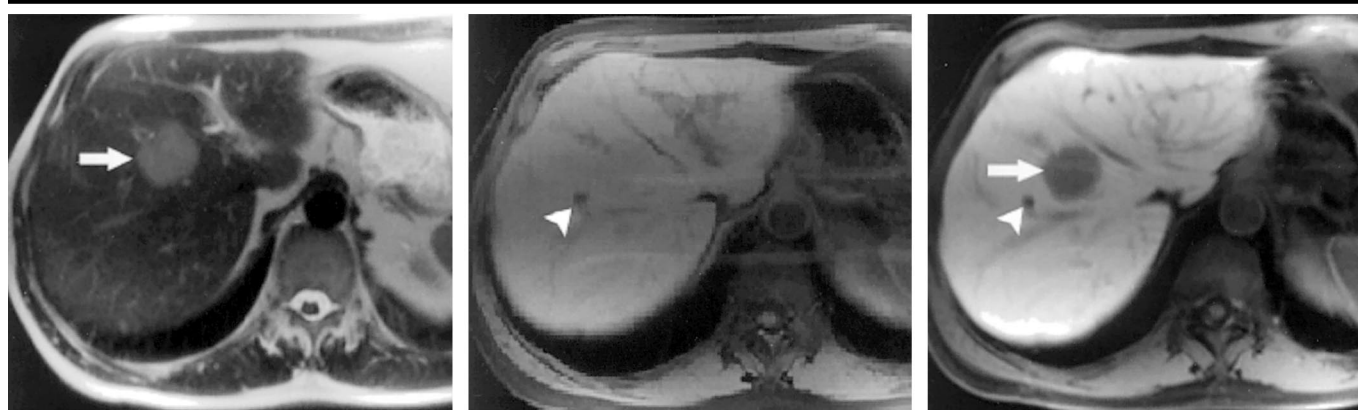


Figure 5. Transverse MR images of the liver obtained at 1.5 T show metastasis of thyroid carcinoma in a 53-year-old man. (a) Nonenhanced half-Fourier single-shot turbo spin-echo image (4.4/64; flip angle, 140°) shows a central, moderately hyperintense lesion (arrow) in segment VIII. (b) On a T1-weighted fat-saturated image (124/4.1; flip angle, 75°), the lesion is not clearly depicted. (c) On an image obtained 20 minutes after administration of 0.025 mmol/kg of gadoxetic acid with the same parameters used to obtain b, the increase of liver-to-lesion contrast allows clear delineation and localization of the lesion (arrow). Note the additional small cyst (arrowhead) in segment VIII depicted in b and c. In a, the lesion is depicted in an anatomically inferior section. Artifacts of nonuniform signal intensity caused by coil geometry are visible in anterior and posterior portions of the liver on b and c.

false-negative results. Hence, with the precontrast MR images, for readers 1, 2, and 3, respectively, sensitivity values were 75.7%, 74.6%, and 66.4%, and specificity values were 83.6%, 84.7%, and 89.0%.

With the postcontrast MR images, reader 1 had 283 true-positive results, 554 true-negative results, 121 false-positive results, and 86 false-negative results, while reader 2 had 278 true-positive results, 583 true-negative results, 92 false-positive results, and 76 false-negative results and reader 3 had 244 true-positive results, 584 true-negative results, 91 false-positive results, and 110 false-negative results. Hence, with the postcontrast MR images, sensitivity increased for all three readers (to 79.9%, 78.5%, and 68.9% for readers 1, 2, and 3, respectively), whereas specificity slightly decreased for two readers (to 82.1%, 86.4%, and 86.5% for readers 1, 2, and 3, respectively).

With the combination of precontrast and postcontrast MR images, reader 1 had 268 true-positive results, 554 true-negative results, 121 false-positive results, and 86 false-negative results, while reader 2 had 277 true-positive results, 581 true-negative results, 94 false-positive results, and 77 false-negative results and reader 3 had 247 true-positive results, 589 true-negative results, 86 false-positive results, and 107 false-negative results. Hence, when a combination of precontrast and postcontrast MR images was evaluated, results comparable to those with postcontrast MR images were obtained (sensitivity: 75.7%, 78.3%, and

69.8% and specificity: 82.1%, 86.1%, and 87.3% for readers 1, 2, and 3, respectively).

Evaluation of Lesion Classification and Characterization at Off-Site Reading

In our evaluation of a secondary end point in the off-site assessment, we again found that administration of gadoxetic acid improved the classification and characterization of focal liver lesions (Fig 6). For two of the three readers, the per-patient sensitivity for classification was significantly higher with postcontrast MR images alone ($P = .001$, $P = .051$, and $P < .001$ for readers 1, 2, and 3, respectively). The per-patient sensitivity for lesion classification with combined precontrast and postcontrast MR images was significantly higher for only one reader ($P = .175$, $P = .001$, and $P = .081$ for readers 1, 2, and 3, respectively). For two of the three readers, the per-patient sensitivity for lesion characterization (Table) was significantly higher with postcontrast MR images alone ($P = .063$, $P = .004$, and $P < .001$ for readers 1, 2, and 3, respectively) or with combined pre- and postcontrast MR images ($P = .041$, $P < .001$, and $P = .480$ for readers 1, 2, and 3, respectively) than with precontrast MR images alone.

Subgroup Analysis

The results of comparison of the data for male and female patients and com-

parison of the data among the three age subgroups were similar and were comparable with the results in the overall patient population in both the on-site and off-site evaluations.

DISCUSSION

MR imaging is an established diagnostic modality for the evaluation of liver lesions. With the advent of high-performance spoiled T1-weighted gradient-echo sequences, coverage of the entire liver during a single breath hold is standard in clinical practice. In combination with the use of nonspecific extracellular contrast media, dynamic imaging now enables differentiation of the phases of hepatic perfusion and, thereby, characterization of focal liver lesions (4).

During the past decade, several liver-specific MR imaging contrast agents have been developed and investigated in clinical studies with the objective of further increasing the performance of MR imaging of the liver, especially in terms of lesion detection (6–8,14). The increase in liver-to-lesion contrast observed when these agents are used enables focal liver lesions to be detected more easily and localized more precisely. Some of these contrast agents, however, cannot be injected as a bolus, making it impossible to use them with dynamic imaging. The new liver-specific contrast medium gadoxetic acid offers the possibility of performing both dynamic and liver-specific (ie, hepatocyte-phase) MR imaging and

may enable high lesion detection rates and the ability to characterize focal liver lesions (17,18).

One of the many requirements for an organ-specific contrast medium is that it have a good safety profile. The high tolerability of currently used extracellular MR imaging contrast agents represents a standard that has not been fully achieved so far with available liver-specific contrast media. The results of our study suggest that the tolerability of gadoxetic acid is within a range that is comparable with reported ranges for the tolerability of extracellular gadolinium-based contrast agents (5,9,17–20).

Better understanding of liver anatomy has led to improvements in segmental resection surgery, and, as a result, patient outcome has improved markedly (21). Resection of malignant hepatic lesions has gained an important role in the management of primary liver tumors and metastatic disease. Results of clinical studies have shown that preoperative hepatic imaging techniques, particularly MR imaging after the administration of a liver-specific contrast agent, have high sensitivity and specificity values for the detection of focal liver lesions (14,22). Results of another study in which intraoperative US was performed revealed that intraoperative US yielded additional information that facilitated segmental resection in nearly 50% of patients and led to changes in the surgical approach in 15% of patients (23). Other researchers investigating primary and secondary liver malignancies reported an intraoperative change of surgical strategy in up to 42% (24) and 44% (25) of cases when intraoperative US was used. These data indicate that the currently available preoperative imaging tools still lack necessary accuracy and further illustrate that sensitivity is a relative measure that depends on the definition of “truth.”

Thus, in comparing our results in detecting lesions by using a liver-specific contrast agent and an independent off-site evaluation with the results of published clinical studies, we should consider the level of reference or “truth.” Studies in which results of histopathologic examination or intraoperative US of the entire liver are used as a standard of reference are relatively rare. Reports of most of these studies describe calculation of sensitivity and specificity values for correct lesion detection on the basis of lesion counting (5,14). In a multicenter phase III study involving the liver-specific contrast agent gadobenate dimeglu-

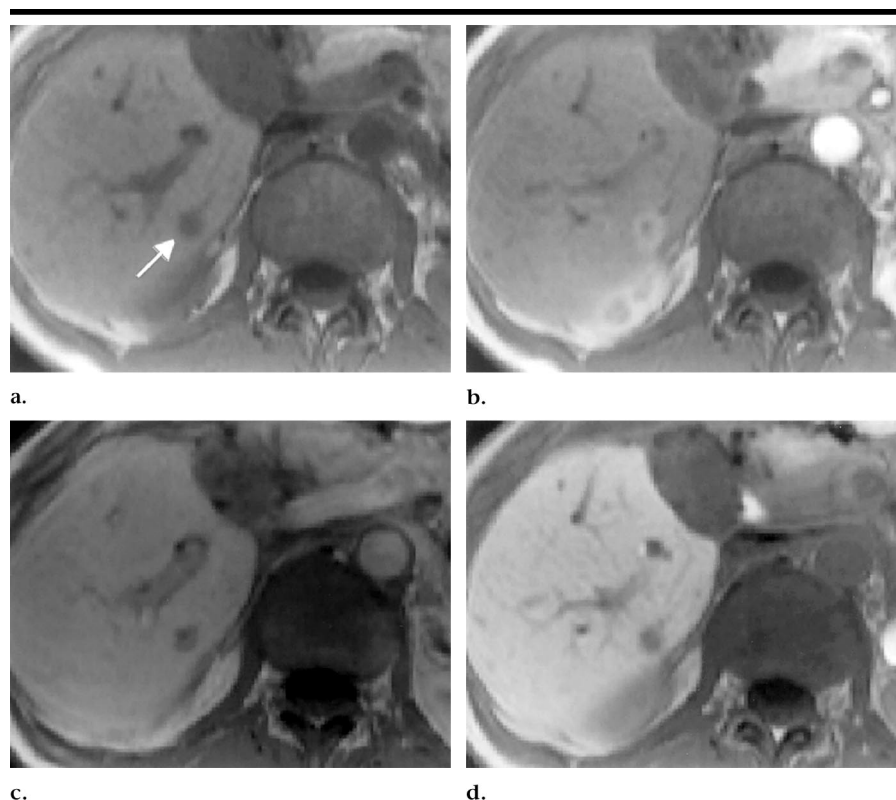


Figure 6. Transverse T1-weighted gradient-echo MR images (141/4.1, 75° flip angle) of the liver obtained at 1.5 T show a hypervascular metastasis from primary gastric leiomyosarcoma in a 61-year-old woman. (a) Nonenhanced image shows a small hypointense lesion (arrow) in segment VI. (b) On an image obtained about 15 seconds after administration of 0.025 mmol/kg of gadoxetic acid (ie, during the arterial phase), the lesion shows high degree of peripheral enhancement, which is characteristic of hypervascular lesions. (c) Image obtained about 60 seconds after contrast agent administration (ie, during the portal venous phase) shows the rapid washout of the contrast agent. (d) On an image obtained 20 minutes after contrast agent injection, the lesion shows no substantial uptake of the liver-specific contrast agent in the delayed phase. These images demonstrate the ability of MR imaging performed with the liver-specific contrast agent gadoxetic acid to yield dynamic information comparable to that provided by MR imaging performed with non-liver-specific extracellular contrast agents.

mine and a study protocol similar to that used in our study, three off-site reviewers had sensitivity values between 61.0% and 67.3% at precontrast MR imaging performed with T1- and T2-weighted spin-echo sequences (6). After contrast enhancement, sensitivity increased to values between 69.3% and 79.9%. A limitation of that study was that not all patients underwent a complete standard-of-reference examination; this complicates a comparison of the results of that study with our results because of the different approach to “truth” in terms of the reference standard and evaluation approach. In addition, lesion matching was not performed in that study.

We hypothesized that the most frequently published values for sensitivity and specificity do not reflect a realistic picture owing to the described method-

ologic limitations. In the present study, we therefore used more strict criteria in the evaluation of sensitivity in lesion detection. In addition to evaluating the ability to detect focal liver lesions by counting lesions per patient—which does not allow a clear distinction between, for example, truly and falsely positive lesions—we also performed a lesion-by-lesion analysis and a per-patient analysis based on lesion matching. These analyses were performed throughout with the highest possible standard of reference—results of histopathologic examination and/or intraoperative US—and for all images to prove the presence and location of each individual lesion. To the best of our knowledge, no previous report of a study involving this kind of individual lesion tracking with only intraoperative confirmation in a compara-

bly large patient population has been published. Given the strict criteria of our study, we expected our results to be numerically lower when compared with those of other published studies.

Our results show a consistent improvement in lesion detection after injection of gadoxetic acid at the level of patient-based and lesion-based analysis in both the on-site and off-site assessments. All existing lesions were correctly identified in the majority of patients and more lesions in total were correctly detected at gadoxetic acid-enhanced MR imaging. Our study data revealed better results for lesion detection and localization in the on-site evaluation, which is hardly surprising in that the on-site evaluation was performed by physicians who were familiar with the imaging equipment, the imaging protocols, and the image review workstations used. Although on one hand, an off-site blinded independent review eliminates much of the potential for bias, on the other hand, it imposes a condition that does not exist in clinical routine by also excluding any knowledge of patient-related information in that only standardized image material is presented.

In the blinded reading, we observed that the readers performed slightly better with the postcontrast MR images alone than with the combined pre- and postcontrast MR images. Two of three readers were able to correctly match all lesions in a slightly higher number of patients when the unenhanced T1-weighted MR images were not available. One explanation for this could be the "visual overflow" that might be experienced by the readers when a higher number of images are available. It could also be that the readers rejected the suspicion of liver lesions on postcontrast T1-weighted MR images in comparison with precontrast MR images because of a lack of experience and confidence with the new contrast agent gadoxetic acid.

The increases (of between 3.3% and 8.3%) in the percentages of correctly detected lesions that we observed between the precontrast and postcontrast MR image assessments in the blinded off-site evaluation can be considered to be relevant. In our study, a high number of lesions that were additionally correctly detected and localized with gadoxetic acid-enhanced MR images were smaller than 10 mm. The size of a hepatic metastasis is an important prognostic factor. Results of a study that included patients with metastatic colorectal cancer revealed that nearly 50% of all liver metastases detected with intraoperative US had a di-

ameter of less than 10 mm (26). This underlines the importance of lowering the detection threshold as a prerequisite for improving patient outcome. According to our study data, use of gadoxetic acid will enable this detection threshold to be lowered.

In our study, the improvement in the number of correctly detected lesions at the various levels of evaluation outweighed the slight increase in false-positive lesion detections. In this context, the use of results of intraoperative US as a standard of reference for the evaluation of the nonresected portions of the liver should be critically discussed as a limitation of this study. Ultimately, only 205 of the 302 standard-of-reference-proved lesions were confirmed at histopathologic examination (which was considered the highest standard of reference). Intraoperative US is believed to be the examination with the highest accuracy when hepatectomy specimens are not available, but sensitivity of intraoperative US is likely to be lower than the sensitivity of pathologic examination. The reported sensitivity of intraoperative US varies between 80% and 98% (24,26,27). False-negative results occur mainly with subcapsular lesions because intraoperative US is limited in its ability to cover the superficial subcapsular regions of the entire liver. Therefore, some lesions detected at MR imaging that were classified as falsely positive owing to nonconfirmation of the lesion by the intraoperative US results might in fact have been positive but missed at intraoperative US.

Despite the superiority of our data to some clinical data from comparisons of the benefits of invasive intraoperative US with the benefits of noninvasive diagnostic imaging methods (24–26), the accuracy of contrast material-enhanced MR imaging in the correct detection and localization of focal liver lesions seems low and the number of false-positive results remains relatively high, revealing the need for further efforts to increase the accuracy of liver MR imaging. The use of three-dimensional sequences with lower section thicknesses and image reconstruction in different planes (28,29) in combination with the use of the liver-specific contrast agent gadoxetic acid could be a promising approach.

The levels of correct classification and characterization of focal liver lesions were only secondary variables in this "detection study." The reason for that was the carefully selected patient population, which included only patients scheduled for surgery. The variety of focal liver le-

sions in our study was therefore relatively limited, and malignant lesions predominated. The distribution of lesions in our study is not typical of that seen in the general population of patients undergoing liver imaging, which includes a higher proportion of patients with benign lesions or no lesions.

In our study, a high percentage of the benign lesions were cystoid lesions, which have unique MR imaging features (eg, long T2, nonenhancement) that improve their conspicuity and facilitate their differentiation from malignancies. These lesions could have artificially increased the sensitivities for all evaluation parameters.

Within the selected population in this study, our data indicate that use of gadoxetic acid has the potential to improve lesion classification and characterization. Results of previous studies have revealed that imaging after injection of gadoxetic acid has dynamic properties very similar to those of dynamic imaging after injection of extracellular gadolinium-based contrast media (17,18), which is the current MR imaging method of choice for characterization of focal liver lesions (30). However, to prove the effectiveness of this new liver-specific contrast medium in lesion classification and characterization in a more general population, additional studies must be performed.

Furthermore, whether the use of gadoxetic acid (as the first liver-specific contrast agent that can be administered as a bolus injection and has an efficient extracellular phase and a liver-specific phase in a clinically acceptable time frame) can change the indications for liver MR imaging must still be proved. The costs of MR imaging, the limited volume coverage at MR imaging compared with that at CT (which complicates screening for widespread metastases with MR imaging), and the duration of the MR imaging examination limit liver MR imaging at present to use in a restricted patient population.

In conclusion, gadoxetic acid is a safe MR imaging contrast agent that can be rapidly injected and improves detection and correct localization of focal liver lesions. In addition, use of this liver-specific contrast agent increases the ability to classify and characterize focal liver lesions correctly.

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Authors: Alexander Huppertz, MD, Thomas Balzer, MD, Ahmed Ba-Salamah, MD, Anthony Blakeborough, MD, Josy Breuer, MD, Lluís Castellés Fusté, MD, Rosa Dominguez-Oronoz, MD, Andrea Giovagnoni, MD, Renate Hammerstingl, MD, Gertraud Heinz-Peer, MD, Werner Judmaier, MD, Michael Laniado, MD, Riccardo M. Manfredi, MD, Didier G. Mathieu, MD, Koenraad J. Mortelé, MD, Dieter Mueller, MD, June F. C. Olliff, MD, Simon P. Olliff, MD, Peter Reimer, MD, Maximilian F. Reiser, MD, Philip J. Robinson, MD, Johannes Seitz, MD, Kohkan Shamsi, MD, Michael Strotzer, MD, Matthias Taupitz, MD, Bernd Tombach, MD, Gianluca Valeri, MD, Bernard E. Van Beers, MD, Thomas J. Vogl, MD.

Author affiliations: Klinikum Grosshadern, University of Munich, Germany (A.H., M.F.R.); Department of Clinical Development Diagnostics, Schering, Berlin, Germany (A.H., T.B., J.B.); Royal Hallamshire Hospital, Sheffield, England (A.B.); Hospital Valle de Hebrón, Barcelona, Spain (L.C.F., R.D.O.); University of Ancona, Italy (A.G., G.V.); Johann-Wolfgang-Goethe-University Frankfurt, Germany (R.H., T.J.V.); Allgemeines Krankenhaus der Stadt Wien, Universitätsklinik für Radiodiagnostik, Vienna, Austria (G.H.P., A.B.S.); University Hospital Innsbruck, Austria (W.J.); Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Germany (M.L.); Policlinico Agostino Gemelli, University Cattolica del Sacro Cuore of Rome, Italy (R.M.M.); Hôpital Henri Mondor, Creteil, France (D.G.M.); Brigham and Women's Hospital, Boston, Mass (K.J.M.); Georg-August Universität, Göttingen, Germany (D.M.); Queen Elizabeth Hospital, Birmingham, England (J.F.C.O., S.P.O.); Städtisches Klinikum Karlsruhe, Germany (P.R.); St James University Hospital Trust, Leeds, England (P.J.R.); Berlex Laboratories, Montville, NJ (K.S.); University Hospital, Regensburg, Germany (J.S., M.S.); Universitätsklinikum Charité, Medizinische Fakultät der Humboldt-Universität, Berlin, Germany (M.T.); Westfälische Wilhelms Universität Münster, Germany (B.T.); and Université Catholique de Louvain, St-Luc University Hospital, Brussels, Belgium (B.E.V.B.).

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