Radiology

Multicenter, Double-Blind, Randomized, Intraindividual Crossover Comparison of Gadobenate Dimeglumine and Gadopentetate Dimeglumine for Breast MR Imaging (DETECT Trial)[1]

Laura Martincich, MD
Matthieu Faivre-Pierret, MD
Christian M. Zechmann, MD
Stefano Corcione, MD
Harrie C. M. van den Bosch, MD
Wei-Jun Peng, MD
Antonella Petrillo, MD
Katja C. Siegmann, MD
Johannes T. Heverhagen, MD
Pietro Panizza, MD
Hans-Björn Gehl, MD
Felix Diekmann, MD
Federica Pediconi, MD
Lin Ma, MD
Fiona J. Gilbert, MD
Francesco Sardanelli, MD
Paolo Belli, MD
Marco Salvatore, MD
Karl-Friedrich Kreitner, MD
Claudia M. Weiss, MD
Chiara Zuiani, MD

Purpose: To intraindividually compare 0.1 mmol/kg doses of gadobenate dimeglumine and gadopentetate dimeglumine for contrast material–enhanced breast magnetic resonance (MR) imaging by using a prospective, multicenter double-blind, randomized protocol.

Materials and Methods: Institutional review board approval and patient informed consent were obtained. One hundred sixty-two women (mean age, 52.8 years ± 12.3 [standard deviation]) enrolled at 17 sites in Europe and China between July 2007 and May 2009 underwent at least one breast MR imaging examination at 1.5 T by using three-dimensional spoiled gradient-echo sequences. Of these, 151 women received both contrast agents in randomized order in otherwise identical examinations separated by more than 2 but less than 7 days. Images, acquired at 2-minute or shorter intervals after contrast agent injection, were evaluated independently by three blinded radiologists unaffiliated with enrollment centers. Histopathologic confirmation was available for all malignant lesions (n = 144), while benign lesions were confirmed either by using histopathologic examination (n = 52) or by at least 12-month diagnostic follow-up (n = 20) with mammography and/or ultrasonography. Determinations of malignant lesion detection rates and diagnostic performance (sensitivity, specificity, accuracy, positive predictive value [PPV], and negative predictive value [NPV]) were performed and compared (McNemar and Wald tests). A full safety assessment was performed.

Results: Significant superiority for gadobenate dimeglumine was noted by readers 1, 2, and 3 for malignant lesion detection rate (91.7%, 93.1%, 94.4% vs 79.9%, 80.6%, 83.3%, respectively; $P \leq .0003$). Readers 1, 2, and 3 reported significantly superior diagnostic performance (sensitivity, specificity, and accuracy) for breast cancer detection with gadobenate dimeglumine (91.1%, 94.5%, 95.2% vs 81.2%, 82.6%, 84.6%; 99.0%, 98.2%, 96.9% vs 97.8%, 96.9%, 93.8%; 98.2%, 97.8%, 96.7% vs 96.1%, 95.4%, 92.8%, respectively; $P \leq .0094$) and significantly superior PPV (91.1%, 85.2%, 77.2% vs 80.7%, 75.5%, 60.9%, respectively; $P \leq .0002$) and NPV (99.0%, 99.4%, 99.4% vs 97.8%, 98.0%, 98.1%, respectively; $P \leq .0003$). No safety concerns were noted with either agent.

Conclusion: Gadobenate dimeglumine is superior to gadopentetate dimeglumine for breast cancer diagnosis.

Clinical trial registration no. NCT00486473 (*http://www.clinicaltrials.gov/*).

Supplemental material: *http://radiology.rsna.org/lookup/suppl/doi:10.1148/radiol.10100968/-/DC1*

[1] From the Department of Diagnostic Imaging, Institute for Cancer Research and Treatment (IRCC), Istituto per la Ricerca e la Cura del Cancro (IRCC), Fondazione piemontese per l'oncologia, Strada Provinciale 142-Km 3,95, 10060 Candiolo, Turin, Italy (L. Martincich). The affiliations of the other authors are listed at the end of this article. Received May 13, 2010; revision requested July 7; final revision received August 24; accepted September 1; final version accepted September 8. **Address correspondence to** L. Martincich (e-mail: *laura.martincich@ircc.it*).

Breast cancer is the second leading cause of cancer deaths after lung cancer worldwide. Approximately 192 370 new cases of invasive breast cancer and 62 280 cases of in situ cancer were estimated to have occurred in the United States alone in 2009, while more than 40 000 women and men were estimated to have died of the disease (1). In the United States, the overall breast cancer incidence rates have remained relatively stable since 2003, although screening programs and improved early cancer detection have led to a steady decrease in the incidence of invasive cancer and an increase in the incidence of in situ cancer (1).

Of the techniques available for breast cancer detection and staging, magnetic resonance (MR) imaging is the most sensitive. However, despite superior diagnostic performance relative to conventional mammography and ultrasonography (US) (2–15), MR imaging is currently recommended by the American Cancer Society as a screening procedure for high-risk women only (16). In looking to refine existing guidelines for surveillance of women at high and moderately increased risk of breast cancer, a large study (the Evaluation of Imaging Methods for Secondary Prevention of Familial Breast Cancer [EVA] trial [17]) has recently confirmed that the highest sensitivity for breast cancer detection is achieved by using MR imaging. Any means to improve the diagnostic performance of MR imaging still further could greatly affect the initial approach to patient work-up and the subsequent treatment and outcome of patients with diagnosed disease and may also have an effect on screening guidelines.

To maximize the diagnostic information attainable, it is essential to optimize image acquisition to better depict and characterize nodules following contrast agent administration. Recently, two intraindividual crossover studies demonstrated improved diagnostic performance with the high relaxivity MR contrast agent gadobenate dimeglumine (MultiHance; Bracco Imaging, Milan, Italy) relative to the standard relaxivity agent gadopentetate dimeglumine (Magnevist; Bayer HealthCare, Berlin, Germany) when administered at equivalent doses of 0.1 mmol per kilogram of body weight (18,19). However, both comparison studies were small-scale single-center studies. Our aim was to intraindividually compare 0.1 mmol/kg doses of these agents for breast MR imaging by using a prospective, multicenter, double-blind design, with images evaluated individually by three independent, blinded readers.

Advances in Knowledge

- Three independent blinded readers reported significantly better cancer detection rate with gadobenate dimeglumine than with gadopentetate dimeglumine when these agents were administered to the same patients at an equivalent dose of 0.1 mmol/kg body weight (91.7%–94.4% vs 79.9%–83.3%, $P \leq .0003$).
- The negative predictive values (NPVs) (ie, the proportion of patients with negative test results who received a correct diagnosis) were always above 97% and were significantly higher for gadobenate dimeglumine (99.0%–99.4% vs 97.8%–98.1%, $P \leq .0003$).
- The positive predictive values (PPVs) (ie, the proportion of patients with positive test results who received a correct diagnosis) were also significantly higher for gadobenate dimeglumine (77.2%–91.1% vs 60.9%–80.7%, $P \leq .0002$).

Implications for Patient Care

- The NPV of breast MR imaging was very close to 100% with both agents, indicating that the risk of overlooking malignant lesions with MR imaging is extremely low; these data confirm that MR imaging is an accurate tool for screening women at high risk of breast cancer and highlight its value for staging breast cancer, determining the most appropriate treatment, and following up patients after breast cancer treatment.
- Gadobenate dimeglumine should be preferred over gadopentetate dimeglumine, because it provided significantly improved diagnostic performance (greater sensitivity, specificity, NPVs, and PPVs).

Materials and Methods

This Phase III, Multicenter, Double-Blind, Randomized, Crossover Study to Compare MultiHance with Magnevist in Contrast-enhanced Magnetic Resonance Imaging of the Breast (DETECT trial) was sponsored by Bracco Imaging. The study was registered at *http://www.clinicaltrials.gov/* (registration no. NCT00486473). Institutional review board and regulatory approval were granted from each center (the 17 enrolling centers correspond to the institutional affiliations of the last 17 authors, excluding the first four authors [L. Martincich, M.F., C.M.Z., and S.C.], who functioned as blinded readers for the study), and all patients gave written informed consent. All investigators and authors had complete access to all study results, and all authors had full control of

Published online before print
10.1148/radiol.10100968

Radiology 2011; 258:396–408

Abbreviations:
CI = confidence interval
DCIS = ductal carcinoma in situ
FPR = false-positive rate
LCIS = lobular carcinoma in situ
NPV = negative predictive value
PPV = positive predictive value
SI = signal intensity

Author contributions:
Guarantors of integrity of entire study, L. Martincich., S.C., A.P., K.C.S., F.D., F.P., M.S.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, L. Martincich, H.C.M.v.d.B., W.J.P., A.P., F.D., F.P., F.S., M.S.; clinical studies, M.F., H.C.M.v.d.B., W.J.P., A.P., K.C.S., J.T.H., P.P., H.B.G., F.D., F.P., L. Ma, F.J.G., F.S., P.B., M.S., K.F.K., C.M.W., C.Z.; statistical analysis, W.J.P., A.P., F.D., F.P.; and manuscript editing, L. Martincich, C.M.Z., H.C.M.v.d.B., W.J.P., A.P., K.C.S., J.T.H., F.D., F.P., M.S.

Potential conflicts of interest are listed at the end of this article.

the data and statistical results included in this report, including data that might represent a conflict of interest to Bracco and employees thereof.

Patients

One hundred sixty-two women with an abnormality at mammography or US (category 3, 4, or 5 for suspicion of malignancy according to the Breast Imaging Reporting and Data System classification [20]) who were highly likely to undergo biopsy or surgery were enrolled at 17 sites in Europe and China between July 2007 and May 2009. Patients were enrolled because of unclear diagnosis at mammography and/or US before histologic confirmation (n = 78), for cancer staging because of equivocal mammographic and/or US findings before histologic confirmation (n = 59), for cancer staging after histologic confirmation but before surgery (n = 11), or for preoperative work-up of a lesion suspected of being malignant (n = 14). No more than 18 women were enrolled at any site. Patients with congestive heart failure (New York Heart Association classification IV) or a known allergy to either agent were ineligible. Patients were also ineligible if they had received or were scheduled to receive another contrast medium within 24 hours before or after either examination, any other investigational compound and/or medical device within 30 days before until 24 hours after administration of the second agent, or were scheduled to undergo any intervention between the two examinations. Finally, patients were ineligible if they were pregnant or lactating or had any medical condition or other circumstance (eg, metallic vascular stent, pacemaker, severe claustrophobia) that would decrease the chances of performing an adequate examination or which would preclude proximity to a strong magnetic field.

The 162 eligible women (mean age, 52.8 years ± 12.3 [standard deviation]; range, 24–87 years) were randomized prospectively to two groups (groups A and B) for breast MR imaging. Patients randomized to group A (n = 82) received gadobenate dimeglumine for the first examination and gadopentetate dimeglumine for the second; patients randomized to group B (n = 80) received the agents in reverse order (Fig 1).

Figure 1

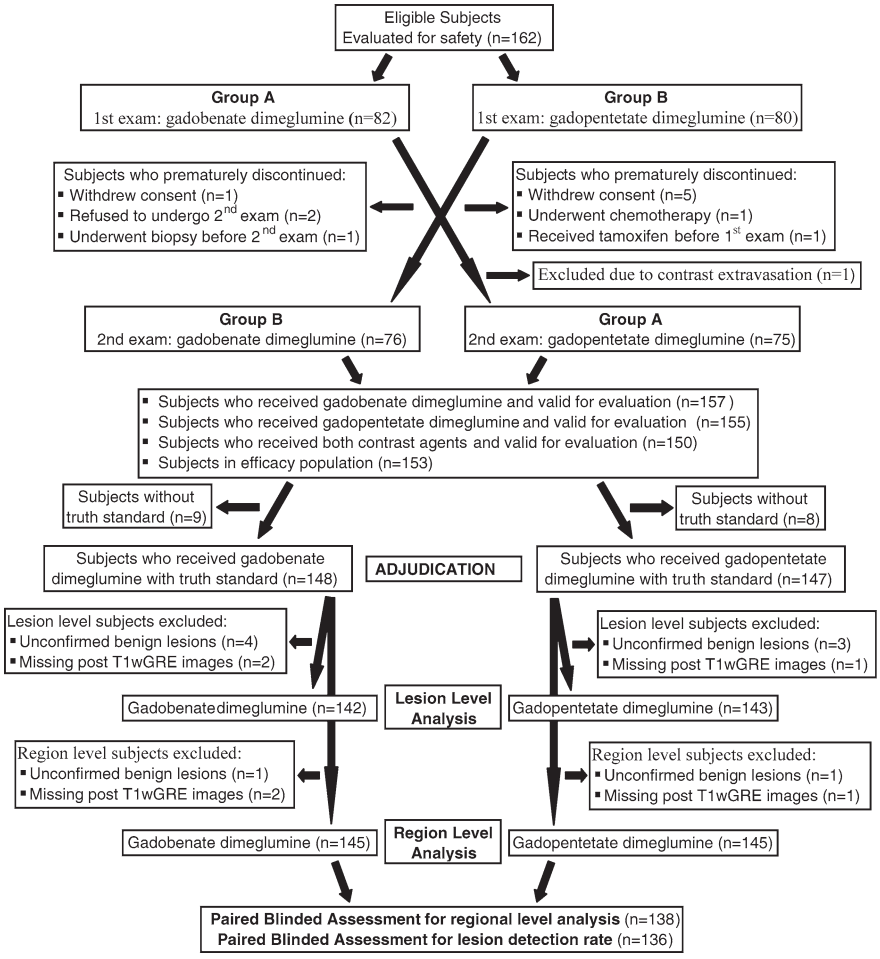

Figure 1: Flow diagram showing subject enrollment and evaluation. *T1wGRE* = T1-weighted gradient echo.

MR Imaging

All procedures were performed at 1.5 T by using commercially available imagers (Sonata [n = 23], Avanto [n = 15], or Symphony [n = 15], Siemens Medical Solutions, Erlangen, Germany; Achieva [n = 30] or Intera [n = 28], Philips Medical Systems, Best, the Netherlands; Signa Excite [n = 43] or Genesis Signa [n = 8], GE Medical Systems, Milwaukee, Wis) equipped with power gradients of at least 30 mT/m. All examinations were performed with the subject in the prone position by using a dedicated double-breast coil. Details of the breast MR imaging examination protocol are given in Appendix E1 (online).

Contrast agent was administered intravenously by using a power injector in 158 (97.5%) women, at a rate of 2 mL/sec in 139 (85.8%) women, 1.8 mL/sec in two (0.01%) women, and 1.5 mL/sec in 17 (0.10%) women, or as a manual bolus in four (2.5%) women at a rate of 1–2 mL/sec for approximately 10 seconds, ensuring that the same rate was used for both examinations in each patient. Each contrast agent was administered at an identical dose of 0.1 mmol/kg (0.2 mL/kg) according to a randomization list and was followed by a 20-mL saline flush. The interval between examinations was longer than 48 hours in all patients to avoid any carryover effect but less than 7 days to ensure full comparability between examinations.

Image Evaluation

All images were evaluated independently by three radiologists (L. Martincich, M.F., C.M.Z., with 5–10 years of experience in breast MR imaging) who were unaffiliated with the study centers and were fully blinded to the contrast agent used in each examination, to all patient clinical and radiologic information, and to the results of all interpretations by on-site investigators.

Images were presented for review on a multimonitor imaging workstation (AquariusNet Viewer for Windows, version 4.4.1.4; TeraRecon, San Mateo, Calif). All routine image processing functions (eg, window and level, zoom, pan) were available. Two independent reading sessions (paired and unpaired assessments) were performed by each reader and are detailed in Appendix E1 (online).

Lesion Tracking (Adjudication)

A fourth independent radiologist (S.C., with 20 years of experience in breast imaging), who was unaffiliated with the study centers and was blinded to all clinical and radiologic information and to the findings of the blinded readers, reviewed all on-site final diagnosis (truth standard) data (patient profiles, original mammographic, US, and histopathologic and/or surgical reports). Histopathologic confirmation was available for all malignant lesions (n = 144). Benign lesions were confirmed either with histopathologic examination (n = 52) or with at least a 12-month diagnostic follow-up (n = 20) with mammography and/or US. All truth-standard lesions were numbered, mapped, and characterized. Lesions identified by each off-site blinded reader were matched against truth-standard lesions characterized by the adjudicator. Lobular carcinoma in situ (LCIS) was considered a malignant lesion, as it is usually a candidate for resection (21,22).

Safety Assessments

All subjects were monitored for adverse events from the time the informed consent was obtained until 24 hours after administration of the first contrast agent, and then from 24 hours before until 24 hours after administration of the second contrast agent. Events were classified as serious or nonserious (mild, moderate, or severe). Event severity and its relationship to the study contrast agent (probable, possible, unrelated, or unknown) were assessed by the investigating radiologist.

Vital sign (blood pressure, heart rate) measurements and 12-lead electrocardiograms were obtained within 1 hour before and after the administration of each contrast agent.

Statistical Analysis

The study was powered to show a difference in sensitivity of approximately 15% between contrast agents for the diagnosis of malignant lesions. By using the McNemar test of equality of paired proportions (nQuery, version 6.01; Statistical Solutions, Cork, Ireland), and assuming 25% discordant pairs, that each subject will have one malignant lesion, and considering a 20% dropout rate, evaluation of 130 subjects was necessary for 90% of power in a two-sided test with an α level of .05.

Comparison of demographic characteristics between groups A and B was performed by using the Student t test for continuous variables and the χ^2 test for categorical variables.

Determinations were performed of the cancer detection rate (number of malignant lesions at MR imaging divided by the number of malignant lesions at histologic examination) and of the diagnostic performance (sensitivity, specificity, accuracy, positive predictive value [PPV], and negative predictive value [NPV] for the diagnosis of malignant lesions) of breast MR imaging at the regional level relative to truth-standard findings. For the latter analysis, a region with at least one confirmed malignant lesion was considered to be a true-positive finding, while a region without a malignant lesion (no lesion or a confirmed benign lesion) was considered to be a true-negative finding. Technically inadequate MR images were considered false-negative, if the region had a malignant lesion at truth standard, or false-positive, if the region had no lesion or a benign lesion. Differences in sensitivity, specificity, and accuracy were determined together with 95% confidence intervals (CIs) and were compared by using the McNemar test. Differences in PPV and NPV were compared by using the Wald test derived from generalized estimating equations with exchangeable working correlation structure.

The false-positive rate (FPR) for malignant lesion detection (malignant lesions detected with MR imaging but not confirmed at histologic examination) and the rate of cancer misdiagnosis (malignant lesions found at histologic examination that were diagnosed as benign with MR imaging) were determined for both contrast agents.

Comparison of lesion conspicuity, lesion border delineation, and diagnostic preference was performed by using the Wilcoxon signed rank test.

Interreader agreement in detecting or assessing lesion nature was determined by using generalized weighted κ statistics and was classified as excellent (κ values > 0.80), good ($\kappa = 0.61$–0.80), moderate ($\kappa = 0.41$–0.60), fair ($\kappa = 0.21$–0.40), or poor ($\kappa \leq 0.20$) (23).

All statistical tests were two sided at the $P < .05$ level of significance and were performed by using dedicated software (SAS, version 8.2; SAS, Cary, NC).

Results

Group A comprised 82 women (mean age, 53.3 years ± 13.4; range, 24–87 years) and group B comprised 80 women (mean age, 52.3 years ± 11.0; range, 24–79 years) (Fig 1). There were no between-group differences in age (P = .63), height (P = .86), or race (P = .36), although the subjects in group B were slightly heavier, with a mean weight of 69.0 kg ± 11.4 versus 65.2 kg ± 9.8 (P = .03). All 162 subjects were evaluated for safety. Of these women, 91 (56.2%) were postmenopausal (24 had surgical menopause), seven (4.3%) were perimenopausal (<1 year without menses), and 64 (39.5%) were premenopausal. Fifty-one (31.5%) subjects had a familial history of breast cancer.

Eleven subjects discontinued after the first examination (seven discontinued after the examination with gadobenate dimeglumine, four discontinued after the examination with gadopentetate

Table 1

Technical Adequacy and Anatomic Coverage

	Reader 1		Reader 2		Reader 3	
Adequacy and Coverage	Gadobenate	Gadopentetate	Gadobenate	Gadopentetate	Gadobenate	Gadopentetate
Technically adequate	146 (98.6)	145 (98.6)	146 (98.6)	145 (98.6)	145 (98.0)	146 (99.3)
Technically inadequate	2 (1.4)	2 (1.4)	2 (1.4)	2 (1.4)	3 (2.0)	1 (0.7)
Anatomic coverage						
Complete	145 (98.0)	143 (97.3)	131 (88.5)	135 (91.8)	135 (91.2)	139 (94.6)
Incomplete	1 (0.7)	2 (1.4)	15 (10.1)	10 (6.8)	10 (6.8)	7 (4.8)

Note.—For the gadobenate dimeglumine group, analysis was based on $n = 148$, and for the gadopentetate dimeglumine group, analysis was based on $n = 147$. Data are numbers of patients. Numbers in parentheses are percentages.

dimeglumine) (Fig 1), while one further patient was excluded from efficacy evaluation because of contrast agent extravasation during the first examination. Therefore, 157 subjects who received gadobenate dimeglumine and 155 who received gadopentetate dimeglumine were assessed. Overall, 150 evaluable subjects received both contrast agents. Truth-standard data were available for 153 subjects (47 who underwent mastectomy [radical or simple], 53 who underwent conservative surgery [segmental or wide excision], 53 who underwent biopsy [core needle, vacuum assisted or surgical]); of these, 148 who received gadobenate dimeglumine and 147 who received gadopentetate dimeglumine were evaluable. These subjects comprised the primary efficacy population for blinded off-site evaluations (separate image sets).

After adjudication, analysis of the cancer detection rate was performed for 142 of 148 subjects who received gadobenate dimeglumine and 143 of 147 subjects who received gadopentetate dimeglumine; blinded paired assessment was performed for 136 subjects who received both contrast agents (Fig 1). At the regional level, analysis was performed for 145 of 148 subjects who received gadobenate dimeglumine and 145 of 147 subjects who received gadopentetate dimeglumine; blinded paired assessment was performed for 138 subjects.

Technical Adequacy and Anatomic Coverage

The three readers considered almost all examinations with both contrast agents to be technically adequate and the coverage to be anatomically complete (Table 1). All technically adequate examinations were included in determinations of diagnostic performance.

Table 2

Size and Grade of 144 Histologically Confirmed Malignant Lesions

Lesion Parameter	Invasive Carcinoma ($n = 127$)	In Situ Carcinoma ($n = 17$)
Size		
≤5 mm	19 (15)	1 (6)
6–10 mm	18 (14)	3 (18)
11–20 mm	44 (35)	3 (18)
>20 mm	36 (28)	4 (24)
Not measurable	10 (8)	6 (35)
Grade		
I, low	7 (6)	1 (6)
II, intermediate	70 (55)	9 (53)
III, high	34 (27)	4 (24)
Not available	16 (13)	3 (18)

Note.—Numbers in parentheses are percentages.

Cancer Detection Rate and FPRs (Lesion-Level Analysis)

A truth-standard diagnosis was available for 216 lesions in 136 (90.7%) of 150 patients available for paired assessment (144 malignant and 52 benign lesions confirmed with histopathologic examination in 132 patients; 20 benign lesions confirmed with follow-up in 10 patients [nota bene, five subjects had histologically confirmed malignant *and* benign lesions, six subjects had histologically confirmed malignant lesions *and* benign lesions confirmed with follow-up]). The 144 histologically confirmed malignant lesions comprised 127 invasive carcinomas (87 invasive ductal, 30 invasive lobular, one invasive tubular, one cribriform, five mixed, and three unspecified) and 17 noninvasive carcinomas (13 DCIS, three LCIS, and one mixed type). The size and grade of the 144 histologically confirmed malignant lesions are summarized in Table 2. The 52 cases of histologically confirmed benign lesions comprised the following: 14 fibrocystic changes, 14 sclerosing adenosis lesions, 10 fibroadenomas, five papillomas, four phylloid tumors, two mastitis, one galactophoritis, one blunt duct adenosis, and one fat necrosis.

Readers 1, 2, and 3 reported significantly superior cancer detection with gadobenate dimeglumine (91.7%, 93.1%, 94.4% vs 79.9%, 80.6%, 83.3%, respectively; $P \leq .0003$) (Table 3). Superiority for gadobenate dimeglumine was reported for all malignant lesion types,

Table 3

Diagnostic Performance for Detection of Malignancies: Cancer Detection in 136 Patients with 144 Malignant Lesions

	Reader 1		Reader 2		Reader 3	
Diagnostic Performance	Gadobenate	Gadopentetate	Gadobenate	Gadopentetate	Gadobenate	Gadopentetate
True cancer lesions at MR imaging	132	115	134	116	136	120
Misdiagnosed cancer lesions	12	29	10	28	8	24
Cancer detection rate (%)*	91.7 (132)	79.9 (115)	93.1 (134)	80.6 (116)	94.4 (136)	83.3 (120)

Note.—Data were based on paired analysis, which includes only lesions with a final truth-standard diagnosis after adjudication. The *P* values were determined with the McNemar test and were $P < .0001$ for readers 1 and 2 and $P = .0003$ for reader 3.

* Numbers in parentheses were used to calculate the percentages on the basis of $n = 144$.

Table 4

Misdiagnosed or Undetected Cancerous Lesions after Administration of Gadobenate Dimeglumine and Gadopentetate Dimeglumine

	After Both Contrast Agents		After Gadopentetate Only		After Gadobenate Only	
Reader and Lesion Type	Misdiagnosed	Not Detected	Misdiagnosed	Not Detected	Misdiagnosed	Not Detected
Reader 1						
IDC	1 (70)	3 (2.5–7)	4 (5–12)	7 (3–15)	0	1 (NA)
ILC	0	0	2 (25,32)	4 (NA, 8–13)	0	0
DCIS	1 (NA)	2 (NA, 100)	0	1 (3)	0	0
LCIS	0	2 (6,40)	0	0	0	0
Unspecified or cribriform	1 (NA)	1 (90)	0	0	0	0
Total	3	8	6	12	0	1
Reader 2						
IDC	0	5 (2.5–10)	4 (9–70)	5 (3–15)	0	0
ILC	0	0	1 (32)	4 (NA, 8–13)	0	0
DCIS	0	3 (NA, 100)	2 (NA, 3)	0	0	0
LCIS	0	2 (6,40)	0	0	0	0
Unspecified or cribriform	0	0	0	2 (NA, 90)	0	0
Total	0	10	7	11	0	0
Reader 3						
IDC	0	4 (3–13)	3 (9,10)	4 (2.5–15)	0	0
ILC	0	1 (13)	3 (6–50)	2 (NA, 10)	0	1 (NA)
DCIS	0	1 (NA)	1 (20)	2 (NA, 100)	1 (40)*	0
LCIS	0	0	0	1 (NA)	0	0
Unspecified or cribriform	0	0	0	2 (NA, 90)	0	0
Total	0	6	7	11	1	1

Note.—All misdiagnosed lesions were characterized as benign. Numbers in parentheses are lesion sizes in millimeters. IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, NA = not available.

* Mixed DCIS and LCIS.

including noninvasive carcinomas (12 [70.6%], 12 [70.6%], and 14 [82.4%] of 17 noninvasive cancers identified with gadobenate dimeglumine compared with 11 [64.7%], 10 [58.8%] and 12 [70.6%] of 17 identified with gadopentetate dimeglumine for readers 1, 2, and 3, respectively). A list of misdiagnosed and undetected cancer lesions with each contrast agent is given in Table 4. No trends in regard to the type or size of the misdiagnosed lesions were apparent. The FPR for malignant lesion detection was similar with the two contrast agents for readers 1 and 2 but was approximately twice as high with gadopentetate dimeglumine for reader 3 (Table 5). All false-positive lesions were between 5 and 10 mm in diameter. The cancer misdiagnosis rates were roughly double with gadopentetate dimeglumine for readers 1, 2, and 3 (4.9%, 6.6%, 11.9% vs 2.6%, 4.0%, 3.5%, respectively) (Table 5). Three-reader agreement for assessing lesion nature was good (76.4%, $\kappa = 0.69$) for gadobenate dimeglumine but only moderate (66.2%, $\kappa = 0.57$) for gadopentetate dimeglumine.

Overall Diagnostic Performance (Region-Level Analysis)

A total of 1530 breast regions were assessed (10 regions per patient;

Table 5

Diagnostic Performance for Detection of Malignancies: FPRs and Cancer Misdiagnosis Rates

	Reader 1		Reader 2		Reader 3	
Diagnostic Performance	Gadobenate	Gadopentetate	Gadobenate	Gadopentetate	Gadobenate	Gadopentetate
No. of lesions at truth standard	227	226	227	226	227	226
No. of additional malignant lesions	14	14	25	18	33	69
No. of misdiagnosed benign lesions	6	11	9	15	8	27
FPR for detection (%)*	5.8 (14/241)	5.8 (14/240)	9.9 (25/252)	7.4 (18/244)	12.7 (33/260)	23.4 (69/295)
Rate of cancer misdiagnosis (%)†	2.6 (6/227)	4.9 (11/226)	4.0 (9/227)	6.6 (15/226)	3.5 (8/227)	11.9 (27/226)

Note.—For the gadobenate dimeglumine group, analysis was based on $n = 142$ patients, and for the gadopentetate dimeglumine group, analysis was based on $n = 143$ patients. Based on unpaired analysis. Includes all lesions detected on MR imaging before adjudication.

* Numbers in parentheses were used to calculate the percentage as follows: number of additional malignant lesions at MR imaging/(number of lesions at truth standard plus additional malignant lesions at MR imaging).

† Numbers in parentheses were used to calculate the rate of cancer misdiagnosis as follows: number of lesions diagnosed wrongly as malignant at MR imaging/number of lesions at truth standard.

Table 6

Diagnostic Performance for Detection of Malignancies: Region-Level Analysis

	Reader 1		Reader 2		Reader 3	
Diagnostic Performance	Gadobenate	Gadopentetate	Gadobenate	Gadopentetate	Gadobenate	Gadopentetate
Total regions	1450	1450	1450	1450	1450	1450
With TP	133	121	138	123	139	126
With TN	1291	1272	1280	1261	1263	1220
With FP	13	29	24	40	41	81
With FN	13	28	8	26	7	23
Sensitivity (%)*	91.1 (133/146)	81.2 (121/149)	94.5 (138/146)	82.6 (123/149)	95.2 (139/146)	84.6 (126/149)
Difference (%)†	10.1 (4.7, 15.5)	. . .	12.2 (6.8, 17.7)	. . .	10.8 (4.6, 17.0)	. . .
P value	.0005	. . .	<.0001	. . .	.0011	. . .
Specificity (%)*	99.0 (1291/1304)	97.8 (1272/1301)	98.2 (1280/1304)	96.9 (1261/1301)	96.9 (1263/1304)	93.8 (1220/1301)
Difference (%)†	1.1 (0.3, 1.9)	. . .	1.3 (0.3, 2.3)	. . .	3.1 (1.5, 4.6)	. . .
P value	.006	. . .	.0094	. . .	.0001	. . .
Accuracy (%)*	98.2 (1424/1450)	96.1 (1393/1450)	97.8 (1418/1450)	95.4 (1384/1450)	96.7 (1402/1450)	92.8 (1346/1450)
Difference (%)†	2.0 (1.1, 2.9)	. . .	2.4 (1.3, 3.4)	. . .	3.8 (2.3, 5.4)	. . .
P value	<.0001	. . .	<.0001	. . .	<.0001	. . .
PPV (%)*	91.1 (133/146)	80.7 (121/150)	85.2 (138/162)	75.5 (123/163)	77.2 (139/180)	60.9 (126/207)
Difference (%)‡	9.9	. . .	10.4	. . .	16.5	. . .
P value	<.0001	. . .	.0002	. . .	<.0001	. . .
NPV (%)*	99.0 (1291/1304)	97.8 (1272/1300)	99.4 (1280/1288)	98.0 (1261/1287)	99.4 (1263/1270)	98.1 (1220/1243)
Difference (0%)‡	1.1	. . .	1.4	. . .	1.3	. . .
P value	<.0001	. . .	<.0001	. . .	.0003	. . .

Note.—Analysis includes only lesions with a final truth standard diagnosis after adjudication. Ellipses indicate that the percentages for differences, 95% CIs (where applicable), and *P* values apply to comparisons of gadobenate dimeglumine with gadopentetate dimeglumine for each reader. FN = false-negative findings, FP = false-positive findings, TN = true-negative findings, TP = true-positive findings.

* Numbers in parentheses were used to calculate the percentages. Sensitivity was calculated as TP/(TP + FN). Specificity was calculated as TN/(TN + FP). Accuracy was calculated as (TP + TN)/(TP + TN + FP + FN). PPV was calculated as TP/(TP + FP). NPV was calculated as TN/(TN + FN).

† Numbers in parentheses are 95% CIs. Differences and 95% CIs were determined by using the paired binary approach. *P* values for differences were determined by using the McNemar test.

‡ *P* values for differences were determined by using the Wald test from generalized estimating equations.

153 patients). After adjudication and exclusion of ineligible subjects, 1450 regions were evaluated for both contrast agents. Readers 1, 2, and 3 reported significantly superior sensitivity (91.1%, 94.5%, 95.2% vs 81.2%, 82.6%, 84.6%, respectively; $P \leq .0011$), specificity (99.0%, 98.2%, 96.9% vs 97.8%, 96.9%, 93.8%, respectively; $P \leq .0094$), and accuracy (98.2%, 97.8%, 96.7% vs 96.1%, 95.4%, 92.8%, respectively; $P < .0001$) with gadobenate dimeglumine for the detection of breast cancer (Table 6). Similarly, highly significant superiority was noted for PPV (91.1%, 85.2%, 77.2% vs 80.7%, 75.5%,

Radiology

Figure 2

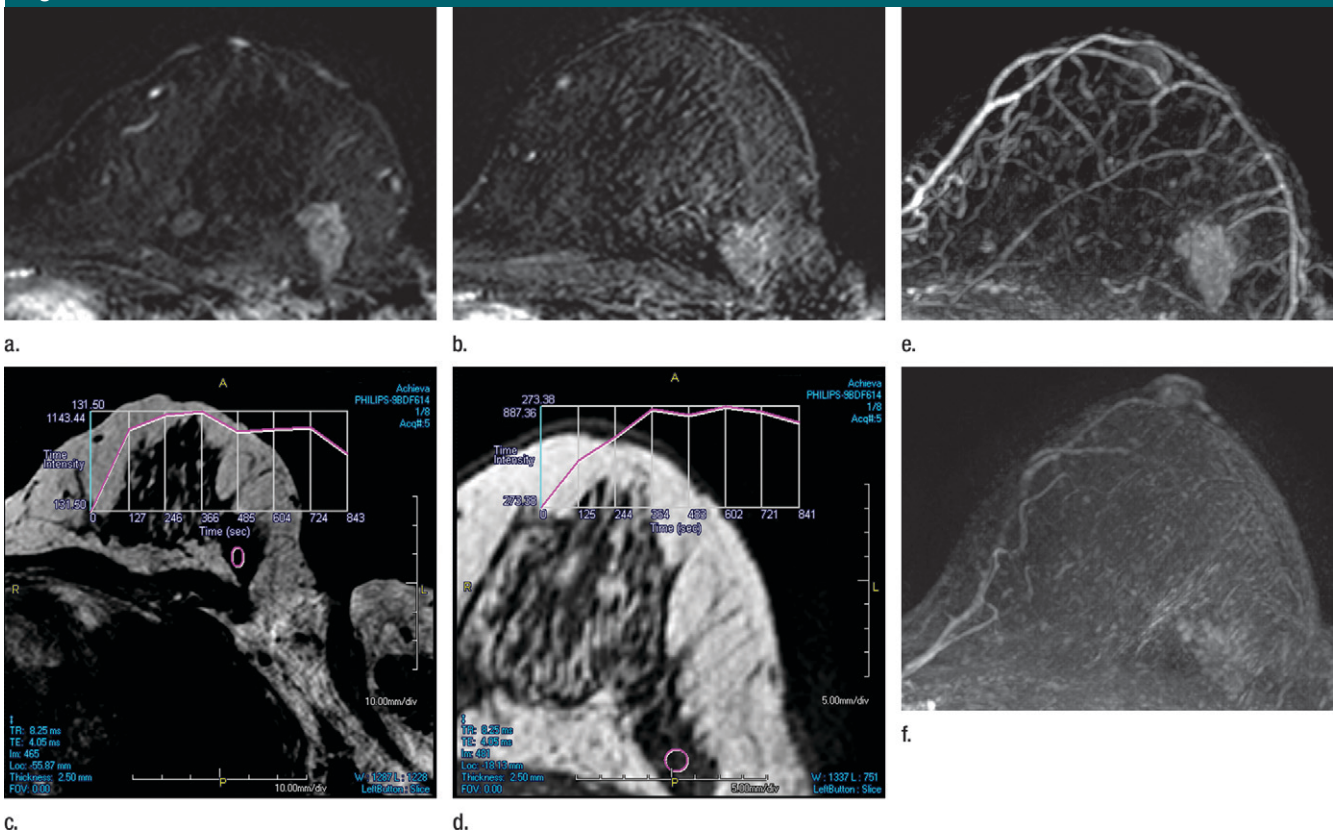

Figure 2: Images obtained in a 50-year-old woman with family history of breast cancer (high-grade ductal carcinoma in situ [DCIS]) who underwent MR imaging because of inconclusive findings at mammography and US before histologic and pathologic examination. **(a)** Subtracted axial image (repetition time msec/echo time msec, 8.24/4.05; flip angle, 25°) from the early acquisition after administration of 0.1 mmol/kg gadobenate dimeglumine reveals a round mass-enhancing area with irregular margins in the left superior external quadrant of the left breast. **(b)** Corresponding subtracted image obtained after administration of 0.1 mmol/kg gadopentetate dimeglumine shows that the lesion is less conspicuous. **(c)** Signal intensity (SI)-time curve after gadobenate dimeglumine administration was classified as type III and indicative of a malignant lesion by all three readers at quantitative analysis. **(d)** SI-time curve after gadopentetate dimeglumine administration was classified as type III by only one reader; the other two readers classified the curve as type II. All readers noted considerably greater SI enhancement after gadobenate dimeglumine administration, as evident from the SI-time curves and the maximum intensity projection reconstructions after **(e)** gadobenate dimeglumine and **(f)** gadopentetate dimeglumine administration. Evaluation of images in matched pairs confirmed unanimous reader preference for gadobenate dimeglumine for lesion conspicuity, border delineation, and overall diagnostic preference.

60.9%, respectively; $P \leq .0002$) and NPV (99.0%, 99.4%, 99.4% vs 97.8%, 98.0%, 98.1%, respectively; $P \leq .0003$). Examples of the improved diagnostic performance with gadobenate dimeglumine are given in Figures 2 and E1 and E2 (online).

Quantitative Assessments

Differences in peak quantitative lesion SI enhancement were determined by readers 1, 2, and 3 for 115, 103, and 112 confirmed malignant lesions and 30, 29, and 28 confirmed benign lesions, respectively. Significantly ($P < .0058$) greater peak SI enhancement with gadobenate dimeglumine was noted by all readers for benign lesions and by readers 1 and 3 for malignant lesions (Fig 3). The mean SI increase with gadobenate dimeglumine relative to gadopentetate dimeglumine ranged between 13.22% (reader 2) and 25.59% (reader 3) for malignant lesions and between 19.27% (reader 1) and 37.63% (reader 3) for benign lesions. No meaningful differences were noted concerning the appearance of SI-time curves.

Matched-Pairs Assessments

Each reader preferred gadobenate dimeglumine over gadopentetate dimeglumine in significantly ($P \leq .0003$) more patients for determinations of lesion conspicuity, lesion border delineation, and overall diagnostic preference (Table 7).

Safety

Eleven adverse reactions to gadopentetate dimeglumine were recorded in seven (4.3%) patients (four reports of nausea, two of dizziness, two of dysgeusia, and one each of vomiting, vertigo, and headache), while eight reactions to gadobenate dimeglumine were recorded in six (3.7%) patients (two of dizziness, two of vertigo, and one each

Table 7

Reader Preference

End Point and Reader	Gadobenate Preferred	No Difference	Gadopentetate Preferred	*P* Value*
Lesion conspicuity				
Reader 1 (*n* = 132)	41 (31.1)	79 (59.8)	12 (9.1)	<.0001
Reader 2 (*n* = 124)	62 (50.0)	47 (37.9)	15 (12.1)	<.0001
Reader 3 (*n* = 134)	94 (70.1)	28 (20.9)	12 (9.0)	<.0001
Lesion border delineation				
Reader 1 (*n* = 132)	36 (27.3)	84 (63.6)	12 (9.1)	.0003
Reader 2 (*n* = 124)	54 (43.5)	60 (48.4)	10 (8.1)	<.0001
Reader 3 (*n* = 134)	78 (58.2)	38 (28.4)	18 (13.4)	<.0001
Overall diagnostic preference†				
Reader 1 (*n* = 139)	60 (43.2)	63 (45.3)	16 (11.5)	<.0001
Reader 2 (*n* = 139)	66 (47.5)	55 (39.6)	18 (12.9)	<.0001
Reader 3 (*n* = 139)	86 (61.9)	33 (23.7)	20 (14.4)	<.0001

Note.—Data are numbers of patients. Numbers in parentheses are percentages of evaluated patients. *n* = number of paired image sets included in the evaluation.

* Determined with the Wilcoxon signed rank test.

† Includes an additional patient without lesions at MR imaging.

Figure 3

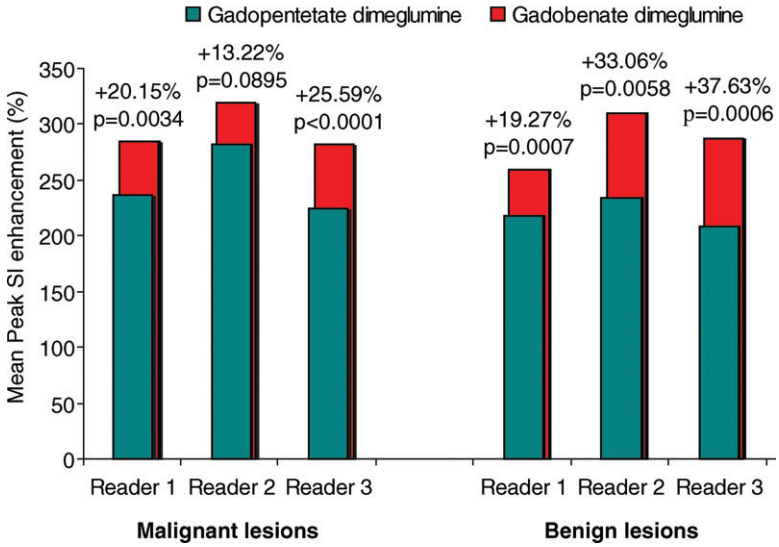

Figure 3: Graph shows peak SI enhancement of malignant and benign breast lesions at MR imaging.

of dysgeusia, decreased blood pressure, increased heart rate, and an abnormal electrocardiogram). All adverse reactions were nonserious, were mild in intensity, and resolved spontaneously within 24 hours. There were no differences in vital sign measurements or electrocardiograms.

Discussion

Multiple studies have shown that breast cancer detection is superior with MR imaging rather than with conventional imaging, both in breasts with known cancer (2–14,17) and in contralateral breasts (24–29). In looking to improve the diagnostic yield of MR imaging, the focus of studies has been primarily on imaging hardware and improved protocol design (30–33) rather than on differences between MR contrast agents. In part, this reflects the similar R1 relaxivity of conventional gadolinium agents (4.3–5.0 $L \cdot mmol^{-1} \cdot sec^{-1}$ at 1.5 T [34]) and, thus, minimal differences in peak lesion SI enhancement and dynamic contrast enhancement behavior when these contrast agents are administered at an equivalent dose. Gadobenate dimeglumine differs from gadopentetate dimeglumine and similar contrast agents in possessing roughly twofold higher R1 relaxivity in vivo owing to weak, transient interaction with serum albumin (34–38). This translates into increased SI enhancement and improved diagnostic performance in breast MR imaging (18,19,39) and other MR applications (40–48). The results of this multicenter, intraindividual crossover study confirm those of earlier single-center (18,19) and interindividual parallel group studies (39) in showing that the greater SI enhancement with gadobenate dimeglumine at 0.1 mmol/kg results in significantly ($P \leq .0003$) greater breast cancer detection and significantly ($P \leq .0094$) better diagnostic performance relative to that achieved with gadopentetate dimeglumine at an equivalent dose. Notably, the improved diagnostic performance with gadobenate dimeglumine was observed for all lesion types, including noninvasive cancers whose accurate identification has previously been considered a potential limitation of MR imaging (12,13). It is important to emphasize that the readers in this study were unaffiliated with the investigational centers, and they were blinded to all patient radiologic and clinical information and to the contrast agent used in each examination. Previous single-center studies to determine the diagnostic performance of breast MR imaging have utilized on-site readers in which the risk of unintentional interpretation bias is inevitably greater, potentially resulting in inflated values for sensitivity, specificity, and overall accuracy. The readers in our study were presented solely with the images from

each examination in randomized order, and all interpretations were made by using standard image interpretation tools.

Given the unreliability of SI-time curves for the confident characterization of lesion nature (22,23,49–51), the better diagnostic performance with gadobenate dimeglumine can be ascribed to improved depiction of lesion morphologic features that are characteristic of either malignancy or benignancy. Features characteristic of invasive malignancy include an irregular shape; irregular, ill-defined, or spiculated margins; and internal inhomogeneous contrast distribution. On the other hand, the features of ductal cancers in situ include the large spectrum of nonmasslike enhancement (52–54). It is likely that the greater SI enhancement with gadobenate dimeglumine enabled better depiction of malignant features, resulting in more true-positive determinations and fewer false-positive and false-negative determinations than with gadopentetate dimeglumine at an equivalent dose. Notably, vital tumor regions indicative of malignant neoangiogenesis are known to be associated with increased microvascular permeability to plasma proteins (55). It is thus possible that gadobenate dimeglumine would prove beneficial in better depicting regions of active tumor growth in which the level of plasma proteins is elevated. In matched-pair assessments of lesion conspicuity, border delineation and overall diagnostic preference, each reader preferred gadobenate dimeglumine in significantly ($P \leq .0003$) more patients than the reader did gadopentetate dimeglumine.

Of particular interest are the predictive values determined by the three readers. The PPV determinations indicate that a breast region with a positive finding determined with gadobenate dimeglumine is up to 91.1% likely to harbor malignant disease and that this percentage is significantly ($P \leq .0002$) higher than the likelihood determined with gadopentetate dimeglumine. In regard to NPV, this value was high (>97%) with both contrast agents, confirming the value of MR imaging in general for breast cancer screening. Nevertheless, a higher NPV was noted with gadobenate dimeglumine by all readers ($P \leq .0003$), indicating that the risk of overlooking malignant disease is significantly lower with this contrast agent.

Concerning the widespread introduction of breast MR imaging into routine practice, this has been hampered by reports of low specificity and high FPRs (56–58). Whereas MR imaging cannot always help to distinguish cancerous from noncancerous abnormalities and while it is not uncommon for the morphologic-kinetic enhancement of benign lesions to simulate malignancy, in our study the cancer misdiagnosis rate was markedly lower with gadobenate dimeglumine for readers 1, 2, and 3 (2.6%, 4.0%, 3.5% for gadobenate dimeglumine vs 4.9%, 6.6%, 11.9% for gadopentetate dimeglumine). Concerning the number of false-positive results, this number was relatively low with both contrast agents for two readers but twice as high with gadopentetate dimeglumine (23.4% vs 12.7%) for the third reader. Although false-positive diagnoses leading to unnecessary biopsies are a concern, from a clinical perspective, the additional true-positive malignant lesions detected should outweigh the occasional misdiagnosis of benign lesions, particularly if patients are at high risk for breast cancer and if the false-positive finding does not prompt the clinician to change the surgical treatment to wider local excision or mastectomy (59,60).

Our study was limited in that there is no comparison with mammography or US and no analysis according to lesion type.

Recently, the EVA trial showed that MR imaging alone provides significantly improved cancer detection relative to mammography and US and that combined MR imaging and mammography provides no significant benefit over MR imaging alone in terms of cancer yield (17). Although no information on the type of gadolinium chelate used in the EVA trial was provided, our results extend these findings to show that the MR contrast agent used can markedly improve the diagnostic performance of breast MR imaging. Specifically, our study findings confirm that gadobenate dimeglumine at a dose of 0.1 mmol/kg is significantly superior to gadopentetate dimeglumine at an equivalent dose for the depiction of malignant breast disease.

Acknowledgments: The authors thank everyone involved in the conducting of this study, especially the following for their invaluable contribution toward the acquisition of data: Liang-ping Zhou, MD (Radiology Department, Cancer Hospital, Fudan University, Shanghai, People's Republic of China); Alfredo Siani, MD (First Department of Radiology, Istituto Nazionale dei Tumori, Fondazione G. Pascale, Naples, Italy); Claus D. Claussen, MD (Department of Diagnostic Radiology, Eberhard Karl University, Tübingen, Germany); Isabella Fedele, MD, and Elena Belloni, MD (Department of Radiology, Scientific Institute, Ospedale San Raffaele, Milan, Italy); Ercan Boga (Department of Diagnostic and Interventional Radiology, Klinikum Bielefeld, Academic Teaching Hospital University of Münster, Bielefeld, Germany); Bernd Hamm, MD (Department of Radiology, Institut für Radiologie, Charité-Universitätsmedizin, Berlin, Germany); Roberto Passariello, MD (Department of Radiological Sciences, University of Rome La Sapienza, Rome, Italy); Liuquan Cheng, MD (Radiology Department, General Hospital of the Chinese People's Liberation Army (PLA), Beijing, People's Republic of China); Senthil Kumar Arcot Ragupathy, MD, and Tanja Gagliardi, MD (Aberdeen Biomedical Imaging Centre, University of Aberdeen, Aberdeen, Scotland); Luca Carbonaro, MD, and Anastassia Esseridou, MD (University of Milan School of Medicine, Department of Medical and Surgical Sciences, Unit of Radiology, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy); Carmine Ierardi, MD, and Enida Bufi, MD (Department of Bioimaging and Radiological Sciences, Institute of Radiology, A. Gemelli Hospital-Catholic University, Rome, Italy); Giovanni Morana, MD, and Raffaella Pozzi-Mucelli, MD (Department of Diagnostic Radiology, Ospedale Cà Foncello, Treviso, Italy); Massimo Bazzocchi, MD (Institute of Radiology, Department of Medical and Morphological Research, University of Udine, Udine, Italy).

Author affiliations: Department of Radiology, Center Oscar Lambret, Lille, France (M.F.); Department of Radiology, German Cancer Research Center, Heidelberg, Germany (C.M.Z.); Senology Unit, University Hospital S. Anna, Ferrara, Italy (S.C.); Department of Radiology, Catharina Hospital, Eindhoven, the Netherlands (H.C.M.v.d.B.); Radiology Department, Cancer Hospital, Fudan University, Shanghai, People's Republic of China (W.J.P.); First Department of Radiology, Istituto Nazionale dei Tumori, Fondazione G. Pascale, Naples, Italy (A.P.); Department of Diagnostic Radiology, Eberhard Karl University, Tübingen, Germany (K.C.S.); Department of Diagnostic Radiology, University Hospital, Philipps University, Marburg, Germany (J.T.H.); Department of Radiology, Scientific Institute, Ospedale San Raffaele, Milan, Italy (P.P.); Department of Diagnostic and Interventional Radiology, Klinikum Bielefeld, Academic Teaching Hospital, University

of Münster, Bielefeld, Germany (H.B.G.); Department of Radiology, Institut für Radiologie, Charité-Universitätsmedizin, Berlin, Germany (F.D.); Department of Radiological Sciences, University of Rome La Sapienza, Rome, Italy (F.P.); Department of Radiology, General Hospital of the Chinese People's Liberation Army (PLA), Beijing, People's Republic of China (L. Ma); Aberdeen Biomedical Imaging Centre, University of Aberdeen, Aberdeen, Scotland (F.J.G.); Department of Medical and Surgical Sciences, Unit of Radiology , University of Milan School of Medicine, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy (F.S.); Department of Bioimaging and Radiological Sciences, Institute of Radiology, A. Gemelli Hospital-Catholic University, Rome, Italy (P.B.); Department of Biomorphological and Functional Sciences, Federico II University, Naples, Italy (M.S.); Department of Diagnostic and Interventional Radiology, Johannes Gutenberg-University, Mainz, Germany (K.F.K.); Department of Diagnostic Radiology, Ospedale Cà Foncello, Treviso, Italy (C.M.W.); and Institute of Radiology, Department of Medical and Morphological Research, University of Udine, Udine, Italy (C.Z.).

Disclosures of Potential Conflicts of Interest: **L. Martincich** Financial activities related to the present article: received €10.000 as a blinded reader for the DETECT study. Financial activities not related to the present article: received $1000 for serving on GE Breast MRI Medical Advisory Board 2010 and €3600 from Bracco for lectures including service on speakers bureaus for European Society of Breast Imaging 2010, European Congress of Radiology 2010, and International Society for Magnetic Resonance in Medicine 2010. Other relationships: none to disclose. **M.F.** No potential conflicts of interest to disclose. **C.M.Z.** Financial activities related to the present article: received a consulting fee from Bracco. Financial activities not related to the present article: none to disclose. Other relationships: none to disclose. **S.C.** Financial activities related to the present article: received support for travel for image review and fees for participation in review activities from Bracco Diagnostics. Financial activities not related to the present article: none to disclose. Other relationships: none to disclose. **H.C.M.v.d.B.** No potential conflicts of interest to disclose. **W.J.P.** No potential conflicts of interest to disclose. **A.P.** No potential conflicts of interest to disclose. **K.S.** Financial activities related to the present article: received payment of costs by study-related breast MR imaging. Financial activities not related to the present article: none to disclose. Other relationships: none to disclose. **J.T.H.** Financial activities related to the present article: received institutional grant and writing assistance, medicines, equipment, or administrative support from Bracco Imaging. Financial activities not related to the present article: received consultancy fees from Sanochernia and Repligen and institutional grants from Bayer Schering, payment for lectures including service on speakers bureaus from Bracco Imaging. Other relationships: none to disclose. **P.P.** No potential conflicts of interest to disclose. **H.B.G.** No potential conflicts of interest to disclose. **F.D.** Financial activities related to the present article: received institutional grant from Bracco. Financial activities not related to the present article: received research grants from BayerSchering, Siemens, GE Healthcare, MeVis, and Sectra for breast cancer diagnostic studies. Other relationships: none to disclose. **F.P.** Financial activities related to the present article: received institutional grant and medicines for the work under consideration from Bracco Imaging. Financial activities not related to the present article: none to disclose. Other relationships: none to disclose. **L. Ma** No potential conflicts of interest to disclose. **F.J.G.** Financial activities related to the present article: NHS Gramplain and University of Aberdeen hospitals were paid for each patient recruited into the study to pay for nurse time for recruitment, MR imaging costs, interpretation costs,, and radiology fees to complete data forms. Financial activities not related to the present article: none to disclose. Other relationships: none to disclose. **F.S.** Financial activities related to the present article: received institutional grant to IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy, related to about 10 patients enrolled in the study. Financial activities not related to the present article: received €11 340.30 for seven different events during the past 36 months from Bracco and €20 000 for participation in ECR and RSNA Congresses in 2007, 2008, and 2009. Other relationships: none to disclose. **P.B.** Financial activities related to the present article: received institutional grant and provision of writing assistance, medicines, equipment, or administrative support from Bracco Imaging . Financial activities not related to the present article: none to disclose. Other relationships: none to disclose. **M.S.** No potential conflicts of interest to disclose. **K.F.K.** No potential conflicts of interest to disclose. **C.W.** Financial activities related to the present article: received a grant for each patient enrolled in the study. Financial activities not related to the present article: none to disclose. Other relationships: none to disclose. **C.Z.** Financial activities related to the present article: received an institutional grant and institutional money for medicines from Bracco. Financial activities not related to the present article: none to disclose. Other relationships: none to disclose.

References

1. Breast Cancer Facts and Figures 2009-2010. National Cancer Institute. http://www.cancer.gov/cancertopics/types/breast. Accessed April 24, 2010.
2. Warner E, Plewes DB, Shumak RS, et al. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. J Clin Oncol 2001; 19(15):3524–3531.
3. Berg WA, Gutierrez L, NessAiver MS, et al. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. Radiology 2004;233(3):830–849.
4. Van Goethem M, Schelfout K, Dijckmans L, et al. MR mammography in the pre-operative staging of breast cancer in patients with dense breast tissue: comparison with mammography and ultrasound. Eur Radiol 2004; 14(5):809–816.
5. Orel SG, Schnall MD. MR imaging of the breast for the detection, diagnosis, and staging of breast cancer. Radiology 2001; 220(1):13–30.
6. Bedrosian I, Mick R, Orel SG, et al. Changes in the surgical management of patients with breast carcinoma based on preoperative magnetic resonance imaging. Cancer 2003;98(3):468–473.
7. Sardanelli F, Giuseppetti GM, Panizza P, et al. Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in fatty and dense breasts using the whole-breast pathologic examination as a gold standard. AJR Am J Roentgenol 2004;183(4):1149–1157.
8. Kuhl C. The current status of breast MR imaging. I. Choice of technique, image interpretation, diagnostic accuracy, and transfer to clinical practice. Radiology 2007;244(2): 356–378.
9. Kuhl CK. Current status of breast MR imaging. II. Clinical applications. Radiology 2007;244(3):672–691.
10. Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol 2008;26(19):3248–3258.
11. Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 2004;292(11):1317–1325.
12. Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 2004; 351(5):427–437.
13. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005;365(9473):1769–1778. [Published correction appears in Lancet 2005; 365(9474):1848.]
14. Hagen AI, Kvistad KA, Maehle L, et al. Sensitivity of MRI versus conventional screening in the diagnosis of BRCA-associated breast cancer in a national prospective series. Breast 2007;16(4):367–374.

15. Berg WA, Zhang Z, Cormack JB, Jong RA, Barr RG, Lehrer DE. Supplemental yield and performance characteristics of screening MRI after combined ultrasound and mammography: ACRIN 666 [abstr]. In: Radiological Society of North America Scientific Assembly and Annual Meeting Program. Oak Brook, Ill: Radiological Society of North America, 2009;103.

16. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57(2):75–89.

17. Kuhl C, Weigel S, Schrading S, et al. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol 2010;28(9):1450–1457.

18. Pediconi F, Catalano C, Occhiato R, et al. Breast lesion detection and characterization at contrast-enhanced MR mammography: gadobenate dimeglumine versus gadopentetate dimeglumine. Radiology 2005;237(1):45–56.

19. Pediconi F, Catalano C, Padula S, et al. Contrast-enhanced MR mammography: improved lesion detection and differentiation with gadobenate dimeglumine. AJR Am J Roentgenol 2008;191(5):1339–1346.

20. American College of Radiology. Breast Imaging Reporting and Data System Atlas. 4th ed. Reston, Va: American College of Radiology, 2003.

21. Foster MC, Helvie MA, Gregory NE, Rebner M, Nees AV, Paramagul C. Lobular carcinoma in situ or atypical lobular hyperplasia at core-needle biopsy: is excisional biopsy necessary? Radiology 2004;231(3):813–819.

22. Li CI, Malone KE, Saltzman BS, Daling JR. Risk of invasive breast carcinoma among women diagnosed with ductal carcinoma in situ and lobular carcinoma in situ, 1988-2001. Cancer 2006;106(10):2104–2112.

23. Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York, NY: Wiley, 1981.

24. Liberman L, Morris EA, Kim CM, et al. MR imaging findings in the contralateral breast of women with recently diagnosed breast cancer. AJR Am J Roentgenol 2003;180(2):333–341.

25. Lee SG, Orel SG, Woo IJ, et al. MR imaging screening of the contralateral breast in patients with newly diagnosed breast cancer: preliminary results. Radiology 2003;226(3):773–778.

26. Slanetz PJ, Edmister WB, Yeh ED, Talele AC, Kopans DB. Occult contralateral breast carcinoma incidentally detected by breast magnetic resonance imaging. Breast J 2002;8(3):145–148.

27. Viehweg P, Rotter K, Laniado M, et al. MR imaging of the contralateral breast in patients after breast-conserving therapy. Eur Radiol 2004;14(3):402–408.

28. Pediconi F, Catalano C, Roselli A, et al. Contrast-enhanced MR mammography for evaluation of the contralateral breast in patients with diagnosed unilateral breast cancer or high-risk lesions. Radiology 2007;243(3):670–680.

29. Brennan ME, Houssami N, Lord S, et al. Magnetic resonance imaging screening of the contralateral breast in women with newly diagnosed breast cancer: systematic review and meta-analysis of incremental cancer detection and impact on surgical management. J Clin Oncol 2009;27(33):5640–5649.

30. Kuhl CK, Schild HH, Morakkabati N. Dynamic bilateral contrast-enhanced MR imaging of the breast: trade-off between spatial and temporal resolution. Radiology 2005;236(3):789–800.

31. Kuhl CK, Jost P, Morakkabati N, Zivanovic O, Schild HH, Gieseke J. Contrast-enhanced MR imaging of the breast at 3.0 and 1.5 T in the same patients: initial experience. Radiology 2006;239(3):666–676.

32. Pinker K, Grabner G, Bogner W, et al. A combined high temporal and high spatial resolution 3 tesla MR imaging protocol for the assessment of breast lesions: initial results. Invest Radiol 2009;44(9):553–558.

33. Schmitz AC, Peters NH, Veldhuis WB, et al. Contrast-enhanced 3.0-T breast MRI for characterization of breast lesions: increased specificity by using vascular maps. Eur Radiol 2008;18(2):355–364.

34. Rohrer M, Bauer H, Mintorovitch J, Requardt M, Weinmann HJ. Comparison of magnetic properties of MRI contrast media solutions at different magnetic field strengths. Invest Radiol 2005;40(11):715–724.

35. Pintaske J, Martirosian P, Graf H, et al. Relaxivity of gadopentetate dimeglumine (Magnevist), gadobutrol (Gadovist), and gadobenate dimeglumine (MultiHance) in human blood plasma at 0.2, 1.5, and 3 tesla. Invest Radiol 2006;41(3):213–221 [Published correction appears in Invest Radiol 2006;41(12):859.]

36. 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(12):780–796.

37. Giesel FL, von Tengg-Kobligk H, Wilkinson ID, et al. Influence of human serum albumin on longitudinal and transverse relaxation rates (r1 and r2) of magnetic resonance contrast agents. Invest Radiol 2006;41(3):222–228.

38. Bleicher AG, Kanal E. A serial dilution study of gadolinium-based MR imaging contrast agents. AJNR Am J Neuroradiol 2008;29(4):668–673.

39. Knopp MV, Bourne MW, Sardanelli F, et al. Gadobenate dimeglumine-enhanced MRI of the breast: analysis of dose response and comparison with gadopentetate dimeglumine. AJR Am J Roentgenol 2003;181(3):663–676.

40. Maravilla KR, Maldjian JA, Schmalfuss IM, et al. Contrast enhancement of central nervous system lesions: multicenter intraindividual crossover comparative study of two MR contrast agents. Radiology 2006;240(2):389–400.

41. Rowley HA, Scialfa G, Gao PY, et al. Contrast-enhanced MR imaging of brain lesions: a large-scale intraindividual crossover comparison of gadobenate dimeglumine versus gadodiamide. AJNR Am J Neuroradiol 2008;29(9):1684–1691.

42. Kuhn MJ, Picozzi P, Maldjian JA, et al. Evaluation of intraaxial enhancing brain tumors on magnetic resonance imaging: intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine for visualization and assessment, and implications for surgical intervention. J Neurosurg 2007;106(4):557–566.

43. Rumboldt Z, Rowley HA, Steinberg F, et al. Multicenter, double-blind, randomized, intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine in MRI of brain tumors at 3 tesla. J Magn Reson Imaging 2009;29(4):760–767.

44. Prokop M, Schneider G, Vanzulli A, et al. Contrast-enhanced MR angiography of the renal arteries: blinded multicenter crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine. Radiology 2005;234(2):399–408.

45. Bueltmann E, Erb G, Kirchin MA, Klose U, Naegele T. Intra-individual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine for contrast-enhanced magnetic resonance angiography of the supraaortic vessels at 3 tesla. Invest Radiol 2008;43(10):695–702.

46. Gerretsen SC, le Maire TF, Miller S, et al. Multicenter, double-blind, randomized, intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine for MR angiography of peripheral arteries. Radiology 2010;255(3):988–1000.

47. 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(2):85–94.

48. Balci NC, Inan N, Anik Y, Erturk MS, Ural D, Demirci A. Low-dose gadobenate dimeglumine versus standard-dose gadopentate dimeglumine for delayed contrast-enhanced cardiac magnetic resonance imaging. Acad Radiol 2006;13(7):833–839.

49. Kinkel K, Helbich TH, Esserman LJ, et al. Dynamic high-spatial-resolution MR imaging of suspicious breast lesions: diagnostic criteria and interobserver variability. AJR Am J Roentgenol 2000;175(1):35–43.

50. Stoutjesdijk MJ, Fütterer JJ, Boetes C, van Die LE, Jager G, Barentsz JO. Variability in the description of morphologic and contrast enhancement characteristics of breast lesions on magnetic resonance imaging. Invest Radiol 2005;40(6):355–362.

51. El Khouli RH, Macura KJ, Barker PB, Habba MR, Jacobs MA, Bluemke DA. Relationship of temporal resolution to diagnostic performance for dynamic contrast enhanced MRI of the breast. J Magn Reson Imaging 2009;30(5):999–1004.

52. Fischer U, Kopka L, Grabbe E. Breast carcinoma: effect of preoperative contrast-enhanced MR imaging on the therapeutic approach. Radiology 1999;213(3):881–888.

53. Baum F, Fischer U, Vosshenrich R, Grabbe E. Classification of hypervascularized lesions in CE MR imaging of the breast. Eur Radiol 2002;12(5):1087–1092.

54. Carbonaro LA, Verardi N, Di Leo G, Sardanelli F. Handling a high relaxivity contrast material for dynamic breast MR imaging using higher thresholds for the initial enhancement. Invest Radiol 2010;45(3):114–120.

55. Knopp MV, Weiss E, Sinn HP, et al. Pathophysiologic basis of contrast enhancement in breast tumors. J Magn Reson Imaging 1999;10(3):260–266.

56. Teifke A, Hlawatsch A, Beier T, et al. Undetected malignancies of the breast: dynamic contrast-enhanced MR imaging at 1.0 T. Radiology 2002;224(3):881–888.

57. Heywang SH, Wolf A, Pruss E, Hilbertz T, Eiermann W, Permanetter W. MR imaging of the breast with Gd-DTPA: use and limitations. Radiology 1989;171(1):95–103.

58. Langer SA, Horst KC, Ikeda DM, Daniel BL, Kong CS, Dirbas FM. Pathologic correlates of false positive breast magnetic resonance imaging findings: which lesions warrant biopsy? Am J Surg 2005;190(4):633–640.

59. Pediconi F, Catalano C, Padula S, et al. Contrast-enhanced magnetic resonance mammography: does it affect surgical decision-making in patients with breast cancer? Breast Cancer Res Treat 2007;106(1):65–74.

60. Lee JM, Kopans DB, McMahon PM, et al. Breast cancer screening in *BRCA1* mutation carriers: effectiveness of MR imaging—Markov Monte Carlo decision analysis. Radiology 2008;246(3):763–771.