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

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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, 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 ≤ .0004) and significantly superior PPV (91.1%, 85.2%, 77.2% vs 80.7%, 75.3%, 60.9%, respectively; P ≤ .0002) and NPV (99.0%, 99.4%, 99.4% vs 97.8%, 98.0%, 98.1%, respectively; P ≤ .0003). No safety concerns were noted with either agent.

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 ≤ .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 ≤ .0004) and significantly superior PPV (91.1%, 85.2%, 77.2% vs 80.7%, 75.3%, 60.9%, respectively; P ≤ .0002) and NPV (99.0%, 99.4%, 99.4% vs 97.8%, 98.0%, 98.1%, respectively; P ≤ .0003). No safety concerns were noted with either agent.

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

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

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 (Multi-Hance; 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.

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 the study design, with images evaluated individually by three independent, blinded readers.

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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
S1 = 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., F.P., H.B.G., F.D., F.P., 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.

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 a significantly improved diagnostic performance (greater sensitivity, specificity, NPVs, and PPVs).
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.

**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 = 39), 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 gadothentate dimeglumine for the first examination and gadopentetate dimeglu- mine for the second; patients randomized to group B (n = 80) received the agents in reverse order (Fig 1).

**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).

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

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 standard) data (patient profiles, original mammmographic, 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; Statistica 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 χ² test for categorical variables.

Differences 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 (κ = 0.61–0.80), moderate (κ = 0.41–0.60), fair (κ = 0.21–0.40), or poor (κ ≤ 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 (36.2%) 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
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.

### 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; $P < .0003$) (Table 3). Superiority for gadobenate dimeglumine was reported for all malignant lesion types.
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%, $k = 0.69$) for gadobenate dimeglumine but only moderate (66.2%, $k = 0.57$) for gadopentetate dimeglumine.

### Overall Diagnostic Performance (Region-Level Analysis)

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

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### Table 3

<table>
<thead>
<tr>
<th>Diagnostic Performance</th>
<th>Reader 1</th>
<th>Reader 2</th>
<th>Reader 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gadobenate</td>
<td>Gadopentetate</td>
<td>Gadobenate</td>
</tr>
<tr>
<td>True cancer lesions at MR imaging</td>
<td>132</td>
<td>115</td>
<td>134</td>
</tr>
<tr>
<td>Misdiagnosed cancer lesions</td>
<td>12</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>Cancer detection rate (%)</td>
<td>91.7 (132)</td>
<td>79.9 (115)</td>
<td>93.1 (134)</td>
</tr>
</tbody>
</table>

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

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

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.

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Comparison of Gadobenate and Gadopentetate for Breast MR

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BREAST IMAGING: Comparison of Gadobenate and Gadopentetate for Breast MR

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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; \( P < .001 \)), specificity (99.0%, 98.2%, 96.9% vs 97.8%, 96.9%, 93.8%, respectively; \( P < .0004 \)), 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%,

Table 5

<table>
<thead>
<tr>
<th>Diagnostic Performance</th>
<th>Reader 1</th>
<th>Reader 2</th>
<th>Reader 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gadobenate</td>
<td>Gadopentetate</td>
<td>Gadobenate</td>
</tr>
<tr>
<td>No. of lesions at truth standard</td>
<td>227</td>
<td>226</td>
<td>227</td>
</tr>
<tr>
<td>No. of additional malignant lesions</td>
<td>14</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>No. of misdiagnosed benign lesions</td>
<td>6 (14/241)</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>FPR for detection (%)(^*)</td>
<td>5.8 (14/241)</td>
<td>5.8 (14/240)</td>
<td>9.9 (25/252)</td>
</tr>
<tr>
<td>Rate of cancer misdiagnosis (%)(^*)</td>
<td>2.6 (6/227)</td>
<td>4.9 (11/226)</td>
<td>4.0 (9/227)</td>
</tr>
</tbody>
</table>

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.

Table 6

<table>
<thead>
<tr>
<th>Diagnostic Performance</th>
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<th>Reader 3</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Gadobenate</td>
<td>Gadopentetate</td>
<td>Gadobenate</td>
</tr>
<tr>
<td>Total regions</td>
<td>1450</td>
<td>1450</td>
<td>1450</td>
</tr>
<tr>
<td>With TP</td>
<td>13 (133/146)</td>
<td>121</td>
<td>138</td>
</tr>
<tr>
<td>With TN</td>
<td>3 (1291/1450)</td>
<td>1272</td>
<td>1280</td>
</tr>
<tr>
<td>With FP</td>
<td>13</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>With FN</td>
<td>13</td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>Sensitivity (%)(^*)</td>
<td>91.1 (133/146)</td>
<td>81.2 (121/149)</td>
<td>94.5 (138/146)</td>
</tr>
<tr>
<td>Difference (%)(^*)</td>
<td>10.1 (4.7, 15.5)</td>
<td>...</td>
<td>12.2 (6.8, 17.7)</td>
</tr>
<tr>
<td>P value</td>
<td>.020</td>
<td>...</td>
<td>.001</td>
</tr>
<tr>
<td>Specificity (%)(^*)</td>
<td>99.0 (1291/1304)</td>
<td>97.8 (1272/1301)</td>
<td>98.2 (1280/1304)</td>
</tr>
<tr>
<td>Difference (%)(^*)</td>
<td>1.1 (0.3, 1.8)</td>
<td>...</td>
<td>1.3 (0.3, 2.3)</td>
</tr>
<tr>
<td>P value</td>
<td>.006</td>
<td>...</td>
<td>.004</td>
</tr>
<tr>
<td>Accuracy (%)(^*)</td>
<td>98.2 (1424/1450)</td>
<td>96.1 (1393/1450)</td>
<td>97.8 (1418/1450)</td>
</tr>
<tr>
<td>Difference (%)(^*)</td>
<td>2.0 (1.1, 2.9)</td>
<td>...</td>
<td>2.4 (1.3, 3.4)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.0001</td>
<td>...</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PPV (%)(^*)</td>
<td>91.1 (133/146)</td>
<td>80.7 (121/150)</td>
<td>85.2 (138/162)</td>
</tr>
<tr>
<td>Difference (%)(^*)</td>
<td>9.9</td>
<td>...</td>
<td>10.4</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.0001</td>
<td>...</td>
<td>.0002</td>
</tr>
<tr>
<td>NPV (%)(^*)</td>
<td>99.0 (1291/1304)</td>
<td>97.8 (1272/1300)</td>
<td>99.4 (1280/1288)</td>
</tr>
<tr>
<td>Difference (%)(^*)</td>
<td>1.1</td>
<td>...</td>
<td>1.4</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.0001</td>
<td>...</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

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.
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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...
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BREAST IMAGING

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·mmol⁻¹·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 < .0003) greater breast cancer detection and significantly (P < .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

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

Table 7

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

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

Graph shows peak SI enhancement of malignant and benign breast lesions at MR imaging.
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 ≤ .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 ≤ .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 ≤ .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 cancers 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.

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