Breast Imaging

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Abbreviations:
DCIS = ductal carcinoma in situ
EIC = extensive intraductal component
IDC = invasive ductal carcinoma
ILC = invasive lobular carcinoma
MIP = maximum intensity projection
MLO = mediolateral oblique

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PURPOSE: To prospectively assess accuracy of mammography, clinical examination, ultrasonography (US), and magnetic resonance (MR) imaging in preoperative assessment of local extent of breast cancer.

MATERIALS AND METHODS: Institutional review board approval and informed patient consent were obtained. Results of bilateral mammography, US, and contrast-enhanced MR imaging were analyzed from 111 consecutive women with known or suspected invasive breast cancer. Results were correlated with histopathologic findings.

RESULTS: Analysis included 177 malignant foci in 121 cancerous breasts, of which 89 (50%) foci were palpable. Median size of 139 invasive foci was 18 mm (range, 2–107 mm). Mammographic sensitivity decreased from 100% in fatty breasts to 45% in extremely dense breasts. Mammographic sensitivity was highest for invasive ductal carcinoma (IDC) in 89 of 110 (81%) cases versus 10 of 29 (34%) cases of invasive lobular carcinoma (ILC) (P < .001) and 21 of 38 (55%) cases of ductal carcinoma in situ (DCIS) (P < .001). US showed higher sensitivity than did mammography for IDC, depicting 104 of 110 (94%) cases, and for ILC, depicting 25 of 29 (86%) cases (P < .001 for each). US showed higher sensitivity for invasive cancer than DCIS (18 of 38 [47%], P < .001). MR showed higher sensitivity than did mammography for all tumor types (P < .001) and higher sensitivity than did US for DCIS (P < .001), depicting 105 of 110 (95%) cases of IDC, 28 of 29 (96%) cases of ILC and 34 of 38 (89%) cases of DCIS. In anticipation of conservation or no surgery after mammography and clinical examination in 96 breasts, additional tumor (which altered surgical approach) was present in 30. Additional tumor was depicted in 17 of 96 (18%) breasts at US and in 29 of 96 (30%) at MR, though extent was now overestimated in 12 of 96 (12%) at US and 20 of 96 (21%) at MR imaging. After combined mammography, clinical examination, and US, MR detected additional tumor in another 12 of 96 (12%) breasts and led to overestimation of extent in another six (6%). US showed no detection benefit after MR imaging. Bilateral cancer was present in 10 of 111 (9%) patients; contralateral tumor was depicted mammographically in six and with both US and MR in an additional three. One contralateral cancer was demonstrated only clinically.

CONCLUSION: In nonfatty breasts, US and MR imaging were more sensitive than mammography for invasive cancer, but both MR imaging and US involved risk of overestimation of tumor extent. Combined mammography, clinical examination, and MR imaging were more sensitive than any other individual test or combination of tests.

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With increasing use of reliable percutaneous biopsy techniques, a current goal in breast cancer management is accurate pretreatment planning to allow neoadjuvant chemotherapy or a
single definitive surgical procedure with lymph node sampling, as appropriate. Complete excision of malignant foci is the standard, with the goal of achieving clear margins of excision.

The sensitivity of mammography to the index cancer ranges from 63% to 98% (1-3) and has been reported to be as low as 30%-48% in dense breasts (4,5). Several groups have evaluated the preoperative use of supplemental magnetic resonance (MR) imaging (6-8), ultrasonography (US) (9,10), and both (11,12) after mammography and clinical breast examination to assess the extent of disease within the breast(s). Across these series, a change in management in 11%-15% of patients resulted from additional imaging after mammography; 27%-34% of breasts had additional malignant foci not seen mammographically (6-10,12,13). The purpose of our study was to prospectively assess the accuracy of mammography, clinical examination, US, and MR imaging in the preoperative assessment of the local extent of breast cancer. We further sought to determine whether the accuracy of detection methods varied with breast density or tumor type.

**MATERIALS AND METHODS**

Entrance criteria consisted of women older than 18 years with newly diagnosed invasive breast cancer by means of core biopsy and/or high clinical or mammographic suspicion of invasive breast cancer. Women ultimately selected to have ductal carcinoma in situ (DCIS) either had a larger area of calcifications (>2.5 cm) mammographically or a mass (either clinically or at imaging) and were therefore suspected of having an invasive component. Consecutive patients at the University of Maryland were recruited from September 1999 through January 2002. Women had to (a) agree to undergo bilateral mammography, whole-breast US, and contrast material–enhanced MR imaging of the breasts according to an institutional review board–approved protocol and (b) provide informed consent. Women who were unable to provide consent or undergo MR imaging because of a pacemaker, an aneurysm clip, or a metallic foreign body in or near the eye were excluded, as were patients who had undergone open biopsy before mammography, US, and MR imaging could be performed.

**Imaging and Clinical Examination Techniques**

Bilateral mammography was performed (Lo-Rad MIV unit, Hologic, Danbury, Conn, or DMR Plus, GE Medical Systems, Milwaukee, Wis) and included routine craniocaudal and mediolateral oblique views of the breast(s) and spot- or global-magnification views over the area of the cancer. Findings were recorded prospectively according to the Breast Imaging Reporting and Data System (BI-RADS, lexicon (14) by one of several interpreting radiologists (including W.A.B.) who were qualified according to the Mammography Quality Standards Act and had 2–10 years of experience in mammography. Findings ipsilateral to the cancer, which were mammographically probably benign, suspicious for cancer, or highly suggestive of malignancy, were sampled for biopsy if the patient was a candidate for conservation and if the identification of a malignancy at that site would change the surgical approach. Contralateral findings suspicious for or highly suggestive of malignancy were sampled for biopsy. Mammography had to be performed within 6 weeks of the other imaging studies.

Clinical breast examination was performed by one of two radiologists (including W.A.B.) with 2–10 years of experience in clinical examination at the time of whole-breast US. Any palpable lumps in the breast(s) or axilla, skin thickening or retraction, and nipple discharge or retraction were noted.

Bilateral whole-breast US was performed with knowledge of clinical and mammographic findings either prior to MR imaging or afterward. US was performed by one of two radiologists (including W.A.B.) with 2–10 years of experience in the performance and interpretation of breast US, who were blinded to MR imaging results (US results were recorded prospectively). By using a linear-array broadband transducer with a center frequency of 10 MHz, US was performed and supplemented with a linear-array transducer with a center frequency of 7.5 MHz as needed to penetrate larger breasts (Acoustic Imaging Performa, Tempe, Ariz, or Elegra, Siemens, Issaquah, Wash). For the inner breast, scanning was performed with the patient in the supine position. For the outer breast, the patient was placed in the contralateral posterior oblique position with the ipsilateral arm raised. Survey scanning was performed in transverse and sagittal planes. Discrete lesions were measured in both radial and areolar margins. When multiple suspicious lesions were identified, panoramic display was used whenever possible to document the distance between lesions. Spatial compounding was intermittently used in 20 cases.

Images and perpendicular measurements were documented for all discrete findings other than simple cysts. Biopsy was recommended for all palpable solid masses and for incidental solid masses unless they were (a) circumscribed, oval, uniformly hyperechoic with no posterior features, and nonpalpable or (b) nonpalpable complicated cysts. The latter two classes of lesions were classified as probably benign at US and were recommended for short-interval (6-month) follow-up. If such lesions corresponded to suspicious findings at MR imaging, then biopsy was performed, but the US classification remained probably benign for purposes of analysis. Solid lesions that would otherwise have been considered probably benign but were ipsilateral to cancers were aspirated or sampled for biopsy if a malignant result would change the surgical approach.

MR imaging was performed with the patient in the prone position in a dedicated phased-array breast coil. A 1.5 T (n = 30) or 1.0 T (n = 81) imager (Philips/Marconi Medical Systems, Cleveland, Ohio) was used. Transverse T1-weighted MR images (repetition time msec/echo time msec, 718/14; two signals acquired; field of view, 32–40 cm; section thickness, 5 mm) were obtained in both breasts, followed by sagittal T2-weighted fat-suppressed (6700–7072/68–88; two signals acquired; field of view, 18 cm; section thickness, 4 mm) images at 1.5 T or inversion-recovery (7100/90/90 [inversion time]; flip angle, 90°; one signal acquired; field of view, 18 cm; section thickness, 4 mm) images at 1.0 T acquired in each breast separately. A coronal three-dimensional T1-weighted spoiled gradient-echo volume acquisition (10/3.6; flip angle, 30°; field of view, 34–42 cm; section thickness, 2.0–2.9 mm; matrix, 192 × 256) was then obtained both prior to and then three to six times over a period of 5–8 minutes after intravenous injection of 0.1 mmol per kilogram of body weight of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) over 20 seconds with a power injector.

Zero-filled interpolation was used for a reconstruction matrix of 512 × 512; final resolution was 1.8–2.2 mm in the phase-encoding direction by 1.5–1.9 mm in the frequency-encoding direction with 1.0–1.4-mm section thickness. The dynamic acquisition consisted of three volumes at 1.5 T and six volumes at 1.0 T obtained after administration of contrast material. The dynamic sequence was reviewed with subtraction technique and maximum intensity projection (MIP) technique.
Kinetic analysis was performed for regions of interest that were either drawn around the entire lesion (for lesions ≤ 5 mm) or based on 4 pixels within the lesion for lesions larger than 5 mm. Lesion size was measured on selected MIPs (typically those created from the second postinjection subtraction volume) in sagittal and transverse planes, and hard copies were generated for clinical use.

Morphology (15) and kinetics (16) at MR imaging were evaluated for all enhancing lesions. Enhancement in contiguity with the primary tumor was considered suspicious, regardless of size or morphology. Isolated discrete foci of enhancement that showed at least 70% increase in signal intensity over background in the first 90 seconds after injection and were at least 5 mm in size were considered suspicious unless there was (a) a benign correlate at mammography, US, or unenhanced MR imaging (eg, an intramammary lymph node of normal morphology or a fat-containing mass compatible with fat necrosis at T1-weighted MR imaging and/or at mammography) or (b) a probably benign correlate (such as clustered microcysts at inversion-recovery MR imaging and/or at US).

Lesions smaller than 5 mm with at least 70% increase in signal intensity within the first 90 seconds of injection with washout kinetics (16) were also considered suspicious. Regional areas of enhancement with at least 60% increase in signal intensity within the first 90 seconds after contrast material injection were considered suspicious for malignancy and segmental, or linear clumped enhancement was considered suspicious for DCIS, regardless of kinetics. Lesions that did not meet any of these criteria were considered probably benign, with serial 6-month follow-up MR imaging recommended. Findings were recorded prospectively.

One radiologist (W.A.B.) with 2 years of experience (prior to the study) in contrast-enhanced breast MR imaging interpretation interpreted all MR images; US images and mammograms were reviewed at the time of MR imaging interpretation, and clinical findings were known. Second-look US was performed and targeted to areas of concern on MR images when the lesion was not believed to have been identified at prospective US or mammography.

**Biopsy Technique**

Lesions considered suspicious for or highly suggestive of malignancy with any modality were sampled for biopsy if a malignant result would change the surgical approach. Lesions considered probably benign with any modality were sampled for biopsy if they were ipsilateral to cancer and a malignant result would change the surgical approach. If a lesion was clearly benign with any modality, it was not sampled for biopsy. Core biopsy of more than two separate areas in any given breast was performed if the lesions had a different appearance and malignant results would change the surgical approach.

Preoperative core-needle biopsy was performed with US guidance whenever possible by one of four radiologists (W.A.B.) or fellows who specialized in breast imaging and had 6 months to 10 years of experience. A 14-gauge automated biopsy gun (Monopty; Bard Urological, Covington, Ga) was used to sample lesions with US guidance with a minimum of three passes per lesion. Specimen radiography was performed according to the method of Berg et al (17). A clip (Micromark II; Biopsy division of Ethicon Endo-Surgery, Cincinnati, Ohio) was placed with US guidance for lesions 7 mm or smaller, lesions with poor conspicuity, and those depicted with only US or MR imaging. The clip was placed via an 11-gauge trochar (Bard Urological) according to the method of Kopans (18). When a clip was placed, craniocaudal and true lateral mammographic views were acquired after biopsy. Any malignant or atypical result prompted excision, as did any discordant result. Follow-up was recommended after a benign concordant result.

When a lesion was seen only mammographically and stereotactic biopsy was feasible, the patient was positioned prone on a digital stereotactic table (LoRad DSM; Holologic, Danbury, Conn). An 11-gauge probe (Biopsy division of Ethicon Endo-Surgery) was inserted, positioning was confirmed, and 12 samples were obtained in circumferential fashion with biopsies performed by one of four breast imaging radiologists (W.A.B.) with 2–10 years of experience. Specimen radiography and handling was performed as described earlier. A clip (Micromark II; Biopsy division of Ethicon Endo-Surgery) was placed in the posterior aspect of the biopsy cavity for all stereotactic biopsies.

For lesions first identified at MR imaging, mammograms were reevaluated, and second-look US was performed as needed. MR imaging–guided biopsy was available by using a breast biopsy coil (MRI Devices, Waukesha, Wis, supplied by Philips/Marconi Medical Systems). During the course of this study, no MR imaging–guided biopsies were required, since (a) the lesion could be identified with either US or mammography or (b) wide excision or mastectomy was performed according to patient and physician choice. If the lesion(s) seen only at MR imaging was not identified clearly at initial histopathologic examination, the specimen was resectioned according to the clockface location and distance from the nipple of the MR imaging–depicted abnormality (or abnormalities) after discussion between the radiologist (W.A.B.) and pathologist (O.B.I.).

**Histopathologic Examination**

The reference standard was detailed serial 5-mm slicing of the surgical specimen (lumpectomy or mastectomy) per the method of Egan (19). The histopathologic specimen was viewed by one of two pathologists (O.B.I.) with 3–20 years of experience in breast pathology. Invasive ductal carcinoma (IDC) was graded according to the Nottingham system (20). DCIS was graded according to the nuclear grade (20). The number of slides containing DCIS in relation to the total number of slices was recorded as a surrogate measure of histopathologic size. An extensive intraductal component (EIC) was defined as tumor with an invasive component, where at least 25% of the tumor was DCIS and there were additional discrete foci of DCIS outside the main tumor mass (21,22).

**Analysis**

For each imaging modality, a cancer was considered to be depicted successfully (true-positive) if it appeared to be suspicious for or highly suggestive of malignancy (14,23,24) with that modality. Lesions considered probably benign that proved to be malignant at biopsy were classified as false-negative findings for the modality (or modalities) with which they appeared probably benign (such as a cluster of punctate calcifications or a circumscribed mass at mammography, a complicated cyst at US, or a round or oval focus showing <70% enhancement at MR imaging). If a malignancy was seen only in retrospect or at repeat scanning (such as those seen at second-look US as directed by findings at MR imaging), it was classified as a false-negative finding for that modality. A malignancy was credited with prompting an additional unnecessary biopsy if the biopsy sample was not malignant and that tissue would otherwise not have been sampled histologically. Contralateral probably benign findings were
followed at 6, 12, and 24 months. The rates of additional induced follow-up and compliance with these recommendations were recorded.

The extent of disease was classified as follows by using prospectively defined criteria. Multifocal disease was defined as multiple discrete discontinuous tumor foci within 4 cm in one breast. Multicentric disease was defined as two or more malignant foci separated by 4 cm or more in one breast (25). Disease was classified as diffuse if more than two quadrants had multiple discrete and/or contiguous tumor foci. Imaging findings could be altogether negative for cancer in that breast. Disease was considered to be underestimated with an imaging modality if the size of the cancer was underestimated by at least 2 cm or if additional malignant foci were missed that would have required a wider surgical excision. Disease was considered to be overestimated if the size of the primary tumor was overestimated by at least 2 cm or if there were additional suspicious foci that would have prompted wider surgical excision (or mastectomy) unnecessarily.

In an effort to avoid artificially inflating or deflating the performance of any imaging modality, we sought practical definitions of disease extent. All suspicious findings at imaging were evaluated histopathologically. However, since we are unaware of a circumstance whereby a breast with more than four distinct malignant foci separated by more than 5 cm total would be recommended for conservation, we considered only the performance of the imaging modality in the detection of no more than four suspicious foci in each breast, even if there were diffuse foci of tumor. Similarly, we did not specifically seek to perform core biopsy in more than four lesions per breast in any circumstance.

Statistical Methods

The sensitivity and accuracy of extent determination with each modality for each tumor type were compared with the sensitivity and accuracy of extent determination with mammography by using the McNemar test and t tests to determine statistical significance. The McNemar test was performed for comparisons of the same group of cases or matched pairs of patients when comparing how different imaging modalities performed in the same group of cases. t tests were performed in separate groups of cases—for example, when comparing across cancer types within the same imaging modality.

The corresponding rates for each imaging modality combination were compared with the rates for mammography and clinical examination by using t tests. Independent comparisons were evaluated with the χ² test. The χ² test was also used to evaluate the effect of breast density on the sensitivity of imaging modalities.

Multivariate logistic regressions were performed with SAS version 8.1 software (SAS Institute, Cary, NC). Logistic multiple regression was used to analyze the possible effect of independent variables, such as modality, tumor type, patient age, and breast density, on (a) accurate detection of the presence of cancer and (b) accurate depiction of the extent of cancer (not over- or underestimated). In addition to the use of the McNemar test when comparing matched pairs of cases, we controlled for cluster and/or dependency issues that stemmed from the presence of multiple imaging studies read in the same patient and the presence of multiple lesions by using random-effects logistic regression. We treated the variability across multiple imaging studies read in the same patient as a random effect.

RESULTS

A total of 120 patients were eligible for this study. Seven did not participate because of surgeon preference (n = 3, all with fatty breasts), patient claustrophobia (n = 3), or scheduling constraints (n = 1). Results from two patients were excluded because contrast material injection failed during MR imaging (not recognized by the technologist or patient). In the 111 analyzable women enrolled in study, the mean age was 48.7 years; median age was 48 years (age range, 26–81 years). The presenting (index) lesion proved malignant in 110 of 111 (99.1%) patients (with one focus of architectural distortion yielding atypical ductal hyperplasia at excision); 80 (73%) of these 110 lesions were palpable.

A total of 258 discrete lesions, including 177 malignancies, were correlated with histopathologic findings in 121 breasts with cancer. There were 110 foci of invasive ductal cancer (including 51 foci with associated intraductal carcinoma, of which 19 had an EIC, and five had mixed IDC and invasive lobular carcinoma [ILC]), 38 foci of DCIS (not including EIC cases), 29 foci of ILC, 12 atypical lesions (all excised after initial diagnosis at core biopsy, with the same or benign results, including five atypical papillomas, three lobular carcinomas in situ, two cases of atypical lobular hyperplasia, and two cases of atypical ductal hyperplasia), and 69 concordant benign diagnoses (19 fibroadenomas, 19 fibrocystic changes, nine cases of sclerosing adenosis, seven cases of fibrosis, six papillomas, four ruptured cysts, two lymph nodes, and one case each of foreign body granuloma, chronic inflammatory changes, and lactational changes). One patient presented for evaluation of a new area of architectural distortion mammographically in one breast, which proved to be only atypical ductal hyperplasia at excision, with a contralateral tubular cancer found only at MR imaging (Fig 1).

Surgical Approach: Multifocal and Multicentric Disease

Conservation surgery was performed in 54 breasts, including 48 breasts with single definitive lumpectomy, three with wide excision (quadrantectomy), and three with double lumpectomy. Four of 54 (7%) breasts had positive margins that necessitated repeat excision. Mastectomy was performed in 67 breasts with cancer, including 25 recommended on the basis of combined mammography and clinical examination. Of 96 breasts in which conservation or no surgery was planned after mammography and clinical examination, (a) 24 (25%) were recommended for mastectomy on the basis of MR imaging findings, in which five cases were overestimated, and (b) 19 (20%) were recommended for mastectomy on the basis of US findings, in which four cases were overestimated. There were no breasts in which US findings changed the overall management after MR imaging (all those converted to mastectomy on the basis of US were also converted on the basis of MR imaging). Fourteen mastectomies were performed according to patient choice, and another four followed initial lumpectomy with positive margins.

Of the 121 breasts with cancer, 75 (62%) had solitary tumors, of which seven were classified as “diffuse” because they were larger than 7 cm. Eleven (9%) breasts had diffuse foci of cancer in multiple quadrants; 29 (24%) had multifocal cancer within 4 cm surrounding the index lesion, and six (5%) had isolated multicentric foci of cancer.

Overall Performance

Table 1 summarizes the overall performance of each of the imaging modalities.
and combinations of modalities. The combination of mammography, clinical examination, and MR imaging was the most sensitive, depicting 176 of 177 (99.4%) of all malignant foci. This combination was significantly better than the combination of mammography, clinical examination, and US, which depicted 165 of 177 (93.2%) foci (\(P < .001\)) (Tables 1–3). Mammography combined with clinical examination was more accurate overall than clinical examination alone (\(P < .001\)) or mammography alone (\(P < .001\)). With regard to only dense and heterogeneously dense breasts, however, the accuracy of mammography and clinical examination combined was not significantly better than that of clinical examination alone (131 of 168 [78.0%] foci vs 123 of 168 [73.2%] foci). Because of the substantial risk of false-positive findings with both US and MR imaging, the overall accuracy of US or MR imaging alone or in combination with mammography and clinical examination was no higher than the accuracy of mammography alone (Table 1).

For 96 breasts in which conservation or no surgery was planned after mammography and clinical examination, tumor...
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was missed altogether in eight (8.3%) breasts. In 22 of the 96 (23%) breasts, tumor size was underestimated by at least 2 cm, or additional tumor foci were underestimated. In another three (3.1%), tumor size was overestimated by at least 2 cm, or additional suspicious foci led to overestimation of disease extent (Tables 4–6). Supplemental US after mammography and clinical examination depicted additional tumor foci that expanded the surgical approach in 17 of 96 (18%) breasts. For the 96 breasts, after combined mammography, clinical examination, and US, cancer was missed in two (2.1%), underestimated in 15 (16%), and overestimated in 12 (12%). Supplemental MR imaging after mammography and clinical examination depicted additional tumor that appropriately expanded the surgical approach in 29 of 96 (30%) breasts. With mammography, clinical examination, and MR imaging, extent of disease was only underestimated in one (1%) breast but was overestimated in 20 (21%). The addition of US to this combination of tests provided no additional diagnostic yield. After combined mammography, clinical examination, and US, MR imaging depicted additional tumor in 12 of 96 (12%) breasts in which conservation or no surgery had been planned. Five of 12 (42%) of the breasts with more extensive tumor only at MR imaging resulted from depiction of an EIC.

Performance as a Function of Tumor Type

IDC.—Of 110 foci of IDC, 73 (66%) were palpable. Mammography was less sensitive in the depiction of IDC than was either US or MR imaging (P < .01 for each), with no statistically significant difference in sensitivity between US and MR imaging. Specifically, mammography depicted 89 (81%) foci of IDC, US depicted 104 (94.5%), and MR imaging depicted 105 (95.4%) (Table 2). Two small index IDC foci (one 4-mm colloid IDC and one 6-mm grade II IDC with DCIS) were seen only with mammography, and two (one 5-mm tubular IDC [Fig 1] and one 8-mm grade II IDC) were seen only with MR imaging. The combination of mammography and clinical examination depicted 98 of 110 (89.1%) IDC foci. The combination of mammography, clinical examination, and US depicted 108 (98.2%) IDC foci. The combination of mammography, clinical examination, and MR imaging depicted 110 (100%) IDC foci (Table 2). The addition of either US or MR imaging to mammography and clinical examination significantly improved detection (P < .005 for each). Of the 21 mammographically occult foci of IDC, 18 (86%) were depicted at initial US (with another two at second-look US), and 20 (95%) were depicted at MR imaging (Table 3).

Mammographic sensitivity was inversely related to breast density (P < .001), with 18 of 30 (60%) foci of IDC depicted in dense breasts, 31 of 36 (86%) depicted in heterogeneously dense breasts, 34 of 38 (89%) depicted in breasts with minimal scattered fibroglandular density, and six of six (100%) depicted in fatty breasts (Table 2). Of the 18 foci of IDC depicted mammographically in dense breasts, 17 (94%) were palpable. Random-effects logistic regression analysis showed that age did not affect mammographic sensitivity independent of density. Breast density did not affect the sensitivity of US or MR imaging.

Ninety-two breasts were found to have IDC; of these, 43 (47%) had associated DCIS, including 19 (21%) with EIC. Four were mixed IDC and ILC. Of the 92 breasts, six (6.5%) had “incidental” IDC at additional imaging that was not detected at either mammography or clinical examination, with two of those occult to initial US, as well. Of the 92 breasts with IDC, 14 (15%) had diffuse tumor (six according to primary tumor size larger than 7 cm and eight with diffuse foci), four (4.3%) were multicentric, 19 (21%) were multifocal, and 55 (60%) were solitary and smaller than 5 cm.

Twenty-one breasts with IDC were recommended for mastectomy on the basis of mammography and clinical examination findings; indeed, the findings in five (24%) of these 21 were ultimately overstaged not only mammographically but also on the basis of US and MR imaging findings.

Among the 72 breasts with IDC for which conservation or no surgery was planned after mammography and clinical examination, the tumor was missed altogether in six of 72 (8%) breasts, and the extent of tumor was underestimated in another 15 (21%) breasts (Table 4). Of the 15 underestimates, three (20%) were due to EIC alone, two (13%) were due to size, and 10 (67%) were due to discrete additional foci of tumor (three of which also had underestimated EIC). Thus, there were six outright misses and another 10 with missed discrete additional tumor foci, for a total of 16 breasts with missed tumor after mammography and clinical examination. This number represents 17% of the 92 breasts with IDC with additional tumor that potentially would have been missed even if clear margins of excision had been achieved, had management been based on the combination of mammography and clinical examination.

US alone (performed with knowledge of mammographic and clinical findings) was more accurate than mammography in the depiction of disease extent for IDC (P < .05), but the combination of mammography, clinical examination, and US was not significantly more accurate in

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography</td>
<td>120/177 (67.8)</td>
<td>61/81 (75)</td>
<td>120/140 (85.7)</td>
<td>181/258 (70.2)</td>
</tr>
<tr>
<td>Mammography and clinical examination</td>
<td>137/177 (77.4)</td>
<td>58/81 (72)</td>
<td>137/160 (85.6)</td>
<td>195/258 (75.6)</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>89/177 (50.3)</td>
<td>75/81 (92)</td>
<td>89/95 (94)</td>
<td>164/258 (63.6)</td>
</tr>
<tr>
<td>US</td>
<td>147/177 (83.0)</td>
<td>28/81 (34)</td>
<td>147/200 (73.5)</td>
<td>175/258 (68.7)</td>
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<tr>
<td>Mammography and US</td>
<td>162/177 (91.5)</td>
<td>19/81 (23)</td>
<td>162/224 (72.3)</td>
<td>181/258 (70.2)</td>
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<tr>
<td>Mammography, clinical examination, and US</td>
<td>165/177 (93.2)</td>
<td>18/81 (22)</td>
<td>165/228 (72.4)</td>
<td>183/258 (70.9)</td>
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<tr>
<td>MR imaging</td>
<td>167/177 (94.4)</td>
<td>21/81 (26)</td>
<td>167/227 (73.6)</td>
<td>188/258 (72.9)</td>
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<tr>
<td>MR imaging, clinical examination, and MR</td>
<td>176/177 (99.4)</td>
<td>6/81 (7)</td>
<td>176/251 (70.1)</td>
<td>182/258 (70.5)</td>
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</tbody>
</table>

NOTE.—Numbers in parentheses are percentages.
the depiction of disease extent than mammography and clinical examination alone. MR imaging alone (interpreted with knowledge of mammographic and clinical findings) was more accurate than mammography in the assessment of disease extent \( (P < .001) \). The combination of mammography, clinical examination, and MR imaging provided significantly more accurate assessment of disease extent than did mammography and clinical examination alone \( (P < .01) \). The combination of mammography, clinical examination, and MR imaging left no underestimates of extent of IDC, but IDC

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Summary of 258 Histologically Proven Lesions according to Method of Depiction and as a Function of Mammographic Breast Density</th>
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</thead>
<tbody>
<tr>
<td>Diagnosis and Modality</td>
<td>No. of Lesions Depicted</td>
</tr>
<tr>
<td>All malignancies ((n = 177))</td>
<td></td>
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<tr>
<td>Mammmography</td>
<td>120 (68)</td>
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<td>Mammmography and clinical examination</td>
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<td>Mammmography and US</td>
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<tr>
<td>MR imaging</td>
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<tr>
<td>Mammmography, clinical examination, and MR imaging</td>
<td>176 (99)</td>
</tr>
<tr>
<td>IDC ((n = 110))</td>
<td></td>
</tr>
<tr>
<td>Mammmography</td>
<td>89 (81)</td>
</tr>
<tr>
<td>Mammmography and clinical examination</td>
<td>98 (89)</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>73 (66)</td>
</tr>
<tr>
<td>US</td>
<td>104 (94)</td>
</tr>
<tr>
<td>Mammmography and US</td>
<td>107 (97)</td>
</tr>
<tr>
<td>Mammmography, clinical examination, and US</td>
<td>108 (98)</td>
</tr>
<tr>
<td>MR imaging</td>
<td>105 (95)</td>
</tr>
<tr>
<td>Mammmography, clinical examination, and MR imaging</td>
<td>110 (100)</td>
</tr>
<tr>
<td>ILC ((n = 29))</td>
<td></td>
</tr>
<tr>
<td>Mammmography</td>
<td>10 (34)</td>
</tr>
<tr>
<td>Mammmography and clinical examination</td>
<td>14 (48)</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>8 (28)</td>
</tr>
<tr>
<td>US</td>
<td>25 (86)</td>
</tr>
<tr>
<td>Mammmography and US</td>
<td>25 (86)</td>
</tr>
<tr>
<td>Mammmography, clinical examination, and US</td>
<td>25 (86)</td>
</tr>
<tr>
<td>MR imaging</td>
<td>28 (96)</td>
</tr>
<tr>
<td>Mammmography, clinical examination, and MR imaging</td>
<td>28 (96)</td>
</tr>
<tr>
<td>DCIS ((n = 38))</td>
<td></td>
</tr>
<tr>
<td>Mammmography</td>
<td>21 (55)</td>
</tr>
<tr>
<td>Mammmography and clinical examination</td>
<td>25 (66)</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>8 (21)</td>
</tr>
<tr>
<td>US</td>
<td>18 (47)</td>
</tr>
<tr>
<td>Mammmography and US</td>
<td>30 (79)</td>
</tr>
<tr>
<td>Mammmography, clinical examination, and US</td>
<td>32 (84)</td>
</tr>
<tr>
<td>MR imaging</td>
<td>34 (89)</td>
</tr>
<tr>
<td>Mammmography, clinical examination, and MR imaging</td>
<td>28 (96)</td>
</tr>
<tr>
<td>Benign, not atypical ((n = 69)^*)</td>
<td></td>
</tr>
<tr>
<td>Mammmography</td>
<td>14 (20)</td>
</tr>
<tr>
<td>Mammmography and clinical examination</td>
<td>17 (25)</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>3 (4)</td>
</tr>
<tr>
<td>US</td>
<td>42 (61)</td>
</tr>
<tr>
<td>Mammmography and US</td>
<td>51 (74)</td>
</tr>
<tr>
<td>Mammmography, clinical examination, and US</td>
<td>52 (75)</td>
</tr>
<tr>
<td>MR imaging</td>
<td>50 (72)</td>
</tr>
<tr>
<td>Mammmography, clinical examination, and MR imaging</td>
<td>64 (93)</td>
</tr>
<tr>
<td>Benign, atypical ((n = 12)^†)</td>
<td></td>
</tr>
<tr>
<td>Mammmography</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Mammmography and clinical examination</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>3 (25)</td>
</tr>
<tr>
<td>US</td>
<td>11 (92)</td>
</tr>
<tr>
<td>Mammmography and US</td>
<td>11 (92)</td>
</tr>
<tr>
<td>Mammmography, clinical examination, and US</td>
<td>11 (92)</td>
</tr>
<tr>
<td>MR imaging</td>
<td>10 (83)</td>
</tr>
<tr>
<td>Mammmography, clinical examination, and MR imaging</td>
<td>11 (92)</td>
</tr>
</tbody>
</table>

Note.—Numbers in parentheses are percentages. NA = not applicable.

* Lesion appeared suspicious with that modality or any one modality within the combination of tests.

† Atypical includes five atypical papillomas, three lobular carcinomas in situ, two cases of atypical lobular hyperplasia, and two cases of atypical ductal hyperplasia. These were all excised with the same or benign results and are classified as benign but appeared suspicious with that modality or any one modality within the combinations listed.

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exterior extent was overestimated in 10 of 72 (14%) breasts after this combination of tests (Fig 2, Table 4).

One case of IDC was overestimated by more than 2 cm on MR images because of enhancement that included hematoma from recent core biopsy. The combination of mammography, clinical examination, and MR imaging was not significantly more accurate than MR imaging alone or the combination of mammography, clinical examination, and US, but it was more accurate than US alone in the depiction of the extent of IDC (P < .05). US was not of benefit after mammography, clinical examination, and MR imaging in the determination of disease extent (Table 4), though it was used to guide biopsy.

Two mastectomies were prompted only by additional imaging findings in breasts with IDC that proved to have a solitary cancer smaller than 5 cm at excision. One of these was prompted by MR imaging findings alone, and one was prompted by US and MR imaging findings. Another 13 patients chose mastectomy, which exceeded the needed surgery: Five of these women had cancer foci that were mammographically occult, and another three had index cancers at additional evaluation with MR imaging alone (n = 2) or both MR imaging and US (n = 1).

**TABLE 3**

<table>
<thead>
<tr>
<th>Diagnosis and Modality of Depiction</th>
<th>True-Positive</th>
<th>Negative at Mammography</th>
<th>Negative at Clinical Examination (Nonpalpable)</th>
<th>Negative at US</th>
<th>Negative at MR Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDC (n = 110)*</td>
<td>21</td>
<td>37</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Mammaryography</td>
<td>89 (81)</td>
<td>NA</td>
<td>25 (68)</td>
<td>3 (50)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>73 (66)</td>
<td>8 (38)</td>
<td>NA</td>
<td>1 (17)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>US</td>
<td>104 (94)</td>
<td>18 (86)</td>
<td>32 (86)</td>
<td>3 (50)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>MR imaging</td>
<td>105 (95)</td>
<td>20 (95)</td>
<td>34 (92)</td>
<td>3 (50)</td>
<td>NA</td>
</tr>
<tr>
<td>ILC (n = 29)†</td>
<td>19</td>
<td>21</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mammaryography</td>
<td>10 (34)</td>
<td>NA</td>
<td>6 (29)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Clinical examination</td>
<td>8 (28)</td>
<td>4 (21)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>25 (86)*</td>
<td>15 (79)*</td>
<td>17 (81)*</td>
<td>NA*</td>
<td></td>
</tr>
<tr>
<td>MR imaging</td>
<td>28 (97)</td>
<td>18 (95)</td>
<td>20 (95)</td>
<td>3 (75)</td>
<td>NA</td>
</tr>
<tr>
<td>DCIS (n = 38)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammaryography</td>
<td>21 (55)</td>
<td>NA</td>
<td>17 (57)</td>
<td>12 (60)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>8 (21)</td>
<td>4 (24)</td>
<td>NA</td>
<td>2 (10)</td>
<td>NA</td>
</tr>
<tr>
<td>US</td>
<td>18 (47)</td>
<td>9 (53)</td>
<td>12 (40)</td>
<td>4 (20)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>MR imaging</td>
<td>34 (89)</td>
<td>17 (100)</td>
<td>25 (83)</td>
<td>17 (85)</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Two IDC foci were seen only with mammaryography, two were seen only with MR imaging, and one was evident only clinically.
† One focus of ILC was seen only at second-look US and was not considered true-positive.
‡ Three DCIS foci were seen only at mammaryography, and six were seen only at MR imaging.

**TABLE 4**

<table>
<thead>
<tr>
<th>Modality</th>
<th>Accuracy</th>
<th>Negative*</th>
<th>Foci Missed†</th>
<th>Size Underestimated‡</th>
<th>Missed EIC§</th>
<th>Foci Overestimated¶</th>
<th>Size Overestimated‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammaryography</td>
<td>40 (56)</td>
<td>9 (12)</td>
<td>13 (18)**</td>
<td>4 (6)</td>
<td>3 (4)</td>
<td>1 (1)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Mammaryography and clinical examination</td>
<td>48 (67)</td>
<td>6 (8)</td>
<td>10 (14)**</td>
<td>2 (3)</td>
<td>3 (4)</td>
<td>1 (1)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>US</td>
<td>53 (74)</td>
<td>4 (6)</td>
<td>4 (6)</td>
<td>2 (3)</td>
<td>6 (8)</td>
<td>3 (4)</td>
<td>NA</td>
</tr>
<tr>
<td>Mammaryography, clinical examination, and US</td>
<td>55 (76)</td>
<td>2 (3)</td>
<td>3 (4)</td>
<td>1 (1)</td>
<td>5 (7)</td>
<td>4 (6)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>MR imaging</td>
<td>61 (85)</td>
<td>3 (4)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>6 (8)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Mammaryography, clinical examination, and MR imaging</td>
<td>62 (86)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>6 (8)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>All modalities combined</td>
<td>62 (86)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>6 (8)</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

* Cancer not depicted by that modality or combination of modalities.
† Malignant foci were missed that would have prompted wider surgical excision.
‡ Index lesion size underestimated by ≥2 cm.
§ Size and/or foci were underestimated for what proved to be an EIC.
¶ Additional suspicious lesions were noted for which, had surgery been based on that modality or combination of modalities, more extensive surgery would have been performed than necessary on the basis of final histopathologic findings.
# Index lesion size overestimated by ≥2 cm.
** Three cases with missed invasive foci also had missed EIC but are tabulated as “foci missed.”

**EIC.**—A subset of 19 breasts with IDC had an EIC, and in 12 of these, conservation was planned on the basis of mammography and clinical examination findings. In the 19 breasts with an EIC, disease was visible mammographically in 18, and the extent of disease was underestimated by more than 2 cm with mammography in seven of those 18 (39%), compared with 15 of 73 (20%) of all other breasts with IDC, though the difference was not significant. Clinical examination was of no value in the identification of EIC. With US, in seven of 19 (37%) cases of EIC, disease extent was underestimated, though careful attention to detail allowed retrospective iden-
tification in five cases in which second-
look US was performed (Fig 3). In six of
19 (32%) breasts with EIC, only MR im-
gaging depicted the EIC; five of those six
EIC cases seen only at MR imaging were
in breasts in which conservation was an-
ticipated. Findings in only one (5%) breast with EIC were underestimated at MR imaging, with the EIC seen at both mammography and US in that breast.

ILC.—Twenty-nine foci of ILC were
evaluated, of which eight (28%) were pal-
pable. Mammography was less sensitive
to ILC than IDC (P < .001). Mammogra-
phy was less sensitive to ILC than were
US or MR imaging (P < .001 for each comparison), with no statistically signif-
ificant difference in sensitivity between US
and MR imaging. Specifically, mammog-
rapy depicted 10 of 29 (34%) foci of ILC,
US depicted 25 (86%), and MR imaging
depicted 28 (96%) (Table 2). Two foci of
ILC were depicted only at MR imaging,
and one was depicted only at second-
look US. The combination of mammogra-
phy and clinical examination allowed
identification of 14 of 29 (48%) cases of
ILC. Mammography and US with or
without clinical examination depicted 25
of 29 (86%) cases; mammography, clinical
examination, and MR imaging depicted
28 of 29 (96%) cases. The addition of
either US or MR imaging to mammogra-
phy and clinical examination signifi-
cantly improved detection of ILC (P < .001 for each US and MR imaging) (Ta-
bles 2, 3).

As with IDC, mammographic sensitiv-
ity to ILC was again inversely related to
breast density, with one of nine (11%) cases of ILC depicted in dense breasts,
five of 14 (36%) depicted in heteroge-
neously dense breasts, three of five (60%)
depicted in breasts with minimal scat-
tered fibroglandular density, and one of
one (100%) depicted in fatty breasts (P < .001) (Table 2). Of the nine foci of ILC in
dense breasts, all had palpable index le-
sions. As with IDC, breast density did not
affect US or MR imaging sensitivity.

The management of 15 breasts was
based on presence of ILC. Of the 15
breasts with ILC, three (20%) had diffuse
tumor (one according to tumor size larger
than 7 cm and two according to diffuse
foci), one (6.7%) had multicentric tumor,
five (33%) had multifocal tumor, and six

### TABLE 5
Evaluation of Disease Extent in 12 Breasts with Invasive Lobular Cancer for Which Breast Conservation Was Planned

<table>
<thead>
<tr>
<th>Modality</th>
<th>Accuracy</th>
<th>Negative*</th>
<th>Foci Missed¹</th>
<th>Size Underestimated¹</th>
<th>Foci Overestimated¹</th>
<th>Size Overestimated¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography</td>
<td>5 (42)</td>
<td>4 (33)</td>
<td>3 (25)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mammography and clinical exam.</td>
<td>5 (42)</td>
<td>2 (17)</td>
<td>5 (42)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>US</td>
<td>8 (67)</td>
<td>NA</td>
<td>2 (17)</td>
<td>NA</td>
<td>2 (17)</td>
<td>NA</td>
</tr>
<tr>
<td>Mammography, clinical exam., and US</td>
<td>8 (67)</td>
<td>NA</td>
<td>2 (17)</td>
<td>NA</td>
<td>2 (17)</td>
<td>NA</td>
</tr>
<tr>
<td>MR imaging</td>
<td>7 (58)</td>
<td>NA</td>
<td>1 (8)</td>
<td>4 (33)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mammography, clinical exam., and MR</td>
<td>7 (58)</td>
<td>NA</td>
<td>1 (8)</td>
<td>4 (33)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>All modalities combined</td>
<td>7 (58)</td>
<td>NA</td>
<td>1 (8)</td>
<td>4 (33)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Note.—Numbers in parentheses are percentages. NA = not applicable.

* Cancer not depicted by that modality or combination of modalities.
† Malignant foci were missed that would have prompted wider surgical excision.
‡ Index lesion size underestimated by ≥2 cm.
§ Additional suspicious lesions were noted for which, had surgery been based on that modality or combination of modalities, more extensive surgery would have been performed than necessary on the basis of final histopathologic findings. All breasts with overestimated foci of tumor were due to foci of lobular carcinoma in situ.
‖ Index lesion size overestimated by ≥2 cm.
¶ In one breast with ILC, additional tumor was found only at second-look US.

### TABLE 6
Evaluation of Disease Extent in 12 Breasts with DCIS for Which Breast Conservation Was Planned

<table>
<thead>
<tr>
<th>Modality</th>
<th>Accuracy</th>
<th>Negative*</th>
<th>Foci Missed¹</th>
<th>Size Underestimated¹</th>
<th>Foci Overestimated¹</th>
<th>Size Overestimated¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography</td>
<td>6 (50)</td>
<td>4 (33)</td>
<td>1 (8)</td>
<td>1 (8)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mammography and clinical exam.</td>
<td>10 (83)</td>
<td>4 (33)</td>
<td>1 (8)</td>
<td>1 (8)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>US</td>
<td>4 (33)</td>
<td>4 (33)</td>
<td>NA</td>
<td>4 (33)</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Mammography, clinical exam., and US</td>
<td>8 (75)</td>
<td>NA</td>
<td>1 (8)</td>
<td>4 (33)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MR imaging</td>
<td>5 (42)</td>
<td>1 (8)</td>
<td>NA</td>
<td>5 (42)**</td>
<td>1 (8)**</td>
<td>NA</td>
</tr>
<tr>
<td>Mammography, clinical exam., and MR</td>
<td>6 (50)</td>
<td>NA</td>
<td>1 (8)</td>
<td>5 (42)**</td>
<td>1 (8)**</td>
<td>NA</td>
</tr>
<tr>
<td>All modalities combined</td>
<td>6 (50)</td>
<td>NA</td>
<td>NA</td>
<td>5 (42)**</td>
<td>1 (8)**</td>
<td>NA</td>
</tr>
</tbody>
</table>

Note.—Numbers in parentheses are percentages. NA = not applicable.

* Cancer not depicted by that modality or combination of modalities.
† Malignant foci were missed that would have prompted wider surgical excision.
‡ Index lesion size underestimated by ≥2 cm.
§ Additional suspicious lesions were noted for which, had surgery been based on that modality or combination of modalities, more extensive surgery would have been performed than necessary on the basis of final histopathologic findings. All breasts with overestimated foci of tumor were due to foci of lobular carcinoma in situ.
‖ Index lesion size overestimated by ≥2 cm.
¶ In two breasts with DCIS, there were multiple false-positive findings at both US and MR imaging, though the index DCIS was occult. When combined with mammography, disease extent appeared overestimated. These are listed as “overestimated foci,” though they could have been listed as “negative” for each of US and MR imaging.
** Both size and foci were overestimated at MR imaging in one breast, listed as “size overestimated.”
(40%) had solitary tumor. Mastectomy was planned in three (20%) breasts on the basis of combined mammography and clinical examination findings.

Table 5 summarizes the extent of disease according to imaging modality for the 12 breasts with ILC in which breast conservation was anticipated after mammography and clinical examination. US and MR imaging accurately depicted extent in eight and seven of these breasts, respectively, compared with five at mammography, though the differences were not significant. Detection of mammographically and clinically unsuspected...
Contralateral ILC occurred in two breasts on the basis of additional imaging with US and MR imaging (Fig 4). US and MR imaging were both hampered by false-positive findings due to lobular carcinoma in situ (Fig 5). Two patients had potentially unnecessary mastectomy on the basis of US and MR imaging findings (Fig 5).

**DCIS.**—Of 38 foci of DCIS evaluated, 21 (55%) were depicted mammographically, and eight of 38 (21%) were clinically evident (six foci were palpable, and two breasts had Paget disease of the nipple). Three (8%) DCIS foci were seen only mammographically. US was less sensitive for DCIS than for IDC or ILC (P < .001), with 18 of 38 (47%) foci identified initially and another three (8%) seen at second-look US. MR imaging depicted 34 of 38 (89%) DCIS foci, which was significantly more than that depicted with US (P < .001) or mammography (P < .01) (Table 2). Six foci of DCIS were seen only at MR imaging.

The foci of DCIS depicted mammographically included two of eight (25%) in dense breasts, nine of 14 (64%) in breasts with heterogeneously dense parenchyma, nine of 15 (60%) in breasts with minimal scattered fibroglandular density, and one of one (100%) in fatty breasts. Another focus of low-grade DCIS was initially considered probably benign at mammography and manifested as a grouping of four punctate calcifications at stereotactic biopsy performed after intense progressive enhancement seen at MR imaging.

The management of 14 breasts was predicated on DCIS (six high-grade, four intermediate-grade, and four low-grade DCIS). Of the 14 breasts, one (7.1%) showed diffuse foci of DCIS, one (7.1%) had multicentric foci, five (36%) had multifocal disease, and seven (50%) had solitary tumor foci. Of the six with multifocal or multicentric disease, three (50%) were micropapillary DCIS.

Table 6 summarizes the extent of disease according to imaging modality for the 12 breasts with DCIS for which breast conservation was anticipated on the basis of clinical examination and mammo-
graphic findings. Combined mammography and clinical examination depicted extent of DCIS well, but differences compared with other modalities alone or in combination were not significant, likely as a result of the small number of cases. The extent of disease was overestimated with US in four of 12 (33%) breasts and with MR imaging in six of 12 (50%). One mastectomy was prompted by the finding of multiple scattered suspicious foci at both US and MR imaging, with two additional core biopsy results indicating atypical ductal hyperplasia. This case proved to be a solitary 25-mm mass of intermediate-grade DCIS. Another four of 12 (33%) breasts with DCIS for which conservation was planned were negative at US. Two breasts were appropriately converted from planned lumpectomy to mastectomy on the basis of more extensive disease at US and MR imaging (Fig 6).

**Contralateral Cancer**

Of the 111 patients, 10 (9.0%) were shown to have synchronous bilateral cancer, with an 11th patient found to have cancer in the breast opposite a benign presenting lesion (Fig 1) at MR imaging only. Six of the 10 with synchronous contralateral cancers were suspected mammographically, eight were suspected at US, and nine were suspected at MR imaging. One 7-cm recurrent contralateral grade III IDC was only evident clinically 2 months after study evaluation; findings from another US examination and mammogram remained negative at the time of diagnosis. Three of the contralateral cancers seen at US were not seen at mammography (Fig 7). The presenting lesion proved to be IDC in seven patients, ILC in two, and DCIS in one with synchronous bilateral cancer. Histologic examination of the contralateral cancers revealed five IDCs, five ILCs (including diffuse ILC in one [Fig 4], multifocal ILC in another, separate foci of ILC and DCIS in another, separate foci of ILC and IDC in another, and one case of mixed IDC and ILC), and one case of DCIS.
Additional Biopsies

An additional 145 biopsies were performed in tissue beyond the presenting lesion, of which 67 (46%) findings proved malignant and 12 (8.3%) proved atypical (Table 2). Nine of the 67 (13%) additional cancers were palpable. Beyond the presenting lesion, mammographic findings prompted 43 biopsies, of which 23 (53%) findings were malignant and six (14%) were atypical. Findings at US prompted 93 additional biopsies, of which 40 (43%) findings were malignant and 11 (12%) were atypical. There were no cancers seen only at initial US (ie, all cancers were also found at clinical examination, mammography, or MR imaging), though one ILC was seen only at second-look US. Findings at MR imaging helped prompt 115 additional biopsies, of which 54 (47%) findings were malignant and 10 (8.7%) were atypical.

There were 25 suspicious findings seen only at MR imaging, of which 10 (40%) proved malignant (six cases of DCIS, two IDCs, and two ILCs). Second-look US allowed identification of 17 of 25 (68%) lesions seen only at MR imaging, and six of 17 (35%) of those were malignant (two cases of DCIS, two IDCs, and two ILCs). Another two lesions found at MR imaging were evident retrospectively at mammography (including one cluster of four punctate calcifications due to DCIS, initially classified as probably benign at mammography, and one fibroadenoma). The other six lesions seen only at MR imaging, including three malignancies, were excised.
False-Negative Findings

As stated, mammography was relatively insensitive to all cancers in dense breasts—particularly to ILC, with 57 of 177 (32%) malignant foci mammographically occult \( (n = 56) \) or considered probably benign \( (n = 1) \). Of these 57 mammographic “misses,” 26 (46%) were in extremely dense breasts, and none were in fatty breasts. Nineteen (33%) mammographic “misses” were due to ILC.

Of 177 malignant foci, 30 (17%) were missed at US, and 20 (67%) of those misses were DCIS. Also occult were five small foci of IDC (three tubular cancers—3, 5, and 6 mm, respectively—one 4-mm colloid carcinoma [Fig 2], and one 6-mm grade II IDC), of which two were seen at second-look US (Fig 1). The one large 7-cm grade III IDC that was occult to all imaging modalities has been described. Four foci of ILC were also missed at initial US, with one initially interpreted as a complicated cyst, and the other three visible at second-look US.

Of 177 malignant foci, 10 (5.6%) were missed at MR imaging. Two 6-mm tubular cancers were not identified at MR imaging, one of which showed less than 60% enhancement (Fig 8), and the other of which was simply occult. A 4-mm colloid carcinoma was not recognized in a background of diffuse foci of enhancement (Fig 2). Two additional IDCs were not depicted at MR imaging in one patient: One was an 8-mm grade I IDC seen at mammography and US, and the other was a contralateral 7-cm grade III IDC found only clinically 2 months later, though DCIS was visible in this patient.

Four foci of DCIS were occult at MR imaging, as was one ILC. Of the 10 MR imaging misses, nine (90%) were in studies performed at 1.0 T. Lower magnet field strength tended to decrease sensitivity, with 108 of 117 (92.3%) malignancies identified at 1.0 T and 59 of 60 (98%) identified at 1.5 T \( (P < .1) \).
Additional Short-Interval Follow-up

Additional probably benign foci of enhancement in the contralateral breast were common at MR imaging, seen in 54 of 111 (49%) patients, with 25 of the participants requiring follow-up for findings seen only at MR imaging. Probably benign findings were noted mammographically in the contralateral breast in 19 of 111 (17%) patients (seen only at mammography in four of these) and at US in 21 of 111 (19%) patients (seen only at US in three of these). After all three imaging modalities were performed, 64 of 111 (58%) patients had probably benign findings in the contralateral breast. Adequate follow-up was performed for 55 of 64 (86%) of these: Six of these breasts underwent biopsy (or removal) with benign results, and 49 breasts had lesions that were stable, decreasing, or gone. Indeed, three patients opted for contralateral mastectomy on the basis of probably benign findings at MR imaging, which proved benign.

With a median of 24 months (range, 13–60 months) of follow-up when available for patients in this series, there have been no local recurrences. However, five of the 111 (4.5%) patients died of their disease, and another five (4.5%) had distant metastases.

DISCUSSION

Detection of Cancer

Detection of breast cancer is the primary goal of breast imaging. Mammography has proved effective as a screening test for the early detection of breast cancer. In dense and heterogeneously dense breasts, mammographic sensitivity is decreased, with as few as 30%–48% of cancers depicted in extremely dense breasts (4,5). Indeed, in this series, where 50% of cancers were palpable, mammographic sensitivity was 45% (21 of 47 foci) in extremely dense breasts and 70% (45 of 64 foci) in heterogeneously dense breasts and was lower for ILC than for IDC across all grades of breast density. Only one of 19 (5%) invasive cancers depicted mammographically in dense breasts was non-palpable, which further suggests that screening mammography is of limited value in dense breasts.

In this series, cancer was nearly twice as prevalent in dense or heterogeneously dense breasts than in nondense breasts (111 of 177 [62.7%] malignant foci vs 66...
of 177 [37.3%] malignant foci, \( P < .001 \). Increased breast density has been shown to increase the risk of breast cancer from 2.2- to fivefold when breasts with densest grades are compared with fatty breasts (26,27). The combination of decreased mammographic sensitivity and increased prevalence of cancer in denser breasts has prompted interest in the investigation of supplemental screening with US (28) or even MR imaging.

Stomper et al (29) reported that the frequency of dense breasts decreases with increasing age, with 62% of women in their 30s having more than 50% breast density compared with 27% of women in their 60s. Several studies (3,30) have shown decreased mammographic sensitivity in younger women, even after correcting for breast density.

Mammographically occult tumor may help explain the observations that (a) women younger than 40 years with positive margins are at increased risk of having residual tumor in their breasts compared with older women (31) and that (b) women younger than 40 years experience a much higher rate of local recurrence after radiation therapy than do older women, even with a boost to the lumpectomy site (32). We did not find younger age to be an independent predictor of decreased mammographic sensitivity or increased risk of multifocality per se.

ILC presents particular dilemmas in the detection and evaluation of disease extent. ILC tends to be mammographically subtle if it is seen at all. In one series (33), more than one of three mammo-
Graphically depicted ILCs was seen as a vague asymmetry, poorly defined opacity, or area of possible architectural distortion. US is beneficial in the identification of ILC. In the series of Butler et al (34), 81 of 208 (39%) ILCs were mammographically subtle or occult, and 71 of those 81 (88%) were depicted at US. In this series, 19 of 29 (66%) ILCs were mammographically occult (compared with 21 of 110 [19%] IDCs [P < .001]), with 15 of these 19 (79%) seen at US.

In this series, the combination of mammography, clinical examination, and US depicted 165 of 177 (93.2%) malignant foci, with the remainder seen only at MR imaging. The sensitivity of combined mammography and US was 96% each in the screening series of Kolb et al (5) and in the series of 480 symptomatic patients reported by Housami et al (35). Moyer et al (36) reported that 97% of palpable cancers were depicted with a combination of US and mammography.

MR imaging alone depicted 167 of 177 (94.4%) malignant foci. MR imaging sensitivity at 1.0 T tended to be lower than that at 1.5 T. Heywang-Köbrunner et al (37) found equivalent sensitivity at the two field strengths, with improved specificity at 1.0 T. We found no difference in the rate of false-positive findings as a function of field strength.

Of the 17 malignancies seen with only one modality, five (29%) were seen only mammographically, 10 (59%) only at MR imaging, and one (6%) only at second-look US. One (6%) was only clinically evident. This suggests that additional imaging should be considered a supplement to mammography, not a replacement. US provided no benefit over and above combined MR imaging, mammography, and clinical examination in the identification of tumor foci, though US was used to guide biopsy whenever possible.

In this series, 47% of DCIS foci were identified at US. In the series of Moon et al (10), 56 of 76 (74%) DCIS foci were identified. In both the study of Moon et al (10) and the present series, US was performed without being blinded to mammographic findings, and its independent performance may be substantially less. When seen mammographically, 73%–98% of DCIS is manifest as microcalcifications (38–40). Despite spatial compounding, speckle artifact present in breast tissue hampers identification of microcalcifications, as does resolution.

Yang and Tse (41) reported that US was not helpful in the characterization of morphology or extent of calcifications in symptomatic DCIS. Soo et al (42) described that in their experience with US of lesions manifested as suspicious mammographic microcalcifications, only 26 of 111 (23%) lesions could be identified with US. Importantly, lesions seen at US were more likely to be malignant (69% vs 21%) and invasive (72% vs 28%), with underestimation of an invasive component less likely when biopsy was performed sonographically than stereotactically (42). On the basis of our experience with false-positive and false-negative findings, we would not encourage the use of US in the evaluation of the extent of DCIS per se but would reserve its use for biopsy guidance when possible.

As with US, MR imaging supplied problematic in cases of DCIS in this series and was more likely to result in unnecessary biopsy or surgery than to improve treatment planning. MR imaging has proved useful in the evaluation of extent of DCIS in patients with more focal margins of excision (43,44), though that was not the focus of the present series.

**Extent of Disease**

As summarized in the study of Liberman et al (8), across multiple series totaling 1280 breasts with detailed histopathologic evaluation after a preoperative diagnosis of unifocal cancer, 619 (48%) were found to have additional tumor foci unsuspected at mammography. In this series, among 96 breasts in which conservation or no surgery was anticipated after mammography and clinical examination, 30 (31%) had additional mammographically occult tumor foci. Supplemental US more accurately depicted extent, which necessitated wider excision in 17 of 96 (18%) breasts for which conservation was anticipated, corresponding to 17 of 30 (57%) breasts with mammographically or clinically occult tumor (though four remained underestimated). In an earlier nonoverlapping series (9), we found that US depicted additional tumor, which altered the surgical approach in 15% of breasts.

Supplemental MR imaging depicted additional tumor that necessitated wider excision in 29 of 96 (30%) breasts for which conservation was anticipated, corresponding to 29 of 30 (97%) breasts with mammographically or clinically occult tumor. Liberman et al (8) reported additional tumor depiction with MR imaging in 27% of ipsilateral breasts. Orel et al (7) reported additional tumor depiction with MR imaging in 33% of patients.

As stated earlier, the vast majority of additional tumor foci are found in the same quadrant as the index lesion. In this series, in 40 of 46 (87%) breasts with additional foci of tumor, the foci were multifocal in the immediate 4 cm of tissue surrounding the index lesion; 92% of breasts with additional tumor were multifocal in the series of Liberman et al (8). In the present series, 11 of 46 (24%) breasts with additional tumor were both multifocal and multicentric, with diffuse tumor foci involving multiple quadrants. In only six of 121 (5%) breasts were there isolated multicentric foci of tumor. Thus, the vast majority of additional tumor foci are in the same quadrant and within 4 cm of the index cancer. At a minimum, when performing US in a patient known or suspected to have cancer, thorough evaluation of at least that quadrant of the breast is recommended.

Evaluation of the contralateral breast deserves discussion. On the basis of clinical or mammographic evaluation or both, 2%–3% of patients are found to have synchronous bilateral cancer (45). Invasive lobular histologic findings (46) and age younger than 55 years (46,47) increase the risk of contralateral breast cancer. In the present series, 9% of patients had synchronous bilateral cancer, with 3% of patients identified as having unsuspected contralateral cancer at US and MR imaging that was occult at mammography and clinical examination. Similar rates of 4%–6% of unsuspected contralateral breast cancer have been seen in other series (10,11,48–50) on the basis of supplemental imaging beyond mammography.

We found a benefit of MR imaging over and above combined mammography, clinical examination, and US in 12 of 96 (12%) breasts for which conservation (or no surgery) had been planned, similar to the 7% (seven of 104) additional benefit of MR imaging in the series of Hlawatsch et al (12). In five of the 12 (42%) breasts with an additional MR imaging benefit, MR imaging depicted an extensive intraductal component that was otherwise occult; presumably, these patients would have had positive margins at lumpectomy. Ideally, patients with an EIC could be selected to undergo preoperative MR imaging. Mai et al (51) found that EIC could be predicted on the basis of core biopsy findings. If at least three cores had low-grade DCIS or at least two cores had high-grade DCIS, 20 of 23 (87%) patients with IDC had EIC at excision (51). Importantly, nine of 15 (60%) lumpectomies in the group with core biopsy findings suggestive of EIC (according to the criteria of Mai et al) had posi-
Invasive carcinoma, and ILC represents 10%-90% of all invasive carcinoma. IDC represents 85%-90% of all invasive breast cancer. A 5%–10% rate of local recurrence comes at the price of increased risk of unnecessary wider excision or mastectomy. For breasts with cancer in this series, 67 of 121 (55%) underwent mastectomy, with only 23 of 67 (34%) of these recommended on the basis of mammography and clinical examination alone. Fifteen mastectomies were deemed potentially excessive. In five of 15 (33%) of these breasts, atypical lesions had been sampled for biopsy percutaneously and required excision in addition to the known cancer, which in these patients proved problematic in that poor cosmetic results were then anticipated if lumpectomy and separate surgical biopsy (or biopsies) were performed. Three patients opted for bilateral mastectomy because of findings considered probably benign in the contralateral breast at MR imaging (with all proving benign), and another three patients opted for mastectomy (for tumor that could have been removed by means of lumpectomy) because their cancer was seen only at MR imaging (n = 2) or at both US and MR imaging (n = 1) and they lacked confidence in standard imaging follow-up. It is imperative that histopathologic proof of disease extent be obtained preoperatively whenever possible to assist in proper surgical planning, though atypical results and multiplicity of additional suspicious findings (Fig 5) can make this task problematic.

It should be recognized that lack of a US correlate for an abnormality at MR imaging should not deter biopsy of a suspicious finding. In the experience of La Trenta et al (60), lesions found at second-look US were more likely malignant, but 14% of lesions seen only at MR imaging were malignant and required MR imaging–guided biopsy. In the present series, 25 suspicious findings were evident at MR only, and 10 (40%) of these proved malignant. Integration of breast MR imaging interpretation with other breast imaging is critical. Of the 25 suspicious findings at MR imaging, 17 (68%) were identified at second-look US and were sampled for biopsy, including six of 10 (60%) malignancies identified only with MR imaging.

Another malignancy (DCIS) first seen at MR imaging was evident at mammography retrospectively as a group of four punctate microcalcifications, as was a benign fibroadenoma. Of six suspicious findings seen only at MR imaging even after second-look US and review of mammograms, three (50%) proved malignant in the present series. Capability of MR imaging–guided core biopsy is critical to the widespread use of breast MR imaging. Commercially available methods are in development (61) and are to be encouraged.

In addition to the risk of potentially unnecessary wide excision or mastectomy, additional imaging follow-up was required in 48% of patients because of incidental findings at MR imaging. Brown et al (62) reported that 29% of MR imaging studies showed incidental enhancing lesions. Teifke et al (63) found incidental enhancing lesions in 16% of patients. The criteria for classification of enhancing lesions found at MR imaging as benign or probably benign are not well established. When contrast material continues to accumulate within the lesion over time (ie, progressive or persistent kinetics), this tends to correlate with benignancy. Kuhl et al (16) found that nine of 146 (6%) lesions with progressive or initially progressive then delayed plateau enhancement were malignant, and this represented 9% of malignant lesions in their series.

Detailed morphologic analysis is not readily performed for very small lesions (smaller than 5 mm) when bilateral breast MR imaging is performed because of the requirement for imaging both breasts within the first 1–2 minutes after contrast material injection and resulting limited resolution. Experimental contrast agents with prolonged intravascular
phase may facilitate detailed morphologic analysis and biopsy of lesions seen only at MR imaging (64). Importantly, Liberman et al (65) found that nine of 89 (10%) women with lesions considered probably benign at MR imaging proved to have malignancy at a median follow-up of 11 months, though three of nine (33%) of the malignancies were at other sites. Prognosis was not likely adversely affected by short-interval follow-up in that series, as five of nine (56%) cancers were DCIS, and the median size of the IDCs was 6 mm (though two had micrometastases) (65).

One of the limitations of our study was that US was performed without being blinded to mammographic or clinical findings, and MR imaging was performed without being blinded to mammographic, clinical, or US findings. This artificially inflates the performance of supplemental imaging, since findings that might otherwise be dismissed will be targeted specifically. Importantly, US was performed independent of MR imaging results, and we found no supplemental independent benefit of US after mammography and MR imaging, except to guide biopsy.

Full assessment of the local extent of breast cancer also includes the axilla. We did not specifically evaluate the axilla prospectively with US or MR imaging in these patients, though enhancement of lymph nodes in the axilla and even (rarely) internal mammary chain was seen at MR imaging. We have found that when a node is identified at MR imaging that enhances more intensely or is visually strikingly larger than adjacent nodes or has lost its fatty hilum, that subsequent US identification and US-guided fine-needle aspiration biopsy (66) can facilitate surgical planning. If a nodal metastasis is confirmed, the patient will typically proceed straight to full axillary dissection rather than initial sentinel node biopsy and second axillary surgery if the sentinel node is positive. Refinement of criteria and further validation of this approach are warranted.

In summary, US and MR imaging were each more sensitive than mammography for invasive cancer, particularly in heterogeneously dense or extremely dense breasts. Supplemental imaging beyond mammography was problematic for most cases of DCIS and of no value in fatty breasts. Of 96 breasts in which conservation or no surgery was planned after mammography and clinical examination, 30 (31%) were ultimately found to have additional foci of cancer that would change the surgical approach. After combined mammography and clinical examination, US depicted additional tumor foci that changed the surgical approach in 17 of 96 (18%) breasts, and MR imaging depicted additional tumor foci that changed the surgical approach in 29 of 96 (30%) breasts. After combined mammography, clinical examination, and US, MR imaging depicted additional cancer in 12 of 96 (12%) breasts for which conservation was anticipated (with five of 12 (42%) of these due to depiction of an EIC); addition of MR imaging carried a substantial risk of false-positive findings, with extent of disease overestimated in 20 of 96 (21%) breasts (compared with three of 96 [3.1%] overestimated at mammography and clinical examination alone and 12 of 96 (12%) overestimated after mammography, clinical examination, and US).

Combined mammography, clinical examination, and MR imaging were more sensitive to malignancy than any other test alone or in combination, depicting all 177 malignancies. The use of combined US and mammography was nearly as effective as MR imaging, except when an EIC was present, and was equivalent to MR imaging in the assessment of ILC. While useful in guiding biopsy of lesions seen at MR imaging, US had no role in the detection of disease after MR imaging in this series. Bilateral whole-breast US or contrast-enhanced MR imaging was of value in the depiction of magnomorphic and clinically occult synchronous contralateral cancer in three (3%) patients.

References


