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MRI Detection of Distinct Incidental Cancer in Women With Primary Breast Cancer Studied in IBMC 6883

MITCHELL D. SCHNALL, MD, PhD,[1]* JEFFERY BLUME, PhD,[2] DAVID A. BLUEMKE, MD, PhD,[3] GIA A. DEANGELIS, MD,[4] NANETTE DEBRUHL, MD,[5] STEVEN HARMS, MD,[6] SYLVIA H. HEYWANG-KÖBRUNNER, MD, PhD,[7] NOLA HYLTON, PhD,[8] CHRISTIANE K. KUHL, MD,[9] ETTA D. PISANO, MD,[10] PETRINA CAUSER, MD,[11] STUART J. SCHNITT, MD,[12] STANLEY F. SMAZAL, MD,[13] CAROL B. STELLING, MD,[14] CONSTANCE LEHMAN, MD, PhD,[15] PAUL T. WEATHERALL, MD,[16] AND CONSTANTINE A. GATSONIS, PhD[17]

[1]*Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania*
[2]*Center for Statistical Sciences, Brown University, Providence, Rhode Island*
[3]*Russell H. Morgan, Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland*
[4]*Department of Radiology, University of Virginia Health System, Charlottesville, Virginia*
[5]*Department of Radiological Sciences, UCLA School of Medicine, Los Angeles, California*
[6]*Department of Radiology, University of Arkansas School for Medical Sciences, Little Rock, Arkansas*
[7]*Institute of Radiology, Rechts der Isar Hospital, Technical University Munich, Munich, Germany*
[8]*Magnetic Resonance Science Center, Department of Radiology, University of California, San Francisco, California*
[9]*Department of Radiology, University of Bonn, Bonn, Germany*
[10]*Department of Radiology, University of North Carolina, Chapel Hill, North Carolina*
[11]*University of Toronto, Sunnybrook Cancer Care Center, Toronto, Canada*
[12]*Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts*
[13]*Radiology Imaging Associates, Porter Adventist Hospital, Denver, Colorado*
[14]*Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[15]*Department of Radiology, University of Washington, Seattle, Washington*
[16]*Department of Radiology, University of Texas, Southwestern Medical Center, Dallas, Texas*
[17]*Center for Statistical Sciences, Brown University, Providence, Rhode Island*

Background: Prior single institution studies suggest MRI may improve the assessment of the extent of cancer within the breast, and thus reduce the risk of leaving macroscopic disease in the breast following breast conservation therapy. We report on the rate of MRI and mammography detection of foci of distinct incidental cancer in a prospective, multi center trial involving 426 women with confirmed breast cancer at 15 institutions in the US, Canada, and Germany.

Methods: Women underwent mammography and MRI prior to biopsy of the suspicious index lesion. Additional incidental lesions (IL) greater than 2 cm from the index lesion that were detected by mammography and MRI were noted and characterized. Biopsy recommendations were associated with ILs given an assessment of suspicious or highly suspicous (BiRads 4 and 5). These assessments were considered a positive test.

Results: MRI had a significantly higher yield of confirmed cancer ILs than mammography (0.18 (95%CI: 0.142–0.214) for MRI versus 0.072 (95%CI: 0.050–0.100) for mammography). The cancer ILs detected by MRI alone appeared to be similar to those detected by mammography with respect to size and histology. The percentage of biopsies of ILs that resulted in a cancer diagnosis was similar between

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*Correspondence to: Mitchell D. Schnall, MD, PhD, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104, Fax: 215-662-7238, 215-662-3013.
E-mail: schnall@oasis.rad.upenn.edu

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the modalities (MRI 0.72(95%CI: 0.6–0.81); Mammography 0.85 (95%CI: 0.62–0.96))

Conclusions: These results suggest that consideration needs to be given regarding the integration of breast MRI into the pretreatment evaluation of women seeking breast conservation therapy.

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KEY WORDS: **breast cancer; MRI; staging**

INTRODUCTION

Choosing appropriate candidates for breast conservation therapy is critical to reliably achieving local control of breast cancer [1–3], while conserving a women's breast. The assessment of the extent of cancer in an affected breast is significant in the selection of women for breast conservation. Current practice relies on mammography and physical examination to estimate the extent of cancer. Multicentric cancer refers separate foci of disease, distinct from the index lesion. This has been traditionally defined as disease in different quadrants mammographically, while the term multifocality is meant to imply multiple cancer foci within a quadrant. When detected by mammography, multicentric disease is known to be associated with a high local recurrence rate and is considered an exclusion criterion for breast conservation [4].

There have been several single institution studies reporting that MRI detects more extensive disease than mammography and clinical exam [5–10]. This includes the detection of disease distant from the presenting index lesion that would not likely be detected by the surgical margin status. These studies include small and potentially biased patient populations. In addition, the definition of additional foci of disease and the characterization of the MRI detected disease are incomplete across these studies. The International Breast MRI Consortium (IBMC) is a co-operative group organized to perform a diagnostic study of breast MRI (protocol 6883). The analysis presented here, studies the relative performance of MRI and mammography in the detection of distinct incidental cancer foci in patients enrolled in IBMC 6883 whose index lesion was confirmed to represent breast cancer.

MATERIALS AND METHODS

The data used in this analysis was collected under IBMC protocol 6883 by a consortium of 15 institutions in the US, Canada, and Germany. The study protocol was approved by the IRB or Ethic Committees of all participating institutions and funded by the National Cancer Institute. All institutions were operating under a valid assurance from the Office of Human Research Protection (OHRP).

Entrance Criteria

Women that presented with a suspicious or highly suspicious imaging finding on conventional imaging (BiRads 4 and 5) or suspicious clinical findings that were felt to require biopsy were eligible for participation in IBMC 6883. Conventional imaging included mammography; and when appropriate clinically, ultrasound and/or galactography. All participants greater than 40 years were required to have mammography within 6 weeks of their MRI examination. Participants under 40 with clinical findings did not require mammography, consistent with standard clinical care. Participants who underwent core or excisional biopsy in the affected breast within 6 months prior to study entry were excluded. Additional exclusions included a prior history of breast cancer in the affected breast, pregnancy, and contraindication to MRI scanning. Those participants in IBMC in whom the index lesion diagnosis was established to be cancer, form the basis for the current analysis.

MRI Scanning

Participants underwent a high resolution 3D contrast enhanced MRI examination of the breast containing the index lesion at 1 or 1.5 Tesla. The scan protocol consisted of a 3D gradient echo sequence with $TR \leq 20$, $TE \leq 4.5$, and a flip angle of 30–45 degrees over a 16–18 cm FOV and $32–128 \leq 3$ mm slices. The total imaging time for this acquisition was required to be less than 4 min. Scans were acquired prior to and after the intravenous administration of 0.1 mM/kg Gd chelate (0.1 mm/kg = 0.2 ml/dg) over 10 sec. Fat suppression or image subtraction was used in all cases.

MRI Interpretation

Radiologists from participating institutions were trained on the imaging features prior to study initiation. MRI scans were interpreted at host institutions with access to mammograms consistent with normal clinical practice. Mammograms were interpreted blinded to the MRI images and findings. In addition to performing a diagnostic assessment of the index lesion, readers were asked to identify additional potentially suspicious

findings (termed incidental lesions (IL)) on MRI and mammography. In order to be considered as a distinct lesion, a minimum of 2 cm separation between the IL and index lesion was required. This definition was used, as 2 cm is beyond the usual planned surgical margin for index lesions. If there were more than one suspicious finding observed on the mammogram, the most suspicious finding was defined as the index lesion and additional findings as ILs. Each IL was recorded, and its visibility on each imaging modality was specifically queried. A final assessment was assigned for each IL according to the ACR BI-RADS standard (1: normal, 2: benign, 3: probably benign, 4: suspicious, and 5: highly suspicious) [11]. Biopsy was recommended for all suspicious and highly suspicious ILs in patients with index lesions that represented cancer. An assessment of 4 or 5 was considered a positive for malignancy, while an assessment of 1, 2, or 3 was considered negative. The recommended biopsy procedure was a needle localization excisional biopsy performed under MRI guidance at the time of the primary cancer excision. An MRI core needle biopsy was acceptable only if it were positive. Ultrasound was not routinely performed.

Pathology Evaluation

Each site was responsible for correlating lesions identified on pathology specimens with the MRI and other imaging findings. Participating sites sent representative slides and the original pathology report for each lesion (including the index lesion, ILs that underwent biopsy and lesions discovered by pathology alone) to a pathology core facility for review when available. Otherwise, pathology diagnosis was extracted from local pathology clinical reports. The study reference pathologist reviewed and determined pathologic status for all index lesions. All pathology interpretations were categorized as benign, atypical, in situ carcinoma, and invasive carcinoma. Within each of these major categories, specific diagnoses were also collected.

Statistical Methods

The goal of this analysis was to estimate the yield of mammography alone, and the yield of MRI performed as an adjunct to mammography, in the detection of cancer ILs in a breast containing an index cancer. The analysis set consisted of all eligible women who had a confirmed malignant index lesion.

For this analysis, MRI and mammography BI-RADS assessments were dichotomized as 1, 2, or 3 as negative and 4 or 5 as positive for malignancy. Histology findings of invasive cancer or ductal carcinoma in situ (DCIS) were classified as malignant; all others were classified as not malignant. Exact confidence intervals were computed for diagnostic yield estimates. Comparisons of yields were made using McNemar test, which accounts for the paired design by using each women as her own ''control.'' Yield estimates were adjusted for the presence of missing pathology data. A missing at random assumption was used and corroborated by comparing key characteristics of cases with and without pathology information.

ROLE OF THE SPONSOR

The National Cancer Institute provided advice regarding study design but was not involved in collection, analysis, or interpretation of data; writing of the paper; or the decision to submit the paper for publication. Gadolinium contrast agents were provided by General Electric Healthcare, Berlex Laboratories, and Bracco Diagnostics, who had no role in the design or conduct of the study or analysis. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

One thousand four eligible women enrolled in IBMC 6883. In 426 of these women, the index lesion was confirmed to be cancer. This cohort of women forms the analysis set and is described in Table I. Pathology was established by the reference pathologist in 65% of the ILs and 98% of the index lesions. The disagreement between the reference and local site pathologist in terms of diagnosing cancer, defined as DCIS or invasive carcinoma, was less than 0.5% on those cases reviewed by the reference pathologist, supporting the use of individual site pathology reports in this analysis.

Of the 426 women in the analysis set, 423 successfully completed the MRI examination while 417 underwent mammography. Yield comparisons by McNemar test

TABLE I. Population Characteristics

Characteristic	
Age	52 ± 11 years
Family history of breast CA[a]	39.7%
Index lesion size (mean)	24.7 ± 1.3 mm
Index lesion size (median)	18 mm
Index lesion palpable	51.4%
Index lesion visible on mammography	88.5%
Index histology	
Invasive ductal (NOS)	59.6%
DCIS	14.3%
Invasive lobular	7.3%
Mixed lobular/ductal	11.7%
Tubular carcinoma	2.1%
Colloid carcinoma	1.4%
Other	3.6%

[a]Defined as primary, secondary, or tertiary relative.

TABLE II. Findings of Incidental Lesions in 426 Women With Breast Cancer

	Findings by mammography	Findings by MRI	Findings by MRI only
Women with complete scans	417	423	423
Women with at least one IL	41 (9.8%)	129 (30.5%)	101 (23.9%)
Women with at least one suspicious IL	36 (8.6%)	103 (24.3%)	83 (19.6%)
Women with at least one suspicious ILs with pathology data	20 (4.8%)	78 (18.4%)	61 (14.4%)
Percent verified by pathology	55.5% (20/36)	75.7% (78/103)	73.5% (61/83)
Women with verified cancer IL	17	56	41
Percent of cancer IL in biopsied women	85% (17/20)	72.8% (56/78)	67.2% (41/61)

were conducted on the 414 women who completed both exams. Data on the incidental lesions detected by each modality are presented in Table II.

In addition to the ILs, described in Table II, five ILs seen by MRI but given an assessment of 3 (probably benign) underwent biopsy and yielded three additional cancer ILs. All three of these cancer ILs were not seen on mammography. These are excluded from the positive cases reported in Table II since a classification of BI-RADS 4 or 5 was required for a lesion to be considered positive. In addition, three lesions seen on mammography, but not classified as suspicious underwent biopsy and yielded malignant results. All three of these lesions were seen and classified as suspicious by MRI. Thus they are included in the 56 confirmed cases of MRI detected cancer ILs.

A biopsy for a suspicious IL was recommended in 36 (8.6%) women by mammography and in 103 (24.3%) women by MRI (Table II). Pathology data were available in 20 (55.5%) of the mammography recommended biopsy cases and 78 (75.7%) of the MRI cases. There was no significant difference between the full cohort of women with a MRI suspicious IL and the subset with pathology information (Table III). Assuming that the pathology verified cases were a random sample of all cases with a suspicious IL, the adjusted estimates of the yield for detection of cancer ILs were 0.18 (95%CI: 0.142–0.214) for MRI and 0.072 (95%CI: 0.050–0.100) for mammography. The MRI yield was significantly higher than the mammography yield (difference 0.103 (95%CI: 0.059–0.147), McNemar test P-value <0.0001). If all unverified ILs were assumed benign, the yields would be 0.13 and 0.041 for MRI and mammography, respectively. The yields were not significantly different between institutions. The difference remains significantly different from zero. The percentage of biopsies of ILs that resulted in a cancer diagnosis was similar between the modalities MRI 0.72 (95%CI: 0.6–0.81); Mammography 0.85 (95%CI: 0.62–0.96).

Women with cancer ILs detected by mammography tended to have lower mammographic breast density while women with cancer ILs detected by MRI only tended to have higher breast density [Table IV]. The median maximum diameter of the index lesions were larger for women with MRI only detected cancer ILs (2.4 cm) compared to those cases detected by mammography (±MRI) (1.5 cm).

The characteristics of the true positive cancer ILs detected by mammography and MRI are listed in Table V. Most of the ILs detected by both modalities were invasive cancer. There was no significant difference in the size and invasive fraction or histologic subtype of cancer ILs detected by mammography or by MRI.

DISCUSSION

In 1993, Harms et al. [5] reported finding mammographically occult foci of carcinoma by MRI in 37% of a cohort of 30 women undergoing mastectomy. Since that time, a number of investigators have reported case series with incidence of MRI detected multifocal/multicentric carcinoma varying from 12% to 88% [6,7,12–14].

TABLE III. Comparison of the Population With Suspicious ILs on MRI With Those Who Underwent Biopsy

Characteristic	Suspicious IL	Suspicious IL with biopsy	Suspicious IL with missing biopsy
Number of women	103	78	25
Age (mean, SD)	54.3 (11) years	54.6 (11) years	53.4 (10) years
Post menopausal (% of total; % missing of total)	48 (46.6%; 0%)	35 (44.9%; 0%)	13 (52%; 0%)
Family history of breast cancer (% of total; % missing of total)	38 (36.9%; 0%)	28 (35.9%, 0%)	10 (40%; 0%)
Index lesion size (mean, SD)	25.3 (2.7) mm	26.4 (3) mm	22.4 (6) mm
Index DCIS (% of total; % missing of total)	9 (8.7%; 0%)	6 (7.8; 0%)	3 (12%; 0%)
IL size (mean, SD)	17.4 (17) mm	18.8 (18) mm	13.0 (16) mm
Upper ½ of breast density scale (% of total; % missing of total)	59 (57.3%; 4.9%)	43 (55.7%; 5.2%)	16 (64%; 0%)

TABLE IV. Mammographic Density in Women With Confirmed Cancer IL Detected by Mammography and MRI Only[a]

Breast density (n)	Mammography detected cancer IL (±MRI) (20)	MRI only detected cancer IL (41)
Fatty (n)	35% (7)	2% (1)
Scattered fibroglandular density (n)	25% (5)	24% (10)
Heterogeneously dense (n)	30% (6)	49% (20)
Extremely dense (n)	10% (2)	12% (5)
Not available (n)	0% (0)	12% (5)

[a]This analysis includes three cases detected but not classified as suspicious.

Although it is generally accepted that MRI can detect foci of breast cancer occult to mammography, variability in the definition of multifocal/multicentric cancer, variability in patient cohorts, incomplete characterization of the MRI detected additional cancer foci and concerns over mammographic technique have made it difficult to generalize the results of these studies. IBMC 6883 accrued a diagnostic population, and thus it was anticipated that the cancer patients in the trial would be reflective of a general cancer population. In fact, the population does appear generalizable in terms of the family history of cancer, index cancer size, and invasive fraction. The age of the population may be lower than the median age for a women with a new diagnosis of breast cancer [15]. The trial adopted a clear definition of an incidental lesion, requiring a 2 cm distance from the index lesion. The precise 3-dimensional image data associated with MRI makes adoption of the traditional definition of multicentricity as disease in different quadrants problematic. Foci of disease that straddle 12:00 and 6:00 but are geographically very close would be considered multicentric and disease in the same quadrant, but separated by large distances would not. This led us to adopt a standard for incidental lesions that appeared to be clinically relevant by requiring a separation beyond the expected surgical margin. Although this does not correspond precisely to the traditional standard for multicentric cancer, we believe that our standard for incidental lesions is more reproducible for cross sectional imaging and serves as a surrogate for traditional multicentricity

TABLE V. Characteristics of Most Advanced Lesion Diagnosed as Cancer IL[a]

	Mammo detected	MRI only detected
Number of women with cancer IL	20	41
IL histology		
Invasive	16 (80%)	32 (78.1%)
Invasive lobular	2 (10%)	6 (15%)
Invasive lob/ductal	3 (15%)	3 (7.3)
Tubular	1 (5%)	2 (4.9%)
DCIS	4 (20%)	9 (21.9%)
Median size	12 mm	11 mm
% grade 2 or 3	70%	84%

[a]This table includes three lesions detected but not classified as suspicious. Characteristics are from the most advanced lesion confirmed in each women diagnosed with a cancer IL.

The results presented demonstrate that MRI detects significantly more cancer ILs than mammography. The MRI yield was 2.4 times greater than that of mammography. However, this study did not directly measure the ultimate impact on local recurrence. The local recurrence rates for breast conservation therapy (BCT) vary from 3% to 19% at 10 years [16–23]. Mammogram detected multicentric disease and positive surgical margins are correlated with a high risk of local recurrence. Although there is clear benefit of radiation therapy in terms of reducing recurrence rates, proper patient selection for BCT is required to achieve acceptable local recurrence rates. Current recommendations include the exclusion of women with mammogram detected multicentric cancer or positive surgical margins [4].

A major concern raised with respect to integrating MRI into the selection of women for BCT is the potential that the disease MRI detects could be controlled with radiation, and may not significantly impact recurrence [24]. Our data show little difference in the characteristics of the cancer ILs detected by MRI and mammography in terms of size, invasive fraction, and grade. Given the known impact on local recurrence rates from excluding women with mammogram detected cancer ILs from BCT, our data would suggest that there would be an additional impact from excluding women with MRI cancer ILs. Our data indicates that approximately 10% of women presenting with breast cancer have MRI only detected cancer ILs, and approximately half of these ILs are greater than 1 cm. Under an assumption that radiation therapy would not control breast cancer foci greater than 1 cm [25], it can be estimated that eliminating women with MRI detected cancer ILs from BCT would reduce recurrence rates by 5%. Although this may be associated with a minor decrease (no more than 10%) in the rate of traditional BCT, the improved anatomic visualization has the potential to expedite the implementation of more

elaborate breast conserving partial mastectomies (bat wing mastopexies, etc) in order to achieve negative surgical margins while saving the breast.

It has been suggested that MRI would have maximal value in women with radiographically dense breasts. Although the data demonstrate that the population of women with MRI only visible cancer IL is skewed toward higher breast density, one-third of the cases were detected in women in the lower half of the breast density scale. Similarly, the median index lesion size for women with MRI only cancer ILs (2.4 cm) was higher than that of women with mammogram detected cancer ILs (1.5 cm) and than the general cancer population enrolled in this study (1.1 cm).

The reported low specificity of breast MRI in a diagnostic setting has caused some concern regarding its application to evaluate cancer patients for BCT. Previous reports of the impact of MRI on breast cancer management do raise the concern of patients receiving additional surgery or mastectomy based on false positive MRI findings [8]. This data was collected before technology for vacuum assisted core biopsy under MRI was available [26]. This technology is being disseminated and allows sampling of MRI findings percutaneously with minimal associated morbidity. In addition, the cancer yield from MRI guided biopsy in this study was quite high. The high pretest probability in the cancer setting may mitigate some of the specificity concerns.

It is possible that some of the disease detected by MRI would ultimately be detected by positive surgical margins, however the 2 cm distance from the index lesion definition, used in this study, suggests that these lesions would be beyond the typical surgical margin. In addition, there is an advantage of detecting the disease prior to surgery since a single operative procedure could be performed, reducing re-excision and improving cosmesis. Further more, using more modern technology it is possible to achieve similar image quality while imaging both breasts simultaneously. Small studies have estimated that MRI will detect occult contra-lateral cancer in 4–5% of women with newly diagnosed breast cancer [27,28], suggesting an additional advantage of breast MRI in this setting.

One limitation of this study is the incomplete pathology verification. This was primarily related to participants undergoing treatment at non-consortium institutions, patient choice, and physician choice. No apparent verification bias was detected with respect to participant age, index lesion size, clinical presentation, index lesion imaging characteristics, and index lesion histology. In addition, results remain consistent under the conservative assumption that all unverified cases are negative and the matching of our design makes inferences robust to participant level confounders. Follow up of these lesions would be difficult to interpret in the face of adjuvant radiation and chemotherapy. The interpretation paradigm allowed the MRI reader to be unblinded with respect to the mammogram. Thus the study evaluates the added value of MRI when applied as an adjunct to mammography. This is the expected clinical implementation of MRI evaluation of breast cancer. Another limitation is that the actual distance between the index lesions and IL is not available in all cases, other than the requirement that it is greater than 2 cm. Additionally, although this study provides important data to allow us to estimate the potential impact of MRI on local recurrence, it does not directly measure the local recurrence rate. Unfortunately, this would require long-term data collection and could not be available for several more years. In addition, data regarding the ultimate treatment of women enrolled on this protocol is not available at this time. This data would provide some insight into the potential for MRI to influence treatment decisions.

CONCLUSION

These results demonstrate that MRI performed according to the IBMC standards will detect additional mammogram occult cancer foci greater than 2 cm from the index cancer in approximately 10% of women. These additional cancer foci are similar to those detected by mammography and are therefore likely to be associated with an increased risk of local recurrence for breast conservation therapy. Although follow-up studies to document the effect of breast MRI on local recurrence should be performed to confirm these estimates, consideration needs to be given regarding the integration of breast MRI into the pretreatment evaluation of women seeking breast conservation therapy. This is particularly true in women with radiographically dense breasts and larger index cancers, where data shows a higher relative yield of MRI for additional cancer foci. In addition, MRI should be considered in developing guidelines for patient selection for newer approach to breast cancer treatment such as partial breast irradiation and tumor ablation.

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