Comparison of breast magnetic resonance imaging clinical tumor size with pathologic tumor size in patients status post-neoadjuvant chemotherapy

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KEYWORDS: Breast cancer; Magnetic resonance imaging; Neoadjuvant chemotherapy

Abstract

\textbf{BACKGROUND:} Neoadjuvant chemotherapy (NACT) is used in breast cancer to evaluate the response to treatment. We examined the usefulness of breast magnetic resonance imaging (MRI) in the evaluation of tumor response after NACT.

\textbf{METHODS:} Breast MRIs of 87 women with MRI after NACT were reviewed. The Spearman coefficient was used for estimating the correlation between MRI and pathologic tumor sizes (ypTs).

\textbf{RESULTS:} The median age was 50 years (range 25 to 83 years). The median MRI size was 1.25 cm (range 0 to 10 cm). The median ypT was 1.20 cm (range 0 to 10.4 cm). The Spearman coefficient between MRI and ypT was .78 (95% confidence interval, .67 to .85; \( P < .0001 \)). MRI was found to have a positive predictive value of 92% and a negative predictive value of 64% for residual in-breast disease. The sensitivity and specificity of MRI were 86% and 77%, respectively.

\textbf{CONCLUSIONS:} MRI correlates well with the final pathology and can be a useful modality to predict residual disease after NACT and aid in surgical planning.

Historically, neoadjuvant chemotherapy (NACT) was used to convert inoperable and locally advanced breast cancers into operable cancers. Currently, NACT is used to shrink the size of the cancer, making breast conservation an option. Regardless of surgical choice, tumor response after NACT is measured by residual in-breast and nodal disease. The amount of response (none, partial, or complete) can subsequently be used as an indicator of survival and recurrence risk because the remaining disease is considered an “in vivo” marker of chemotherapeutic efficacy.\textsuperscript{1,2} Although the National Breast and Bowel Project B-18 Trial showed no difference in disease-free or overall survival between the study arms (administration of chemotherapy before or after surgery), it did show that a complete pathologic response after NACT was correlated
to a decreased recurrence risk. As more effective chemotherapeutic regimens are developed, the primary goal of NACT may transition from a reduction in tumor size to achieving a complete pathologic response.

For the current time, the focus remains on elucidating potential candidates for breast preservation. In the early 1990s, the questions of reducing the tumor size before surgical intervention and the potential for breast-conserving therapy were evaluated by several centers. In randomized trials, the use of NACT reduced the mastectomy rate by about 30% in patients deemed to have tumors too large for lumpectomy at presentation. In addition, several large randomized trials have shown comparable clinical outcomes between mastectomy and breast-conserving therapy. However, 1 of the limiting factors is accurately determining the residual in-breast tumor size after NACT to allow for breast-conserving surgery. Thus, NACT in combination with an accurate indicator of residual in-breast disease may help to improve patients’ eligibility for breast-conserving therapy.

Mammography is the most common imaging modality used in breast cancer detection; however, studies have shown that the sensitivity of mammography for detecting multiple malignant foci is often less than 50%. Multiple studies have shown the increased sensitivity of magnetic resonance imaging (MRI) for breast disease over mammography, ultrasound, and clinical examination. Post-NACT MRI has been gaining acceptance as a noninvasive method to measure tumor response for surgical planning. Compared with ultrasound and clinical examination, MRI was found to be the best predictor of the pathologic response in patients who underwent NACT. In addition, the American College of Radiology Imaging Network trial 6657, the imaging component of the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular analysis (I-SPY trial) (Cancer and Leukemia Group B [CALGB] 150007/150012), showed that tumor response measured volumetrically by MRI showed a stronger correlation with the final pathologic tumor size (ypT) compared with clinical examination or the tumor diameter measured in the longest single axis by MRI or mammography. Chen et al showed a close correlation of MRI tumor size to histopathologic size for residual tumors and correctly diagnosed complete responses in 74% of patients.

MRI is a highly sensitive imaging modality for detecting primary breast cancer. However, although some sources have found MRI to be an accurate measure of tumor response after chemotherapy, others have found it to underestimate residual disease, resulting from decreased enhancement in the breast after chemotherapy. Despite the increased use of MRI, the use of routine MRI imaging remains controversial because of the lack of prospective data. MRI is further hampered by the limitations of cost, a lengthy imaging time, contrast injection, and a relatively low specificity. To address some of the questions regarding the usefulness of MRI in accurately measuring tumor size when NACT is administered, we embarked on an institutional review of those patients having both pre- and post-NACT breast MRI.

Methods

This study is an institutional review board–approved retrospective review of patients receiving MRI as part of their evaluation for breast cancer and having surgery at Moffitt Cancer Center, Tampa, FL, between January 2004 and November 2009. Patient chart information was retrieved from the electronic medical records and recorded in an Excel (Microsoft Excel 2007, Seattle, WA) spreadsheet with patient identifiers. Patients included in the study were pathologically diagnosed with breast cancer by core needle biopsy or excisional biopsy and underwent at least 1 breast MRI at our institution. A subset of patients who underwent NACT was separated and analyzed for age at diagnosis, race, sex, family history, axillary status at diagnosis, diagnostic imaging, biopsies, hormone receptor status, type of chemotherapy agents, surgical procedure performed, margin assessment, pathologic tumor size and nodal involvement, and stage according to the American Joint Committee on Cancer Version 6. For those patients who underwent post-NACT MRI, their information was analyzed to retrospectively determine the accuracy of MRI in predicting the pathologic response to chemotherapy. In addition, we analyzed tumor response to NACT according to receptor status and performed a subset analysis to determine if post-NACT MRI was more accurate in predicting final pathologic tumor size according to the receptor status. We used the Response Evaluation Criteria in Solid Tumors for response assessment according to receptor status. Complete response is the disappearance of all target lesions. Partial response is a 30% decrease in the sum of the longest diameter of target lesions. Progressive disease is a 20% increase in the sum of the longest diameter of target lesions. Stable disease is categorized by small changes that do not meet the criteria for progressive disease or partial response

MRI examination

Breast MRI studies were performed using a dedicated 1.5T scanner with channel Sentinelle bilateral breast coil (General Electric, Fairfield, CT). The imaging protocol consisted of an axial precontrast T1-weighted nonfat saturated sequence followed by bilateral dynamic contrast-enhanced images using the 3D VIBRANT pulse sequence (GE). All post-contrast images were obtained at 2.2-mm slice thickness. The VIBRANT pulse sequence was based on a fast 3-dimensional gradient echo sequence with T1 weighting and fat suppression and had special modifications to optimize the image quality for breast imaging. Axial T2-weighted and...
recovery (STIR) sequence and axial T1 high-resolution (slice thickness of .8 mm) images were also obtained. The gadolinium-based contrast agent (.1 mmol/kg body weight Magnevist, Bayer HealthCare Pharmaceuticals, Seattle, WA) was injected followed by 20 mL saline flush. The first post-contrast axial sequence was obtained at 90 seconds after the injection of contrast medium (20 seconds after the completion of contrast injection) followed by 4 more acquisitions at 60- to 90-second intervals. CADstream software (General Electric, Fairfield, CT) was used to analyze the images and determine the tumor size or volume in 3 dimensions. For the purposes of this study, tumor size was recorded as the single long-axis measurement in millimeters. Lesion morphology and enhancement were described using Breast Imaging-Reporting and Data System MRI Lexicon as recommended by the American College of Radiology.

Pathologic examination

All breast specimens were received fresh in the pathology gross room and were fixed after gross evaluation in 10% buffered formalin for 6 to 48 hours. Specimens were then serially sectioned at 2- to 4-mm intervals. All biopsy sites with surrounding nonfatty tissue and any separately identified grossly suspicious lesions were entirely submitted for histologic evaluation. Additionally, for mastectomy specimens, representative sections of grossly unremarkable breast parenchyma, skin, and nipple were submitted for evaluation. All axillary lymph nodes, if present, were entirely submitted if grossly unremarkable, and representative sections of grossly positive lymph nodes were sampled. Specimen blocks were then paraffin-embedded and processed according to routine methods.

Statistical analyses

Pathologic measurement of the tumor size was used as the “gold standard” and compared with the tumor size derived from MRI. The difference between pathologic measurements and post-NACT MRI measurements was assessed using the Wilcoxon signed rank test. Because the measurements fail to hold normality assumption (both P values <.005 with the Anderson-Darling test), the Spearman correlation coefficient and Fisher z transformation were used to compute the correlation coefficient and its 95% confidence intervals, respectively. The association of the response to NACT with patients’ receptor status was assessed by the Fisher exact test, and the odds of pathologic complete response for Her2/neu-positive and triple-negative patients were compared with the hormone receptor-positive, Her2/neu-negative patients.

Results

Eighty-seven women were identified who underwent neoadjuvant chemotherapy and had both pre-NACT and post-NACT breast MRI. The median age was 50 years (range 25 to 83 years). Demographics, the chemotherapy regimen, and receptor status for this patient population were tabulated (Table 1). Initially, seventy-six patients (87%) had clinically T2 or greater tumors; after NACT, 26 patients (30%) still had T2 or greater tumors. Fifty-three patients (61%) had palpable lymphadenopathy at presentation. Of those, 45 (52%) were biopsy-proven positive for metastatic disease in an axillary lymph node.

The median invasive tumor size determined by pre-NACT MRI was 3.75 cm (range .9 to 10 cm). Patients with pre-NACT MRI-determined T1 tumors were more likely to be triple negative or Her2/neu positive. The median post-NACT MRI size was 1.25 cm (range 0 to 10 cm). The median post-NACT size was 1.20 cm (range 0 to 10.4 cm). The median size difference between the post-NACT MRI and the ypT was .60 cm (range 0 to 4.2 cm, P = .51). The correlation coefficient for median post-NACT size and median post-NACT ypT was .78 (P < .0001; 95% confidence interval [CI], .67 to .85; Fig. 1).

The Response Evaluation Criteria in Solid Tumors criteria were used to assess the response to NACT. Patients were divided into groups who either showed a complete clinical response or a residual tumor based on MRI. In each group, patients were then further subdivided by their final pathology into groups who had shown a pathologic complete response or a pathologic residual tumor. Of the 26 patients who had a complete response to NACT on MRI, 17 (65%) had a complete response on pathologic review. Of the 61 patients with residual disease on MRI after NACT, pathology showed 56 (92%) to actually have residual disease. Of those with residual carcinoma, 64% had Invasive ductal carcinoma (IDC), 22% had IDC/DCIS, 12% had ILC, and 2% had only DCIS remaining (Table 1). Post-
NACT MRI had a 92% positive predictive value and a 64% negative predictive value for residual in-breast disease. The sensitivity and specificity of post-NACT MRI for residual disease was 86% and 77%, respectively (Table 2). Sixty percent of MRI tumor sizes were within 1 cm of the final pathology tumor size.

Complete response and partial response were more likely to be achieved in triple-negative patients compared with hormone receptor–positive patients although this was not statistically significant (odds ratio = 6.8; 95% CI, .79 to 59.0; \( P = .081 \)). Complete response and partial response were also more likely to be achieved in Her2/neu-positive patients compared with hormone receptor–positive, Her2/neu-negative patients (odds ratio = 5.5; 95% CI, 1.07 to 27.7; \( P = .041 \)). There was not a significant median size difference between the post-NACT MRI and the post-NACT ypT according to the receptor status; the correlation coefficients between the median size differences were highly significant (Fig. 2).

After NACT, 36 patients (41%) had lumpectomy, and 51 patients (59%) had mastectomy as their surgical procedure. Eight patients (22%) undergoing lumpectomy required re-excision with only 3 of 8 (38%) having residual tumor present on re-excision. Seven lumpectomy patients (19%) ultimately required mastectomy secondary to close or positive margins (defined as < .2 cm from the margin). Of these 7 patients, only 3 (43%) had residual tumor on the final pathology. After the salvage mastectomies, 29 patients (33%) underwent lumpectomy, and 58 patients (67%) underwent mastectomy.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinicopathologic data</th>
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</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>87</td>
</tr>
<tr>
<td>Median age (y)</td>
<td>50 (range 25–83)</td>
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<tr>
<td>Race (%)</td>
<td>White 62 (71.3) Hispanic 11 (12.6) Black 8 (9.2) Asian/Pacific Islander 4 (4.6) Unknown 2 (2.3)</td>
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<tr>
<td>Neoadjuvant chemotherapy (87) (%)</td>
<td>Herceptin (Genentech, Inc, South San Francisco, CA)-based therapy 25 (29.1) Anthracyclin-based therapy 8 (9.3) Anthracyclin + taxane-based therapy 54 (62.8)</td>
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<tr>
<td>Clinical T stage at presentation (%)</td>
<td>T1 9 (10.3) T2 41 (47.1) T3 33 (37.9) T4 2 (2.3) Unknown 2 (2.3)</td>
</tr>
<tr>
<td>Clinical nodal status at presentation (%)</td>
<td>Palpable adenopathy 53 (60.9) Biopsy-positive palpable adenopathy 45 (52.3) No palpable adenopathy 34 (39.1)</td>
</tr>
<tr>
<td>Post-NACT histology (%)</td>
<td>pCR 22 (25.3) IDC 75 (86.2) ILC 10 (11.4) DCIS 2 (2.3)</td>
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<tr>
<td>Receptor status (%)</td>
<td>Estrogen receptor + 46 (52.9) Progesterone receptor + 35 (40.2) Her-2 neu + 29 (33.3) Triple negatives 18 (20.7)</td>
</tr>
<tr>
<td>Post-NACT yT stage (%)</td>
<td>T0 22 (25.3) Tis 2 (2.3) T1 37 (42.5) T2 20 (23.0) T3 6 (6.9) T4 0 (.0)</td>
</tr>
<tr>
<td>Post-NACT yN stage (%)</td>
<td>N0 30 (34.4) N1 37 (42.5) N2 12 (13.8) N3 8 (9.2)</td>
</tr>
</tbody>
</table>

DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LCIS = lobular carcinoma in situ; pCR = pathologic complete response; yN = nodal status post NACT; yT = tumor size post NACT.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Statistical data</th>
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<tr>
<td>Number of patients (%)</td>
<td>87</td>
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<tr>
<td>True-negatives</td>
<td>17 (19.5)</td>
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<tr>
<td>True-positives</td>
<td>56 (64.4)</td>
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<tr>
<td>False-negatives</td>
<td>9 (10.3)</td>
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<tr>
<td>False-positives</td>
<td>5 (5.7)</td>
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<td>Positive predictive value (%)</td>
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<tr>
<td>Negative predictive value (%)</td>
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<tr>
<td>Sensitivity (%)</td>
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<td>Specificity (%)</td>
<td>77.3</td>
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<tr>
<td>False-positive rate (%)</td>
<td>22.7</td>
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<tr>
<td>False-negative rate (%)</td>
<td>13.8</td>
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<tr>
<td>Area under the ROC curve</td>
<td>.82</td>
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ROC = receiver operating characteristic.
A review of the literature has shown MRI to be more accurate than conventional imaging in the detection of breast cancer. MRI performed after NACT has been shown to be accurate in predicting tumor response in 57% to 76% of cases, with size being overestimated in 13% to 33% of cases and underestimated in 10% to 11% of cases.\(^{17,20,31}\) Correlation coefficients ranged from .65 to .93.\(^{17,31}\) In our study, we conducted a systematic analysis to investigate how the post-NACT MRI imaging findings compare with the tumor size on final pathology. Post-NACT mammograms could not be compared with post-NACT MRI with regards to the prediction of actual tumor size because of the smaller percentage of patients receiving post-NACT mammograms. Post-NACT MRI had a positive predictive value of 92% and a negative predictive value of 64%. The sensitivity of post-NACT MRI was 86%, the specificity was 77%, and the area under the receiver operating characteristic curve was .82 (Table 2). This is comparable with studies reported in the literature\(^{10,13}\) correctly identifying complete responses or residual tumors in 84% of patients and predicting a tumor size within 1 cm in 60% of patients.

The neoadjuvant setting also provides an opportunity to determine in vivo tumor responses to chemotherapy.\(^{1,2}\) The National Breast and Bowel Project B-27 trial of NACT showed a higher rate of pathologic complete response in estrogen receptor–negative tumors compared with estrogen receptor–positive tumors.\(^{32}\) Similar outcomes have been observed in Her2/neu-positive tumors compared with estrogen-positive tumors in the neoadjuvant setting.\(^{5,33}\)

Our study supports the literature with complete pathologic response more likely achieved in triple-negative patients and Her2/neu-positive patients compared with hormone receptor–negative, Her2/neu-negative patients (\(P = .081\) and \(P = .041\), respectively). Although this was not statistically significant in triple-negative patients, likely because of a small sample size, it was statistically significant in Her2/neu-positive patients. These outcomes show that the response to NACT may be more efficacious in triple-negative and Her2/neu-positive patients. The accuracy of post-NACT MRI for predicting pathologic tumor size was not significantly different according to the receptor status of the tumor, with correlation coefficients ranging from .73 and .75 (Table 3).

Several studies have convincingly shown that NACT can allow breast-conserving therapy in some patients for whom mastectomy was initially the preferred option for local-regional control.\(^{3,6,7}\) Christy et al\(^{14}\) showed that for tumors

### Comments

Neoadjuvant chemotherapy is a well-established treatment strategy for the management of women with operable, greater than or equal to T2, or node-positive breast cancers that can offer an increased opportunity for breast-conserving therapy and to achieve negative margins. In addition, multiple studies have shown improved outcomes in patients achieving pathologic complete response at the time of definite surgery after NACT.\(^{19,23,24}\) With the opportunity to increase the rate of breast-conserving therapy and the prognostic role of NACT leading to a complete pathologic response, the use of NACT will likely continue to grow. Thus, patient selection is important for both adequate local control and an esthetic result.

An increased local recurrence rate in patients treated with breast-conserving therapy after NACT has been reported and was formerly seen in patients with large tumors.\(^{4,13,25}\) As a result of this uncertainty, many have been hesitant to fully embrace breast-conserving therapy for patients who meet the criteria for this treatment modality after NACT. However, many studies have suggested that breast-conserving therapy after NACT results in acceptably low rates of locoregional recurrence in appropriately selected patients, even in those who initially have T3/T4 cancers.\(^{13,26}\)

Before the routine use of MRI, tumor size evaluation before and after NACT uses physical examination, mammography, and ultrasonography. These conventional techniques are generally poor estimates of residual disease on final pathology. Correlation coefficients have wide ranges from .42 to .79 for physical examination, .33 to .84 for conventional imaging using mammography, and .29 to .89 for sonography.\(^{17,27,28}\) Peintinger et al\(^{26}\) showed that the combined use of 2 or more modalities, specifically ultrasonography and mammography, may increase the accuracy of preoperative assessment of tumor size in patients undergoing NACT. However, conventional imaging relies on changes in gross tumor size; this may be confounded by a nonuniform pathologic response or treatment effect, which may mask the true tumor size.\(^{29}\) Furthermore, tumors may not shrink concentrically, and the actual regression may resemble that of a cookie crumbling.\(^{30}\) Improving the preoperative accuracy of tumor size and the extent of residual disease estimates after NACT may help in patient selection and may lead to an increase in the use of breast-conserving surgery in the setting of NACT.
between 2 and 4 cm, NACT was associated with a significantly decreased rate of re-excision after lumpectomy, not only resulting in fewer mastectomies but also avoiding the morbidity and inferior cosmetic results of re-excision lumpectomy. Our re-excision rate after lumpectomy was 22%, which is lower than most of the literature quoted rates of 20% to 60%. However, we still had 67% of patients opting for mastectomies, whereas only 33% received breast-conserving therapy. It is difficult to ascertain the multiple factors that go into surgical decision making, but one limitation of our study was the inability to identify who initially and post-NACT were considered candidates for breast-conserving therapy. In addition, MRI may not detect scattered cells or clusters of tumor distributed in a large fibroptic region, which could account for the some of the inaccurate post-NACT MRI measurements. Our conversion to mastectomy rate was higher (19%) than what is reported in the literature (6.6% to 12%).

References


