Published in final edited form as:
Cancer. 2009 March 15; 115(6): 1194–1202. doi:10.1002/cncr.24154.

Accuracy of Clinical Evaluation of Locally Advanced Breast Cancer in Patients Receiving Neoadjuvant Chemotherapy

Raquel Prati, M.D.[1], **Christina A. Minami**[2], **Jeff A. Gornbein, Ph.D.**[3], **Nanette Debruhl, M.D.**[4], **Debbie Chung, Pharm.D.**[5,2], and **Helena R. Chang, M.D., Ph.D.**[1,2]

[1]Department of Surgery, Revlon/UCLA Breast Center, David Geffen School of Medicine, UCLA, Los Angeles, CA

[2]David Geffen School of Medicine, UCLA, Los Angeles, CA

[3]Department of Biomathematics, David Geffen School of Medicine, Los Angeles, CA

[4]Department of Radiological Sciences, Iris Cantor Breast Imaging Center, David Geffen School of Medicine, UCLA

[5]Clinical Trials Unit, Revlon/UCLA Breast Center, David Geffen School of Medicine, UCLA Los Angeles, CA

Abstract

Physical examination (PE), mammography (MG), breast MRI, FDG-PET and pathologic evaluation are used to assess primary breast cancer. Their accuracy has not been well studied in patients receiving neoadjuvant chemotherapy. Accuracies of each modality in tumor and nodal assessment in patients with T3/4 tumors receiving neoadjuvant chemotherapy were compared.

METHODS—45 patients of a prospective clinical trial studying T3-T4M0 tumors were included. Patients received neoadjuvant chemotherapy: docetaxel/carboplatin with or without trastuzumab before and/or after surgery (depending on HER-2/neu status and randomization). Tumor measurements by PE, MG, and MRI and nodal status by PE and PET were obtained before and after neoadjuvant chemotherapy. Concordance among different clinical measurements was assessed and compared with the tumor and nodal staging by pathology. Spearman corr (r) and root mean square error (RMSE) were used to measure the accuracy of measurements among all modalities and between modalities and pathological tumor size.

RESULTS—Comparing to the tumor size measured by PE, MRI was more accurate than MG at baseline (***r*** 0.559, ***RMSE*** 35.4% vs. ***r*** 0.046, ***RMSE*** 66.1%). After neoadjuvant chemotherapy, PE correlated better with pathology than MG or MRI (***r*** 0.655, ***RMSE*** 88.6% vs. ***r*** 0.146, ***RMSE*** 147.1% and ***r*** 0.364, ***RMSE*** 92.6%). Axillary nodal assessment after neoadjuvant chemotherapy showed high specificity but low sensitivity by PET and PE.

CONCLUSION—Findings suggested that MRI was a more accurate imaging study at baseline for T3/T4 tumor and PE correlated best with pathology finding. PET and PE both correctly predicted positive axillary nodes but not negative nodes.

Corresponding Author: Name: Helena Chang, M.D., Ph.D., Director, Revlon/UCLA Breast Center, Address: 200 UCLA Medical Plaza, Suite B265-1, Los Angeles, CA 90095-7028, Phone: (310) 825-2144, Fax: (310) 206-2982, hchang@mednet.ucla.edu.

An earlier version of this study was presented in poster form at the Short Term Training Program poster fair at the David Geffen School of Medicine on August 24, 2006 and at San Antonio Breast Cancer Symposium on December 13, 2007.

INTRODUCTION

Neoadjuvant chemotherapy has gained acceptance in treating locally advanced breast cancer. While neoadjuvant chemotherapy affords the same survival rates as postoperative chemotherapy in women with operable breast carcinoma,1 the advantages of neoadjuvant treatment over conventional adjuvant chemotherapy are manifold. First, and most importantly, chemotherapy given before surgery may shrink the large tumors to improve the respectability in some and to allow for breast conservation surgery in others which is otherwise impossible. Second, it allows for assessment of tumor response in each patient. Third, the upfront nature of this treatment provides the earliest chance to treat micrometastatic disease, saving time that could potentially be lost to local treatment.2 Lastly, the intact neovasculature associated with cancer can be exploited to the advantage of the patient. Because surgical excision may alter the tumor's vasculature, neoadjuvant chemotherapy may have the advantage of enhancing the local effect through a non-disturbed blood supply.[3،4]

The assessment of residual tumor size is important in determining the surgical course of action following preoperative chemotherapy. Physical examination is the accepted clinical standard in the evaluation of tumor size before and after neoadjuvant chemotherapy. Pathologic evaluation is the ultimate assessment of the residual tumor size after the chemotherapy.[3،4] Other clinical tools, such as mammography and MRI, are also used in the assessment of tumor response to neoadjuvant treatment.

However, imprecision in tumor measurements accompanies any of these modalities. All three modalities (physical examination, mammography, and MRI) have been found to carry both significant false positive [5،6،7.8] and false negative rates.[4،5،7،9] In addition, chemotherapy itself may induce significant biological changes of the tumor, affecting imaging findings differently. As a result, correlation made among mammography, MRI, PET, and physical examination findings may not be consistent.

Despite these shortcomings, these disease assessment tools are mainstays of current clinical practice that guides treatment and their relative accuracy must be determined. Outcomes in previous studies varied. Some studies have found all three correlate well with final pathologic findings.10 Others have shown physical examination to have a higher predictive value.11 Recently, MRI was found to have the highest correlative value. [2،4،5،6،12،13] Many data from direct comparisons between physical examination, mammography, and MRI, highlight MRI as the most accurate way to assess residual tumor size following neoadjuvant chemotherapy but other studies disagree.[2، 3، 4، 5، 6، 18]

Clinical assessment of axilla is another important evaluation that guides the choice of axillary management. Clinical nodal evaluation is conventionally determined by physical examination, and is not the focus of mammography and MRI. In recent years, fluorodeoxyglucose positron emission tomography (FDG-PET) has emerged as a promising imaging technology for clinical evaluation of nodal metastases. The PET scan has been shown to have low sensitivity when compared to both axillary lymph node dissection and sentinel lymph node biopsy.[14، 21] Nonetheless, the positive predictive value and high specificity of the PET scan would still be valuable in staging patients with more advanced disease and guiding the choice of surgical management of the axilla.[14،15]

The purpose of this study was to prospectively evaluate the accuracy of all available tools—PE, MG, MRI, and PET scan—for clinical staging of primary breast cancer and axillary lymph nodes in women receiving neoadjuvant chemotherapy.

MATERIALS AND METHODS

PATIENTS AND STUDY DESIGN

Forty eight patients reported in this study were participants of an ongoing trial approved by the Institutional Review Board of the University of California, Los Angeles. Eligible patients had confirmed primary adenocarcinoma of the breast either greater than 2 cm or with skin/chest wall involvement (T2, T3, and T4). Women with evidence of distant metastasis, any prior radiation to the breast, or docetaxel (75mg/m^2), carboplatin (AUC=6), or trastuzumab chemotherapy, or breast cancer diagnosis within the past five years were excluded. In this study, patients were treated with four cycles of preoperative docetaxel and carboplatin (with or without trastuzumab) followed by surgery. Neoadjuvant trastuzumab therapy was randomly assigned to the patient whose tumor was HER2/*neu* positive by FISH (fluorescence in situ hybridization). All HER2/*neu* positive patients received postoperative trastuzumab, with both treatment arms receiving a total of twelve months treatment. Baseline breast disease was evaluated by physical examination, mammography, and PET scan. The breast MRI was required for those with discrepancies between the physical examination and mammography findings or with non-measurable disease and was optional for others. The MRI findings were available in most cases. The same baseline breast evaluations were repeated after the completion of four cycles of neoadjuvant chemotherapy. The clinical findings of different modalities were compared and the residual tumor in the breast and axilla were then compared to the pathologic evaluations following their definitive surgery.

Of the original 48 patients, only the T3 and T4 patients were included in the current analysis, totaling 47 patients. One of the 47 patients refused surgery because of a clinical complete response. Another went off study as her tumor did not respond well to the trial chemotherapy drugs and she received a second chemotherapy regimen prior to her surgery. A total of 45 analyzable patients were left.

STUDY ASSESSMENTS

Patient demographics, tumor characteristics, and the longest diameter of the multidimensional tumor measurement obtained by physical examination, mammography, and MRI before and after four cycles of neoadjuvant chemotherapy were recorded. The MRI was required on all who had non-evaluable or non-measurable disease on mammography or had large discrepancies between the measurements obtained by physical examination and mammography at both baseline and after neoadjuvant chemotherapy. Pathologic tumor dimensions were measured separately for invasive and DCIS components of the tumor. In the rare case that a patient underwent additional surgeries for margin clearance, only the longest unidimensional measurement of the cancer from the first definitive surgery was used. An absence of invasive cancer in the mastectomy or lumpectomy specimen was coded as a complete pathologic response of the tumor.

Histological subtype, nuclear grade, histological differentiation, and lymphvascular invasion together with estrogen/progesterone receptors, and HER2/neu status were included in the analyses. Tumor biomarkers from the initial biopsy report were used for analysis to avoid the changes that may be induced by the neoadjuvant therapy.

Clinical assessment on axillary nodal status was recorded both at baseline and following neoadjuvant chemotherapy by PET scan and physical examination. The findings were compared with pathologic nodal staging. Both number of positive nodes and total number of nodes examined pathologically were recorded.

STATISTICAL ANALYSIS

Statistical analysis included mean and standard deviation (SD) of the differences between tumor measurements, as well as the root mean square error (RMSE). The RMSE is similar to the SD except that it compares all the deviations among the differences to zero rather than to the mean difference. The RMSE incorporates lack of agreement between the measurement in question and the measurement of the standard from both systematic bias (one is higher than the other) and random variation from patient to patient. The “best” measurement compared to the standard is the one that has the smallest RMSE. Bias, the difference between the mean gold standard measurement (the chosen method to be measured against) and the mean measurement of the modality in question, was also calculated. Measurement correlation was calculated using both parametric Pearson correlations and the non parametric rank based Spearman correlations. The R square (R^2), the square of the Pearson correlation, represents the percentage of the variation in one measurement that is accounted for by variation in the other measurement.

RESULTS

The median age of the 45 patients included in this report was 50 (range, 29–68 years). The majority of the patient population was white (62%), followed by Hispanic (18%), Asian (16%), and black (4%). By T staging, T3 tumors accounted for 69% of the population, followed by inflammatory breast cancer or T4d (22%) and T4a-c tumors (9%). Infiltrating ductal histology (82%) and moderate to poor histological differentiation (82%) were the most common tumor characteristics. Lymphvascular invasion (LVI) was seen in 16 (35%) of the patients. More than one third of patients had hormone receptor negative tumors (38%) (Table 1). Tumor characteristics (LVI, histological differentiation, tumor type, and nuclear grade) were taken from the pathology report of the tumor biopsy procedures.

Forty patients had the clinical tumor measurements at baseline and post-neoadjuvant chemotherapy. Incomplete data in five patients was due to lack of evaluable films or missing pathological measurement of the size of their residual tumor. Forty three patients at baseline and forty four patients after neoadjuvant chemotherapy had tumor size measurable on physical examination. Two patients at baseline and one following neoadjuvant chemotherapy did not have tumor size measured by physical examination because of the diffuse nature of the inflammatory disease in these three patients. Forty four patients had baseline mammographies of which thirty patients had tumor measurements; forty one patients had post-neoadjuvant mammographies with twenty-nine of them containing tumor measurements. One patient did not receive mammography at baseline because of the extremely painful inflammatory cancer, fourteen others had disease that was either not visible, measurable, or evaluable by mammography. Four patients did not undergo mammography following their neoadjuvant chemotherapy, one did not have a baseline mammography and three had non-evaluable disease on the baseline mammography. In the remaining, twelve had evaluable but non-measurable disease or non-evaluable mammographies after four cycles of chemotherapy. Architectural distortion and asymmetrical density were the main abnormalities responsible for a non-measurable tumor.

Thirty-three patients had tumor measurements by MRI at baseline and thirty-four had MRI measurements following their neoadjuvant chemotherapy. At baseline, 10 patients did not receive MRIs and two patients had non-evaluable MRIs due to technical problems. The ten patients who did not undergo baseline MRI did not receive a post-neoadjuvant chemotherapy MRI. Post-neoadjuvant chemotherapy MRI was reported as non-evaluable in one case.

Twenty-one patients had tumor measurements by all three modalities (physical examination, mammography, and MRI) at baseline. The median tumor size by physical examination at baseline was 6.5 cm (range, 3.5–20 cm), 3.5 cm by mammography (range 1.5–9 cm), and 6.2 cm by MRI (range, 2.9–15 cm) - patients were deemed a T3 if a tumor measurement over 5.0 cm was seen on baseline PE, baseline mammography, or baseline MRI. Comparison of the RMSE (root mean square error) showed that the MRI finding (RMSE = 2.9) was highly agreeable with physical examination. This was in contrast to the poor correlation between mammography and physical examination (RMSE = 4.8). Similarly, Spearman correlation values showed that MRI had a greater agreement with physical examination in assessing tumor size (r=0.559) than mammography (r=0.046).

At the end of the neoadjuvant treatment, twenty-three patients had all three clinical measurements including physical examination, mammography, and MRI, and subsequent pathological measurements of the residual tumors (Table 3). Thirty-nine had tumor measurements by PE and final pathology (the definitive measurement of tumor size), with a median tumor size of 2.0 cm by PE (range, 0 and 11 cm) and 3 cm by pathology. Median measurement by mammography (n = 28) was 1.5 cm (range of 0 and 12 cm) and 2.1 cm by pathology. The 34 patients with MRI and pathology size yielded a median measurement of 2.6 cm (range, 0 and 11 cm), 3.0 cm by pathology.

Given the data in Table 3, it may appear that MRI is superior to PE in assessing post-neoadjuvant tumor measurements as the differences in median tumor size by MRI is 0.4 cm as compared with the 1.0 cm difference by PE. However, post-neoadjuvant PE actually had a smaller RMSE, or root mean square error, a statistical calculation that is akin to standard deviation, except RMSE compares deviations among the measurement differences to zero rather than to the mean difference. If there was perfect agreement between the measurement in question and the gold standard (e.g. PE minus pathology measurement) all the differences would be zero, making the mean difference zero, the SD of the differences zero and the RMSE zero. Compared to final pathological findings, physical examination, mammography, and MRI had an RMSE of 3.1, 3.8, and 3.5 respectively. Physical examination had a Spearman correlation value of 0.655, which was shown to correlate the best with pathological measurement (Table 4) and it was slightly better than MRI. Although the RMSE for post-neoadjuvant physical examination versus final pathology differences was smaller than that of post-neoadjuvant MRI, the physical examination differences were more biased, with a 1.2 cm bias for PE as opposed to the 0.2 cm bias (mean difference) for MRI.

Eleven of the 45 patients had a complete pathologic response (pCR) of the primary cancer. All of the pCR cases were T3 invasive ductal carcinomas (24.4%), and were mainly ER/PR- (55%), high grade (73%), with no lymphvascular invasion (82%) (Table 5). Two of these patients with no residual cancer had positive nodes by PET scan and were node negative by physical examination. Upon final pathological examination, one was node positive, the other, node negative. Physical examination correctly predicted a complete tumor resolution in nine of the eleven patients with pathologic complete response. An absence of architectural distortion, mass, or abnormal calcifications on the mammographies was found in five patients with pathologic complete response. Of the patients with pathologic complete response, 9 had post-neoadjuvant MRI evaluation and only two patients were correctly predicted by a negative MRI.

Our study suggested that clinically positive axillary nodes found by either post-neoadjuvant PE or PET were suggestive of pathologically positive nodes. Three patients did not undergo post-neoadjuvant chemotherapy PET scan and one patient had a study deemed not-evaluable by the radiologist. All patients were assessed by physical examination for post-neoadjuvant chemotherapy nodal status. Seventy percent of node-positive patients by PE or PET were

proven to have pathologic positive nodes (Table 6). In contrast, only 41% of patients (17 of the 41 patients by PE and 14 of the 35 patients by PET) with clinically negative axilla had true pathologic negative lymph nodes.

Therefore, pathologically negative nodes were poorly predicted by either modality alone or in combination. In addition, the negative findings on PE and/or PET did not predict a negative finding on pathology; that is, the 41 “node-negative” patients identified by post-chemotherapy physical examination did not wholly contain the 35 PET “node-negative” patients.

We found very high specificity (94% and 88%) associated with both post-chemotherapy PE and PET for predicting negative nodes and low sensitivity (11% and 16% respectively), for predicting positive nodes, with an accuracy of 52% by the two modalities. When compared with post-neoadjuvant evaluation, baseline PE and PET were found to be more accurate in predicting pathology nodal status: PE had 65% accuracy, with 56% specificity and 74% sensitivity, while PET had 72% accuracy, with 63% specificity and 81% sensitivity (Table 7).

DISCUSSION

Tumor assessment is important both in planning the initial treatment course and in monitoring disease response to the treatment. Baseline assessment of a palpable breast cancer can steer the treatment decision either towards or away from the option of neoadjuvant chemotherapy. Should neoadjuvant chemotherapy be chosen, monitoring tumor response to treatment by assessing the residual tumor size is essential to determine the best course of surgical action. Monitoring and assessment, however, rely on the relative accuracy of available clinical tools.

Tumor measurement at baseline by physical examination was used as reference to judge the relative accuracy of mammography against MRI. Our results found MRI to hold closer to physical examination measurements than mammography. Furthermore, the tumor measurements by physical examination were possible in all while almost one third of the mammograms were not evaluable or not measureable. Our study suggested that mammography should not be the sole breast imaging study in patients with T3 or T4 breast cancer.

Some studies have found all three correlate well with final pathologic findings.10 Others have shown physical examination to have a higher predictive value.11 Recently, MRI was found to have the highest correlative value. [2،4،5،6،12،13] Many data from direct comparisons between physical examination, mammography, and MRI, highlight MRI as the most accurate way to assess residual tumor size following neoadjuvant chemotherapy but other studies disagree.[2، 3، 4، 5، 6،14]

When compared with the pathologically measured tumor size, the absolute superiority of MRI for tumor assessment was not confirmed in the post-neoadjuvant chemotherapy setting in these women. Previous studies have touted MRI as the most accurate way of assessing residual disease when compared to final pathology measurements in populations including patients not limited to locally advanced disease.[2،3،4،6،15،16] Partridge et al. found MRI to be exceedingly accurate (MR correlation with pathology: r = 0.89 vs. r = 0.6 for PE correlation with pathology) despite reduced tumor contrast uptake following neoadjuvant chemotherapy.16 Londero et al. reported MRI capable of accurately evaluating the extent of residual tumor in 80% of patients, a superior rate, when compared to the accuracy of mammography in their study (53%).2 Like Yeh et al., they implicated post-chemotherapeutic fibroglandular changes as the main reason for the inaccuracies frequently

associated with mammographic findings.4 Such fibrotic tissues can confound physical examination findings as well, as Balu-Maestro et al. postulated in their study of 51 patients comparing physical examination, mammography, ultrasound, and MRI before and after neoadjuvant chemotherapy.5

In this study, we found physical examination to be a reliable method to evaluate size of residual breast carcinoma, reinforcing Rieber et al.'s observation that MRI is a less reliable evaluation in determining size of residual cancer.8 Our study indicated that MRI might overestimate the residual tumor among patients with a complete pathologic response.

Complete response to neoadjuvant chemotherapy was also assessed most accurately by physical examination. In our study, six of the patients with complete response had apparent residual disease on mammography and seven complete responders had measurable disease on MRIs. Unlike Schott et al., who reported MRI to be the most accurate in the determination of pathologic complete response 14, a complete response by physical examination appeared in our study to be the best predictor of pathologic complete response. However, Schott et al. had only four patients with a complete pathologic response, and they suggested that the high sensitivity and low specificity of MRI might be superior in patient cohorts unlikely to achieve complete response. Therefore, MRI may be less accurate in a population with a higher pathologic complete response rate.

Given the body of evidence that supports the utility and specificity of MRI imaging, our results should be interpreted as reinforcing the importance of physical examination by experienced practitioners rather than detracting the role of MRI in patient management. Physical examination findings, particularly the large primary breast cancer assessment, remain essential in the treatment decision-making and not to be omitted and replaced by the measurements garnered from imaging technologies.

In women with locally advanced disease, large tumors are often accompanied by axillary node involvement. Disease staging, especially in this population, necessitates accurate assessment of nodal status. FDG-PET is an emerging technology that has the potential to provide valuable staging information and possibly predicting tumor response, but its role in the evaluation of lymph node involvement following neoadjuvant chemotherapy has yet to be clearly defined. The PET scan has been shown to have low sensitivity when compared to both axillary lymph node dissection and sentinel lymph node biopsy.[17, 18] Nonetheless, the positive predictive value and high specificity of the PET scan would still be valuable in staging patients with more advanced disease and guiding the choice of surgical management of the axilla.[17,19] Inoue et al. found encouraging results, showing PET scan to have a higher specificity, sensitivity and accuracy in the diagnosis of axillary lymph node status than physical examination.20 FDG-PET was more accurate in the diagnosis of axillary lymph node status than physical examination. We also examined nodal assessment by physical examination, and FDG-PET and compared negative and positive findings to patients' nodal staging by pathology. Our results showed physical examination and PET scan after neoadjuvant chemotherapy to be highly specific, but poor for sensitivity and accuracy. This is comparable to the results reported by Fehr et al., who also found a sensitivity of 20% and a specificity of 93% for nodal assessment by PET. While these results might suggest that PET scan had an inherent low sensitivity after neoadjuvant treatment though others have reported sensitivity rates of up to 100%.[18,21] In our study, baseline PET and PE were shown to be more accurate and sensitive in predicting the final nodal status than the post-neoadjuvant evaluation by either PE or PET, but none was sufficient to replace pathological staging.

Limitations of our study included a small cohort of patients, using only the longest dimension for tumor size determination which may not be the best way to measure tumor response to neoadjuvant chemotherapy and heterogeneous medical teams at numerous clinical sites that participated in this study.

In summary, tumor assessment in patients with locally advanced breast cancer by PE is accurate, clinically useful, and can be attained in all patients. Our study suggests that breast cancer size determined by PE in these women is highly accurate when compared with breast imaging and pathology finding. The varied experiences of different physicians and the retrospective nature of many studies may all play a role in the relative unreliability found by some reports. In addition, pathological nodal staging is still necessary even when PE and PET are negative. Further studies focusing on the role of FDG-PET in breast disease assessment are warranted.

Acknowledgments

Study supported by PHS/NCI R01 CA 93736-01A, Aventis Pharmaceuticals, Genentech, Inc. and Friends of the Breast Program at UCLA.

REFERENCES

1. Kaufman M, von Minckwitz G, Smith R, et al. International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: review and recommendations. J Clin Oncol. 2003; 21:2600–2608. [PubMed: 12829681]
2. Londero V, Bazzocchi M, Del Frate C, et al. Locally advanced breast cancer: comparison of mammography, sonography and MR imaging in evaluation of residual disease in women receiving neoadjuvant chemotherapy. Eur Radiol. 2004; 14:1371–1379. [PubMed: 14986052]
3. Rosen EL, Blackwell KL, Baker JA, et al. Accuracy of MRI in the detection of residual breast cancer after neoadjuvant chemotherapy. Am J Roentgenol. 2003; 181:1275–1282. [PubMed: 14573420]
4. Yeh E, Slanetz P, Kopans D. Prospective Comparison of Mammography, Sonography, and MRI in Patients Undergoing Neoadjuvant Chemotherapy for Palpable Breast Cancer. Am J Roentgenol. 2005; 184:868–877. [PubMed: 15728611]
5. Balu-Maestro C, Chapellier C, Bleuse A, et al. Imaging in evaluation of response to neoadjuvant breast cancer treatment benefits of MRI. Breast Cancer Res Treat. 2002; 72:145–152. [PubMed: 12038705]
6. Partridge SC, Gibbs JS, Lu Y, et al. Accuracy of MR imaging for revealing residual breast cancer in patients who have undergone neoadjuvant chemotherapy. Am J Roentgenol. 2002; 179:1193–1199. [PubMed: 12388497]
7. Chagpar A, Middleton L, Sahin A, et al. Accuracy of physical examination, untrasonography, and mammography in predicting residual pathologic tumor size in patients treated with neoadjuvant chemotherapy. Ann Surg. 2006; 243:257–264. [PubMed: 16432360]
8. Rieber A, Zeitler H, Rosenthal H. MRI of breast cancer: influence of chemotherapy on sensitivity. Br J Radiol. 1997; 70:452–458. [PubMed: 9227225]
9. Nakamura T, Fukutomi T, Tsuda H, et al. Changes in finds of mammography, ultrasonography and contrast-induced computed tomography of three histological complete responders with primary breast cancer before and after neoadjuvant chemotherapy: case reports. Jpn J Clin Oncol. 2000; 30:453–457. [PubMed: 11185893]
10. Akashi-Tanaka S, Fukutomi T, Watanabe T, et al. Accuracy of contrast-enhanced computed tomography in the prediction of residual breast cancer after neoadjuvant chemotherapy. Int J Cancer. 2001; 96:66–73. [PubMed: 11241331]
11. Herrada J, Iyer RB, Atkinson N, et al. Relative value of physical examination, mammography, and breast sonography in evaluating the size of the primary tumor and regional lymph node metastases

in women receiving neoadjuvant chemotherapy for locally advanced breast carcinoma. Clin Cancer Res. 1997; 3:1565–1569. [PubMed: 9815844]

12. Esserman L, Kaplan E, Partridge S, et al. MRI phenotype is associated with response to doxorubicin and cyclophosphamide neoadjuvant chemotherapy in stage III breast cancer. Ann Surg Oncol. 2001; 8:548–559.
13. Cheung YC, Chen SC, Su MY. Monitoring the size and response of locally advanced breast cancers to neoadjuvant chemotherapy (weekly paclitaxel and epirubicin) with serial enhanced MRI). Breast Cancer Res Treat. 2003; 78:51–58. [PubMed: 12611457]
14. Schott A, Roubidoux M, Helvi M, et al. Clinical and radiologic assessments to predict breast cancer pathologic complete response to neoadjuvant chemotherapy. Breast Cancer Res Treat. 2005; 92:231–238. [PubMed: 16155794]
15. Partridge S, Gibbs J, Lu Y, et al. Accuracy of MR imaging for revealing residual breast cancer in patients who have undergone neoadjuvant chemotherapy. Am J Roentgenol. 2002; 179:1193–1199. [PubMed: 12388497]
16. Akazawa K, Tamaki Y, Taguchi T, et al. Preoperative evaluation of residual tumor extent by three-dimensional magnetic resonance imaging in breast cancer patients treated with neoadjuvant chemotherapy. Breast J. 2006; 12:130–137. [PubMed: 16509837]
17. Kumar R, Zhuang H, Schnall M, et al. FDG PET positive lymph nodes are highly predictive of metastasis in breast cancer. Nucl Med Commun. 2006; 27:231–236. [PubMed: 16479242]
18. Byrne AM, Hill AD, Skehan SJ, et al. Positron emission tomography in the staging and management of breast cancer. Br J Surg. 2004; 91:1398–1409. [PubMed: 15499650]
19. Lovrics P, Chen V, Coates G, et al. A prospective evaluation of positron emission tomography scanning, sentinel lymph node biopsy, and standard axillary dissection for axillary staging in patients with early stage breast cancer. Ann Surg Oncol. 2004; 11:813–814. [PubMed: 15313735]
20. Inoue T, Yutani K, Taguchi T, et al. Preoperative evaluation of prognosis in breast cancer patients by [(18)F]2-Deoxy-2-fluoro-D-glucose-positron emission tomography. J Cancer Res Clin Oncol. 2004; 130:273–278. [PubMed: 14986112]
21. Fehr MK, Hornung R, Varga Z, et al. Axillary staging using positron emission tomography in breast cancer patients qualifying for sentinel lymph node biopsy. Breast J. 2004; 10:89–93. [PubMed: 15009033]

Table 1

Patient and Tumor Characteristics

Feature	Value
Median age (range)	50 (29–68)
Ethnicity (%)	
White	28 (62%)
Black	2 (4%)
Hispanic	8 (18%)
Asian	7 (16%)
Tumor Stage [total (%)]	
T3	31 (69%)
T4a–c	4 (9%)
T4d	10 (22%)
Tumor Histology (%)	
IDC	37 (82%)
ILC	8 (18%)
Histological Differentiation (%)	
Well	5 (11%)
Moderate	12 (27%)
Poor	25 (55%)
Not Specified	3 (7%)
Nuclear Grade (%)	
High	23 (51%)
Intermediate	10 (23%)
Low	6 (13%)
Not Specified	6 (13%)
Lymphvascular Invasion (%)	
Present	16 (35%)
Absent	26 (58%)
Not Specified	3 (7%)
Estrogen/Progesterone receptor (ER/PR) status (%)	
ER+ / PR +	18 (40%)
ER+ / PR −	9 (20%)
ER− / PR +	1 (2%)
ER− / PR−	17 (38%)
HER2/*neu* status (%)	
HER2/*neu* +	20 (44%)
HER2/*neu* −	25 (56%)

Note: IDC = infiltrating ductal carcinoma; ILC = infiltrating lobular carcinoma

Table 2

Number of Patients with Tumor Size Measured by Modality

Clinical Assessment	Baseline (n)	Post-Neoadjuvant (n)
Physical Examination (PE)	43	44
Mammography (MG)	30	29
Magnetic Resonance Imaging (MRI)	33	34
Combination of modalities (PE, MG, and MRI)	21	23*

Note: n = number of patients;

* = this number also includes pathological measurement in addition to the clinical modalities

Table 3

Post-Neoadjuvant Tumor Measurements in cm in Patients with Measurements by Modality and Pathological Examination

Clinical Assessment	n	minimum	mean	median	maximum
Physical examination	39	0	2.28	2.0	11.0
Pathological examination	39	0	3.45	3.0	16.0
Mammography	28	0	2.3	1.5	12.0
Pathological examination	28	0	2.6	2.1	11.4
MRI	34	0	3.6	2.6	11.0
Pathological examination	34	0	3.8	3.0	16.0

Note: n = number of patients

Table 4

Correlation of Tumor Sizes (Baseline comparison between imaging finding and PE, and post-neoadjuvant treatment, with final pathological finding)

Clinical assessment	n	Spearman corr	RMSE	Bias in cm (%)
Baseline MG	30	0.046	66.1%	−3.4 (−46.1%)
Baseline MRI	32	0.559	35.4%	−1.2 (−14.8%)
Post-neoadjuvant PE	39	0.655	88.6%	−1.2 (−33.8%)
Post-neoadjuvant MG	28	0.146	147.1%	−0.3 (−11.6%)
Post-neoadjuvant MRI	34	0.364	92.6%	−0.2 (−5.3%)

Note: PE = physical examination; MG = mammography; MRI = Magnetic resonance imaging; corr = correlation

Table 5

Complete Response of Primary Invasive Cancer by Tumor Characteristics

	pCR	w/DCIS only	w/(+) nodes
ER+/PR+	2	2	0
ER−/PR−	6	0	2
ER+/PR−	2	0	1
ER−/PR+	1	0	0
LVI (−)	9	1	3
Not specified	2	1	0
HER-2/neu (+)	5	2	1
HER-2/neu (−)	6	0	2
T3	11	2	3
High Grade	8	1	3
Int. Grade	1	1	0
Not specified	2	0	0

Note: pCR = pathological complete response; DCIS = ductal carcinoma in situ; ER = estrogen receptor; PR = progesterone receptor; LVI = lymphvascular invasion; Int. = intermediate

Table 6

Post-Neoadjuvant Treatment Lymph Node Status by Physical Examination, PET, and Pathology Finding

# Patients by the Modality		(+) LN by Pathology (#pts)	(−) LN by Pathology (#pts)
(+) LN by PE	4	3	1
(+) LN by PET	6	4	2
(+) LN by either PE or PET	10	7	3
(+) LN by both PE and PET	0	0	0
(−) LN by PE	41	24	17
(−) LN by PET	35	21	14
(−) LN by both PE and PET	32	19	13
(+) LN by PE, (−) by PET	3	2	1
(+) LN by PET, (−) by PE	5	4	1

Note: LN = lymph node; PE = physical examination

Table 7

Specificity, Sensitivity, and Accuracy of Baseline and Post-Neoadjuvant PE and PET

	TP	FN	Sensitivity	TN	FP	Specificity	Accuracy
Baseline PE	20	7	74%	10	8	56%	65%
Baseline PET	21	5	81%	10	6	63%	65%
Post-neoadjuvant PE	3	24	11%	17	1	94%	53%
Post-neoadjuvant PET	4	21	16%	14	2	88%	52%

Note: PE = physical examination; PET = positron emission tomography; TP = “true positive”—positive by modality, lymph node positive by pathology; FN = “false negative”—negative by modality, positive by lymph node pathology; TN = “true negative”—negative by modality, lymph node negative by pathology; FP = “false positive”—positive by modality, negative by lymph node pathology