

Prospective Comparison of Mammography, Sonography, and MRI in Patients Undergoing Neoadjuvant Chemotherapy for Palpable Breast Cancer

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OBJECTIVE. The objective of our study was to determine the relative accuracy of mammography, sonography, and MRI in predicting residual tumor after neoadjuvant chemotherapy for breast cancer as compared with the gold standards of physical examination and pathology.

SUBJECTS AND METHODS. Forty-one women with stage IIB–III palpable breast cancer were prospectively enrolled in a study investigating the effects of sequential single-agent chemotherapy (doxorubicin followed by paclitaxel or vice versa) on tumor imaging. The study cohort consisted of the first 31 patients (age range, 31–65 years; mean, 45 years) who completed the protocol. All underwent physical examination, mammography, sonography, and MRI before and after receiving each neoadjuvant chemotherapeutic drug. Imaging studies were reviewed by two radiologists using conventional lexicons for lesion analysis, and the findings were compared with clinical response and pathology results.

RESULTS. Complete, partial, and stable clinical response as defined by clinical examination was seen in 15, 14, and two of the 31 patients, respectively. Agreement rates about the degree of response were 32%, 48%, and 55%, respectively, for mammography, sonography, and MRI compared with clinical evaluation and did not differ statistically. Agreement about the rate of response as measured by clinical examination, mammography, sonography, and MRI compared with the gold standard (pathology) was 19%, 26%, 35%, and 71%, respectively. Of the four, MRI agreed with the gold standard significantly more often ($p < 0.002$ for all three paired comparisons with MRI). When there was disagreement with the gold standard, none of the four exhibited a significant tendency to either under- or overestimate.

CONCLUSION. MRI appears to provide the best correlation with pathology—better than physical examination, mammography, and sonography—in patients undergoing neoadjuvant chemotherapy. However, MRI may overestimate (6%) or underestimate (23%) residual disease in approximately 29% of the patients (95% confidence interval, 14–48%).

Neoadjuvant chemotherapy followed by surgery and radiation has been shown to be as effective as surgery followed by adjuvant chemotherapy and radiation in the treatment of palpable breast carcinoma [1]. The advantages to neoadjuvant chemotherapy are multiple. By reducing tumor volume for patients with large breast tumors, this approach may permit breast-conservation surgery rather than mastectomy [2–6]. Unlike conventional adjuvant chemotherapy that may be delayed for several months because of surgical scheduling and the need for wound healing, neoadjuvant chemotherapy allows earlier treatment of micrometastatic disease [7].

The *in vivo* assessment of tumor response to specific chemotherapeutic regimens may permit the oncologist to tailor preoperative or

postoperative chemotherapy more effectively. If the tumor decreases in size with a particular chemotherapeutic agent while the tumor is *in vivo*, then the referring clinician will know that the agent is effective and may continue the agent. Conversely, if the tumor increases in size, the oncologist may elect to change to a different chemotherapeutic agent. The neoadjuvant chemotherapy model allows the study of biologic markers that may predict response. It might even provide important information for the treatment of a recurrence, if this were to occur later.

Finally, the effectiveness of chemotherapeutic agents in treating the primary breast malignancy and potential metastatic disease may be enhanced because of the neovascularity associated with cancers. If chemotherapy is given before surgery while the tumor vas-

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culature remains intact, the chemotherapeutic agent (or agents) may be better able to reach the tumor and peritumoral structures to increase the effectiveness of the chemotherapeutic agent. Because of these potential advantages of neoadjuvant chemotherapy in the treatment of palpable breast carcinoma, this approach has become widely adopted over the past several years [8].

At this time, physical examination is the gold standard for assessing initial tumor size and response to neoadjuvant chemotherapy. Pathologic analysis is the gold standard for assessing the size of the residual tumor after surgery. Routinely, patients undergo mammography and possibly sonography for initial assessment, diagnosis, and staging of breast cancers. All of these methods (including physical examination, mammography, and sonography) have been shown to be suboptimal in the accurate assessment of response to neoadjuvant chemotherapy [7, 9–12]. Some have suggested that the lack of concordance may be related to chemotherapy-induced fibrosis [13].

Contrast-enhanced MRI of the breast has been shown in a number of studies to detect breast cancers with a high degree of sensitivity ranging from 95% to 100% and with variable specificity ranging from 37% to 97% [13–28]. One of the major limitations of breast MRI is that false-positive enhancement can occur in benign breast lesions, resulting in relatively low specificity. Recent advances in imaging sequences, however, appear to be improving the specificity while still achieving high sensitivity [26, 29, 30]. Given reasonable sensitivity and specificity, many investigators are now determining the role of MRI in the screening of women at high risk for breast cancer and in the clinical management of patients with breast cancer [31–36].

Another area of interest has been breast MRI and neoadjuvant chemotherapy. Recent studies have investigated breast MRI for measuring the size of residual tumor after neoadjuvant chemotherapy, MRI enhancement patterns in predicting response to neoadjuvant chemotherapy, and functional MRI as a marker of tumor response to neoadjuvant chemotherapy [37–39]. To our knowledge at this time, no one has prospectively evaluated the relative value of the imaging techniques of mammography, sonography, and MRI in predicting residual tumor in patients receiving neoadjuvant chemotherapy for palpable breast cancer.

We undertook this study to investigate prospectively the relative value of mammography, sonography, and MRI in predicting

residual tumor in patients receiving neoadjuvant chemotherapy for palpable breast cancer compared with the gold standards of physical examination and pathology.

Subjects and Methods

From June 2000 through March 2003, 41 consecutive women (age range, 31–65 years; mean, 47 years) with palpable breast cancer, stage IIB–III, were prospectively enrolled in a multidisciplinary study at a tertiary referral academic center. Eligibility criteria included women with clinically palpable breast cancer of at least 3 cm diagnosed by fine-needle aspiration or percutaneous core biopsy. Patients with palpable axillary or supraclavicular lymph nodes (or both) were allowed to participate provided definitive local therapy was judged to be clinically indicated as determined by the team caring for the patient. Patients with inflammatory breast cancer and distant metastatic disease were excluded.

Among the 41 women enrolled in the study, 27 were diagnosed with invasive ductal cancer, eight with invasive cancer (type not specified), one with invasive ductal and lobular cancer, and five with invasive lobular cancer. The protocol was designed to investigate the effects of sequential single-agent chemotherapy (doxorubicin followed by paclitaxel or vice versa) on tumor imaging. The research study was approved by

the hospital's subcommittee on human studies and the institutional review board.

All patients underwent physical examination, mammography, breast sonography, and breast MRI before and after the administration of each chemotherapeutic agent (Fig. 1). At enrollment in the protocol, patients underwent clinical examination performed by a breast oncologist. A standard bilateral mammogram with additional views as necessary was obtained using conventional mammography units accredited by the American College of Radiology: Lorad M-4 (Hologic), DMR (GE Healthcare), Sophie (Planned), and FFD 2000D Senographe (GE Healthcare).

Real-time breast sonography of the tumor was performed by a radiologist using an HDI 5000 unit (ATL), a broadband linear array transducer (5–12-MHz), and the Logic 400 and Logic 500 (GE Healthcare), broadband multifrequency linear array transducers (9–11-MHz). A board-certified radiologist specializing in breast imaging obtained all sonograms. Targeted sonograms were obtained at the site indicated by the patient. The radiologist was blinded to the size of the tumor as measured by the referring clinician. One radiologist performed most of the sonography examinations included in this study and prospectively recorded the information. The remaining handful of studies was performed by other board-certified radiologists specializing in breast imaging,

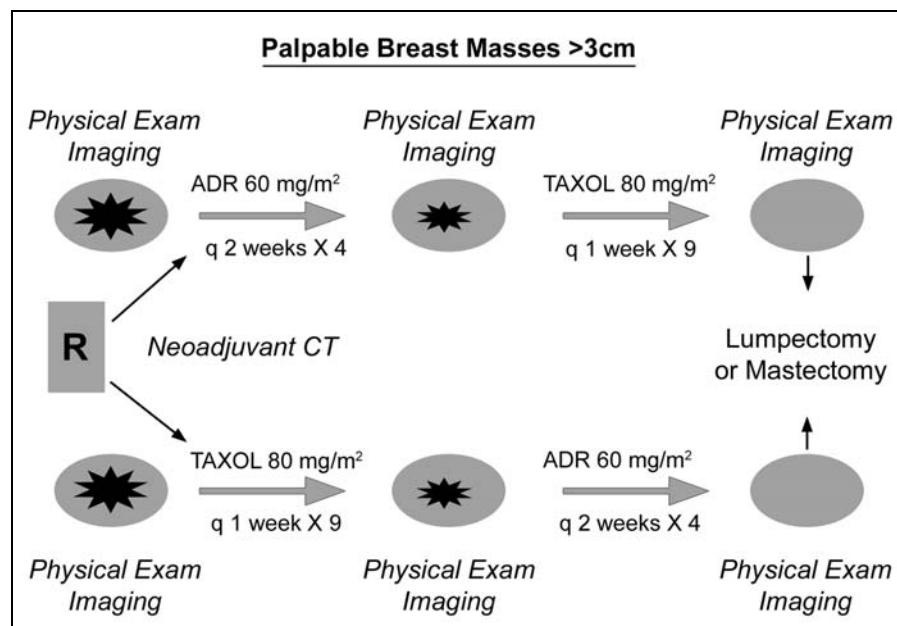


Fig. 1.—Schematic diagram of sequence of protocol used for our pilot study. Patients were randomized (R) to neoadjuvant chemotherapy (CT), either doxorubicin (ADR, Pharmacia Inc.) followed by paclitaxel (Taxol, Bristol-Myers Squibb Company) or vice versa. Physical examination and imaging (i.e., mammography, breast sonography, and breast MRI) were performed. Each patient received single-agent neoadjuvant chemotherapy; then physical examination and imaging examinations were repeated. Second chemotherapeutic agent was given to patient, and physical examination and imaging examinations were repeated. Patient underwent surgery, either lumpectomy or mastectomy, and final pathology results were obtained.

and the radiologist who obtained most of the sonograms reviewed the images. This was done to eliminate potential bias by different sonographers.

Dynamic high-resolution MRI of both breasts was performed on a 1.5-T scanner with a dedicated breast coil (Signa, GE Healthcare) in the first 11 patients. An IV catheter was placed into an antecubital vein before imaging and connected to a power injector (Medrad) containing gadopentetate dimeglumine (Magnevist, Berlex Laboratories).

Two MRI protocols were used; the protocol was changed after the first 11 patients to optimize the high-resolution images. Localization with a gradient-echo sequence was performed (TR/TE, 18/5), followed by an axial fast spin-echo acquisition (3,500/17; inversion time, 165 msec). After manual shimming on the volume of interest, a 3D spoiled gradient-echo sequence (23/6; flip angle, 30°; number of excitations, 1) was used to acquire high-resolution images. Fat suppression was performed using a binomial water-selective pulse. The matrix size was 512×256 , with a field of view ranging from 28 to 35 cm. Sixty slices with 2.0- to 2.7-mm thickness were acquired to provide full coverage of the volume of interest, with a voxel size ranging from $0.5 \times 1 \times 2$ to $0.7 \times 1.4 \times 2.7$ mm³. The functional MRI protocol included two echoplanar spin-echo acquisitions. Before the administration of the contrast agent, the T1 of breast tissue was measured with an echo-planar inversion recovery sequence (6,000/30; inversion time, 50–1,400 msec, with ten steps of 150 msec; number of excitations, 1). The matrix size was 128×128 , with a field of view varying between 35 and 40 cm. Seventeen to 19 slices of 5- to 7-mm thickness with a gap of 1.5 mm were acquired. The voxel size ranged from $2.7 \times 2.7 \times 5$ to $3.1 \times 3.1 \times 7$ mm³. The tissue contrast uptake was monitored before, during, and after the administration of contrast agent with an echoplanar inversion recovery sequence (8,000/30). A fixed inversion time of 160 msec was used to minimize the contribution of fat to the total MRI signal. The other parameters were the same as those used for T1 mapping. Twenty-six images were acquired at 8-sec intervals over a total imaging time of 3 min 29 sec. Five to seven images were acquired before an IV bolus of gadopentetate dimeglumine (0.1 mmol/kg at 3.5 mL/sec). Immediately after the data acquisition with echoplanar inversion recovery, a second set of postcontrast high-resolution images was acquired using a fat-suppression 3D spoiled gradient-echo sequence with the parameters used before injection. The time of acquisition was 4 min 30 sec.

In the latter 30 patients, a sagittal localization with a spoiled gradient-echo sequence was performed (TR/TE, 18/minimum TE), followed by an axial high-resolution gradient-echo acquisition

(nonselectable TR/minimum TE; flip angle, 15°; number of excitations, 1). Fat suppression was performed using a binomial water-selective pulse. The matrix size was 256×256 , with a field of view of 34 cm. Sixty-eight slices with 4.8-mm thickness with no skip were acquired in two slabs with overlap of four slices in the first group and four slices in the second group to provide full coverage of the volume of interest. The voxel size was $1.3 \times 1.3 \times 4.8$ mm³. After administration of an IV bolus of gadopentetate dimeglumine (0.1 mmol/kg at 3.5 mL/sec), three serial postcontrast high-resolution images through the breasts were acquired using a fat-suppression 3D gradient-echo sequence with the parameters used before the injection of gadolinium. The time of acquisition per postcontrast series was 1 min 6 sec. T2-weighted axial images were then obtained (5,000/102). Postprocessing included 2D registration and subtraction of the pre- and postcontrast images and 3D reconstructions with rotations including a bilateral breast tumble rotation with downward rotation and segmentation of each breast with rotation of the right breast to the right side and rotation of the left breast to the left side.

Percutaneous sonographically guided core biopsy using a 14-gauge coaxial system (Monopty, Bard) was performed using a 13-gauge introducer. All tumors were visualized and biopsied under sonographic guidance. Seven to 10 cores were obtained from the dominant tumor mass. If the patient had multiple nodules, the largest mass was biopsied. Immediately after the biopsy, under sonographic guidance, a nonferromagnetic clip (Tissue Marker, Biopsy Medical [now MicroMark Tissue Marker, Ethicon-Endosurgery] or UltraClip Tissue Marker, Inrad) was inserted in the center of each tumor before beginning neoadjuvant chemotherapy [40–42]. This clip was used to guide localization and surgical removal of the residual tumor in patients who became eligible for conservative breast surgery on the basis of the tumor's response to neoadjuvant chemotherapy.

Neoadjuvant chemotherapy was administered to the patients as sequential single-agent therapy using doxorubicin (four cycles of 60 mg/m² every 2 weeks) and then paclitaxel (nine cycles at 80 mg/m² weekly). Patients were randomized to two groups: group 1 received doxorubicin first and group 2 received paclitaxel first. After the first phase of chemotherapy (doxorubicin or paclitaxel), which lasted approximately 2 months, each patient underwent physical examination and breast MRI, mammography, breast sonography, and core biopsy. The second chemotherapeutic agent was administered, lasting approximately 2 months, and the patients subsequently underwent clinical examination and breast MRI, mammography, and breast sonography. This was then followed by definitive surgery of

lumpectomy or mastectomy, which was determined at the discretion of the physicians. The patients were offered lumpectomy if the patient's breast surgeon believed that breast-conservation surgery would yield a cosmetically acceptable result.

The sequence of imaging examinations of the study patients was as follows: all patients underwent mammography followed by sonography and then a subsequent fine-needle aspiration or core biopsy with a histologic diagnosis of breast cancer. After the patient enrolled in the study, bilateral breast MRI was performed first and was immediately followed by repeat mammography and sonography the same day so that all imaging results could be compared.

If the imaging studies were performed at different times—for example, weeks apart, there may be a question as to the accuracy of the tumor dimensions of the given technique (mammography, sonography, or MRI) versus whether the tumor had changed in size.

The imaging examinations were repeated after the first and then the second neoadjuvant chemotherapy in the same order as described earlier, with MRI first followed by the mammography and the sonography. This sequence of imaging examinations was used because at the time of the sonography, repeat core biopsies and invasive physiologic measurements were made part of a larger study protocol and we did not want artifact or hemorrhage from the procedure to alter the MRI images.

Imaging studies were reviewed by two board-certified radiologists with fellowship training in breast imaging using the conventional BI-RADS [43] lexicon for lesion analysis for mammography. Using terminology from the American College of Radiology's BI-RADS [43] lexicon, the sonographic size, shape, margins, and echotexture were evaluated. Disease extent on MRI was assessed on the basis of the size of the lesion and using morphologic and dynamic criteria. The MRI morphologic features were categorized according to the MRI lexicon developed by the International Working Group [44, 45]; for example, a spiculated mass was considered a suspicious lesion. Dynamic features were assessed on the basis of the early rapid uptake of contrast material (i.e., within the first 3 min) [28–30, 44, 46, 47].

Two radiologists reviewed the imaging studies independently and separately. When there was a discrepancy, the two radiologists reviewed the cases together and came to a consensus. The radiologists were blinded to the clinical response and pathology. To provide the best clinical care for the patient, the radiologist did have access to the mammogram obtained before the sonogram if necessary. Because MRI was performed immediately before mammography and sonography, the MR images

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were not available to the radiologist at the time of the mammography and sonography for logistical reasons (the images were processed before interpretation with subtractions and 3D rotations as described earlier) and also for study purposes. The 3D tumor size was recorded on mammography, sonography, and MRI. Imaging studies were compared with clinical response and pathology results.

Of the 41 patients, 31 have completed the protocol and make up our study cohort. Eight patients have yet to complete the protocol at this time. One patient withdrew due to anaphylaxis to paclitaxel and one patient voluntarily withdrew after completion of the first chemotherapeutic drug. Of the study cohort of 31 patients, the age range was 31–65 years, with a mean of 45 years. At initial biopsy diagnosis, 23 had invasive ductal cancer, five had invasive cancer (type not specified), one had mixed invasive ductal and lobular cancer, and two patients had invasive lobular cancer.

Of the 31 study patients, five of the first six patients received a single chemotherapeutic agent before their final surgery (doxorubicin, $n = 3$; paclitaxel, $n = 2$). This decision was based on the initial protocol that recommended surgery after the first chemotherapy drug if the residual tumor was less than 2 cm. However, the criteria were subsequently changed because the oncologists wanted to maximize the tumor response and decided to give both drugs to all patients unless no residual tumor remained. If no residual tumor remained after the first chemotherapeutic agent was given, the patient did not receive the second agent and went directly to surgery. The remaining 26 patients received two sequential single chemotherapeutic agents before surgical excision (13 patients received doxorubicin followed by paclitaxel and 13 patients received paclitaxel followed by doxorubicin).

Assessment of Tumor Response

The size of the tumor was measured by physical examination and imaging before the patient began receiving neoadjuvant chemotherapy, after receiving the first chemotherapeutic agent, and after receiving the second agent before surgery (when appropriate). A dedicated breast oncologist recorded the size of the tumor in 2D at physical examination. The same oncologist recorded the tumor size for a given patient, but different patients had different oncologists. The size of the tumor on the mammogram, sonogram, and MRI was measured in 3D. The pathologic response to treatment was assessed by direct examination of the excised tumor specimens by a dedicated breast pathologist.

The clinical response to chemotherapy was categorized into four groups: complete response, partial response, progressive disease, and stable disease. Complete clinical response was defined as

the complete disappearance of all measurable and assessable disease, including no new lesions and no disease-related symptoms. Partial clinical response was defined as a greater than 50% decrease in the product of the bidimensional diameters as assessed by physical examination if there was one definable lesion. If there were more than one lesion, partial clinical response was defined as a greater than 50% decrease in the sum of the products of the bidimensional diameters as assessed by physical examination, no progression of assessable disease, and no new lesions. Progressive disease was defined as any increase in the sum of the products of the bidimensional diameters of all measurable lesions from the smallest sum observed (from baseline if no confirmed response); the reappearance of any lesion that had disappeared; or the appearance of any new or deteriorating condition, unless clearly unrelated to this cancer. Stable disease was defined as not fulfilling the criteria for complete or partial response or progressive disease.

On imaging, complete response was defined as no measurable disease. Progressive disease was defined as a 30% or more increase in the longest diameter of the tumor. The new World Health Organization criteria for tumor response were used to correlate tumor size on physical examination, which was measured in 2D, with tumor size on imaging, which was measured in 3D [48, 49]. A 30% or more decrease in the longest diameter of tumor has been shown to be equivalent to a partial response or a greater than 50% volume reduction [50].

The tumor response after neoadjuvant chemotherapy was categorized as described for physical examination, mammography, sonography, and MRI. The response at physical examination was then compared with the response on each of the individual imaging techniques—that is, the response as measured at physical examination was compared with the response as measured on mammography, with that measured on sonography, and with that measured on MRI. The response agreement between physical examination and each imaging technique was calculated for each combination pair.

The pathologic response was then compared with the response by physical examination, mammography, sonography, and MRI. The excised pathologic specimens were directly examined by a pathologist and the size of the residual tumor was measured. If the patient had a reexcision, the sum of the size of the tumor of each specimen was used as the total amount of residual tumor.

Tumor measurements by physical examination, mammography, sonography, and MRI after neoadjuvant chemotherapy were categorized as underestimating, being equal to, or overestimating the amount of residual tumor compared with the gold standard of pathology. Because there is no stan-

dardized method by which to compare the size of tumor on imaging with the size of tumor at pathology, we arbitrarily decided to use the same percentage—30% of the longest diameter—as described by the World Health Organization for comparison with physical examination. We defined tumor size on imaging as equal to that at pathology if the longest diameter was within 30% of the size at pathology. If the size on imaging was not deemed equal (e.g., was not within the range from 70% to 130% of the pathology size), the imaging technique size was defined as an underestimate if it was less than (70% of) the size at pathology and an overestimate if the imaging size was greater than (130% of) the size as determined at pathology.

Statistical Analysis

The extents of agreement or disagreement for treatment response of the three imaging techniques with physical examination were compared using the McNemar test. Similarly, the agreement–disagreement rates for size at physical examination and that on the imaging techniques were also compared with size at pathology using the McNemar test.

The tendencies of all methods to underestimate or overestimate the size were tested using the Wilcoxon's signed rank test where an underestimate was scored as -1 and an overestimate was scored as 1 . Significance levels were determined by the Bonferroni correction for multiple comparisons ($p \leq 0.05/3$ for pairwise comparisons of response, $p < 0.05/6$ for pairwise comparisons of size, and $p \leq 0.05/4$ for trends in size).

Results

The size of the tumor at initial clinical examination before chemotherapy ranged from 3 to 10 cm in the longest dimension with a mean of 4.9 cm. The delay between the MRI study performed after treatment and surgery ranged from 3 to 56 days, with a median of 14 days. Surgery was targeted at least 2–3 weeks after the last chemotherapy session because the patients had extensive chemotherapy and needed time to recover their WBC counts before surgery. The patients who received doxorubicin as the second agent needed a longer delay because of the myelosuppressive effects of that particular chemotherapeutic agent. Longer delays occurred in patients with complications from chemotherapy such as fever and neutropenia.

Of the 31 patients, 18 patients had a lumpectomy and 13 patients had a mastectomy as the final surgery. A lumpectomy was initially performed in 21 patients. Of the 21 patients, seven required reexcision because of positive margins, three of whom had comple-

tion mastectomy. Ten patients underwent modified radical mastectomy as the initial surgery. Pathology results were as follows: 16 patients had invasive ductal cancer and ductal carcinoma in situ (DCIS); six, invasive ductal cancer; four, invasive lobular cancer; four, DCIS; and one, no residual tumor. Of the seven patients requiring reexcision, one had invasive cancer with ductal and lobular features. The others had invasive ductal carcinoma.

Tumor Response and Response Agreement of Clinical Examination Compared with Imaging After Neoadjuvant Chemotherapy

According to physical examination findings, 15 of the 31 patients had a complete clinical response, 14 had a partial clinical response, and two patients had stable disease (Table 1). Mammography findings indicated that seven of the 31 patients had a complete response, six had a partial response, 10 had stable disease, and one patient had progressive disease. Seven patients had mammographically “not visible” lesions because of adjacent dense breast tissues. On sonography, nine of the 31 patients had a complete response, 12 had a partial response, and eight patients had stable disease. The remaining two patients had “not measurable” lesions on sonography that was due to extensive abnormal shadowing with no discrete mass identified. On MRI, six of the 31 patients had a complete response, 17 had a partial response, and eight patients had stable disease.

Response agreement of mammography, sonography, and MRI with the clinical response rate was 32%, 48%, and 55%, respectively. The mammographically “not visible” lesions due to dense breast tissues and sonographically “not measurable” lesions were regarded as nonagreement with respect to physical examination versus the respective imaging technique. These

rates did not differ statistically ($p > 0.12$ for all pairwise comparisons).

Mammographically, most patients had a mass. Twenty-four patients had a mass (12 of which had calcifications associated with the mass), one patient had extensive calcifications with no associated mass seen mammographically, and six patients had no abnormality visualized.

The majority of the patients had dense breast tissues mammographically. Twenty-four patients had an American College of Radiology BI-RADS parenchymal pattern of 3 or 4, and seven patients had a BI-RADS parenchymal pattern of 1 or 2 [43]. In 18 patients, the margins of the mass were more than 80% obscured by the adjacent dense breast tissues, seven of which were not visible at all on mammography because of the adjacent dense breast tissues.

All patients had a hypoechoic irregular mass on sonography. All patients had an enhancing mass on MRI.

Tumor Response and Response Agreement of Clinical Examination and Imaging Compared with Pathology After Neoadjuvant Chemotherapy

Response agreement of clinical examination, mammography, sonography, and MRI with pathology was 19%, 26%, 35%, and 71%, respectively (Table 2). MRI agreed with pathology significantly more often than did clinical examination, mammography, or sonography ($p = 0.0005, 0.0010, \text{ and } 0.0010$, respectively). The rates for the latter three did not differ significantly from each other ($p > 0.30$ for all pairwise comparisons).

There was a 19% response agreement of physical examination with pathology. Clinical examination underestimated pathology in 55% and overestimated pathology in 26% of cases ($p = 0.11$). Fifteen patients had com-

plete response by physical examination after neoadjuvant chemotherapy. Of these 15 patients, 14 had residual tumor at pathology and one patient had no residual tumor. The size of the residual tumor at pathology in the 14 patients was as follows: two patients had an invasive ductal carcinoma that was less than 0.1 cm, one of whom also had extensive DCIS spanning greater than 5.7 cm and the other had extensive DCIS; two patients had two nodules each of invasive ductal carcinoma (0.4 and 0.6 cm, 0.6 and 0.7 cm, respectively); and one patient had two nodules of invasive carcinoma with ductal and lobular features (2.5 and 3.3 cm). The range of tumor size in the remaining nine patients was 0.4–2.2 cm (mean, 1.5 cm; median, 1.7 cm).

There was a 26% response agreement of mammography with pathology. Mammography overestimated the amount of residual tumor in 23% and underestimated the amount of residual tumor in 52% ($p = 0.09$). Of the seven patients in whom mammography overestimated the amount of residual tumor, three patients had dense breast tissues and masses with irregular margins or spiculations; therefore, the size of the tumor was difficult to measure accurately. In two patients, tumor size on mammography differed from that at pathology because of a threshold difference (we arbitrarily chose 70% difference in size and the two patients had a difference in size of 67% and 66%). The remaining two patients had extensive calcifications that were not representative of active tumor at pathology.

Of the 16 patients in whom mammography underestimated the amount of residual tumor, three patients had a tumor that was less than 5 mm at pathology, three patients had one mass identified on mammography and two nodules of tumor at pathology, two patients had complete response on mammography and only DCIS at pathology (0.3 and 1.2 cm), and one patient had complete response on mammography and a 2-cm invasive lobular carcinoma at pathology. In the remaining seven patients, the tumor was not visualized on mammography before and after chemotherapy because of dense breast tissues. These cases were counted as underestimates because there was known tumor and mammography was unable to detect the tumor.

There was 35% response agreement of sonography with pathology after neoadjuvant chemotherapy. Sonography overestimated the amount of tumor after chemotherapy in 13% and underestimated the amount of tumor in 52% ($p = 0.01$). Of the four patients in whom

Response to Chemotherapy	Physical Examination	Mammography ^a	Sonography ^b	MRI
Complete response	15	7	9	6
Partial response	14	6	12	17
Stable disease	2	10	8	8
Progressive disease	0	1	0	0

^aSeven patients had mammographically “not visible” lesions due to adjacent dense breast tissues. These lesions were counted as nonagreement with respect to physical examination versus the respective imaging technique.

^bTwo patients had “not measurable” lesions on sonography because of extensive abnormal shadowing with no discrete mass identified. These lesions were counted as nonagreement with respect to physical examination versus the respective imaging technique.

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TABLE 2 Physical Examination, Mammography, Sonography, and MRI Findings Compared with Pathology Results in 31 Patients

Performance of Imaging Technique	Pathology Results Versus			
	Physical Examination	Mammography ^a	Sonography ^b	MRI
Underestimate	17 (55)	16 (52)	16 (52)	7 (23)
Equal	6 (19)	8 (26)	11 (35)	22 (71)
Overestimate	8 (26)	7 (23)	4 (13)	2 (6)

^aIn seven patients, the mass was not visualized on mammography because of dense breast tissues; these cases were regarded as underestimates.

^bIn two patients, after chemotherapy, ill-defined shadowing that was not measurable was seen on sonography; these cases were regarded as underestimates.

sonography overestimated the size of the tumor, three had a difference in size measurement that was classified as an overestimate likely because of the arbitrary criterion of 70%; the difference in size measurement for the three tumors was 67%, 54%, and 50%. The fourth patient had a sonographic measurement of 1.2 cm, but pathology showed dense sclerosis with no residual tumor.

For the 16 patients in whom sonography underestimated the size of tumor, sonography showed complete response in nine patients:

three had only DCIS at pathology (0.3 and 1.2 cm, and extensive DCIS), four had invasive tumor that was less than 5 mm at pathology, and two had an invasive lobular carcinoma (1.2 and 2.0 cm). Three patients had one mass identified on sonography and two discrete nodules at pathology, and two patients had a difference in size measurement (68% and 50%) that was classified as an underestimate likely because of the arbitrary criterion of 70%. In the two remaining patients, there was shadowing after chemotherapy that was not

measurable because of its ill-defined nature; these cases were regarded as underestimates because the imaging technique was unable to determine the amount of tumor.

There was 71% response agreement (95% confidence interval [CI], 52–86%) of MRI after neoadjuvant chemotherapy with pathology. Figure 2 shows images of a patient in whom more tumor was present before chemotherapy on MRI (10 cm) than initially suspected at physical examination (3 cm), on mammography (dense negative), or on sonography (2.1 cm). After chemotherapy, MRI showed complete resolution of enhancement, a finding that was concordant with the pathology results, which showed dense sclerosis and no residual tumor.

MRI overestimated the amount of residual tumor in 6% and underestimated the amount of residual tumor in 23% of patients ($p = 0.18$). In one of the two cases in which MRI overestimated the amount of residual tumor, tumor size on MRI was 6.3 cm, whereas pathology showed two nodules of invasive ductal carcinoma (1.3 and 0.4 cm) that were 0.2 cm apart. In the second case in which MRI overestimated the amount of residual tumor, the MRI size was 2.5 cm and pathology showed scattered small clusters of tumor cells of invasive ductal carcinoma and DCIS, grade 2, over an area of 1.4 cm (Table 3).

MRI underestimated the amount of residual tumor in 23% of patients. In four of these cases, MRI showed no residual mass or enhancement and pathology revealed an invasive ductal carcinoma (< 0.1 cm) in three of these cases and two foci (0.4 and < 0.02 cm) of invasive ductal carcinoma in the other case. In one of the cases in which MRI underestimated the amount of residual tumor, MRI showed nonspecific patchy enhancement in the area of the previously seen tumor, and pathology showed multiple nodules aggregating to 2 × 1 cm of invasive cancer with lobular features and DCIS. In one case, MRI showed a 2.2-cm mass and pathology revealed two nodules, 2.5 and 3.3 cm of invasive carcinoma with ductal and lobular features. In the seventh case, MRI depicted a 1.8-cm mass and pathology revealed a 3.5-cm invasive ductal carcinoma (Table 3).

In two patients, MRI detected a second abnormality that was subsequently biopsied and shown to be an additional focus of tumor that had not been detected prospectively by the other techniques, including physical examination, mammography, and sonography. In one of the two patients, the dominant tumor

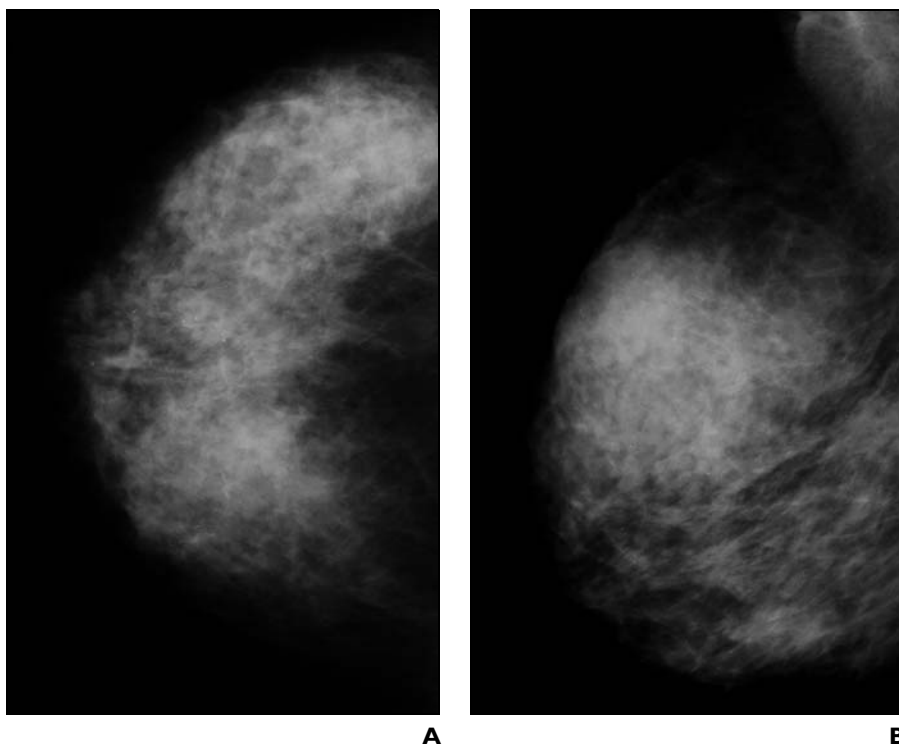


Fig. 2.—46-year-old woman with left breast lump. After chemotherapy, patient had lumpectomy with pathology results showing dense sclerosis and no residual tumor.

A. Left breast craniocaudal mammogram shows dense parenchyma and was interpreted as negative.

B. Left breast mediolateral oblique mammogram shows dense parenchyma and was interpreted as negative.

(Fig. 2 continues on next page)

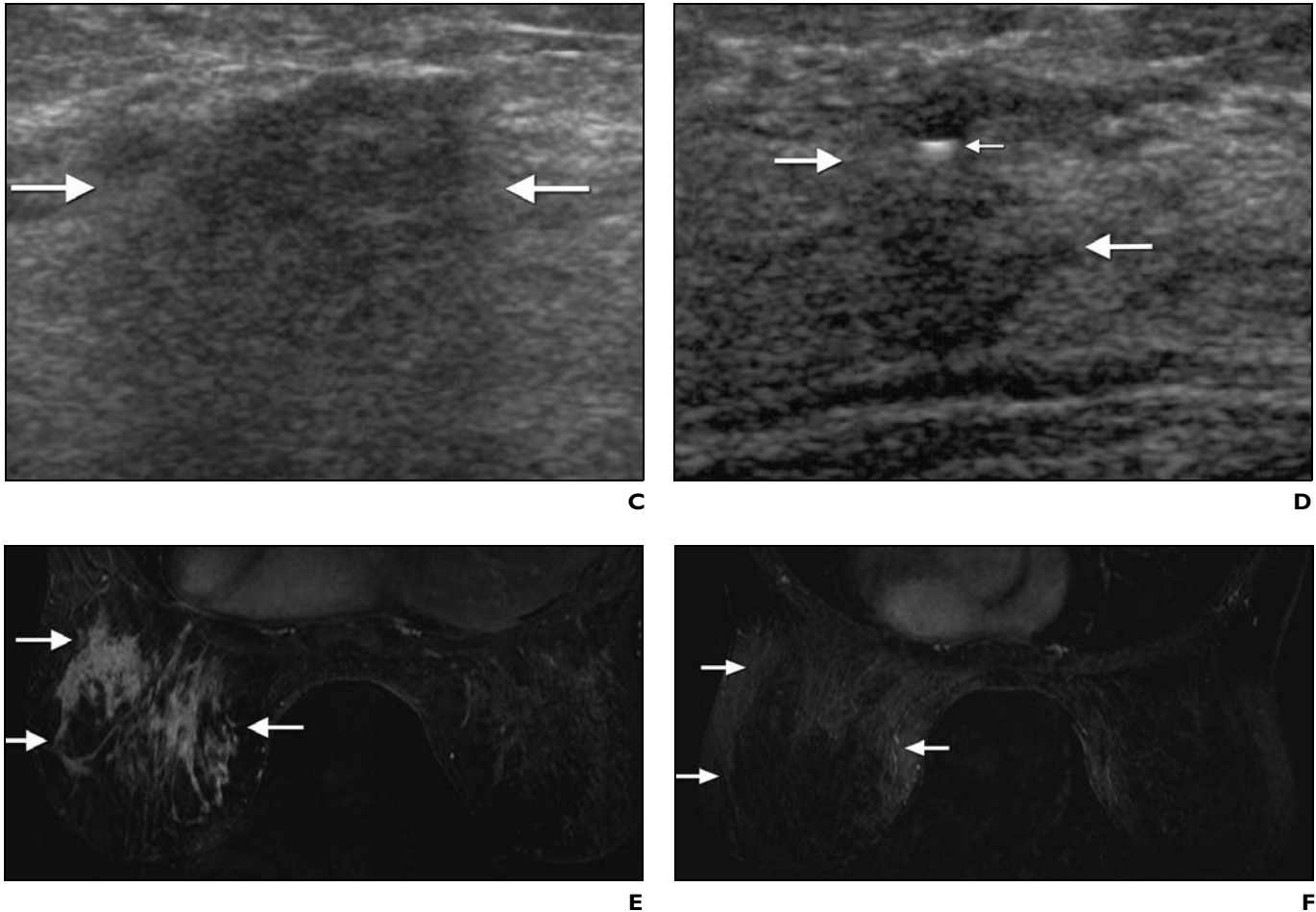


Fig. 2. (continued)—46-year-old woman with left breast lump. After chemotherapy, patient had lumpectomy with pathology results showing dense sclerosis and no residual tumor. **C**, Sonogram obtained before chemotherapy shows irregular hypoechoic shadowing and 2.1-cm mass (arrows) in left breast at 2-o'clock position in transverse plane. **D**, Sonogram obtained after chemotherapy shows discrete residual mass (large arrows) in transverse plane. Micromark clip is present within mass (small arrow). **E**, Axial subtraction MRI obtained before chemotherapy shows extensive enhancement (arrows) in left breast. Before patient received chemotherapy, more tumor was detected on MRI (10 cm) than initially was suspected on basis of physical examination (3 cm), mammography (dense negative), or sonography (2.1 cm) findings. **F**, Axial subtraction MRI obtained after chemotherapy shows complete resolution of enhancement (arrows).

was in the upper inner quadrant and an additional enhancing area was identified in the upper outer quadrant by MRI. Focused sonography showed a 1-cm mass, but a second focus of invasive ductal carcinoma was seen at sonographically guided core biopsy. A clip was placed at both sites of tumor: the dominant mass and the smaller second focus in a different quadrant. After chemotherapy, needle localization and surgical excision were performed at both sites of tumor. Pathology showed a 1-cm invasive ductal carcinoma and grade 1 DCIS at the dominant tumor site and a 0.6-cm invasive ductal carcinoma at the secondary site.

In the second patient, multiple nodules were seen before chemotherapy on MRI. After chemotherapy, one residual mass was identified on mammography and sonography, for which the patient underwent a lumpec-

tomy. On the MR images obtained after neoadjuvant chemotherapy, a 5-mm focus of enhancement over 3 cm away from the dominant mass was identified. It was not depicted on additional mammographic or focused sonographic images. CT-guided needle localization [51] was performed to determine that the site of tumor was separate from the dominant tumor mass.

In summary, we found that MRI findings correlated better with pathology results than physical examination, mammography, and sonography. The response agreement of mammography with physical examination was 32%, sonography with physical examination was 48%, and MRI with physical examination was 55%. The response agreement of physical examination with pathology was 19%, mammography with pathology was

26%, sonography with pathology was 35%, and MRI with pathology was 71%.

Discussion

Because neoadjuvant chemotherapy followed by surgery and radiation is being used with increasing frequency in the treatment of patients with palpable breast cancer, noninvasive methods of assessing response to chemotherapy are increasingly important. A sensitive and specific method would be particularly advantageous because early recognition of nonresponse might lead to changing to a more effective agent sooner, minimize toxicity, and permit optimal timing of surgery. A lack of response to a particular agent in vivo may also help guide additional chemotherapy after surgical removal.

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TABLE 3 MRI Overestimation or Underestimation of Final Pathology

MRI Findings vs Pathology Results	Lesion Size (cm) on MRI	Pathology Results	
		Invasive Carcinoma	Ductal Carcinoma In Situ
Overestimate	6.3	Two nodules: 1.3 and 0.4 cm ^a ; ductal	0
Overestimate	2.5	Scattered small clusters of tumor cells over 1.4 cm; ductal	Mixed with invasive component
Underestimate	1.8	3.5 cm; ductal	0
Underestimate	0.0	Two foci: 0.4 and <0.02 cm; ductal	0
Underestimate	0.0	Multiple nodules aggregating to 2 × 1 cm; lobular	Mixed with invasive component
Underestimate	0.0	Small tumor nests, aggregate <0.1 cm; ductal	5.7 cm
Underestimate	0.0	<0.1 cm; ductal	Microscopic focus
Underestimate	0.0	<0.1 cm; ductal	0.4 cm
Underestimate	2.2	Two nodules: 2.5 and 3.3 cm; ductal and lobular	Extensive ^b

^aThe second nodule was 0.2 cm away from the main tumor nodule.

^bThis patient had invasive carcinoma with ductal and lobular features and extensive in situ component with ductal and lobular features.

Physical examination serves as the gold standard for assessing clinical response to chemotherapy. In this pilot study, we compared physical examination findings with mammography, sonography, and MRI findings and compared all techniques with pathology results regarding the ability of each technique to assess tumor response to neoadjuvant chemotherapy.

The presence of dense tissue on mammography likely contributed to the fact that the response agreement of mammography compared with pathology was less than that of MRI compared with pathology. Dense breast tissue often obscured the tumor on mammography making size determination difficult. Of the 31 patients whom we studied, 24 had dense breast tissues with a BI-RADS parenchymal pattern of 3 or 4 [43]. In 18 of the 31 patients, greater than 80% of the margins of the tumor mass were obscured by dense tissue, thereby making the mass difficult to detect. In seven of the patients, the tumor mass was not visible on mammography because of the dense breast tissues, although some of these patients did have calcifications.

Of the noninvasive methods of tumor assessment in patients undergoing neoadjuvant chemotherapy that we measured, MRI correlated better with pathology than physical examination, mammography, and sonography. However we did find that MRI overestimated and under-

estimated residual tumor in 29% (95% CI, 14–48%) of the patients. We had two cases in which MRI overestimated residual tumor. It is unclear whether the specific chemotherapeutic agent altered gadolinium uptake or induced surrounding inflammation. Preliminary studies have suggested that taxanes increase vascular permeability and may induce a capillary protein leakage, thereby contributing to increased gadolinium uptake by the tumor [39]. Further study into the effects of specific chemotherapeutic agents is warranted.

Chemotherapy-induced fibrosis can be difficult to differentiate from residual disease on physical examination and conventional imaging [7, 9–12]. Clinical examination potentially can overestimate residual tumor; morphologic response has been shown to be more accurately assessed using contrast-enhanced MRI [52, 53]. In our two cases in which MRI overestimated residual disease, perhaps the residual enhancement was from reactive inflammation that was caused by tumor response and healing.

In seven of our cases, MRI underestimated residual disease. In four of these cases, MRI showed no residual mass or enhancement. Pathology results for these cases showed very small foci of invasive carcinoma, including an invasive ductal carcinoma (<0.1 cm) in three of these cases and two foci (0.4 and <0.02 cm) of invasive ductal carcinoma in the other

case. Two of the seven cases were an invasive cancer with lobular features. It has previously been shown that lobular carcinomas may have variable enhancement on MRI [54–56].

Four of the six cases had associated DCIS. Previous studies have shown a 10–90% sensitivity of detection of ductal carcinoma in situ on contrast-enhanced MRI [57–62]. The reason for the wide range in sensitivity of detection of ductal carcinoma in situ is likely related to the underlying pathology of the early noninvasive disease and the fact that gadolinium uptake is related to tumor angiogenesis and neovascularity. MRI enhancement patterns in DCIS have been described in prior studies with small numbers of patients as ductal enhancement, segmental or regional nonmass enhancement, and mass enhancement [61, 63]. Two studies have compared the MRI enhancement patterns in high-grade and non-high-grade DCIS and have found no significant difference in the enhancement patterns [57, 58].

Limitations of our study include the small number of patients. However, this cohort of patients represents a pilot project that is part of an ongoing protocol that is investigating imaging and physiologic and molecular markers in patients with palpable breast cancer greater than 3 cm who are receiving neoadjuvant chemotherapy.

The radiologist was blinded to the clinical size of the tumor and the pathology results, but to provide the best clinical care for the patient, the radiologist had access to the other imaging studies, with the exception that the MRI results were not known to the radiologist at the time of the mammogram and sonogram. This study design may be associated with potential bias; however, we think that this design provided the best clinical care to the small number of patients enrolled in this study. Another potential limitation of the study is that it is possible that the chemotherapeutic agents may affect the imaging appearance, especially on MRI with regard to the gadolinium uptake [39].

In summary, MRI appears to correlate better with pathology than physical examination, mammography, and sonography in patients undergoing neoadjuvant chemotherapy. MRI is not, however, perfect. It may overestimate or underestimate residual disease in some patients. These results support the need to conduct further studies to assess the value of MRI in the prediction of in vivo morphologic and pathologic tumor response to specific neoadjuvant chemotherapeutic regimens in women with palpable breast cancer.

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