Breast MRI for Evaluation of Response to Neoadjuvant Therapy

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Abbreviations: ACRIN = American College of Radiology Imaging Network, ADC = apparent diffusion coefficient, DCE = dynamic contrast enhanced, DCIS = ductal carcinoma in situ, DW = diffusion weighted, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, pCR = pathologic complete response, PR = progesterone receptor, RECIST = Response Evaluation Criteria in Solid Tumors

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Recognize the appearance of complete, partial, and noncomplete responses to neoadjuvant therapy at breast MRI.
- List causes of over- and underestimation of residual breast cancer at MRI.
- Discuss limitations of MRI in evaluating the response to therapy in the axilla and the rationale for targeted axillary dissection.

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Neoadjuvant therapy is increasingly being used to treat early-stage triple-negative and human epidermal growth factor 2–overexpressing breast cancers, as well as locally advanced and inflammatory breast cancers. The rationales for neoadjuvant therapy are to shrink tumor size and potentially decrease the extent of surgery, to serve as an in vivo test of response to therapy, and to reveal prognostic information for the patient. MRI is the most accurate modality to demonstrate response to therapy and to help ensure accurate presurgical planning. Changes in lesion diameter, volume, and enhancement are used to predict complete response, partial response, or nonresponse to therapy. However, residual disease may be overestimated or underestimated at MRI. Fibrosis, necrotic tumors, and residual benign masses may be causes of overestimation of residual disease. Nonmass lesions, invasive lobular carcinoma, hormone receptor–positive tumors, nonconcentric shrinkage patterns, the use of antiangiogenic therapy, and late-enhancing foci may be causes of underestimation of residual disease. In patients with known axillary lymph node metastasis, neoadjuvant therapy may be followed by targeted axillary dissection to avoid the potential morbidity associated with an axillary lymph node dissection. Diffusion-weighted imaging, radiomics, machine learning, and deep learning methods are under investigation to improve MRI accuracy in predicting treatment response.

Introduction

The current available options for breast cancer treatment include local-regional therapy (surgery and radiation) and systemic therapy (chemotherapy or endocrine therapy), depending on the type of breast cancer, receptor status, tumor size, and cancer stage. Chemotherapy and endocrine therapy may be given after surgery (as adjuvant therapy) or may be given before surgery (as neoadjuvant therapy). There is no difference in overall survival and disease-free survival between patients treated with neaodjuvant and adjuvant therapy (1). The rationale for neoadjuvant treatment is based on three potential benefits. First, the therapy may be expected to shrink tumor size to permit breast-conserving therapy in patients who would otherwise have needed a mastectomy, allow surgery in previously inoperable tumors, improve cosmesis of surgery, and downstage axillary lymph node disease to avoid axillary dissection. Second, neoadjuvant therapy serves as an in vivo evaluation of tumor response to therapy, allowing an oncologist to change the treatment regimen if it is not effective. Third, the degree of response to neoadjuvant therapy reveals important prognostic information as response is associated with improved survival.

TEACHING POINTS

- The rationale for neoadjuvant treatment is based on three potential benefits. First, the therapy may be expected to shrink tumor size to permit breast-conserving therapy in patients who would otherwise have needed a mastectomy, allow surgery in previously inoperable tumors, improve cosmesis of surgery, and downstage axillary lymph node disease to avoid axillary dissection. Second, neoadjuvant therapy serves as an in vivo evaluation of tumor response to therapy, allowing an oncologist to change the treatment regimen if it is not effective. Third, the degree of response to neoadjuvant therapy reveals important prognostic information as response is associated with improved survival.
- Comparisons of clinical breast examination, mammography, US, and MRI have found that MRI is the most accurate method for detecting tumor response and residual tumor.
- Before surgery, medical oncologists and breast surgeons use physical examination and imaging to assess tumor response to therapy and to plan surgery.
- At MRI, the extent of residual disease may be overestimated because of enhancing benign foci of fibrosis or treatment change, enhancing benign masses, and residual nonenhancing masses representing treated tumor.
- The extent of residual disease may be underestimated at MRI because of tumors with nonmass morphology such as invasive lobular carcinomas and luminal tumors, which are more difficult to accurately measure.

Given these benefits, neoadjuvant therapy is currently the standard of care for locally advanced and inflammatory breast cancers and is becoming the standard of care for early-stage triple-negative and human epidermal growth factor receptor 2 (HER2)–overexpressing breast cancers (2). This review focuses on response to neoadjuvant chemotherapy and HER2-directed therapy, which are the most commonly administered neoadjuvant therapies. Other neoadjuvant therapies such as endocrine therapy alone (without chemotherapy), cyclin-dependent kinase 4 and 6 (CDK4 and CDK6) inhibitors, and immunotherapy have little or no published literature on response patterns at breast MRI.

Response to neoadjuvant therapy can be mixed depending on the molecular subtype of cancer, with an average pathologic complete response (pCR) rate of 19% (3). Before surgery, response to therapy is assessed at clinical examination and imaging. Comparisons of clinical breast examination, mammography, US, and MRI have found that MRI is the most accurate method for detecting tumor response and residual tumor (4–6). The American College of Radiology Imaging Network (ACRIN) 6657 trial compared MRI to clinical examination and mammography and found that MRI was the most accurate for detecting pCR and also showed the strongest association with final pathologic size in patients without pCR (4). A meta-analysis of 44 studies also showed that MRI had better accuracy for predicting both pCR and residual disease than did clinical examination and mammography (7).

The objectives of this article are to review the evaluation of response to neoadjuvant therapy at MRI, illustrate causes of overestimation and underestimation of residual disease at MRI, and discuss the management of the axilla after neoadjuvant therapy.

Assessing Tumor Response at Pathologic Analysis

After neoadjuvant therapy, patients undergo surgery for local-regional control, and final pathologic response can be assessed. pCR is defined as no residual invasive tumor at pathologic assessment (8). Note that it is the lack of an invasive component that determines pCR, although some institutions and studies may also require the absence of ductal carcinoma in situ (DCIS). Most typically, pCR refers to response in the breast and in the axilla. However, some trials may report pCR when there is no residual invasive disease in the breast but there is residual nodal disease in the axilla. Since 2014, this has been specifically discouraged by the U.S. Food and Drug Administration (9).

For patients whose disease does not demonstrate pCR, a residual cancer burden (RCB) score is commonly used to predict survival. In calculating the RCB score, four parameters are evaluated: the primary tumor dimension (in situ and invasive), cellularity of the invasive tumor, size of the largest nodal metastasis, and number of positive lymph nodes (8). Increasing RCB scores represent increasing degrees of residual disease and are correlated to a worse prognosis, including higher rates of distant recurrence (10).

Breast cancer is a heterogeneous disease, and the rates of pCR after neoadjuvant therapy range from 0.3%–50.3% depending on tumor subtype (3,6). Differences among individual tumors occur because of underlying variability in gene expression. In clinical practice, immunohistochemical markers of estrogen receptor (ER) and progesterone receptor (PR) positivity and HER2 overexpression are used to classify tumors into four subtypes, each with unique prognoses that may require different therapies (Table 1) (11). The two more aggressive subtypes are triple-negative tumors (that do not express genes for ER, PR, or HER2) and HER2-positive tumors (that overexpress HER2). These more aggressive tumors are more chemosensitive because of high cellular proliferation and are therefore commonly treated with neoadjuvant chemotherapy even when in an early stage (12). HER2-overexpressing cancers are additionally treated with HER2-targeted monoclonal antibody therapies. The two less aggressive subtypes

Table 1: Four Clinical Subtypes of Invasive Breast Cancer

Subtype	Immunochemical Results and Usual Grade	Frequency (%)	Treatment Notes	Morphology at Presentation	Imaging Findings after Neoadjuvant Therapy
Luminal A	ER+ PR+ HER2– Low proliferation Low grade	50–55	Best prognosis Treated with hormonal therapy May not need chemotherapy	Mass or NME	Low pCR rates May show nonconcentric shrinkage Low correlation between size of residual enhancement and pathologic size MRI may underestimate residual disease
Luminal B	ER+ and/or PR+ HER2– or HER2+ High proliferation Intermediate or high grade	15	More aggressive than luminal A Usually needs chemotherapy in addition to hormonal therapy	Mass or NME	Low pCR rates May show nonconcentric shrinkage Low correlation between size of residual enhancement and pathologic size MRI may underestimate residual disease
HER2 enriched	HER2+ Usually ER– or PR– (may be ER+ or PR+) Intermediate to high grade	15	Prognosis has improved with HER2-targeted therapies Often treated with neoadjuvant chemotherapy and HER2-targeted therapies	Mass	High pCR rates with targeted therapy Concentric shrinkage most common pattern MRI accurately predicts pCR
Triple negative	ER– PR– HER2– High grade	10–20	Most aggressive Often treated with neoadjuvant chemotherapy	Mass Unifocal	High pCR rates with targeted therapy Concentric shrinkage most common pattern MRI accurately predicts pCR

Source.—Frequency data are from reference 11.
Note.—ER+ = tumor expresses estrogen receptor, ER– = tumor does not express estrogen receptor, HER2+ = tumor overexpresses HER2, HER2– = tumor does not overexpress HER2, NME = nonmass enhancement, PR+ = tumor expresses progesterone receptor, PR– = tumor does not express progesterone receptor.

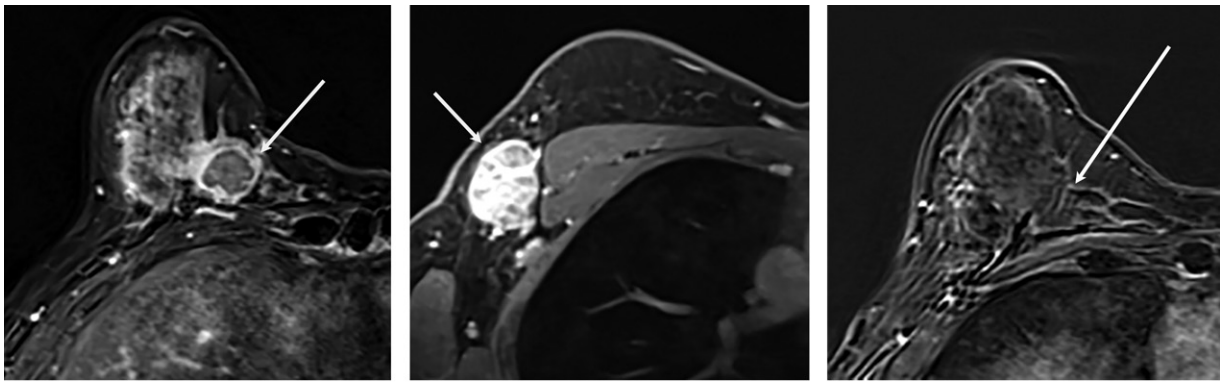
are cancers that are ER and/or PR positive, and these are grouped into luminal A and luminal B subtypes. Luminal B tumors are more likely to be higher grade with higher markers of proliferation and a less favorable prognosis. Luminal cancers are less likely to be treated with neoadjuvant therapy, as these tumors have the lowest rates of pCR because of lower chemosensitivity (12).

Assessing Tumor Response at MRI

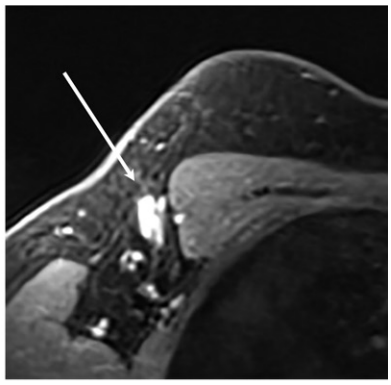
Before surgery, medical oncologists and breast surgeons use physical examination and imaging to assess tumor response to therapy and to plan surgery. Interpretation of posttreatment MR images hinges on changes in tumor size and/or enhancement compared with pretreatment MR images.

At our institution, our imaging protocol to help assess treatment response is to perform one precontrast and three postcontrast axial T1-weighted sequences. The timing is 90 seconds for the first postcontrast sequence and 6 minutes for the last postcontrast sequence. We have found the third postcontrast image to be helpful in identifying residual disease, as enhancement may be delayed because of the antiangiogenic effect of chemotherapy (13).

Either diameter or volume measurements may be used to evaluate changes in tumor size. The Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines are widely used in oncology trials and recommend tumor measurement in at least one dimension (at least the longest diameter in the plane of measurement) (14). Four categories of response are recognized: complete response, partial response, stable disease, and progressive disease (Figs 1–3, Table 2) . The RECIST 1.1 guidelines specify that MRI is the preferred imaging modality to follow breast lesions in the neoadjuvant setting but is not used in axillary lymph node evaluation.



a. b. c.



d.

Figure 1. Complete imaging and pathologic response to therapy in a 38-year-old woman with poorly differentiated invasive ductal carcinoma (IDC) (ER positive, PR positive, HER2 negative) with fine-needle aspiration–proven metastasis to an axillary lymph node. **(a)** Axial contrast-enhanced T1-weighted subtraction MR image obtained before treatment shows a round rim-enhancing mass (arrow) in the right breast. **(b)** Axial pretreatment contrast-enhanced T1-weighted MR image shows an enlarged heterogeneously enhancing lymph node in the right axilla (arrow). A total of five abnormal lymph nodes were identified in the right axilla (not shown). **(c)** Axial contrast-enhanced T1-weighted subtraction MR image obtained after treatment shows complete resolution of enhancement in the breast (arrow). **(d)** Axial posttreatment contrast-enhanced T1-weighted MR image shows a normal-appearing axillary lymph node (arrow). The imaging findings are compatible with complete response. Final pathologic analysis (not shown) yielded no residual carcinoma in the breast and 16 normal lymph nodes.

In multifocal or multicentric breast cancers, up to two lesions are measured in each breast, preferably the largest lesions, and are considered the target lesions that are to be measured at follow-up imaging. Any additional enhancing lesions in the breast are nontarget lesions and should be evaluated at follow-up imaging but do not require measurement.

Across all tumor types, pCR is achieved in 19% of patients, partial response in 45%, nonresponse in 17%, and progression in 20% (3). Response rates vary by cancer subtype, with luminal A tumors achieving the lowest rates of pCR (0.3%), luminal B reaching pCR in 8.3%, triple negative in 23.2%, and HER2-positive tumors in 38.7% (3).

Changes in volume have been found to be more accurate in predicting response than changes in the longest diameter. The ACRIN 6657 trial was a multicenter study of MRI performed before, during, and after neoadjuvant chemotherapy (15). The investigators found that functional tumor volume measurements were not only more accurate in predicting response than were longest diameter measurements, but functional tumor volume could help predict recurrence-free survival (16). The functional tumor volume incorporates enhancement thresholds to determine which portions of the tumor to include in a measurement, combining functional criteria with a volume measurement. Visual assessment of decreased enhancement also indicates response to therapy, as effective chemotherapy reduces tumor neoangiogenesis (17) (Fig 4).

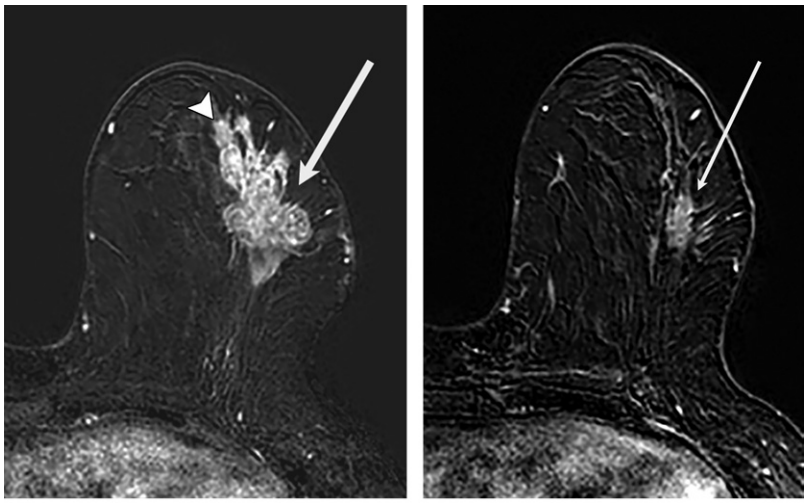
At our institution, we report tumor size by measuring the diameters of the enhancing lesion in three dimensions and do not calculate the tumor volume. When assessing therapeutic response at imaging, we report imaging complete response when there is no residual enhancement at posttreatment MRI. When there is residual enhancement, we measure the enhancing lesion in three dimensions and compare with pretreatment measurements. We also semiquantitatively estimate change in the degree of enhancement. If the extent and degree of enhancement is clearly stable or has clearly decreased, then we report nonresponse or partial response. In cases where imaging response is more subtle or equivocal, we follow the RECIST 1.1 criteria and require at least a 30% decrease in the diameter of the lesion to report partial response. However, in cases where the diameter of the lesion is unchanged but the degree of enhancement is decreased, we report the decreased enhancement and note that it may represent partial response to therapy, as tumor cellularity may decrease without change in overall size of the tumor.

Almost all patients proceed to surgery after neoadjuvant therapy, regardless of whether MRI helps predict pCR. Therefore, the use of MRI in practice is not to help distinguish pCR from

Table 2: Evaluation of Target and Nontarget Lesions according to RECIST Version 1.1

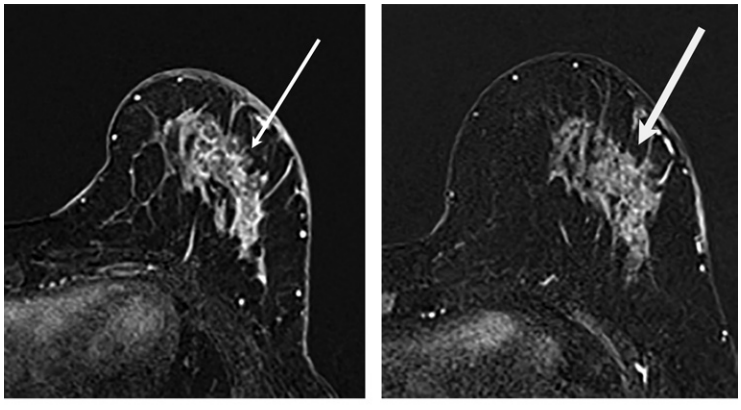
Type of Lesion and Pathologic Response	Criteria
Target lesions (up to two per breast)	
Complete response	Disappearance of all target lesions
Partial response	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the sum of baseline diameters
Progressive disease	At least a 20% increase in the sum of diameters of target lesions In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm The appearance of one or more new lesions is also considered progression
Stable disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease
Nontarget lesions (additional lesions beyond two target lesions per breast)	
Complete response	Disappearance of all nontarget lesions
Noncomplete response or nonprogressive disease	Persistence of one or more nontarget lesions
Progressive disease	Unequivocal progression of existing nontarget lesions Appearance of one or more new lesions

Note.—Adapted and reprinted, with permission, from reference 5.



a. **b.**

Figure 2. Partial imaging and pathologic response to therapy in a 64-year-old woman with a moderately differentiated IDC (ER positive, PR positive, HER2 negative). **(a)** Axial contrast-enhanced T1-weighted subtraction MR image obtained before treatment demonstrates an irregular mass (arrow) with linear nonmass enhancement (arrowhead) in the lateral left breast. **(b)** Axial contrast-enhanced T1-weighted subtraction MR image obtained after treatment demonstrates residual nonmass enhancement (arrow) that is decreased in the longest diameter and in the degree of enhancement, which is compatible with residual tumor and partial response. Final pathologic analysis yielded multiple foci of residual IDC.



a. **b.**

Figure 3. Stable disease at imaging and pathologic analysis in a 26-year-old woman with a poorly differentiated IDC (ER positive, PR positive, HER2 negative). Axial contrast-enhanced T1-weighted subtraction MR images obtained before **(a)** and after **(b)** treatment demonstrate confluent nonmass enhancement (arrow) throughout the central and lateral breast, with no response to treatment. Final pathologic analysis yielded IDC spanning 4.5 cm.

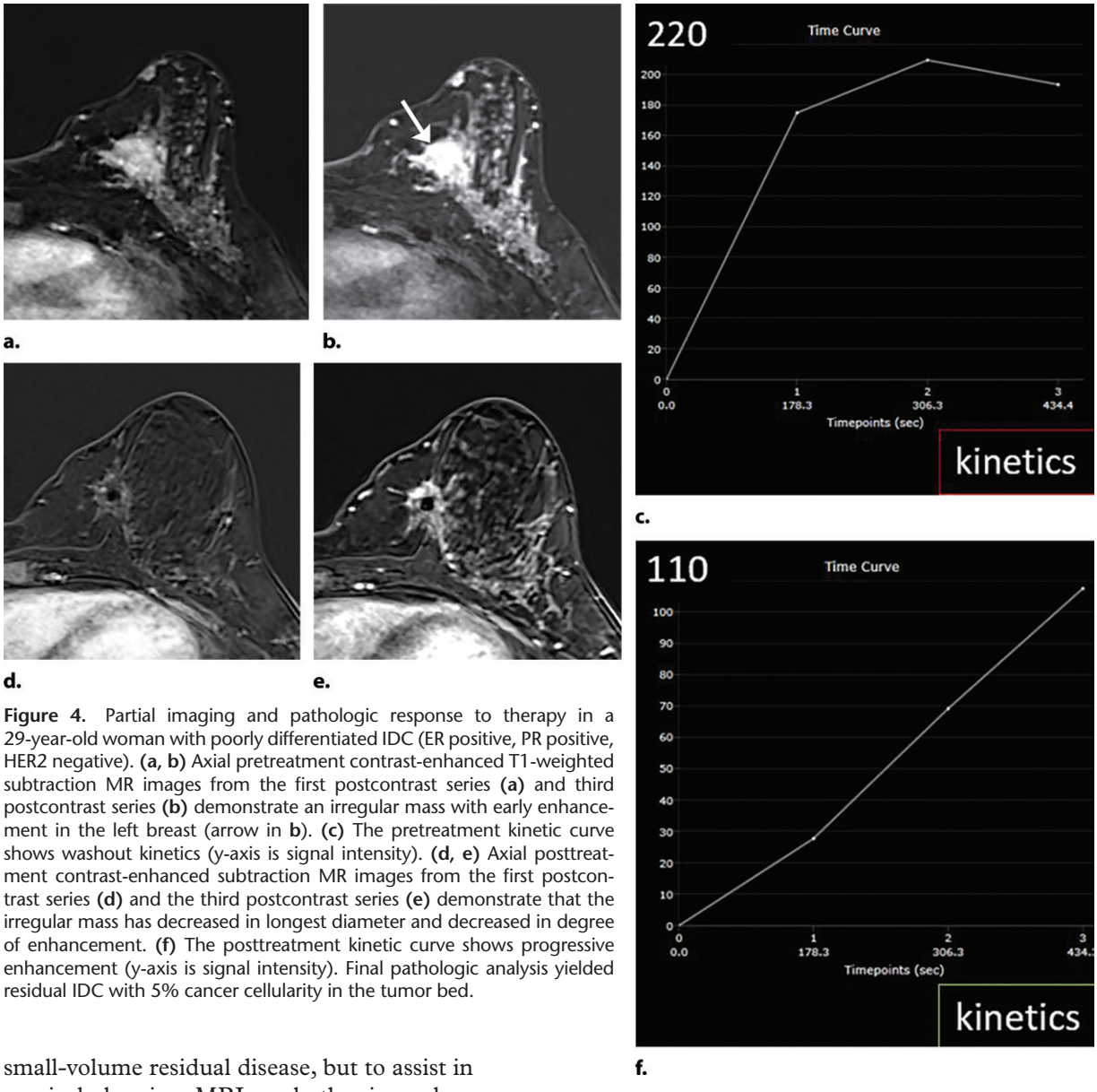


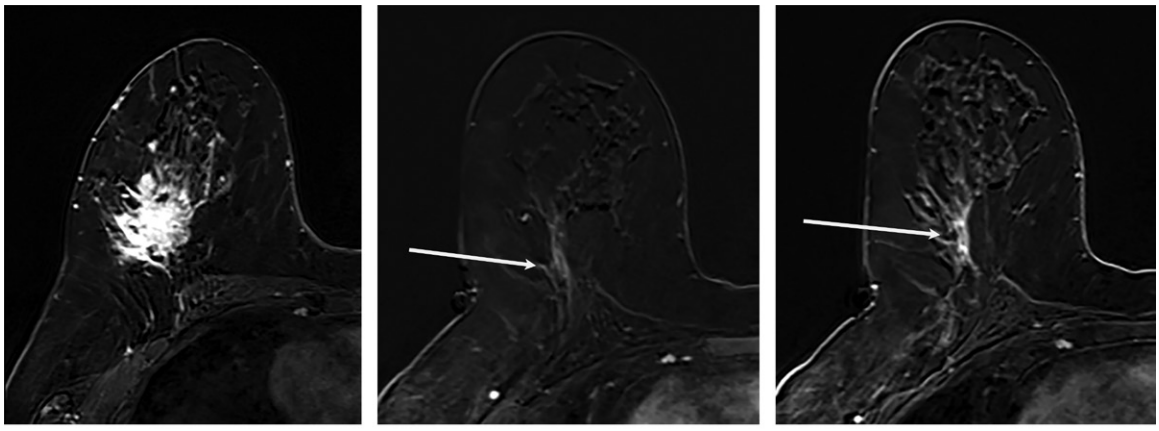
Figure 4. Partial imaging and pathologic response to therapy in a 29-year-old woman with poorly differentiated IDC (ER positive, PR positive, HER2 negative). **(a, b)** Axial pretreatment contrast-enhanced T1-weighted subtraction MR images from the first postcontrast series **(a)** and third postcontrast series **(b)** demonstrate an irregular mass with early enhancement in the left breast (arrow in **b**). **(c)** The pretreatment kinetic curve shows washout kinetics (y-axis is signal intensity). **(d, e)** Axial posttreatment contrast-enhanced subtraction MR images from the first postcontrast series **(d)** and the third postcontrast series **(e)** demonstrate that the irregular mass has decreased in longest diameter and decreased in degree of enhancement. **(f)** The posttreatment kinetic curve shows progressive enhancement (y-axis is signal intensity). Final pathologic analysis yielded residual IDC with 5% cancer cellularity in the tumor bed.

small-volume residual disease, but to assist in surgical planning. MRI can both miss and overestimate residual disease. Sensitivity of MRI depiction for residual disease is 63%–88% in meta-analyses, and specificity is 54%–91% (17). Studies have found that 6%–19% of cases are overestimated at MRI, and 7%–28% of cases are underestimated (18). Overestimating residual disease may result in more extensive surgery: mastectomy instead of breast conservation and axillary dissection instead of sentinel lymph node biopsy. Missing residual disease may result in positive margins and the need for surgical reexcision. Here we present examples of both over- and underestimation of disease.

Causes of Overestimation of Residual Disease

Fibrosis or Treatment Change.—Fibrosis or benign posttreatment change, including postinflammatory changes after neoadjuvant chemotherapy, may enhance and mimic residual carcinoma (Fig 5). Several large studies have found that of patients with enhancement at MRI, 13%–17% have no residual tumor at pathologic analysis (which is considered pCR) (19,20). In discordant cases in which MRI predicted residual disease but none was found, researchers have identified fibrous granulation tissue that contains small vessels and inflammatory cells such as macrophages, accounting for the enhancement (21,22).

Studies comparing early and late enhancement at posttreatment MRI show decreased specificity of the later phase of enhancement, suggesting that the false positives (interpreted as residual disease but achieving pCR at pathologic analysis) are caused by fibrosis or posttreatment change that is late enhancing (7,23). However, residual



a. b. c.

Figure 5. Partial response at imaging but pCR in a 37-year-old woman with a poorly differentiated IDC (ER positive, PR positive, HER2 positive). **(a)** Axial contrast-enhanced T1-weighted subtraction MR image obtained before treatment demonstrates a heterogeneously enhancing irregular mass. **(b, c)** Axial posttreatment contrast-enhanced T1-weighted subtraction MR images from the first postcontrast series **(b)** and the last postcontrast series **(c)** demonstrate 2.3-cm linear nonmass enhancement (arrow) in the tumor bed, which is better seen on the delayed postcontrast image **(c)**. Final pathologic analysis yielded no residual invasive or in situ carcinoma and treatment effect only within a 2.9-cm tumor bed.

tumors may also demonstrate delayed enhancement, particularly luminal tumors as discussed later. Therefore, delayed enhancement remains important for maintaining sensitivity in depiction of residual disease.

Necrotic Tumors.—Tumors that become necrotic, hemorrhagic, or fibrotic during therapy may leave behind residual masses that can be palpated or seen at mammography and US. However, these masses may not contain viable tumor cells, and clinical examination and imaging may lead to overestimation of residual disease. Dynamic contrast-enhanced (DCE) MRI provides functional evaluation of the residual mass, and lack of contrast enhancement indicates either no or low cellularity (22,24). Similarly, mucinous tumors may leave residual pools of acellular mucin that have the appearance of a mass but lack internal enhancement (Fig 6).

Residual Benign Masses.—Fibroadenomas and other benign masses may remain stable or decrease in size and enhancement after therapy and may be mistaken for residual disease (Fig 7). Studies have shown that both benign and malignant lesions decrease in size after chemotherapy, but malignant lesions demonstrate a relatively greater decrease in size (25). Benign lesions and background parenchyma may also decrease in enhancement after neoadjuvant therapy, but this is more commonly seen in patients treated with taxanes, while patients treated with non-taxane–containing regimens have only mild or no decrease in enhancement of benign masses (26). Baseline MRI is important to help accurately evaluate the extent of disease before the start of neoadjuvant therapy, and biopsy may be necessary to help distinguish benign masses from the extent of disease.

In addition, it should be noted that DCIS as well as benign proliferative lesions (such as intraductal papilloma or atypical ductal hyperplasia) may enhance (27–29). While DCIS in the absence of invasive disease may be counted as a pCR, the presence and extent of DCIS is important for surgical planning and to obtain negative surgical margins.

Causes of Underestimation of Residual Disease

Tumors with Nonmass Morphology.—Nonmass lesions are more likely than masses to result in a false-negative MRI, in which there is complete imaging response to therapy but residual tumor is identified in the pathologic specimen (30). Nonmass lesions also have greater size discrepancies between MRI and pathologic analysis than do mass lesions (18,31–33). For example, Chen et al (18) found that the difference between the predicted size of the residual lesion at MRI and the measurement at pathologic analysis was 2.06 cm for nonmass lesions, which was significantly greater than the difference of 0.69 cm for mass lesions.

Given that invasive lobular carcinoma (ILC) is most likely to manifest as a nonmass lesion, it is not surprising that ILC is more likely to yield a false-negative MRI after neoadjuvant therapy than is invasive ductal carcinoma (IDC) (18) (Fig 8). ILC and mixed ductal and lobular invasive cancers also have larger discrepancies between size at MRI and pathologic analysis compared with IDC (34). The growth pattern of

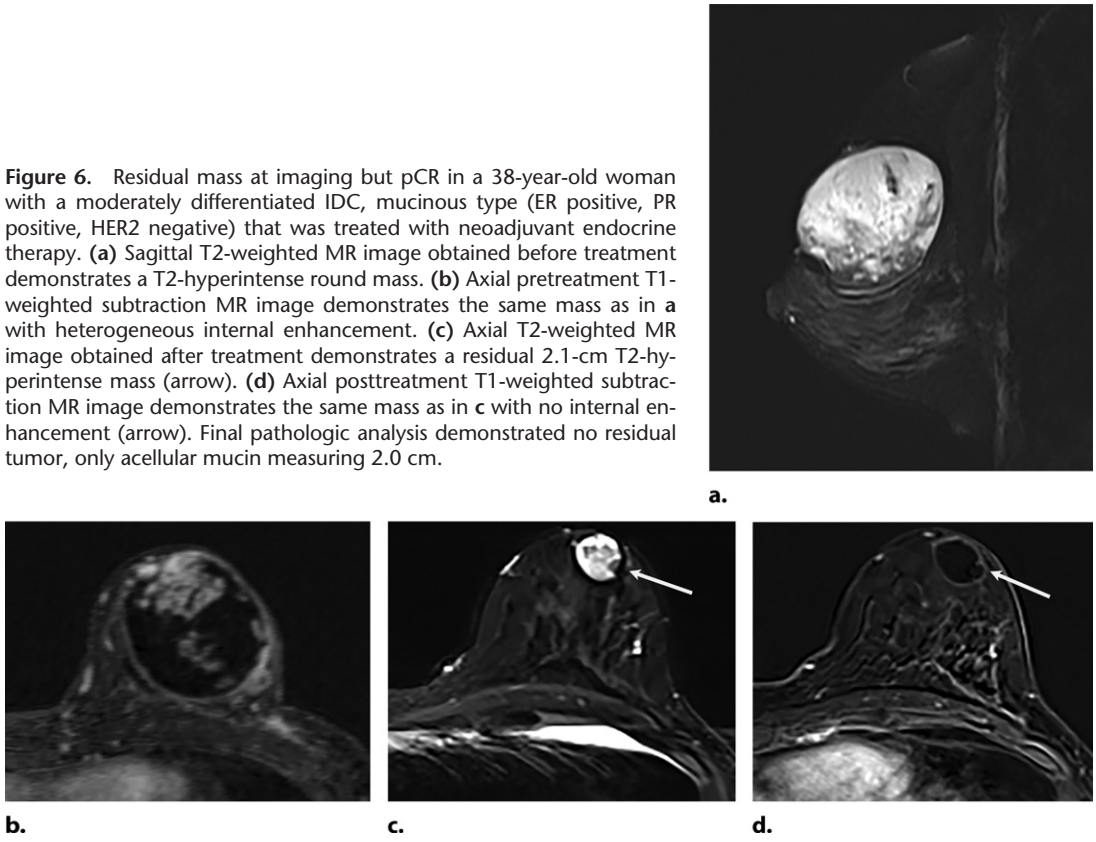


Figure 6. Residual mass at imaging but pCR in a 38-year-old woman with a moderately differentiated IDC, mucinous type (ER positive, PR positive, HER2 negative) that was treated with neoadjuvant endocrine therapy. **(a)** Sagittal T2-weighted MR image obtained before treatment demonstrates a T2-hyperintense round mass. **(b)** Axial pretreatment T1-weighted subtraction MR image demonstrates the same mass as in **a** with heterogeneous internal enhancement. **(c)** Axial T2-weighted MR image obtained after treatment demonstrates a residual 2.1-cm T2-hyperintense mass (arrow). **(d)** Axial posttreatment T1-weighted subtraction MR image demonstrates the same mass as in **c** with no internal enhancement (arrow). Final pathologic analysis demonstrated no residual tumor, only acellular mucin measuring 2.0 cm.

ILC, characterized by diffuseness, multicentricity, and loss of cell-cell adhesion, may account for the lower accuracy of posttreatment MRI in this histologic tumor type.

Luminal (hormone receptor–positive and HER2-negative) tumors are also more likely to be underestimated at posttreatment MRI (21,32,34,35). Although most commonly manifesting as spiculated masses, these tumors may also manifest as a nonmass or diffuse lesion, as compared with triple-negative and HER2-positive tumors, which usually manifest as discrete masses (Figs 2, 7) (31). It is important for surgeons and radiologists to know that there are larger size discrepancies between imaging and pathologic analysis and a higher chance for positive margins after breast conservation therapy for hormone receptor–positive and HER2-negative tumors (33,36).

Tumors with Nonconcentric Shrinkage.—Tumors responding to neoadjuvant therapy may demonstrate different shrinkage patterns: complete response, concentric shrinkage, and nonconcentric shrinkage (37–40). Concentric shrinkage describes a pattern in which the pretherapy MRI demonstrates a mass without surrounding nonmass enhancement or foci. Then, the posttherapy MRI demonstrates a reduction in the longest diameter of the mass, possibly with some residual foci around the dominant mass. Nonconcentric shrinkage is any other pattern of shrinkage and has also been called a crumbling pattern or multinodular lesions. In the nonconcentric shrinkage pattern, it is difficult to determine whether residual enhancement may represent invasive cancer, DCIS, or reactive change after therapy, and both over- and underestimation of residual disease is possible. MR images may appear falsely negative in the setting of small scattered residual disease, as residual tumor cells may be too small to be identified at MRI or may be mistaken for benign foci (Fig 9).

Shrinkage patterns are associated with tumor subtypes (Table 1). HER2-positive and triple-negative tumors more commonly manifest as masses that demonstrate concentric shrinkage after neoadjuvant therapy. In contrast, luminal tumors more commonly manifest as nonmass enhancement that demonstrates nonconcentric shrinkage. Importantly, the shrinkage pattern in luminal tumors is associated with prognosis, and patients with luminal tumors that demonstrate concentric shrinkage have improved rates of survival compared with those with tumors that demonstrate nonconcentric shrinkage, despite similarly low pCR rates (1.6% overall) (38).

Given the variable rates of response, baseline morphology, and shrinkage patterns among the tumor subtypes, it is not surprising that the rates

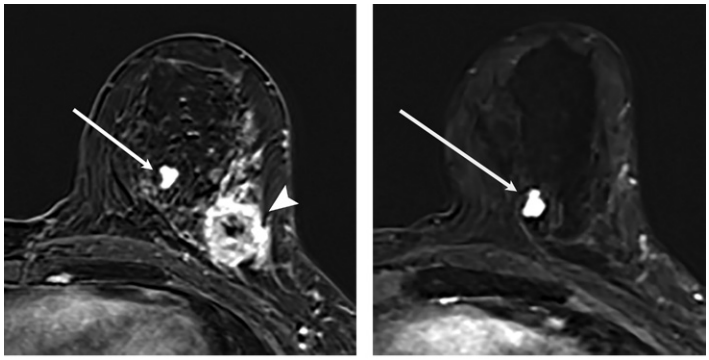
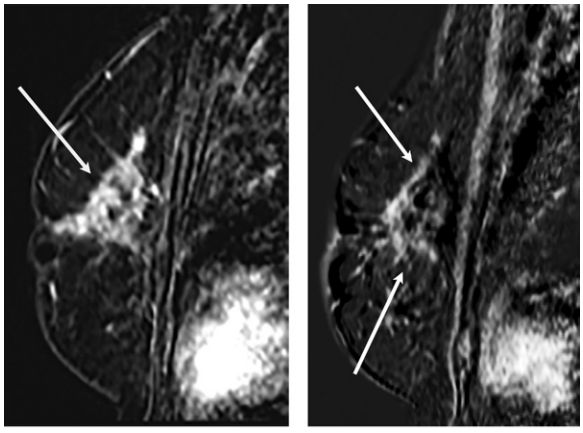


Figure 7. pCR in a 52-year-old woman with a poorly differentiated IDC (ER negative, PR negative, HER2 positive). **(a)** Axial contrast-enhanced T1-weighted subtraction MR image obtained before treatment demonstrates an irregular rim-enhancing mass in the lateral breast (arrowhead) as well as a lobulated mass in the central breast (arrow). **(b)** Axial contrast-enhanced T1-weighted subtraction MR image obtained after treatment demonstrates complete resolution of the irregular mass and no change in the lobulated central mass (arrow), which is a benign fibroadenoma that was diagnosed at presurgical biopsy.

a. **b.**



a. **b.**

Figure 8. Partial imaging and pathologic response in a 59-year-old woman with a moderately differentiated ILC. **(a)** Sagittal pretreatment contrast-enhanced T1-weighted subtraction MR image demonstrates nonmass enhancement (arrow) involving all four quadrants of the breast. **(b)** Sagittal contrast-enhanced T1-weighted subtraction MR image obtained after treatment demonstrates moderate residual nonmass enhancement that is unchanged in extent but has decreased in volume and enhancement, spanning 5.6 cm (arrows). Final pathologic analysis yielded multifocal residual invasive lobular carcinoma, with the largest focus measuring 6.5 cm.

of false-positive and false-negative MRI studies vary by tumor subtype (35). Accuracy of breast MRI for predicting pCR is highest in triple-negative and HER2-positive cancers (21).

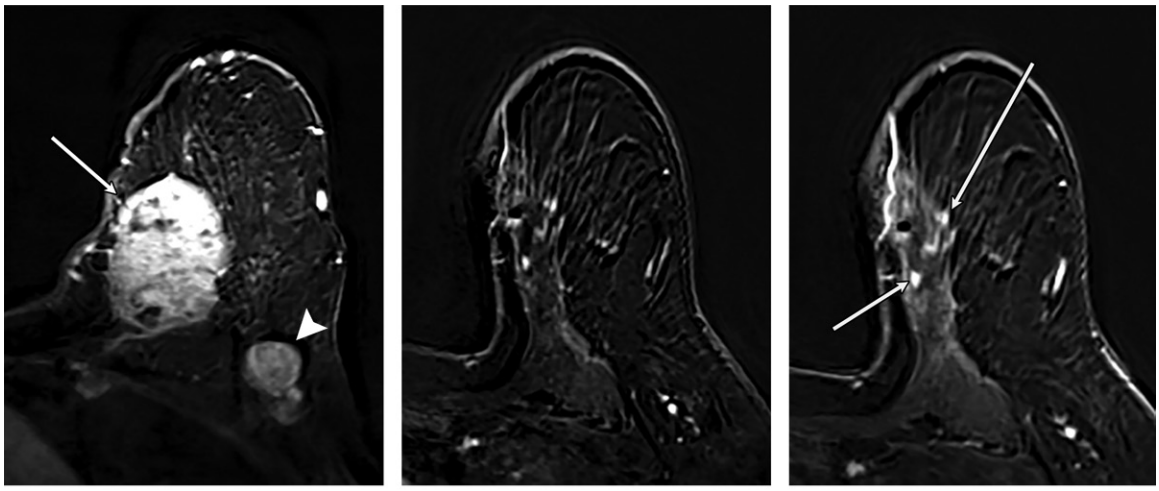
Antiangiogenic Therapy.—Conventional chemotherapy agents such as taxanes and anthracyclines have known antiangiogenic effects. Studies have shown that patients treated with taxane-containing regimens have suppressed enhancement in breast cancers as well as in benign lesions and background parenchyma (26,41,42) (Fig 10). In a study comparing patients treated with multiagent chemotherapy with and without taxanes, the use of taxanes resulted in 66.7% false-negative MRI findings in patients with residual disease (compared with a 20% false-negative rate in patients treated without taxanes) (26). Global reduction in background parenchymal enhancement may indicate treatment effect, and the reader should be aware of the possibility of false negatives in this setting.

Late-enhancing Foci.—Residual tumor after neoadjuvant therapy may demonstrate late enhancement because of the antiangiogenic effect of chemotherapy. This is particularly true for luminal tumors, which are more frequently underestimated than are triple-negative and HER2-positive cancers because of their initial manifestation as nonmass lesions and their nonconcentric shrinkage pattern, resulting in delayed enhancement.

In a study comparing residual tumor size at imaging and at pathologic analysis, early phase images (obtained 90 seconds after beginning administration of intravenous gadolinium-based contrast material) were compared with images obtained later (360 seconds or later). There was no difference in accuracy for depiction of residual invasive disease, but residual DCIS was underestimated on early phase images (34). Therefore, DCE MRI protocols should include sequences performed at least 360 seconds after contrast material administration for evaluation in patients who undergo postneoadjuvant treatment to accurately identify residual in situ disease and ensure accurate surgical planning (Fig 9).

Lymph Node Evaluation

Neoadjuvant therapy can be used to downstage the extent of disease in the breast to enable breast conservation therapy, and similarly, in patients with known axillary lymph node metastases, neoadjuvant therapy can be used to downstage the axilla, with pCR rates of 35%–68% in the lymph nodes (43). The sensitivity of postneoadjuvant therapy MRI to depict persistent lymph node metastasis is moderate, with studies reporting 61%–72% sensitivity (44,45). A study of patients with abnormal lymph nodes at pretreatment MRI, and subsequently with normal-appearing lymph nodes at posttreatment MRI, found that 32% had



a. b. c.

Figure 9. Partial imaging and pathologic response in a 58-year-old woman with a poorly differentiated ILC. **(a)** Axial contrast-enhanced T1-weighted subtraction MR image obtained before treatment demonstrates a heterogeneous mass in the breast (arrow) and enlarged axillary lymph nodes (arrowhead). **(b, c)** Axial posttreatment contrast-enhanced T1-weighted subtraction MR images from the first postcontrast series **(b)** and the last postcontrast series **(c)** demonstrate a marked decrease in the diameter of the mass with a few enhancing 0.5-cm foci in the tumor bed, which are best seen on the delayed image (arrows). Final pathologic analysis yielded multiple foci of residual ILC, with the largest measuring 0.5 cm.

metastatic disease in the axilla at surgery (46). Specificity of MRI is also moderate, as a study of patients with abnormal lymph nodes at posttreatment MRI found that only 58% were positive for lymph node metastasis at surgery (47). Abnormal lymph nodes at MRI appear distinct from other visible axillary lymph nodes, including those in the contralateral breast (48). Any of the following findings is abnormal: cortical thickening, loss of the fatty hilum, round shape, irregular margin, heterogeneous cortex, and surrounding edema. Lymph nodes can be considered normal when they are symmetric, are homogeneously enhancing, and have a thin cortex and preserved fatty hilum.

Management of the Axilla after Neoadjuvant Therapy.—In patients who are not treated with neoadjuvant chemotherapy, a preoperative biopsy-proven diagnosis of metastasis to an axillary lymph node traditionally entailed axillary lymph node dissection at the time of surgery, meaning excision of levels I and II axillary lymph nodes. However, this changed with the publication of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial in 2011, when axillary lymph node dissection was not shown to improve survival or local control compared with sentinel lymph node biopsy for patients with one or two lymph nodes with macrometastases and stage T1 or T2 primary tumor (49). In sentinel lymph node biopsy, only tumor-draining lymph nodes are identified and excised (usually one to four lymph nodes), making this procedure less morbid than axillary lymph node dissection, which carries the risk of lymphedema, seroma, and paresthesias.

The widespread acceptance of sentinel lymph node biopsy for patients with low-volume metastatic disease in the axilla brought into question whether sentinel lymph node biopsy might also be safe in patients with known axillary lymph node metastases treated with neoadjuvant therapy (6,48). For patients with no or low-volume residual disease in the axilla, the goal is to avoid axillary lymph node dissection because of the morbidity of this procedure. However, it was not initially known whether sentinel lymph node biopsy would accurately represent the volume of residual disease in the axilla. Therefore, two large prospective trials were undertaken. The ACOSOG Z1071 and sentinel lymph node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA) trials evaluated false-negative rates for sentinel lymph node biopsy compared with those for axillary dissection. The two trials found sentinel lymph node biopsy to have 12.6% and 14.2% false-negative rates, respectively, which were higher than the accepted rate of 10% and deemed clinically unsatisfactory (50,51). Attempts to reduce false-negative rates included retrieval of more than two sentinel lymph nodes and using dual-tracer techniques with both blue dye and radiolabeled colloid mapping agents.

Since then, the false-negative rate has been lowered further to 2%–7% by the development of the targeted axillary dissection technique (48,52). Sentinel lymph node biopsy may underrepresent residual disease when the sentinel lymph node is so packed with tumor cells that lymphatic flow is disrupted and the lymph node does not map during blue dye or radiolabeled colloid mapping.

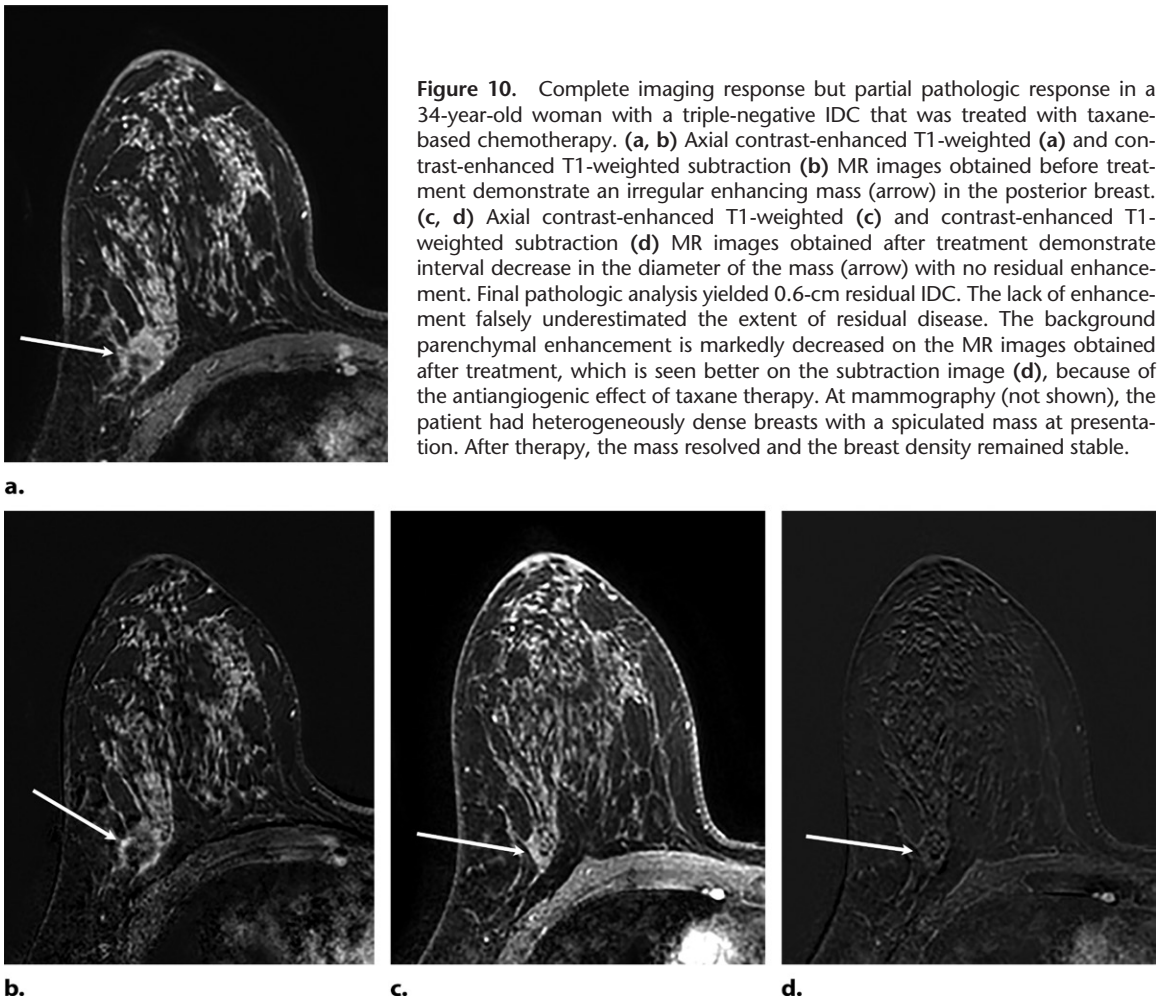


Figure 10. Complete imaging response but partial pathologic response in a 34-year-old woman with a triple-negative IDC that was treated with taxane-based chemotherapy. **(a, b)** Axial contrast-enhanced T1-weighted **(a)** and contrast-enhanced T1-weighted subtraction **(b)** MR images obtained before treatment demonstrate an irregular enhancing mass (arrow) in the posterior breast. **(c, d)** Axial contrast-enhanced T1-weighted **(c)** and contrast-enhanced T1-weighted subtraction **(d)** MR images obtained after treatment demonstrate interval decrease in the diameter of the mass (arrow) with no residual enhancement. Final pathologic analysis yielded 0.6-cm residual IDC. The lack of enhancement falsely underestimated the extent of residual disease. The background parenchymal enhancement is markedly decreased on the MR images obtained after treatment, which is seen better on the subtraction image **(d)**, because of the antiangiogenic effect of taxane therapy. At mammography (not shown), the patient had heterogeneously dense breasts with a spiculated mass at presentation. After therapy, the mass resolved and the breast density remained stable.

a. **b.** **c.** **d.**

In the targeted axillary dissection technique, the axillary lymph node that was biopsy-proven to be metastatic before therapy must be excised at the time of sentinel lymph node biopsy. Therefore, this lymph node must be localized by the radiologist with either wire localization or wire-free localization before surgery. Practically speaking, it is preferable to place a US-visible biopsy marker within the positive lymph node at the time of biopsy or soon after biopsy so the same lymph node can be identified after therapy and localized for excision (Fig 11).

Advanced Imaging Techniques

Diffusion-weighted Imaging.—Diffusion-weighted (DW) MRI is a nonenhanced method that may complement DCE MRI for evaluating tumor response to therapy (17) (Fig 12). DW MRI measures water mobility that is quantified by the apparent diffusion coefficient (ADC). An increasing ADC value after therapy is associated with cell lysis and necrosis, with larger increases in patients responding to therapy compared with those in nonresponders (6,17).

A large multi-institution clinical trial (ACRIN 6698) showed that change in ADC can help predict pCR, and that the course of tumor response differed across tumor subtypes (53). Change in ADC at midtreatment (at 12 weeks) MRI and posttreatment MRI were both predictive. Studies of multiparametric protocols have demonstrated that DW MRI can improve the accuracy of response prediction when added to DCE MRI, and that DW MRI is sensitive while contrast-enhanced MRI is specific in predicting pCR (13,54,55). There is a lack of standardization in the literature, but recommendations for clinical DW with *b* values of 0 and 800 sec/mm^2 have been published by a working group of the European Society of Breast Imaging (56).

Future Directions.—Radiomics, machine learning, and deep learning methods have been studied to predict response to therapy (57). As these techniques detect small changes in imaging parameters that are not visible to radiologists, they may be used to compare pretreatment MR images to early posttreatment MR images (obtained after only one or two cycles of chemotherapy). Studies

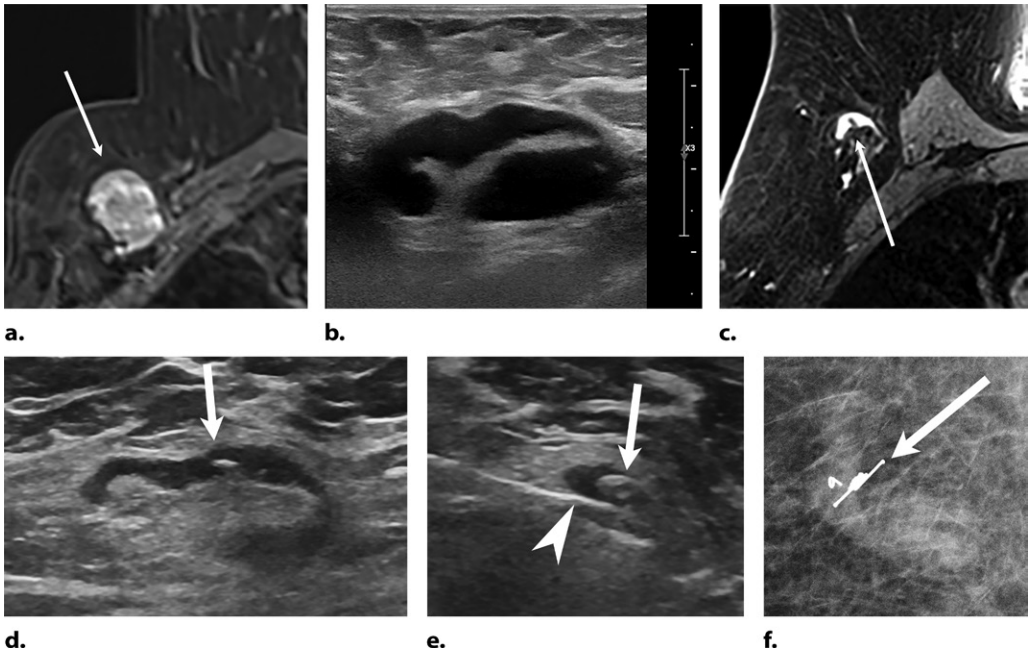


Figure 11. Management of the axilla in a 68-year-old woman with poorly differentiated IDC (ER negative, PR negative, HER2 positive) with a positive axillary lymph node. **(a)** Axial contrast-enhanced T1-weighted MR image obtained before treatment demonstrates an enlarged rounded axillary lymph node lacking a fatty hilum (arrow). **(b)** US image obtained before treatment demonstrates that the same lymph node is enlarged with a thickened cortex. The lymph node underwent fine-needle aspiration with a diagnosis of metastasis, and a biopsy marker was placed. **(c)** Axial contrast-enhanced T1-weighted MR image obtained after treatment demonstrates that the lymph node (arrow) is now normal in size with a thin cortex and contains artifact from the biopsy marker. **(d)** US image obtained after treatment demonstrates that the same lymph node is normal in size with a thin cortex and contains the hyperechoic biopsy marker (arrow). **(e)** US image shows how under US guidance, a Savi Scout reflector (Merit Medical) was placed into the lymph node (arrow) with a needle (arrowhead). **(f)** Mammogram demonstrates the Savi Scout reflector (arrow) adjacent to the biopsy marker within the lymph node. The lymph node was removed at the time of sentinel lymph node biopsy, yielding no residual carcinoma as well as treatment effect.

have found that even after one cycle of treatment, changes in size, enhancement, and heterogeneity of tumors were good predictors of response (58–60). Predicting response after only one or two cycles of treatment would be valuable, as medical oncologists could change the regimen early in treatment if it is not effective. However, predicting response at pretherapy imaging alone is the ultimate goal. This would allow clinicians to better plan the timing of surgery and to provide the patient with an individualized prognosis. Multiple radiomics and deep learning studies have attempted to predict pCR on the basis of pretreatment MR images, mostly evaluating kinetic, textural, and morphologic tumor features (57). Adding peritumoral and background parenchymal features improves performance when compared with tumor-specific features alone (61–63). Not surprisingly, studies have found that separating tumors into their subtypes improves accuracy and that different features are predictive in different tumor subtypes (61,64).

Machine learning and deep learning techniques have not yet achieved clinical applicability. These rapidly evolving methods may bring us closer to the goal of personalized breast cancer treatment, in which each patient receives tailored therapy with accurate prediction of treatment response and risk of relapse.

Conclusion

The sensitivity of MRI for depiction of residual disease is 63%–88% and the specificity is 54%–91% (17). Despite the imperfect sensitivity and specificity, MRI remains the most accurate imaging method to help assess tumor response to neoadjuvant therapy and to plan surgery, outperforming mammography, US, and clinical examination (4). Accurate surgical planning is important, not only to determine which patients are eligible for breast conservation or mastectomy, but also to decrease the positive margin rate and decrease surgical re-excision rates.

At MRI, the extent of residual disease may be overestimated because of enhancing benign foci of fibrosis or treatment change, enhancing benign masses, and residual nonenhancing masses representing treated tumor. The extent of residual disease may be underestimated at MRI because of tumors with nonmass morphology, such as invasive lobular carcinomas and luminal tumors,

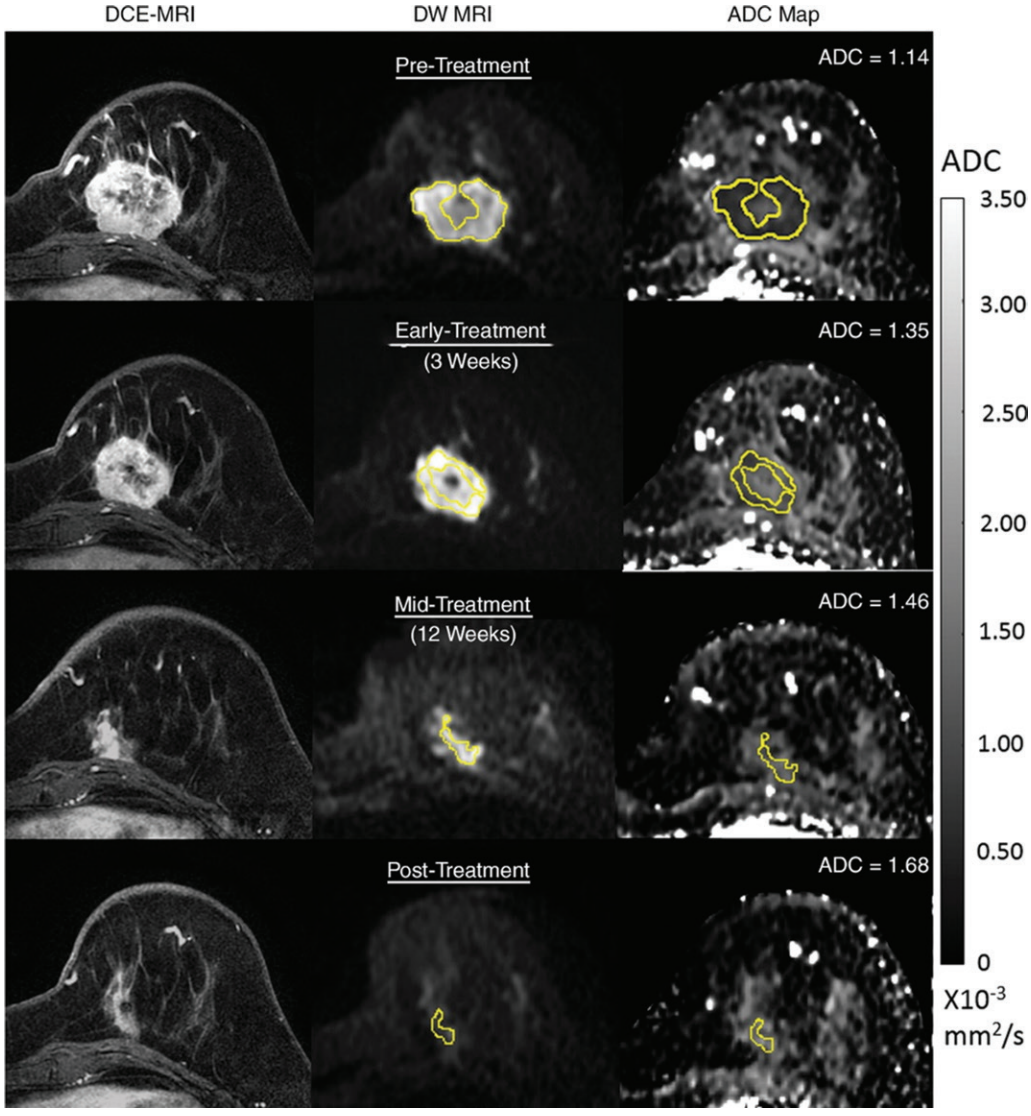


Figure 12. pCR in a 54-year-old woman who underwent neoadjuvant treatment of grade 3 triple-negative cancer. Images were obtained with a 3.0-T MRI unit. Axial DCE MR images (left column), nonenhanced DW MR images (b = 800 sec/mm^2) (middle column), and ADC maps (right column) show the response to treatment. At each time point, a whole-tumor region of interest (ROI) was defined across multiple sections at DW MRI, and mean ADC was calculated for all voxels in the composite ROI. The tumor manifested as a 4.2-cm mass on pretreatment DCE MR images (top row), and the ROI was defined to avoid a central necrotic region. Serial ADC measurements increased progressively with treatment, with the following percentage changes in ADC from the pretreatment value: 18% at early treatment (3 weeks), 28% at midtreatment (12 weeks), and 47% at posttreatment. (Adapted and reprinted, with permission, from reference 53.)

which are more difficult to accurately measure. Similarly, tumors with nonconcentric shrinkage patterns leaving behind small scattered residual disease may be undermeasured. Treatment with antiangiogenic chemotherapy can falsely decrease enhancement of residual tumor, leading to underestimation of residual disease. Readers must also be aware of the possibility of late-enhancing foci, which are more common in luminal tumors and nonconcentrically shrinking tumors and often represent residual DCIS.

As neoadjuvant therapy decreases the burden of disease in the breast, it may also decrease the burden of disease in the axilla and allow patients with known axillary metastatic disease to avoid axillary lymph node dissection. If imaging demonstrates response to therapy in the axilla, then patients may be eligible for targeted axillary dissection, in which the radiologist localizes the previously biopsied positive lymph node for excision along with the sentinel lymph nodes.

In the future, radiomics, machine learning, and deep learning methods may improve our ability to predict response to therapy, perhaps before treatment even begins.

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