Published in final edited form as:

NMR Biomed. 2011 July ; 24(6): 712–720. doi:10.1002/nbm.1739.

MRI in breast cancer therapy monitoring

Rebekah McLaughlin^a and Nola Hylton^{a,b,*}

^aThe UC Berkeley–UCSF Graduate Program in Bioengineering, University of California San Francisco and University of California Berkeley, CA, USA

^bDepartment of Radiology and Biomedical Imaging, University of California San Francisco, CA, USA

Abstract

Breast MRI has several roles in the clinical management of breast cancer, including as a screening method for high-risk women, as a diagnostic tool used as an adjunct to mammography and ultrasound, and for the staging of disease extent prior to treatment. In addition to these uses, MRI is also employed to track small changes in tumor size and microenvironment. MRI has produced several early indicators of treatment response in clinical trials over the last 10 years, including initial lesion pattern, changes in lesion size, kinetic parameters, apparent diffusion coefficient and T_2 value; the related technique of ^1H MRS has also shown that choline concentration, T_2 value and water-to-fat ratio are response indicators. In addition to measuring anatomical changes in the lesion size, as performed in traditional radiology, MRI has the ability to track vascular and cellular changes using dynamic contrast-enhanced MRI and diffusion-weighted MRI, respectively. By adding ^1H MRS to MRI examinations, metabolic changes can also be determined. These functional imaging techniques allow studies to focus on early time points relative to neoadjuvant treatment. Early treatment response predictors may allow therapy to be tailored to individual patients and thus aid in the realization of the goal of personalized medicine.

Keywords

MRI; breast cancer; neoadjuvant chemotherapy; treatment monitoring; dynamic contrast-enhanced imaging; diffusion-weighted imaging; ^1H MRS

INTRODUCTION

Over the past 20 years, MRI has emerged as an important diagnostic tool for breast cancer. Relative to conventional methods of breast imaging, mammography and ultrasound, MRI has shown greater sensitivity to breast cancer, with moderate and variable specificity. Considered in the light of its technical complexity, limited ability to guide biopsy and high cost, the benefit of MRI for breast cancer management is not firmly established and continues to be debated. However, a clear advantage of MRI over conventional techniques is

*Correspondence to: N. Hylton, Department of Radiology and Biomedical Imaging, University of California San Francisco, 1600 Divisadero St., Room C255, Box 1667, San Francisco, CA 94115, USA. nola.hylton@radiology.ucsf.edu.

its superior accuracy for demonstrating the size and extent of cancer in the breast (1–15). This information is essential for disease staging and treatment determination.

The last two decades have also seen a shift in the treatment of invasive breast cancer with the administration of chemotherapy prior to (neoadjuvant) rather than following (adjuvant) surgery for those women requiring systemic therapy. Systemic chemotherapy improves survival for patients with invasive breast cancer. It is considered to be the standard of care for node-positive patients with large primary tumors and is used for many patients with high-risk node-negative disease (16). The National Surgical Adjuvant Breast and Bowel Project B-18 and other clinical trials comparing neoadjuvant and adjuvant chemotherapy found no difference in disease-free or overall survival; however, more women receiving preoperative chemotherapy were able to undergo breast conservation (17,18). These findings have led to the increased use of neoadjuvant chemotherapy. Further findings from these studies have demonstrated that the response of the primary tumor to treatment, as measured clinically or by histopathology, is predictive of disease-free and overall survival (17,18). The National Surgical Adjuvant Breast and Bowel Project B18 found significant disease-free and overall survival differences among women demonstrating complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) determined by clinical examination. Thus, an additional advantage to preoperative chemotherapy over postoperative chemotherapy is that it provides the opportunity to monitor the primary tumor response.

A natural hypothesis arising from these two sets of evidence is that the greater accuracy of MRI for staging the extent of the primary tumor will translate into greater ability of MRI over clinical or conventional imaging assessment to predict the risk of recurrence following neoadjuvant chemotherapy. A secondary hypothesis, and perhaps more significant in the emerging paradigm of individually tailored treatments, is that MRI can accurately measure response early during the course of neoadjuvant treatment and thereby guide treatment modifications for patients not on a trajectory to a good response. According to Schegerin *et al.* (19), if the use of imaging to track treatment response leads to chemotherapeutic regimen changes that result in a notable benefit for patients, neoadjuvant imaging is cost-effective: ‘As long as the initial chemotherapy was less than 90% effective, most imaging systems would be cost effective, and if the cure rate of the disease could be increased as little as 1% through a change to alternate therapy, then the cost effectiveness of the system would be acceptable.’

Although X-ray mammography and physical examination are the standard of care and routinely used as screening methods for breast cancer, they are ineffectual for tracking subtle lesion changes in response to chemotherapy. MRI is a three-dimensional imaging technique with high sensitivity and resolution. It does not expose the patient to ionizing radiation, allowing it to be used repeatedly during treatment and making it effective for monitoring the response to therapy. Several MRI approaches have been used to monitor breast cancer treatment response, including standard contrast-enhanced MRI and more advanced functional MRI techniques, such as dynamic contrast-enhanced (DCE) MRI and diffusion-weighted (DW) MRI. ¹H MRS is a technique related to MRI and, although it is not technically an MRI technique, it is often grouped with DCE MRI and DW MRI as a functional imaging technique used to monitor treatment response. Many studies have

focused on the measurement of changes early during the course of neoadjuvant treatment because effective predictors of response could save the patient from ineffective treatment (4). Because radiological imaging has traditionally followed anatomical changes, the most commonly used MRI indicator is the change in lesion size based on the enhancing area after contrast injection. However, DCE MRI, DW MRI and spectroscopy reflect different aspects of cancer biology and thus provide additional information regarding a lesion's response to treatment. Recent advances in technology have made these functional imaging methods more practical for clinical implementation. This review focuses on the results of clinical studies from the last 10 years that have evaluated various MRI techniques for monitoring the response to therapy.

STAGING OF RESIDUAL DISEASE

Breast MRI is effective for the measurement of residual disease after a full course of neoadjuvant chemotherapy, making it useful as a surgical planning tool (4–15,20–26). Several studies have compared MRI with mammography, physical examination and/or ultrasound for the measurement of residual disease after neoadjuvant chemotherapy. In two studies of 32 and 68 patients, respectively, Bhattacharyya *et al.* (15) and Segara *et al.* (14) found that MRI was superior to clinical examination and ultrasound for the assessment of the post-chemotherapy, pre-surgical tumor size, as determined by agreement with histopathology. Bhattacharyya *et al.* (15) also attempted to compare tumor size determined by MRI and mammography, but found that mammography was unable to define the tumor margins in 18 of the 32 patients. Generally, MRI was found to be superior to other standard techniques for the determination of the extent of residual disease in numerous studies (4–15).

To assess the accuracy of MRI in the measurement of residual disease, clinical studies have compared the pre-surgical lesion size determined by MRI with the current gold standard: pathological lesion size after surgery (4–9,11–15,20–26). Most studies determined that the correlation coefficient (r) of MRI size to pathological size was 0.7–0.8 (8–11,14,15,27,28). However, one study found a lower correlation value of 0.6 (20), and a few studies reported a very high correlation coefficient of 0.9 or above (5,13,21). Although the correlation coefficient ranged in value among the studies, all of the studies found that tumor size determined by MRI correlated significantly with pathological size.

However, several studies have provided examples of MRI significantly underestimating (4,8,9,11,14,29,30) or overestimating (4,8,9,14,15,22,23) residual tumor extent. Rosen *et al.* (8) found that, in 21 patients, MRI overestimated the residual tumor size by more than 1 cm in seven patients and underestimated the residual tumor size by more than 1 cm in two patients. They attributed the underestimation to decreased contrast enhancement on post-chemotherapy MRI. Rosen *et al.* (8) believed that this effect was overcome in the cases in which they overestimated the residual tumor size because of the diffuse nature of the malignant tissue in these cases. Kim *et al.* (23) attributed MRI overestimation and underestimation to the pattern of tumor response. They observed more accurate MRI size measurements in a shrinking mass as opposed to a nest or rim pattern of disease.

Some studies have observed general trends in overestimation or underestimation. In a study of 58 patients, Rieber *et al.* (29) found that MRI tended to underestimate the residual size of tumors, especially in patients who responded well to chemotherapy. This finding may be caused by the lack of signal observed in contrast-enhanced MRI as a result of the significant decrease in size of the lesion, reduced vascular function of the tumor or a greater effect of partial volume averaging in the case of disseminated residual disease. Londero *et al.* (10) examined the change in mean diameter of the tumor and observed that MRI overestimated the residual size but not significantly. In a study of 208 patients, Straver *et al.* (31) created an MRI model to guide surgery following neoadjuvant chemotherapy; however, they found that MRI significantly underestimated the tumor size in 35 patients (17%), which would have led to an incorrect indication of breast-conserving surgery in 27 patients (13%). Although MRI size shows significant correlations with pathological size in residual tumor, it is not absolutely accurate, and therefore the absence of residual tumor in MR images cannot obviate surgery.

MEASUREMENT OF TUMOR RESPONSE

Standard methods for the quantification of changes in lesion size are required for the monitoring of tumor response with imaging, clinical examination or pathology. A single diameter is the simplest measurement and the current standard based on guidelines of the World Health Organization (WHO). The original WHO criteria grouped lesion response into four groups: CR, PR, no change (NC) and PD. Although the criteria were based on unidimensional measurement, the WHO guidelines recommended the measurement of the longest diameter and perpendicular diameter and the calculation of the tumor area whenever possible (32). The original WHO criteria defined CR as the total disappearance of invasive cancer, PR as a decrease of 50%, PD as an increase of 25% and NC as the level between PR and PD (32). The Response Evaluation Criteria for Solid Tumors (RECIST) is the updated standard method for measuring the response to treatment (33). Based on the maximum diameter, RECIST defines CR as the total disappearance of target lesions, PR as a decrease of 30%, PD as an increase of 20% and stable disease (SD) as the level between PR and PD (33). The RECIST update has not eliminated discrepancies between therapeutic response definitions among breast MRI studies, and many still use a bidimensional measurement.

Although it is recognized that a volumetric measurement is likely to give a better estimate of tumor extent than single or bidirectional linear dimensions, manual measurement of the volume from cross-sectional images is considerably more difficult and automated approaches are not generally available. A number of recent studies have used volumetric approaches to measure breast tumor response by MRI (27,28,34–44). In a study of 30 patients, Martincich *et al.* (27) found that MRI tumor volume yielded less false positive results than the product of the orthogonal maximum diameters measured by palpation, mammography and/or ultrasonography. Using MRI volume instead of the product of the maximum diameters allowed the specificity to be increased from 53% to 84% and the positive predictive value from 53% to 77% (27). In 58 patients undergoing neoadjuvant chemotherapy, Partridge *et al.* (38) found that initial MRI volume was the strongest predictor of recurrence-free survival ($p = 0.002$), performing better than initial MRI

diameter ($p = 0.003$) and initial clinical examination ($p = 0.033$); they also found that the final change in MRI volume ($p = 0.015$) was more predictive of recurrence-free survival than was the final change in MRI diameter ($p = 0.077$) or the final change in palpated diameter ($p = 0.27$).

Despite these findings, the use of volume to measure lesion size has not yet been endorsed by a major organization, and there is no standard method for the determination of volume. Investigators have used many different methods to determine MRI volume, from computer-generated three-dimensional estimates (22,27,28,38,39) to the sum of areas of each slice multiplied by the slice thickness (34,35,37,43,44) to the calculation of the volume using the average diameter in a sphere equation (28). Lorenzon *et al.* (28) compared two MRI volume determination methods (calculating the volume with the average diameter in the equation $V=4/3\pi r^3$ versus three-dimensional imaging software), and found that the two methods produced significantly similar results.

In addition, there are no clear guidelines for determining the response with volume measurements as a result of the exclusion of volume from the RECIST guidelines. The 2000 RECIST guidelines noted that, although volumetric methods have the potential to be more effective, the techniques were 'not yet widely available, and many have not been validated' (33). Some volume studies use the volume cut-offs for tumor response given in the RECIST appendix: 65% decrease for PR and 20% increase for PD (28,34,37,40,42). Martincich *et al.* (27) used their volume and pathological response data to calculate a cut-off value from a receiver operating characteristics analysis; from their experimental data, they also determined that a decrease of 65% indicated a responder. Not all studies utilize a decrease of 65% to determine response. Chang *et al.* (35) and Sharma *et al.* (43) used a volume decrease of 50% to define responders. This is similar to the WHO criteria of a bidimensional decrease of 50% for PR; Chang *et al.* (35) compared the volume response with the bidimensional response and found a correlation coefficient of $r = 0.93$. Thus, one major translational challenge is to standardize volume response definitions in a clinical setting.

The argument for using volume rather than diameter is particularly compelling for lesions that are irregular in size and shape, such as lobular carcinomas. For diffuse lesion patterns, the utilization of diameter to determine size can be extremely insensitive. Chen *et al.* (30) saw that 'a patient with lobular cancer had a 0.5 cm residual tumor [by MRI], but this patient actually had scattered residual cancer cells distributed throughout a 6.0 cm region by histopathology'. In such cases, volume may prove to be a more accurate measure. However, despite its possible superiority to diameter for the determination of the therapeutic response, volume calculations are a metric based on criteria for signal enhancement and may not be a true reflection of the absolute volume of the tumor. Unlike maximum diameter, volume cannot be easily determined by clinical examination, mammography or pathology. Thus, MRI volume determination must be rigorously tested in large, multicenter clinical trials before it can be used instead of diameter as the standard for tumor response measurement.

PREDICTION OF THE TREATMENT RESPONSE

Findings in several studies have shown equivalent survival outcomes with preoperative and postoperative chemotherapy (17,18,45,46). As a result, the use of neoadjuvant chemotherapy has increased as it favors breast-conserving surgery. A consequence of this development is the need for better monitoring methods to ensure that lesions are responding rather than progressing whilst surgery is delayed by neoadjuvant chemotherapy. Although MRI following treatment is useful for surgical planning, early indicators of response during neoadjuvant therapy may allow better treatment strategies for individual patients by providing noninvasive tracking of primary tumor characteristics.

Ultimately, an increase in disease-free, recurrence-free or overall survival is the goal of breast cancer treatment. However, few breast MRI studies have included survival rates as their outcome measure because of the time and cost requirements to obtain this endpoint. The studies that have tracked survival have shown that MRI has predictive value (25,38,44). Because pathological response determined after surgery has been shown to be a good indicator of survival (17,47,48), it is the most established response endpoint. However, many neoadjuvant breast MRI studies have defined the response endpoint by other clinical or histopathologic measures, clinical examination or MRI size change.

Breast MRI has the potential to track small changes in tumor size and microenvironment, which would be useful for the monitoring of response to therapy during the course of treatment. Thus, several MRI indicators are being evaluated for treatment response assessment in clinical trials. MRI features that have been shown to be correlated with clinical response include initial lesion morphological pattern, changes in lesion size, enhancement kinetic parameters, apparent diffusion coefficient (ADC) and T_2 values. Choline concentration, T_2 values and water-to-fat ratio, measured by ^1H MRS, have also shown a correlation with response. These indicators are discussed in the following sections.

Contrast-enhanced breast MRI

Radiologic imaging traditionally tracks the responsiveness of a cancer to treatment by measuring anatomical changes in the lesion size. For breast imaging, the sensitivity of MRI allows for more accurate lesion pattern and size assessment than does mammography, physical examination or ultrasound. Breast MRI studies use contrast enhancement to detect breast lesions and define their extent. Gadolinium-based contrast agents, which shorten the T_1 and T_2 of tissue, are used in combination with T_1 -weighted imaging to highlight areas with increased vessel density and/or permeability. Because malignant lesions have poorly developed and leaky microvasculature, the intravenously injected contrast agent concentrates in the lesion faster than in the surrounding breast tissue. Therefore, as long as the image acquisition is timed to quickly follow the injection of contrast, MRI will produce an image in which the lesions appear as the brightest tissue within the breast.

Changes in lesion size can be used to predict pathological response to neoadjuvant treatment (7,9,10,14,21,27,28,30,37,40,42–44,49–55). Figure 1 shows an example of a breast lesion shrinking in response to neoadjuvant chemotherapy. This patient demonstrated significant tumor size reduction – a 72.6% decrease in volume – after the first of four cycles of

adriamycin–cytoxan chemotherapy and went on to have a complete clinical response by palpation. Using a functional volume measurement based on enhancement criteria, the final MRI shows a residual tumor volume of 0.174 cm³. The small amount of residual disease seen on the final MRI was supported by histopathology following surgery, which showed 2mm of residual tumor. Padhani *et al.* (50) also showed that early changes in lesion size during neoadjuvant chemotherapy are predictive of pathological response. They found a significant lesion size decrease in 12 of 14 responders and NC or an increase in six of seven nonresponders, 21 days after the start of treatment; in addition, several other studies have found a significant size change after the first cycle of chemotherapy (21,44,51). Significant changes in lesion size have also been observed after the second cycle of chemotherapy (27,40,42,43,49). However, in a study of 35 patients, Baek *et al.* (55) found that changes in lesion size were not significant 20 days after the start of treatment, but were significant at 69 days; several other studies did not observe significant results after the first cycle, but did so after the second and/or third cycle (42,43,49).

Although many studies have shown correspondence between pathological response and changes in early lesion size (21,27,40,42–44,49–51), not all of these studies produce images of the same quality. Clinical MR images typically fulfill the requirements of submillimeter spatial resolution, homogeneous fat suppression and full bilateral coverage. The achievement of this image quality makes it easier for radiologists to assess lesion morphology, including size, shape, margins and internal enhancement pattern, the clinical criteria used for diagnosis according to the American College of Radiology MRI-BIRADS (56). In addition to size changes, the three-dimensionality of high-quality MR images allows the accurate depiction of the initial lesion pattern, which Esserman *et al.* (57) found could predict treatment response. They found that the five distinct lesion pattern categories shown in Fig. 2 were predictive of response to neoadjuvant chemotherapy. The unicentric mass lesions in category 1 responded the best to treatment, whereas category 5 septal spread lesions responded very poorly (57). Because the quality of MR images is related directly to clinical utility, a challenge for new MRI techniques is to maintain high image quality standards whilst providing functional information.

DCE breast MRI

Functional MRI techniques provide information that can be useful for the characterization of the biologic properties of tumors. These techniques gain information from a series of images, rather than a single, static MR image. The most basic example of this is DCE MRI, which follows the passage of the contrast enhancement through the tissue over time. DCE MRI is essentially vascular information because the flow of contrast agent through the blood vessels is being imaged in real time.

The previous section discussed the use of contrast enhancement to create an image that highlights the lesion locations in the breast. By collecting a rapid succession of MR images before and after contrast injection, a kinetic curve of tissue enhancement can be mapped, as shown in Fig. 3. The dynamic flow of the contrast agent through each type of tissue gives information about the vasculature in that tissue. As mentioned previously, malignant lesions have poorly developed and leaky microvasculature, which causes the contrast agent to

quickly pool in the lesion and then escape. Benign lesions, however, have more normal vasculature, and the contrast agent concentration steadily increases in this tissue until it is saturated, at which point the concentration plateaus. By mapping the dynamic contrast enhancement over time, various types of tissue can be distinguished by their differing vasculature.

However, as a result of hardware limitations, DCE MRI must compromise between image quality – signal-to-noise ratio (SNR), spatial resolution, volume coverage – and temporal resolution. This amounts to choosing either images at many time points, producing a kinetic plot of the enhancement, or better resolved images at a few time points, which allows for greater anatomical accuracy but little kinetic information. Bluemke *et al.* (58) reported the results of the International Breast MRI Consortium multicenter trial of 821 patients, and concluded that DCE MRI did not improve the diagnostic ability over three-dimensional contrast-enhanced MRI alone; however, in other studies, changes in kinetic parameters obtained from DCE MRI curves have shown significance for the prediction of the therapeutic response (25,27,29,34,35,37,39,40,44,50–53,59–62).

In kinetic MRI studies, sufficient DCE MR images must be acquired quickly to accurately plot the kinetic curve. Study protocols have been reported, ranging from a 1–2-min temporal resolution for three to six time points (25,27,29,52) to 42–56-s temporal resolution for 10–16 time points (39,44,51,61,62) to 8–23-s temporal resolution for 26–50 time points (34,35,37,40,50,53,59,60). After fitting the dynamic images to a kinetic curve, some investigators attempted to calculate pharmacokinetic parameters using a pharmacokinetic model (34,35,37,39,40,50,51,53,59,60,62), whereas others chose to use heuristic kinetic parameters (25,27,29,44,52,61).

In 1997, Tofts (63) reviewed several models of DCE MRI tracer kinetics adopted from pharmacokinetic models. Tofts (63) showed that all of the models measured some combination of three parameters – the volume transfer constant K^{trans} (min^{-1}), the volume of extravascular extracellular space per unit volume of tissue v_e ($0 < v_e < 1$) and the flux rate constant between the extravascular extracellular space and plasma k_{ep} ($k_{\text{ep}} = K^{\text{trans}}/v_e$). Tofts *et al.* (64) proposed to standardize k_{ep} , K^{trans} and v_e as the main kinetic terms for DCE MRI tracer models; the terms denoted by Tofts *et al.* are often used to describe the dynamic uptake curve parameters in breast DCE MRI studies (40,50,51,53,62). Tofts' model requires that T_1 and the arterial input function be estimated. An extra scan is needed to determine T_1 . The arterial input function can only be estimated if the signal intensity can be measured in an artery that is visible in the imaging field of view. The procedure for calculating T_1 and the arterial input is not standard and requires more imaging time, which is an additional burden and a greater limitation on the total MRI time. However, it is important to carefully calculate these parameters. Armitage *et al.* (39) showed that inaccurate measurements of T_1 can produce 'false enhancement' and show significance between the therapeutic response and pharmacokinetic changes when there is none. This group presented a more reliable method for measuring T_1 for their pharmacokinetic model.

Reports based on pharmacokinetic modeling have found that decreases in K^{trans} (37,50,51,53,62), k_{ep} (37,51,60) and the amplitude of signal enhancement (53,60) are

significant for treatment response, whereas an increase in v_e (37,62) is significant for nonresponse. After two cycles of chemotherapy in 28 patients, Ah-See *et al.* (53) found that changes in K^{trans} , k_{ep} and v_e , as well as maximum contrast concentration, relative blood volume, relative blood flow and mean transit time for contrast to pass through tissues, correlated significantly with clinical and pathological response, even though changes in lesion size were not significant at that time point.

Because of the difficulty in measuring accurately the pharmacokinetic parameters, some investigators have chosen to use heuristic kinetic parameters; these studies have shown that general reductions in enhancement correlate with response to treatment (27,29,44,61). Partridge *et al.* (38) found that MRI volume quantified using the signal enhancement ratio, rather than the full kinetic curve, was able to predict recurrence-free survival. Loo *et al.* (52) looked at a variety of variables related to timing of the contrast enhancement, including washout. They found that analysis of the fast (10 s after injection) and late (450 s after injection) enhancement of the lesion produced several significant parameters relative to response to therapy; the most significant of these parameters was the change in maximum diameter of the late enhancement after the second chemotherapy cycle. Johansen *et al.* (44) calculated the relative signal intensity and area under the enhancement curve, and found that both parameters were reduced significantly after the first cycle of chemotherapy in patients who responded clinically. Hattangadi *et al.* (25) used the signal enhancement ratio to quantify contrast washout in the stromal tissue and showed its significance for the prediction of disease-free survival. Regardless of the quantification approach used, it is clear that kinetic parameters have the potential to provide additional information about treatment response.

DW breast MRI

DW imaging, another type of functional imaging, captures cellular information from MRI using motion-sensitizing gradients. DW imaging measures the water mobility that results from thermally induced random motion (also known as Brownian motion) which naturally occurs in tissues. It is possible to extract a quantitative parameter, ADC, from DW imaging. ADC has been shown to correlate with tissue cellularity; ADC is typically lower in lesions relative to normal tissue, which is generally attributed to the increased cell density associated with cancerous tissue (65).

In a DW sequence, a diffusion gradient is applied to dephase the protons and, after some time () has passed, an identical diffusion gradient is applied to rephase the protons. The movement of the protons during , quantified as the ADC value, is proportional to the diffusion gradient strength. The ADC value is then calculated from the data using $ADC = -\ln[S(b)/S(0)]/b$, where $S(0)$ denotes the signal intensity with no diffusion gradient, b is a term determined by the magnitude and duration of the diffusion-sensitizing gradient applied and $S(b)$ is the signal intensity resulting from the application of the diffusion gradients determined by the b value (49,62). The most important acquisition parameter for DW MRI is the b value, which has inverse units to ADC and represents the overall sensitivity of the pulse sequence to motion.

ADC is calculated from at least two images that have different known b values. These images are used to solve the equation in the previous paragraph for ADC. In breast DW MRI, two b values are typically acquired. Ideally, more b values would be acquired, but each additional b value increases the acquisition time. In addition, b values that require stronger gradients produce less SNR in the image. Because DW MRI typically uses an echo planar imaging acquisition, the images already have lower SNR and resolution than typical contrast-enhanced MR images. Thus, DW images cannot replace DCE MR images, and DW MRI is being evaluated to determine the value of the cellular information gained from ADC maps.

Studies have found that increases in ADC values predict response to treatment (43,49,62). Sharma *et al.* (43) showed that the mean percentage increase in ADC values using $b=0$, 500 and 1000 s/mm², measured before treatment and after the first cycle of chemotherapy in nine patients, was significantly higher in responders *versus* nonresponders. The mean percentage decrease in both MRI diameter and volume, measured before treatment and after the first cycle, was not predictive of response. In a 10-patient study, Pickles *et al.* (49) used $b=0$ and 700 s/mm² and also saw significance in ADC and treatment response as early as the first chemotherapy cycle, whereas significant changes in lesion diameter were not observed until after the second cycle. Yankeelov *et al.* (62) conducted a study of T_1 , ADC and DCE MRI parameters in 11 patients. Using $b = 0$ and 300 s/mm², they found that ADC and K^{trans} were the most sensitive to the therapeutic response. Sharma *et al.* (43) suggested that the increase in ADC after treatment may be caused by cell damage from therapy, which compromises the cell membrane and allows greater mobility within cells. If the increasing ADC values are a result of therapy-induced cell damage, the type of therapy and the duration of treatment of the patient could affect the magnitude of the ADC increase.

A more advanced approach is diffusion tensor imaging (DTI). Beyond measuring the magnitude of diffusion, DTI provides information on the directionality of diffusion in tissue(s). It has been used extensively in the brain to map neuronal networks. However, DTI has not been used to any great extent in the breast.

Breast ¹H MRS

Although the majority of the MR signal arises from fat and water protons, spectroscopic techniques can be used to distinguish additional metabolites by utilizing the small magnetic field differences created by their protons. ¹H MRS is used more extensively in other organs, such as the brain, prostate and liver, but also has application in breast cancer. The most common metabolite associated with malignancy that can be measured with *in vivo* ¹H MRS is choline. Breast lesions demonstrate elevated levels of choline-containing compounds – free choline, phosphocholine and glycerophosphocholine – relative to normal breast tissue. These separate choline compounds are not usually distinguishable *in vivo* and generally are measured as a single total choline (tCho) peak at 3.2ppm (66). The tCho peak is mostly attributed to elevated phosphocholine levels as a result of several metabolic changes in malignant tissue (67).

Although studies have shown that tCho concentrations from proton spectroscopy are indicators of treatment response (55,68–70), progress in breast ¹H MRS has been retarded

by the technical difficulties of acquiring spectroscopic data. These challenges include a low concentration of tCho *in vivo*, a highly variable fat content in the breast, an inhomogeneous magnetic field because of the air–tissue interface of the breast and biopsy clips, and the difficulty in quantifying a single visible metabolite. For these reasons, both diagnostic and therapy-responsive breast ^1H MRS, unlike other organs, typically uses a single voxel instead of multiple voxels, although several multivoxel studies in breast have been published (70–72). Single-voxel ^1H MRS lacks spatial localization of tCho signals in different parts of the lesion, which means that the heterogeneity of the tumor is not represented.

MRS monitoring of the treatment response in other organs usually relies on changes in the ratio of specific metabolites. In the breast, only tCho, fat and water concentrations are visualized by proton spectroscopy. Bolan *et al.* (73) developed a method to utilize water as an internal reference signal to determine the tCho concentration. Their approach compensates for the partial volume of fat that is inevitably included in the voxel because of the structure of breast tissue and requires the water peak to be thoroughly characterized. Baik *et al.* (74) adapted this method for use in a diagnostic study of 34 patients at 1.5 T and found similar results to Bolan *et al.* (73).

In normal breast tissue, tCho is not usually detected *in vivo* because it is present at less than 1.05 mmol/kg according to Meisamy *et al.* (66); they calculated that the detected tCho concentration in lesions is in the millimolar range. Thus, the acquisition parameters must be optimized in order to improve detection. In particular, the homogeneity of the magnetic field must be optimized in order to obtain the sharpest linewidths possible. This process can be difficult because of magnetic field inhomogeneities in the breast tissue caused by the proximity to the air–tissue interface and biopsy clips inserted in the center of the lesion. Most investigators attempt to avoid the skin and biopsy clip whilst still covering as much of the lesion as possible with a single voxel; this can be difficult depending on the shape and orientation of the lesion. In addition, as the lesion shrinks during neoadjuvant chemotherapy, it can become more difficult to place the voxel over the lesion whilst avoiding the clip.

Voxel placement is further complicated by the variability of fat and water in breast tissue. In some women, the presence of fat in the breast tissue can be extensive, producing a large fat peak in the spectroscopy data. A large broad fat peak can overlap the tCho peak. Thus, fat suppression is a critical issue in breast ^1H MRS. In addition, if the fat peak is much larger than the tCho peak, sidebands caused by the fat can begin to overlap the tCho signal. Bolan *et al.* (75) solved this problem with TE averaging of the spectrum to ensure that the sidebands were eliminated. Ideally, the spectroscopic region of interest would not include fat; however, because of the composition of the breast, it is often difficult to exclude all fat from the spectroscopic voxel.

Another challenge to ^1H MRS is that no commercial software exists for MRI spectroscopy analysis. Each study that monitors MRS utilizes a different, in-house software program to analyze the data. MRS is similar to volume measurements in this respect: a major translational challenge is to find a method to calculate the tCho concentration easily and reproducibly in a clinical setting and to standardize clinical platforms. However, improvements in clinical ^1H MRS of other organs, such as the use of higher magnetic fields

and improved fat suppression, may also advance breast ^1H MRS. As the utility of breast proton spectroscopy for treatment response monitoring is validated, the translational problems will be addressed and the technique will become more clinically available.

Despite these challenges, several studies have found that a reduction in tCho concentration generally indicates that a lesion is responding to therapy (55,68–70). In data from 13 patients, Meisamy *et al.* (69) showed significant tCho concentration decreases in responders as early as 24 h after the start of chemotherapy. In the only multivoxel therapy response study to date, Danishad *et al.* (70) saw a significant SNR decrease in tCho of responders.

^1H MRS is also capable of measuring the water-to-fat ratio, and some investigators have linked changes in the water-to-fat ratio to the therapeutic response (40,41,76). Jagannathan *et al.* (76), Manton *et al.* (40) and Kumar *et al.* (41) showed that the water-to-fat ratio, which is elevated in malignant tissue, decreases in response to therapy. This ^1H MRS technique is less demanding than choline monitoring because water and fat have a much greater SNR because of the high concentrations in breast tissue. However, the biochemical relevance of the water-to-fat ratio to tumor cell viability has yet to be adequately explained.

Changes in the T_2 value of water, which can be measured by ^1H MRS and T_2 -weighted MR images, have also shown significance for the prediction of the therapeutic response; Manton *et al.* (40) and Tan *et al.* (42) have shown a decrease in the T_2 value of water with response to therapy. Like the water-to-fat ratio, a clear explanation of why water T_2 values decrease has not been determined. Indeed, Tan *et al.* (42) proposed that the decrease in water T_2 values may be linked to the decrease seen in the water-to-fat ratio. Both of these predictors need additional research and background in order to be used for therapeutic response monitoring.

CONCLUSIONS

Breast MRI has shown the ability to track small changes in tumor size and microenvironment and has produced several indicators of treatment response in clinical studies over the last 10 years. These indicators include initial lesion pattern (57), changes in lesion size (7,9,10,14,21,27,28,30,35,37,40,42–44,49–55,61), kinetic parameters (25,27,29,34,35,37,39,40,44,50–53,59–62) and ADC (43,49,62), as well as choline concentration (55,68–70), T_2 value (40,42) and water-to-fat ratio (40,41,62) obtained from ^1H MRS.

MRI can measure anatomical changes in lesion size as performed in traditional radiology. Functional imaging can track vascular, cellular and metabolic changes using DCE MRI, DW MRI and MRS, respectively. These functional imaging techniques allow studies to focus on early time points relative to neoadjuvant treatment. Early treatment response predictors may allow therapy to be tailored to individual patients and thus help to realize the goal of personalized medicine.

Abbreviations used

ADC	apparent diffusion coefficient
CR	complete response
DCE	dynamic contrast-enhanced
DTI	diffusion tensor imaging
DW	diffusion-weighted
NC	no change
PD	progressive disease
PR	partial response
RECIST	Response Evaluation Criteria for Solid Tumors
SD	stable disease
SNR	signal-to-noise ratio
tCho	total choline
WHO	World Health Organization

References

1. Boetes C, Mus RD, Holland R, Barentsz JO, Strijk SP, Wobbes T, Hendriks JH, Ruys SH. Breast tumors: comparative accuracy of MR imaging relative to mammography and US for demonstrating extent. *Radiology*. 1995; 197:743–747. [PubMed: 7480749]
2. Harms SE, Flamig DP, Hesley KL, Meiches MD, Jensen RA, Evans WP, Savino DA, Wells RV. MR imaging of the breast with rotating delivery of excitation off resonance: clinical experience with pathologic correlation. *Radiology*. 1993; 187:493–501. [PubMed: 8475297]
3. Soderstrom CE, Harms SE, Copit DS, Evans WP, Savino DA, Krakos PA, Farrell RS, Flamig DP. Three-dimensional RODEO breast MR imaging of lesions containing ductal carcinoma *in situ*. *Radiology*. 1996; 201:427–432. [PubMed: 8888235]
4. Esserman L, Hylton N, Yassa L, Barclay J, Frankel S, Sickles E. Utility of magnetic resonance imaging in the management of breast cancer: evidence for improved preoperative staging. *J Clin Oncol*. 1999; 17:110–119. [PubMed: 10458224]
5. Weatherall P, Evans GF, Metzger GJ, Saborrian MH, Leitch AM. MRI vs. histologic measurement of breast cancer following chemotherapy: comparison with x-ray mammography and palpation. *J Magn Reson Imaging*. 2001; 13:868–875. [PubMed: 11382946]
6. Drew PJ, Kerin MJ, Mahapatra T, Malone C, Monson JRT, Turnbull LW, Fox JN. Evaluation of response to neoadjuvant chemoradiotherapy for locally advanced breast cancer with dynamic contrast-enhanced MRI of the breast. *Eur J Surg Oncol*. 2001; 27:617–620. [PubMed: 11669587]
7. Balu-Maestro C, Chapellier C, Bleuse A, Chanalet I, Chauvel C, Largillier R. Imaging in evaluation of response to neoadjuvant breast cancer treatment benefits of MRI. *Breast Cancer Res Treat*. 2002; 72:145–152. [PubMed: 12038705]
8. Rosen EL, Blackwell KL, Baker JA, Soo MS, Bentley RC, Yu D, Samulski TV, Dewhirst MW. Accuracy of MRI in the detection of residual breast cancer after neoadjuvant chemotherapy. *Am J Roentgenol*. 2003; 181:1275–1282. [PubMed: 14573420]
9. Thibault F, Nos C, Meunier M, El Khoury C, Ollivier L, Sigal-Zafrani B, Clough K. MRI for surgical planning in patients with breast cancer who undergo preoperative chemotherapy. *Am J Roentgenol*. 2004; 183:1159–1168. [PubMed: 15385323]

10. Londero V, Bazzocchi M, Del Frate C, Puglisi F, Di Loreto C, Francescutti G, Zuiani C. Locally advanced breast cancer: comparison of mammography, sonography and MR imaging in evaluation of residual disease in women receiving neoadjuvant chemotherapy. *Eur Radiol.* 2004; 14:1371–1379. [PubMed: 14986052]
11. Bodini M, Berruti A, Bottini A, Allevi G, Fiorentino C, Brizzi M, Bersiga A, Generali D, Volpi D, Marini U, Aguggini S, Tampellini M, Alquati P, Olivetti L, Dogliotti L. Magnetic resonance imaging in comparison to clinical palpation in assessing the response of breast cancer to epirubicin primary chemotherapy. *Breast Cancer Res Treat.* 2004; 85:211–218. [PubMed: 15111758]
12. Yeh E, Slanetz P, Kopans DB, Rafferty E, Georgian-Smith D, Moy L, Halpern E, Moore R, Kuter I, Taghian A. Prospective comparison of mammography, sonography, and MRI in patients undergoing neoadjuvant chemotherapy for palpable breast cancer. *Am J Roentgenol.* 2005; 184:868–877. [PubMed: 15728611]
13. Akazawa K, Tamaki Y, Taguchi T, Tanji Y, Miyoshi Y, Kim SJ, Ueda S, Yanagisawa T, Sato Y, Tamura S, Noguchi S. Preoperative evaluation of residual tumor extent by three-dimensional magnetic resonance imaging in breast cancer patients treated with neoadjuvant chemotherapy. *Breast J.* 2006; 12:130–137. [PubMed: 16509837]
14. Segara D, Krop IE, Garber JE, Winer E, Harris L, Bellon JR, Birdwell R, Lester S, Lipsitz S, Iglehart JD, Golshan M. Does MRI predict pathologic tumor response in women with breast cancer undergoing preoperative chemotherapy? *J Surg Oncol.* 2007; 96:474–480. [PubMed: 17640031]
15. Bhattacharyya M, Ryan D, Carpenter R, Vinnicombe S, Gallagher CJ. Using MRI to plan breast-conserving surgery following neoadjuvant chemotherapy for early breast cancer. *Br J Cancer.* 2008; 98:289–293. [PubMed: 18219287]
16. Esteve FJ, Hortobagyi GN. Integration of systemic chemotherapy in the management of primary breast cancer. *Oncologist.* 1998; 3:300–313. [PubMed: 10388120]
17. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, Wickerham DL, Begovic M, DeCillis A, Robidoux A, Margolese RG, Cruz JAB, Hoehn JL, Lees AW, Dimitrov NV, Bear HD. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol.* 1998; 16:2672–2685. [PubMed: 9704717]
18. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from national surgical adjuvant breast and bowel project B-18. *J Natl Cancer Inst Monogr.* 2001; 30:96–102. [PubMed: 11773300]
19. Schegerin M, Tosteson A, Kaufman P, Paulsen K, Pogue B. Prognostic imaging in neoadjuvant chemotherapy of locally-advanced breast cancer should be cost-effective. *Breast Cancer Res Treat.* 2009; 114:537–547. [PubMed: 18437559]
20. Partridge SC, Gibbs JE, Lu Y, Esserman LJ, Sudilovsky D, Hylton NM. Accuracy of MR imaging for revealing residual breast cancer in patients who have undergone neoadjuvant chemotherapy. *Am J Roentgenol.* 2002; 179:1193–1199. [PubMed: 12388497]
21. Cheung YC, Chen SC, Su MY, See LC, Hsueh S, Chang HK, Lin YC, Tsai CS. Monitoring the size and response of locally advanced breast cancers to neoadjuvant chemotherapy (weekly paclitaxel and epirubicin) with serial enhanced MRI. *Breast Cancer Res Treat.* 2003; 78:51–58. [PubMed: 12611457]
22. Belli P, Costantini M, Malaspina C, Magistrelli A, LaTorre G, Bonomo L. MRI accuracy in residual disease evaluation in breast cancer patients treated with neoadjuvant chemotherapy. *Clin Radiol.* 2006; 61:946–953. [PubMed: 17018307]
23. Kim HJ, Im YH, Han BK, Choi N, Lee J, Kim JH, Choi YL, Ahn JS, Nam SJ, Park YS, Choe YH, Ko YH, Yang JH. Accuracy of MRI for estimating residual tumor size after neoadjuvant chemotherapy in locally advanced breast cancer: relation to response patterns on MRI. *Acta Oncol.* 2007; 46:996–1003. [PubMed: 17851879]
24. Chou CP, Wu MT, Chang HT, Lo YS, Pan HB, Degani H, Furman-Haran E. Monitoring breast cancer response to neoadjuvant systemic chemotherapy using parametric contrast-enhanced MRI: a pilot study. *Acad Radiol.* 2007; 14:561–573. [PubMed: 17434070]
25. Hattangadi J, Park C, Rembert J, Klifa C, Hwang J, Gibbs J, Hylton N. Breast stromal enhancement on MRI is associated with response to neoadjuvant chemotherapy. *Am J Roentgenol.* 2008; 190:1630–1636. [PubMed: 18492917]

26. Chen JH, Feig B, Hsiang DJB, Butler JA, Mehta RS, Bahri S, Nalcioglu O, Su MY. Impact of MRI-evaluated neoadjuvant chemotherapy response on change of surgical recommendation in breast cancer. *Ann Surg.* 2009; 249:448–454. [PubMed: 19247033]
27. Martincich L, Montemurro F, De Rosa G, Marra V, Ponzzone R, Cirillo S, Gatti M, Biglia N, Sarotto I, Sismondi P, Regge D, Aglietta M. Monitoring response to primary chemotherapy in breast cancer using dynamic contrast-enhanced magnetic resonance imaging. *Breast Cancer Res Treat.* 2004; 83:67–76. [PubMed: 14997056]
28. Lorenzon M, Zuiani C, Londero V, Linda A, Furlan A, Bazzocchi M. Assessment of breast cancer response to neoadjuvant chemotherapy: is volumetric MRI a reliable tool? *Eur J Radiol.* 2009; 71:82–88. [PubMed: 18472240]
29. Rieber A, Brambs HJ, Gabelmann A, Heilmann V, Kreienberg R, Kühn T. Breast MRI for monitoring response of primary breast cancer to neo-adjuvant chemotherapy. *Eur Radiol.* 2002; 12:1711–1719. [PubMed: 12111062]
30. Chen JH, Feig B, Agrawal G, Yu H, Carpenter PM, Mehta RS, Nalcioglu O, Su MY. MRI evaluation of pathologically complete response and residual tumors in breast cancer after neoadjuvant chemotherapy. *Cancer.* 2008; 112:17–26. [PubMed: 18000804]
31. Straver ME, Loo CE, Rutgers EJ, Oldenburg HS, Wesseling J, Vrancken Peeters MJ, Gilhuijs KG. MRI-model to guide the surgical treatment in breast cancer patients after neoadjuvant chemotherapy. *Ann Surg.* 2010; 251:701–707. [PubMed: 20224378]
32. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer.* 1981; 47:207–214. [PubMed: 7459811]
33. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst.* 2000; 92:205–216. [PubMed: 10655437]
34. Delille JP, Slanetz PJ, Yeh ED, Halpern EF, Kopans DB, Garrido L. Invasive ductal breast carcinoma response to neoadjuvant chemotherapy: noninvasive monitoring with functional MR imaging—pilot study. *Radiology.* 2003; 228:63–69. [PubMed: 12775851]
35. Chang YC, Huang CS, Liu YJ, Chen JH, Lu YS, Tseng WYI. Angiogenic response of locally advanced breast cancer to neoadjuvant chemotherapy evaluated with parametric histogram from dynamic contrast-enhanced MRI. *Phys Med Biol.* 2004; 49:3593–3602. [PubMed: 15446790]
36. Schott AF, Roubidoux MA, Helvie MA, Hayes DF, Kleer CG, Newman LA, Pierce LJ, Griffith KA, Murray S, Hunt KA, Paramagul C, Baker LH. Clinical and radiologic assessments to predict breast cancer pathologic complete response to neoadjuvant chemotherapy. *Breast Cancer Res Treat.* 2005; 92:231–238. [PubMed: 16155794]
37. Pickles MD, Lowry M, Manton DJ, Gibbs P, Turnbull LW. Role of dynamic contrast enhanced MRI in monitoring early response of locally advanced breast cancer to neoadjuvant chemotherapy. *Breast Cancer Res Treat.* 2005; 91:1–10. [PubMed: 15868426]
38. Partridge SC, Gibbs JE, Lu Y, Esserman LJ, Tripathy D, Wolverson DS, Rugo HS, Hwang ES, Ewing CA, Hylton NM. MRI measurements of breast tumor volume predict response to neoadjuvant chemotherapy and recurrence-free survival. *Am J Roentgenol.* 2005; 184:1774–1781. [PubMed: 15908529]
39. Armitage P, Behrenbruch C, Brady M, Moore N. Extracting and visualizing physiological parameters using dynamic contrast-enhanced magnetic resonance imaging of the breast. *Med Image Anal.* 2005; 9:315–329. [PubMed: 15950895]
40. Manton DJ, Chaturvedi A, Hubbard A, Lind MJ, Lowry M, Maraveyas A, Pickles MD, Tozer DJ, Turnbull LW. Neoadjuvant chemotherapy in breast cancer: early response prediction with quantitative MR imaging and spectroscopy. *Br J Cancer.* 2006; 94:427–435. [PubMed: 16465174]
41. Kumar M, Jagannathan N, Seenu V, Dwivedi S, Julka P, Rath G. Monitoring the therapeutic response of locally advanced breast cancer patients: sequential *in vivo* proton MR spectroscopy study. *J Magn Reson Imaging.* 2006; 24:325–332. [PubMed: 16786567]
42. Tan PC, Pickles MD, Lowry M, Manton DJ, Turnbull LW. Lesion T2 relaxation times and volumes predict the response of malignant breast lesions to neoadjuvant chemotherapy. *Magn Reson Imaging.* 2008; 26:26–34. [PubMed: 17573224]

43. Sharma U, Danishad KKA, Seenu V, Jagannathan NR. Longitudinal study of the assessment by MRI and diffusion-weighted imaging of tumor response in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy. *NMR Biomed*. 2009; 22:104–113. [PubMed: 18384182]
44. Johansen R, Jensen LR, Rydland J, Goa PE, Kvistad KA, Bathen TF, Axelson DE, Lundgren S, Gribbestad IS. Predicting survival and early clinical response to primary chemotherapy for patients with locally advanced breast cancer using DCE-MRI. *J Magn Reson Imaging*. 2009; 29:1300–1307. [PubMed: 19472387]
45. van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European organization for research and treatment of cancer trial 10902. *J Clin Oncol*. 2001; 19:4224–4237. [PubMed: 11709566]
46. Mauri D, Pavlidis N, Ioannidis JPA. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst*. 2005; 97:188–194. [PubMed: 15687361]
47. Kuerer HM, Newman LA, Smith TL, Ames FC, Hunt KK, Dhingra K, Theriault RL, Singh G, Binkley SM, Sneige N, Buchholz TA, Ross MI, McNeese MD, Buzdar AU, Hortobagyi GN, Singletary SE. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol*. 1999; 17:460–469. [PubMed: 10080586]
48. Ogston KN, Miller ID, Payne S, Hutcheon AW, Sarkar TK, Smith I, Schofield A, Heys SD. A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival. *The Breast*. 2003; 12:320–327. [PubMed: 14659147]
49. Pickles MD, Gibbs P, Lowry M, Turnbull LW. Diffusion changes precede size reduction in neoadjuvant treatment of breast cancer. *Magn Reson Imaging*. 2006; 24:843–847. [PubMed: 16916701]
50. Padhani AR, Hayes C, Assersohn L, Powles T, Makris A, Suckling J, Leach MO, Husband JE. Prediction of clinicopathologic response of breast cancer to primary chemotherapy at contrast-enhanced MR imaging: initial clinical results. *Radiology*. 2006; 239:361–374. [PubMed: 16543585]
51. Yu HJ, Chen JH, Mehta RS, Nalcioglu O, Su MY. MRI measurements of tumor size and pharmacokinetic parameters as early predictors of response in breast cancer patients undergoing neoadjuvant anthracycline chemotherapy. *J Magn Reson Imaging*. 2007; 26:615–623. [PubMed: 17729334]
52. Loo CE, Teertstra HJ, Rodenhuis S, van de Vijver MJ, Hannemann J, Muller SH, Peeters MJV, Gilhuijs KGA. Dynamic contrast-enhanced MRI for prediction of breast cancer response to neoadjuvant chemotherapy: initial results. *Am J Roentgenol*. 2008; 191:1331–1338. [PubMed: 18941065]
53. Ah-See MLW, Makris A, Taylor NJ, Harrison M, Richman PI, Burcombe RJ, Stirling JJ, d'Arcy JA, Collins DJ, Pittam MR, Ravichandran D, Padhani AR. Early changes in functional dynamic magnetic resonance imaging predict for pathologic response to neoadjuvant chemotherapy in primary breast cancer. *Clin Cancer Res*. 2008; 14:6580–6589. [PubMed: 18927299]
54. Bahri S, Chen JH, Mehta R, Carpenter P, Nie K, Kwon SY, Yu H, Nalcioglu O, Su MY. Residual breast cancer diagnosed by MRI in patients receiving neoadjuvant chemotherapy with and without bevacizumab. *Ann Surg Oncol*. 2009; 16:1619–1628. [PubMed: 19333654]
55. Baek HM, Chen JH, Nie K, Yu HJ, Bahri S, Mehta RS, Nalcioglu O, Su MY. Predicting pathologic response to neoadjuvant chemotherapy in breast cancer by using MR imaging and quantitative ^1H MR spectroscopy. *Radiology*. 2009; 251:653–662. [PubMed: 19276320]
56. American College of Radiology (ACR). Breast Imaging Reporting and Data System (BI-RADS) Breast Imaging Atlas. 4. American College of Radiology; Reston, VA: 2003. BI-RADS - magnetic resonance imaging.
57. Esserman L, Kaplan E, Partridge S, Tripathy D, Rugo H, Park J, Hwang S, Kuerer H, Sudilovsky D, Lu Y, Hylton N. MRI phenotype is associated with response to doxorubicin and cyclophosphamide neoadjuvant chemotherapy in stage III breast cancer. *Ann Surg Oncol*. 2001; 8:549–559. [PubMed: 11456056]

58. Bluemke DA, Gatsonis CA, Chen MH, DeAngelis GA, DeBruhl N, Harms S, Heywang-Kobrunner SH, Hylton N, Kuhl CK, Lehman C, Pisano ED, Causer P, Schnitt SJ, Smazal SF, Stelling CB, Weatherall PT, Schnall MD. Magnetic resonance imaging of the breast prior to biopsy. *J Am Med Assoc.* 2004; 292:2735–2742.
59. Wasser K, Sinn H, Fink C, Klein S, Junkermann H, Lajdemann H, Zuna I, Delorme S. Accuracy of tumor size measurement in breast cancer using MRI is influenced by histological regression induced by neoadjuvant chemotherapy. *Eur Radiol.* 2003; 13:1213–1223. [PubMed: 12764635]
60. Wasser K, Klein S, Fink C, Junkermann H, Sinn H, Zuna I, Knopp M, Delorme S. Evaluation of neoadjuvant chemotherapeutic response of breast cancer using dynamic MRI with high temporal resolution. *Eur Radiol.* 2003; 13:80–87. [PubMed: 12541113]
61. Khoury CE, Servois V, Thibault F, Tardivon A, Ollivier L, Meunier M, Allonier C, Neuenschwander S. MR quantification of the washout changes in breast tumors under preoperative chemotherapy: feasibility and preliminary results. *Am J Roentgenol.* 2005; 184:1499–1504. [PubMed: 15855104]
62. Yankeelov TE, Lepage M, Chakravarthy A, Broome EE, Niermann KJ, Kelley MC, Meszoely I, Mayer IA, Herman CR, McManus K, Price RR, Gore JC. Integration of quantitative DCE-MRI and ADC mapping to monitor treatment response in human breast cancer: initial results. *Magn Reson Imaging.* 2007; 25:1–13. [PubMed: 17222711]
63. Tofts PS. Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. *J Magn Reson Imaging.* 1997; 7:91–101. [PubMed: 9039598]
64. Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, Larsson HB, Lee TY, Mayr NA, Parker GJ, Port RE, Taylor J, Weisskoff RM. Estimating kinetic parameters from dynamic contrast-enhanced t1-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging.* 1999; 10:223–232. [PubMed: 10508281]
65. Galons JP, Altbach MI, Paine-Murrieta GD, Taylor CW, Gillies RJ. Early increases in breast tumor xenograft water mobility in response to paclitaxel therapy detected by non-invasive diffusion magnetic resonance imaging. *Neoplasia.* 1999; 1:113–117. [PubMed: 10933044]
66. Meisamy S, Bolan PJ, Baker EH, Pollema MG, Le CT, Kelcz F, Lechner MC, Luikens BA, Carlson RA, Brandt KR, Amrami KK, Nelson MT, Everson LI, Emory TH, Tuttle TM, Yee D, Garwood M. Adding in-vivo quantitative ¹H MR spectroscopy to improve diagnostic accuracy of breast MR imaging: preliminary results of observer performance study at 4.0 T. *Radiology.* 2005; 236:465–475. [PubMed: 16040903]
67. Ackerstaff E, Glunde K, Bhujwalla ZM. Choline phospholipid metabolism: a target in cancer cells? *J Cell Biochem.* 2003; 90:525–533. [PubMed: 14523987]
68. Jagannathan NR, Kumar M, Seenu V, Coshic O, Dwivedi SN, Julka PK, Srivastava A, Rath GK. Evaluation of total choline from in-vivo volume localized proton MR spectroscopy and its response to neoadjuvant chemotherapy in locally advanced breast cancer. *Br J Cancer.* 2001; 84:1016–1022. [PubMed: 11308247]
69. Meisamy S, Bolan PJ, Baker EH, Bliss RL, Gulbahce E, Everson LI, Nelson MT, Emory TH, Tuttle TM, Yee D, Garwood M. Neoadjuvant chemotherapy of locally advanced breast cancer: predicting response with *in vivo* ¹H MR spectroscopy—a pilot study at 4 T. *Radiology.* 2004; 233:424–431. [PubMed: 15516615]
70. Danishad KKA, Sharma U, Sah RG, Seenu V, Parshad R, Jagannathan NR. Assessment of therapeutic response of locally advanced breast cancer (LABC) patients undergoing neoadjuvant chemotherapy (NACT) monitored using sequential magnetic resonance spectroscopic imaging (MRSI). *NMR Biomed.* 2010; 23:233–241. [PubMed: 20175134]
71. Jacobs MA, Barker PB, Bottomley PA, Bhujwalla Z, Bluemke DA. Proton magnetic resonance spectroscopic imaging of human breast cancer: a preliminary study. *J Magn Reson Imaging.* 2004; 19:68–75. [PubMed: 14696222]
72. Baek HM, Chen JH, Yu HJ, Mehta R, Nalcioğlu O, Su MY. Detection of choline signal in human breast lesions with chemical-shift imaging. *J Magn Reson Imaging.* 2008; 27:1114–1121. [PubMed: 18425841]
73. Bolan PJ, Meisamy S, Baker EH, Lin J, Emory T, Nelson M, Everson LI, Yee D, Garwood M. *In vivo* quantification of choline compounds in the breast with ¹H MR spectroscopy. *Magn Reson Med.* 2003; 50:1134–1143. [PubMed: 14648561]

74. Baik HM, Su MY, Yu H, Nalcioğlu O, Mehta R. Quantification of choline-containing compounds in malignant breast tumors by ^1H MR spectroscopy using water as an internal reference at 1.5 T. *Magn Reson Mater Phys.* 2006; 19:96–104.
75. Bolan PJ, DelaBarre L, Baker EH, Merkle H, Everson LI, Yee D, Garwood M. Eliminating spurious lipid sidebands in ^1H MRS of breast lesions. *Magn Reson Med.* 2002; 48:215–222. [PubMed: 12210929]
76. Jagannathan N, Singh M, Govindaraju V, Raghunathan P, Coshic O, Julka PK, Rath GK. Volume localized *in vivo* proton MR spectroscopy of breast carcinoma: variation of water–fat ratio in patients receiving chemotherapy. *NMR Biomed.* 1998; 11:414–422. [PubMed: 10221584]

Figure 1. Contrast-enhanced MR images showing breast cancer responding to neoadjuvant chemotherapy. The images were collected before chemotherapy (a), after one cycle (b) and after the full course of chemotherapy (c).

Figure 2.

The five lesion pattern categories: 1, unicentric mass, well marginated; 2, multilobulated mass, well marginated; 3, area enhancement, irregular margins, nodular; 4, area enhancement, irregular margins, without nodularity; 5, septal spread.

Figure 3.

Typical signal enhancement uptake curves illustrating the differences in enhancement over time for malignant, benign, parenchymal and fatty tissues. Reproduced from Armitage *et al.*, Med. Image Anal. 2005; 9: 315–329.