Magnetic resonance imaging for primary breast cancer management: current role and new applications

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Abstract

Techniques for magnetic resonance (MR) imaging of the breast have been evolving over the past decade. The opportunities for integration of MR imaging into clinical breast cancer management and clinical research are increasing. In this paper, we will review the principles behind the creation of standard and MR images and use this as a platform to evaluate clinical studies and indications for the use and study of MR. In particular, we will focus on those areas where MR has the capability of changing care and/or improving our understanding of the biology of breast cancer. In addition, we will address areas where MR is not yet capable of adding value or where MR may lead to unnecessary procedures.

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Introduction

Magnetic resonance imaging (MRI) was introduced as an imaging technique in medicine over 20 years ago, but it is only in the last 3–5 years that it has been used with any consistency to image the breast. Although several centers have been using breast MRI for many years, it has not disseminated rapidly because of the variability of techniques, the difficulty in image processing and interpretation, the lack of MRI-guided biopsy systems, and the absence of a standard, useable platform for demonstrating relevant features to clinicians. Many of these difficulties are being overcome and there are several areas where breast MRI is emerging as a useful clinical tool in the diagnosis, staging, and management of breast cancer.

Clinical studies using contrast-enhanced breast MRI have shown that essentially all breast malignancies enhance with gadolinium (Revel *et al*. 1986, Heywang *et al*. 1989, Kaiser & Zeitler 1989, Stack *et al*. 1990, Pierce *et al*. 1991, Orel *et al*. 1994, Harms 1999). These studies also provide evidence that contrast-MRI is highly sensitive to cancers in the breast as small as a few millimeters in size. Reported sensitivities are in the range of 95–100%. The limitation to MRI of the breast is low-to-moderate specificity ranging from 37 to 97%, with false positive enhancement occurring frequently in benign breast lesions (Heywang *et al*. 1988, 1989, Kaiser & Zeitler 1989, Stack *et al*. 1990, Rubens *et al*. 1991, Gribbestad *et al*. 1992, Dao *et al*. 1993, Flickinger *et al*. 1993, Gilles *et al*. 1993, Harms *et al*. 1993, Boetes *et al*. 1994, Hulka *et al*. 1995).

The actual and potential value of MRI in breast imaging may perhaps best be understood in the context of how images are created by all of the breast imaging modalities and where traditional imaging has failed to diagnose or define disease. By understanding what MRI enables us to visualize, it can help us to understand which clinical situations or problems will be addressed by the introduction of MRI into the clinical management of breast cancer.

How are images created?

Conventional imaging

Mammography

The primary purpose of mammography is to produce fine-detail images of the breasts that can be used to screen for breast cancer and to evaluate signs and symptoms of breast disease. Mammography uses ionizing radiation that passes

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through the compressed breast and then exposes a sheet of film placed on the opposite side of the breast. The image that is produced results from variation in breast tissues that the X-ray beam has encountered along the way to the film. Structures that more strongly attenuate the X-ray beam appear as whiter (or denser) areas on the film, and include thick areas of fibroglandular tissue, calcifications, and masses (Kopans 1998).

Because masses and dense fibroglandular tissue similarly attenuate the X-ray beam, cancers that present as small masses can be obscured by overlapping dense fibroglandular tissue. Hence, the sensitivity of mammography for the detection of small breast cancers is potentially reduced in women with dense breast tissue. Larger cancers may also not be evident mammographically if the growth of the cancer is diffuse, which is true in the case of invasive lobular carcinoma (Kopans 1998). In this situation, there may be insufficient density difference between the carcinoma and adjacent fibroglandular tissue, such that these carcinomas can be quite large when detected, often presenting only as increasing breast 'thickening' on physical examination (see Fig. 1).

Clustered microcalcifications, which can be one of the earliest signs of breast cancer or ductal carcinoma *in situ* (DCIS), appear as whiter particles on the image, and are ordinarily not hidden by dense breast tissue, although their small sizes may make this particular finding rather subtle and easy to miss (Birdwell *et al.* 2001).

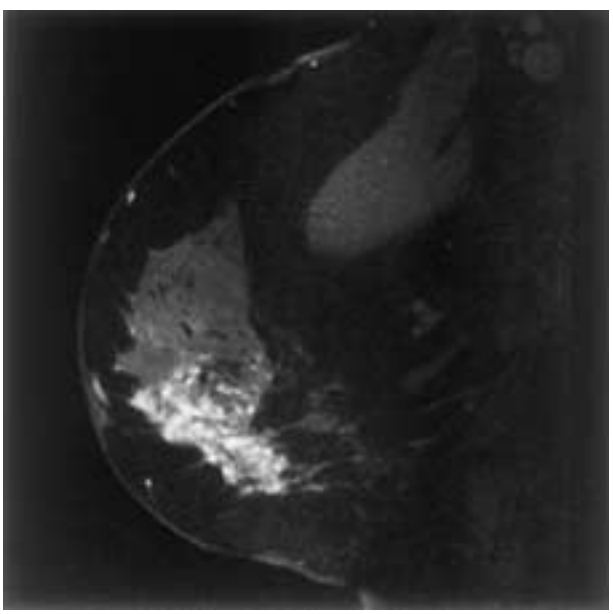

Figure 1 Lobular cancer can be difficult to detect with any modality. This patient had disease that was undetected for several years and presented clinically as an increased density in the lower outer quadrant of the breast. Mammography demonstrated a small architectural distortion in the range of 1–1.5 cm. The MR shows extensive disease of over 6 cm of lobular cancer, which was confirmed at the time of mastectomy. Note that the background density of the breast tissue is likely responsible for the lack of contrast between tumor and normal breast tissue, making detection with standard imaging difficult.

The usual screening mammography examination consists of two views of each breast, craniocaudal and mediolateral oblique views. When necessary, this routine examination may be supplemented with tailored additional views, such as spot compression magnification mammography, to more closely evaluate potential lesions.

Ultrasound

Mammography may also be supplemented by breast ultrasound examination for the further evaluation of mammographically identified masses and other space-occupying lesions. Ultrasound examination may also be used to evaluate palpable breast lesions in very young women as clinically indicated. Ultrasound uses very high frequency sound waves transmitted through a medium (in this case, breast tissue) that are reflected back to the transmitting transducer. The reflected information is translated into an image that is related to the speed of sound through the various breast tissues and fluid (when present), as well as the strength of the reflected ultrasound wave (Tohno *et al.* 1994).

Ultrasound traditionally is very useful at differentiating solid from cystic breast lesions, but can also be used in a limited fashion to characterize solid breast masses. Benign ultrasound features have been described, but should not be used to avert a biopsy when a mammographically or clinically suspicious lesion is present (Stavros *et al.* 1995). When suspicious features are identified, they may provoke a biopsy recommendation, but have a lower positive predictive value as compared with a mammographically prompted biopsy recommendation (Kuhl *et al.* 2000). Ultimately, the addition of ultrasound to mammography in the evaluation of breast lesions can improve the overall sensitivity of conventional breast imaging for the detection of breast cancer (Skaane 1999). Screening ultrasound examination has also been evaluated and found to be useful in the detection of breast cancers over those found by screening mammography in women with dense breast tissue (Kolb *et al.* 1998). This use of ultrasound as a primary screening tool, however, is controversial due to the operator-dependent nature of ultrasound and the low cancer-to-biopsy yield, and is not recommended by the American College of Radiology.

As with mammography, diffuse disease that does not form a mass, such as invasive lobular cancer, is not likely to be visualized with ultrasound unless the operator is extremely experienced and familiar with the subtle architectural changes that may occur in these cases.

MRI

Unlike mammography and ultrasound, MRI produces a set of images of contiguous thin slices of tissue, giving a three-

dimensional representation of one or both breasts. The MRI signal is generated by protons in water molecules. Differences in water content and the local molecular environment give rise to contrast between types of soft tissue. Intrinsic differences between cancerous and non-cancerous breast tissue have not proven sensitive or specific enough for breast cancer detection. To better detect cancerous breast tissue, an exogenous contrast agent, typically a small molecular weight compound containing gadolinium, is given intravenously and causes signal brightening in areas where the agent accumulates. This is expected to occur in cancers because of their increased angiogenesis and thus this phenomenon is exploited by MRI to improve cancer detection. Not all increased vascularity is associated with neoangiogenesis. False positive enhancement can occur in benign tissue such as fibroadenomas, and proliferative breast disease.

The techniques for breast MRI continue to evolve. However there is consensus on general requirements. Surface coils are necessary to achieve adequate spatial resolution while maintaining high signal-to-noise levels. A contrast agent must be used for MRI to be sufficiently sensitive to breast cancer. MRI images must be acquired within a few minutes of contrast injection to observe an early, preferential signal enhancement associated with increased vascularization of malignant tumors. After the first few minutes, benign breast tissue may also show enhancement, making diagnosis less reliable. The time constraint means that a compromise must be made between temporal and spatial resolution. Imaging strategies such as high spatial resolution, large volume of coverage to include the entire breast or both breasts, and the use of fat-suppression techniques will all improve the sensitivity of breast MRI to small and multi-focal lesions, but will incur longer scan times of several minutes (Pierce *et al.* 1991, Harms *et al.* 1993, Hylton *et al.* 1994). Other investigators have reported that the time-course of contrast uptake can be better defined if images are acquired at minute intervals or shorter, resulting in increased specificity (Rubens *et al.* 1991, Boetes *et al.* 1994, Hulka *et al.* 1995). Such 'dynamic' techniques achieve the higher temporal resolution by reducing spatial resolution, scanning only a portion of the breast, and/or foregoing fat suppression. Alternative approaches such as those proposed by Hylton *et al.* (1995) and Degani *et al.* (1997) combine low temporal resolution kinetic information with high spatial resolution anatomic information as a means to achieve high sensitivity and high specificity in a single scan technique.

Where does traditional imaging fall short and MRI add value over traditional imaging?

Mammographic and sonographic images of cancer are created by masses that absorb, deflect, or reflect ionizing radiation or sound waves. Mammography has the additional capability of visualizing calcifications deposited in the lumen of ducts or the necrotic center of a mass as tumors grow. Ultrasound has the additional capacity to assess blood flow, although not necessarily to the degree necessary to discriminate benign from malignant lesions. The ability of either of these techniques to discriminate malignancies within tissue of similar density or echotexture is very limited. Consequently, the ability to detect low density neoplastic processes such as DCIS (particularly those lesions not associated with calcifications) and invasive lobular cancer will also be limited, especially, but not only, in the setting of dense breast tissue. Thus it is not surprising that the clinical areas where traditional imaging falls short include: the detection of breast cancer in high risk young women; the detection as well as the characterization of invasive lobular cancer; the determination of the extent of DCIS that may be incompletely represented by amorphous or pleiomorphic calcifications; the cancer that presents as an axillary mass with an unknown primary (usually small high grade lesions in the setting of dense breast tissue); the multifocal cancer that appears as a solitary cancer on mammogram; and the staging or characterization of locally advanced cancer and its response to chemotherapy.

In this section we will address each of these areas and try to match the biology of the disease process to the principles that lie behind the imaging technique and provide evidence to help determine whether MRI will be of value now or in the future. In general, MRI excels where there is a highly vascularized malignant process in dense breast tissue. Patterns of angiogenesis in less well-vascularized neoplasms can also be of value in discriminating or managing breast cancer. All current imaging techniques will be least robust where neither the density nor vascularity of the malignant process can be discriminated from that of the surrounding breast tissue.

Screening young women at risk for breast cancer

Mammographic screening is not considered to be useful in younger age groups (less than age 40) because of the extremely low frequency of breast cancer found in younger women (<5% of the total breast cancers diagnosed each year). The population of women in this age group is very large and the absolute frequency of breast cancer is well less than 1 in 2000. It thus makes it ineffective and very expensive to screen with a test like mammography, with its attendant sensitivity and specificity. The relatively greater density of breast tissue in young premenopausal women may also interfere with breast cancer detection, potentially reducing the sensitivity of mammography for these women. The combination of a screening tool that is not as sensitive and a disease that is not prevalent have resulted in the uniform recommendation not to screen this population.

However, young women who have strong family histories of breast and/or ovarian cancer and have a known

predisposition to breast cancer on the basis of an inherited mutation of BRCA 1 or 2 have a much higher prevalence of breast cancer at a young age (Cummings *et al*. 1998, Frank *et al*. 1998). The *sine qua non* of BRCA 1 and 2 mutations is the development of breast cancer at a relatively early age (Couch *et al*. 1997, Shattuck-Eidens *et al*. 1997). At least two studies suggest that the frequency of breast cancer is likely to be in the range of 3–6 per 100 women screened (Warner *et al*. 2001). This compares to an incident screening frequency of 3–6 per 1000 in women who are 50 years of age (Nystrom *et al*. 1993). The projected probability of developing *in situ* or invasive breast cancer at 10, 20 and 30 years is calculated for high-risk women, according to the model developed by Gail. Fabian *et al*. (2000) found that women with a 10-year Gail risk of 4.0 had a 7% chance of developing breast cancer over a 3-year period (Fabian *et al*. 2000). Women who also had atypia on random fine-needle aspiration (FNA) had a 15% chance of developing cancer over years. Algorithms such as these that define a very high risk population of women, combined with knowledge of breast density, define populations worth studying to determine the best modality for screening, MRI or mammography.

Because MRI examination has been found to be highly sensitive in the detection of breast carcinoma, and its sensitivity is not affected by the presence of dense breast tissue, MRI has been investigated for its potential role in screening young women at high risk for breast carcinoma. In a comparison of imaging techniques for screening high risk women, Warner *et al*. (2001) found that MRI had the greatest sensitivity for the detection of breast cancer in comparison with mammography, ultrasound examination, and physical examination. In this study, MRI detected all six invasive cancers out of 196 women in contrast to three detected by ultrasound, two by mammography, and two by physical examination. Kuhl *et al*. (2000) also found a higher accuracy of MRI in the evaluation of high risk women. The sensitivity of MRI in the Kuhl *et al*. (2000) study was 100% compared with mammography and ultrasound, each of which had sensitivities of 33% and 44% when combined. The specificity of MRI was also higher, 64% compared with mammography at 30% and ultrasound at 12%.

Given the cost of MRI, is it feasible to screen young women with MRI? Certainly, MRI would be prohibitively expensive where the prevalence of breast cancer is low, such as the average woman in her late thirties or early forties, where the incidence is less than 1–2 per 1000 or less, or even women in their fifties where the incidence is 4–6 per 1000 and mammographic screening is considered to be cost effective. MRI is approximately ten times more expensive than mammography. In very high risk populations of women, studies have demonstrated that there is a frequency of 3–6 cancers per 100 women. If the prevalence is ten times higher, a test that is ten times more expensive may turn out to be cost effective as a screening tool if it proves to be very sensitive and specific. Ongoing studies should be able to validate this assumption. As MRI continues to evolve, specificity of MRI is likely to improve. The positive biopsy rate from a mammographic screening population is fairly low, with only 10–40% of biopsies showing cancer (Brown *et al*. 1995, Denny *et al*. 2001). The specificity of MRI can exceed that of mammography and, if the cost of scans become less, MRI might serve an important role as a screening tool for women with dense breast tissue.

Because MRI is a three-dimensional technique and can look at thin slices of tissue, it is not impeded by breast density. In fact, MRI is probably more effective in dense tissue where there is less effect of partial volume averaging of fat and water that can obscure small features. The sensitivity of breast MRI is quite high and can demonstrate small cancers, DCIS, and multifocal disease quite effectively. Validation of the lexicon and criteria for malignancy are in progress but must be standardized before high risk screening can be implemented. For MRI to be useful as a screening tool, sufficient specificity will be required. In addition, the development of MR-compatible biopsy tools will be necessary. Small enhancing foci of unknown significance could lead to unnecessary and overly aggressive treatments in otherwise asymptomatic women. At the same time, the greater risk and potentially higher cancer growth rates in this population will necessitate more aggressive follow-up, which may include costly short interval follow-up MRIs. These issues should be resolved through ongoing clinical studies.

Multifocality and the determination of extent of disease

When breast carcinoma is diagnosed, the extent of disease may not be apparent either by palpation or mammographically. In fact, pathologic evaluation of mastectomy specimens has revealed additional foci of carcinoma in 30–63% of cases (Berg & Gilbreath 2000). Frequently, mammography combined with ultrasound will detect more extensive disease than is clinically evident. This is the reason that meticulous diagnostic mammography is so important before surgical treatment is performed. However, even well-performed conventional imaging will not always identify the full extent of carcinoma. The presence of very dense breast tissue will obscure small masses, and when calcifications are present that prove to be DCIS, the extent of the calcifications may under-represent the extent of disease, especially if the DCIS is low-to-intermediate grade.

Because of its very high sensitivity, MRI is particularly well suited for staging women diagnosed with breast cancer, especially those women with very dense breast tissue, difficult mammograms, or extensive indeterminate calcifications. Esserman *et al*. (2001) demonstrated such improved staging in 58 cases where MRI accurately defined the anatomic extent of disease in 98% of cancers, in contrast to mammography which

was accurate in only 55% of cases. The value of MRI was demonstrated in those cases where extensive intraductal cancer or multifocal cancer was present.

MRI is quite sensitive to multifocality, provided the scan has been performed to cover the entire breast, or both breasts. There are important trade-offs that are made, however, when selecting the use of MRI. To achieve large volume coverage at high spatial resolution, and obtain good image quality, longer scan times become necessary. While these measures may contribute to greater sensitivity, specificity may suffer as scan time increases. The ability to differentiate malignant and benign disease on the basis of different patterns of contrast uptake and washout decreases as the sample time increases.

Lobular cancer

Invasive lobular carcinoma grows in a pattern where single small cells form columns of cells infiltrating into the breast tissue, and thus these cancers frequently do not form discrete masses, especially when they are small. They often grow slowly and can present clinically as a gradual developing density or thickening of the breast. FNA performed on lobular cancers tends to yield samples of sparse cellularity, reflective of the growth pattern of such tumors. A developing density and an FNA that is insufficiently cellular should raise concern about the possibility of lobular cancer, and a core biopsy or surgical biopsy should be performed (Ljung *et al*. 2001). Lobular cancer is one of the most frequently missed cancers by both mammography and ultrasound. This is probably because the cancer may not be readily detectable until it forms a discrete mass, architectural distortion, or a sufficient quantity of more dense tissue that can attenuate the X-ray beam when mammography is performed. Ultrasound is even more limited, as only the presence of a mass has sufficient specificity to prompt a biopsy recommendation. MRI does not have to detect a mass, but it picks up contrast enhancement generated by neovascularity. The more vascular the tumor, the more visible it will be on MRI. A very low grade tumor with sparse vascularity may also present difficulty on MRI. To detect a lobular cancer, the technique and the parameters are likely to be different from that used to detect and characterize a ductal cancer. Fast rates of contrast uptake and washout are generally associated with an increased likelihood of invasive ductal cancer. Lobular carcinomas often show a more gradual pattern of contrast uptake that is also found in benign disease. A combination of characteristic morphologic features (such as regional enhancement rather than an enhancing mass and less margin definition) and enhancement patterns can help to identify lobular carcinomas on MRI and differentiate them from DCIS, invasive ductal carcinomas, and benign proliferative disease. Local staging of a patient with lobular cancer is a clinical indicator for MRI.

Dense breast tissue and known cancer: diagnosis and follow-up

As described in the section above, MRI performs better in the dense breast. In cases where breast cancer has been diagnosed in a very dense breast, additional smaller occult tumors may be present. The prevalence of additional tumors has not been clearly defined; however, there are many reports of findings of additional tumors in the ipsilateral breast (Schnall *et al*. 2001). If there are multiple foci of mammographically occult disease in the ipsilateral breast, it may also make sense to image the contralateral breast (see below). Examples of the presence of additional cancers in the ipsilateral breast are shown in Fig. 2. As MR techniques evolve and the capability is developed to screen both breasts with equivalent sensitivity and specificity, the frequency of synchronous cancers will be able to be determined.

Several studies have described the utility of MRI to resolve the question of local recurrence in the setting of scar and dense breast tissue, where the breast has been altered through treatment, surgical excision, and/or radiation. Clinical change may or may not be accompanied by a mammographic or ultrasound change. After lumpectomy and radiation, where there is a clinical question of recurrent tumor but mammography and ultrasound cannot differentiate scar from recurrence, MRI has been shown to be very helpful in resolving a question of local recurrence. Again, the setting of dense breast tissue and a well-vascularized tumor are the milieu where MRI performs best. Studies have shown that the absence of enhancement virtually excludes a recurrence and the presence of enhancement is very specific for tumor even in the radiated breast (Dao *et al*. 1993, Mussurakis *et al*. 1995, Murray *et al*. 1996, Rieber *et al*. 1997, Muller *et al*. 1998).

There is no established role for MRI as a post-operative screening tool in women treated with breast conservation. However, women who have the highest risk of local recurrence, e.g. women under the age of 45, who are likely to have dense breasts, may be appropriate candidates for MR screening if their initial tumor was mammographically occult (Veronesi *et al*. 1995). Studies in the population of women with dense breast tissue and mammographically occult cancers should be pursued to determine the prevalence of tumor recurrences, as well as the sensitivity and specificity of MRI.

Contralateral breast imaging

Some preliminary investigations on the use of contralateral breast MRI have found the incidence of synchronous cancers to be as high as 10% (Schnall *et al*. 2001). These are small studies, but they raise the same question about proper local staging as has been raised in the prior discussion of multifocal breast cancer. As in the case of multifocal breast cancer or women with dense breast tissue, conventional imaging

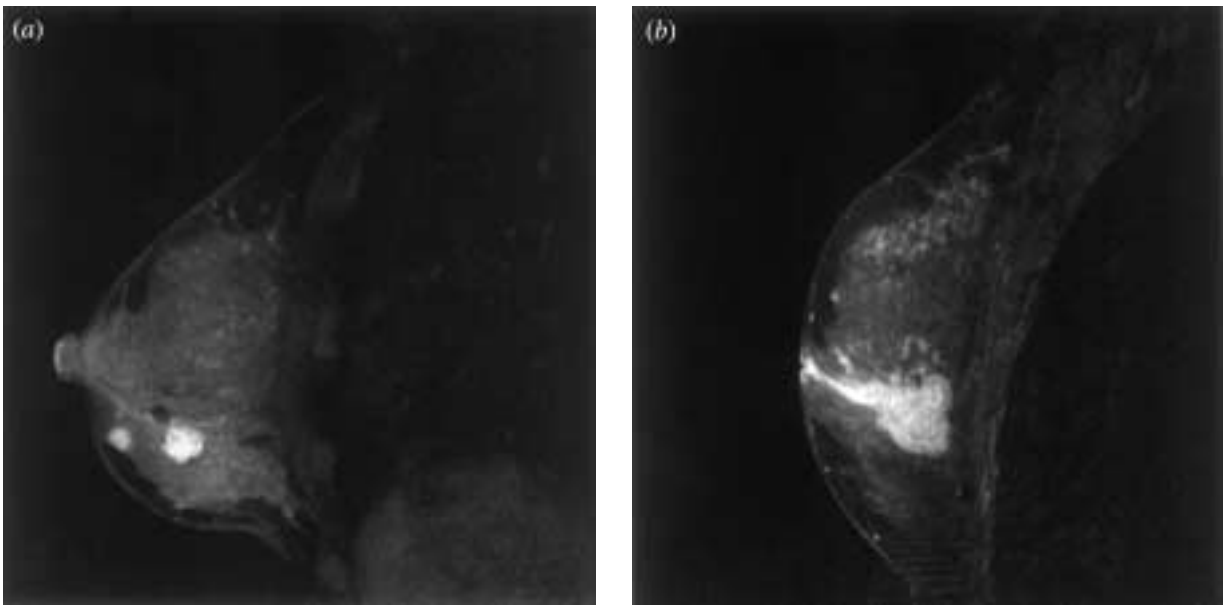

Figure 2 Occult cancers: patients with very dense breasts and a tumor that presents as a palpable mass may harbor additional cancers. In (*a*) the patient had very dense breasts on mammography, and a subtle palpable mass shown to be cancer by fine-needle aspiration (FNA). Contrast enhanced MRI revealed a second, larger cancer behind the palpable mass. In (*b*) a 28-year-old woman, who had a small superficial cancer near the nipple diagnosed by core biopsy, had a normal mammogram. MRI revealed a large 5 cm cancer deep in the breast that was not palpable even in retrospect. Core biopsy proved the diagnosis of adenocarcinoma.

may miss an unsuspected breast cancer in the contralateral breast. The additional screening by MRI of the contralateral breast may be useful, although the relatively lower specificity of MRI is problematic in these cases, and we need easy availability of minimal biopsy techniques before this application is ready for routine use. This is an ideal area for clinical investigation. If the incidence of synchronous cancers is truly 10%, then the rate of breast cancer is over ten times that of the general screening population and would merit a contralateral MRI at the time of diagnosis if mammography truly does not find these lesions. However, if the incidence is, in fact, much lower, e.g. 1% of women at the time of diagnosis are found to have a contralateral clinically relevant breast cancer, then MRI imaging would not be justified. This study must be done in the context of sites that have access to high quality mammography to make sure that we are comparing MRI with the best application of technology that is much more widely available and far less expensive (Esserman *et al*. 2001*a*). It is also possible, in the context of the study, that we would find that there are key features, either of the original tumor (presence of extensive intraductal disease), the density of the breast, or the mammographic findings in the ipsilateral or contralateral breast that would be markers for women who are likely to have a contralateral occult cancer. A study of the contralateral breast assessment with MRI and mammography at the time of diagnosis of a new primary breast cancer would be an ideal study.

Cancer of unknown primary

When a woman presents with palpable axillary lymphadenopathy that proves to be related to carcinoma, but there is no obvious primary lesion within the breast or elsewhere, the most likely origin for the primary is the ipsilateral breast (occult primary breast carcinoma) (Fourquet *et al*. 1996). Traditionally, these women have been treated with mastectomy for the presumptive diagnosis of breast cancer, which may or may not subsequently be proven, or with axillary nodal dissection.

The use of MRI in the evaluation of women with occult primary breast carcinoma significantly increases the chance that the occult lesion will be identified and localized (see Fig. 3). Rates of MRI detection of the occult primary within the breast range from 25 to 80% (Harms *et al*. 1993). When the primary is detected and localized, the option of conservative therapy becomes available to the patient. On occasion, ultrasound examination directed at the site of disease identified on MRI will reveal a lesion that may be easily sampled and subsequently removed. Alternatively, MRI-guided wire localization may be performed. Often, the primary lesions in

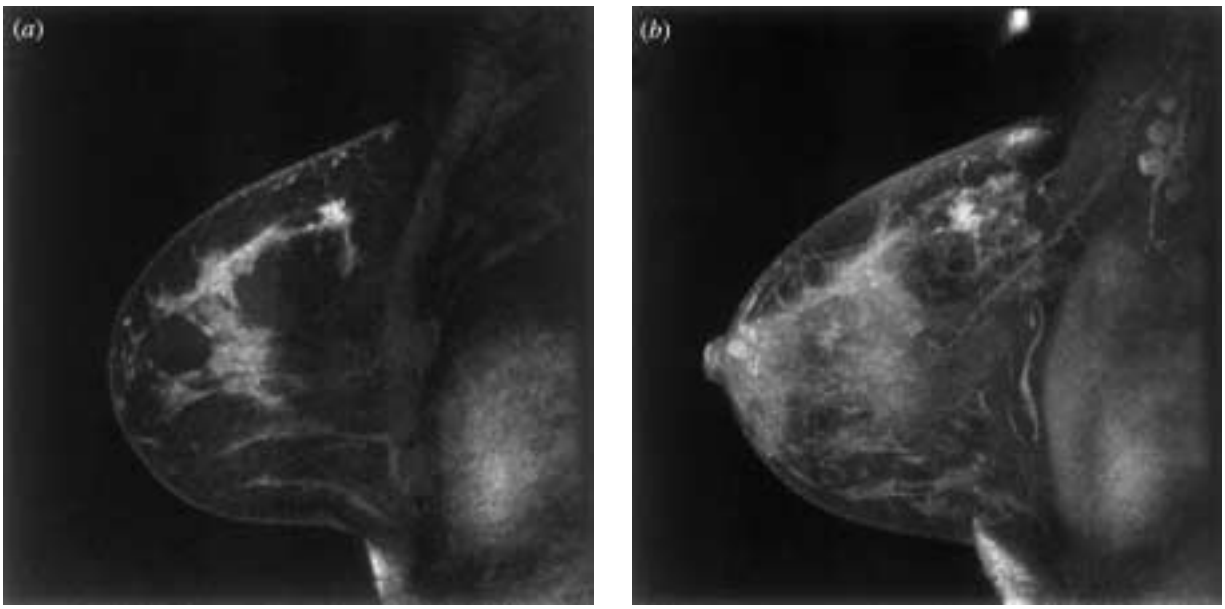

Figure 3 Cancer of unknown primary: a patient who presented with axillary nodes in the left axilla underwent a diagnostic MRI after FNA demonstrating adenocarcinoma. Mammography showed no evidence of disease. The lesion in the breast, once identified on MRI, was localized by ultrasound and an ultrasound-guided FNA confirmed the diagnosis of adenocarcinoma. The patient underwent neoadjuvant chemotherapy and had complete resolution of her primary and axillary cancer. In (*a*) the tumor is shown and (*b*) shows a view of the tumor and lymph nodes.

occult cases are small high grade invasive or *in situ* cancers in the setting of dense breast tissue. For these women, the identification of the primary can change local management, but not systemic management. Particularly because the major life threat is the regional dissemination of disease, and not the local disease itself, a woman with occult cancer should have the option for enhanced breast imaging with MRI. Again, this is a biological setting where MRI will perform best. It is often the only imaging technique that can assist with primary identification and delineation. MRI for this setting should be considered standard practice rather than proceeding to either mastectomy or radiation.

Management of patients with locally advanced disease

It is becoming increasingly common to treat women with locally advanced disease with neoadjuvant therapy. This approach enables the valuable acquisition of information about response to treatment. Clinical response alone is not a very accurate measure of response to therapy however, and many investigators have pursued imaging to track response. MRI is emerging as a very important modality, not only because it can delineate the extent of disease and accurately assess response to therapy (Esserman *et al*. 1999*a*, 2001), but also because it enables us to look at the morphology of tumors and identify tumor patterns that are distinct at initial presentation. Distinguishing different tumor types may be an area where MRI can contribute significantly to the management of breast cancer (Esserman *et al*. 2000*b*). This is an active area of clinical investigation.

Management of DCIS

DCIS now represents a significant component of all cancers diagnosed in screening programs. Since the advent of population-based screening mammography, the incidence of DCIS has increased 500% (Esserman *et al*. 2000*b*). Typically DCIS appears as a cluster of calcifications on a mammogram. There are specific patterns of calcifications that are associated with DCIS: pleomorphic calcifications, linear and branching forms (representing calcifications deposited along the ductal lumen), as well as some amorphous calcifications. Calcifications are thought to represent either debris from cell growth or calcification of necrotic tissue. These calcifications are visible on mammography as they block ionizing radiation. The extent of suspicious calcifications is highly correlated with the extent of high grade DCIS that is replete with comedo changes (calcification and debris in the center of the duct). In lower grade or non-comedo DCIS, where calcifications are less frequent or potentially absent, the extent of calcifications seen on mammography is less likely to represent the actual extent of disease in the breast. The ability to distinguish DCIS lesions with MRI has greatly improved. Although techniques are evolving, consensus is emerging that high-resolution scans are critical to image these lesions

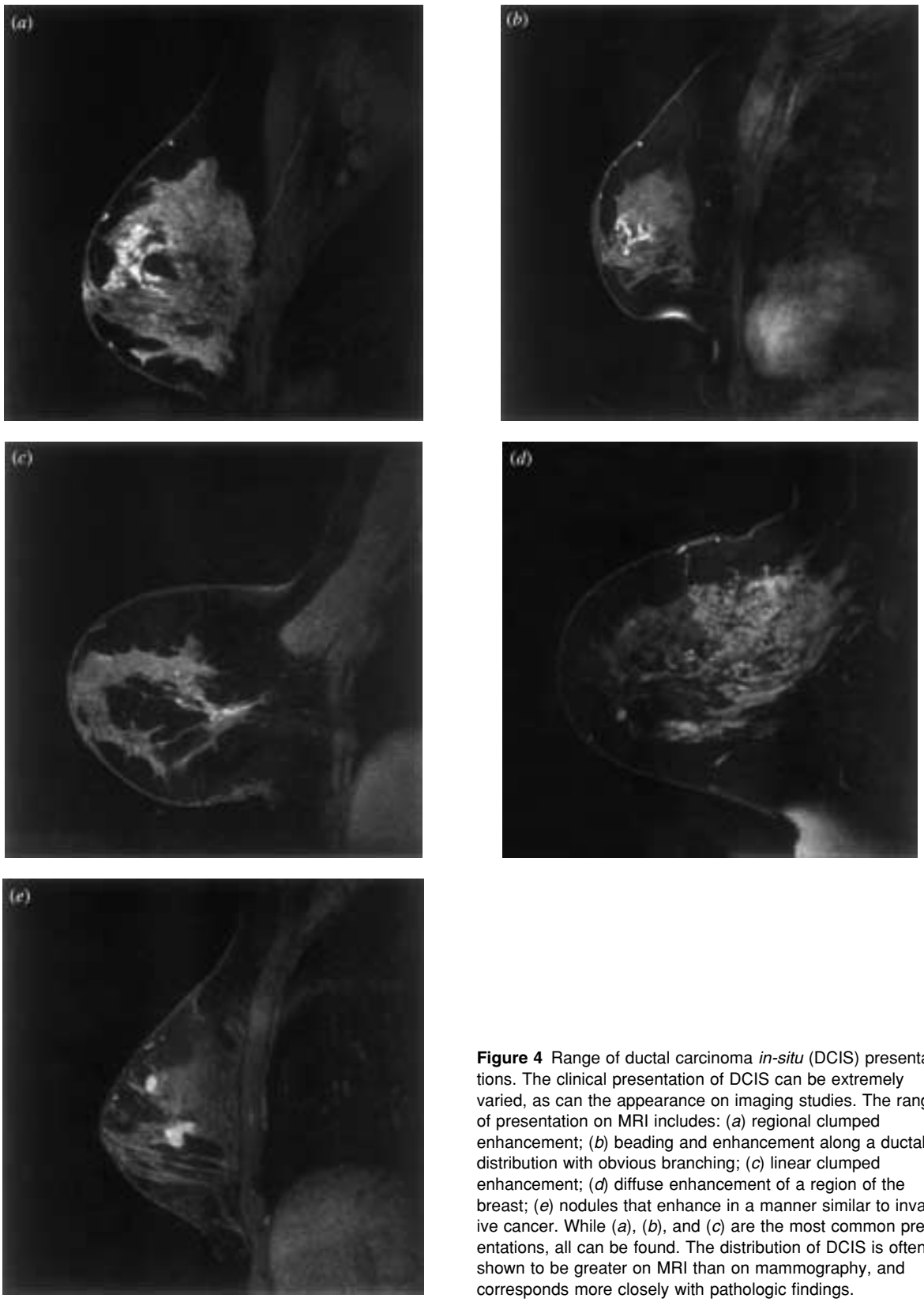

Figure 4 Range of ductal carcinoma *in-situ* (DCIS) presentations. The clinical presentation of DCIS can be extremely varied, as can the appearance on imaging studies. The range of presentation on MRI includes: (*a*) regional clumped enhancement; (*b*) beading and enhancement along a ductal distribution with obvious branching; (*c*) linear clumped enhancement; (*d*) diffuse enhancement of a region of the breast; (*e*) nodules that enhance in a manner similar to invasive cancer. While (*a*), (*b*), and (*c*) are the most common presentations, all can be found. The distribution of DCIS is often shown to be greater on MRI than on mammography, and corresponds more closely with pathologic findings.

well. Again, DCIS usually does not form a mass although, when it does, mammography and ultrasound should be able to image the extent unless it is in the midst of very dense breast tissue (Fig. 4). Biologically, DCIS develops and grows along the duct lumen and thus evidence of contrast enhancement beading along a ductal distribution is considered suspicious for DCIS.

DCIS is often associated with peritumoral cuffing and thus it is not surprising that clumping of contrast is a pattern frequently found on MRI when DCIS is present (Ernster *et al*. 1996). DCIS can present clinically as bloody nipple discharge, and 20–30% of patients with clinically suspicious discharge will have underlying cancer, usually DCIS. Often these patients have normal mammograms. Ductograms can be used to identify a filling defect (papilloma) or the presence of irregularities along the duct lumen (DCIS). Particularly in the dense breast where traditional imaging falls short, MRI can reveal or rule out the presence of DCIS and define its extent.

The range of presentations of DCIS on MR images varies substantially (see Fig. 4) and it is possible that these patterns may help us to better understand and manage DCIS in the future. The evidence suggests that all DCIS will not progress to invasive cancer and that low grade DCIS will progress more slowly than high grade DCIS (Solin *et al*. 1996, Esserman *et al*. 1999*b*). In the future, the degree of MRI abnormality may be able to dictate management. This is an active area of clinical investigation.

What problems are generated by MRI?

MRI examinations are in general more difficult to perform than mammography or ultrasound. Breast MRI studies take longer to perform than mammography or ultrasound, lasting 30–60 min and requiring injection of a contrast agent. The MRI examination may be compromised or unobtainable due to severe claustrophobia, patient size, patient motion, or presence of implanted metal. The large number of variables in the MRI examination can lead to variability between studies performed at different imaging centers or inconsistencies between serial studies performed at the same center. The interpretation of MR images is also challenging. One MRI study produces hundreds of images consisting of many thin sections through the breast, with multiple pre- and post-contrast injection views at each slice location. Assimilation of the available information is a time-consuming process and usually requires computer assistance. Added to the difficulty of interpretation is the combination of high sensitivity and moderate specificity of breast MRI. Many enhancing features on MRI, particularly those with diffuse or regional distribution that show moderate, progressive-to-stabilized enhancement, do not turn out to be cancer. This pattern can also be associated however, with DCIS, lobular carcinoma, or low grade invasive ductal carcinoma. Such findings present a diagnostic dilemma and MR-guided biopsy capabilities are not yet readily available. While MRI can demonstrate enhancing lesions on the order of 1–2 mm in size, it is virtually impossible to obtain histopathologic validation of these small imaging occurrences, making it difficult to determine the true sensitivity of breast MRI.

Areas of active clinical investigations

Clinical research falls into the categories of active clinical studies and efforts to improve technical support and interpretation. Each will be reviewed in turn. There are many active investigations in the field of MRI. We will review some of the multicenter studies and mention important areas of investigation that may change clinical management.

Co-operative group and multicenter studies

MRI for high risk screening and surveillance

Several trials are underway in the United States, Canada, The Netherlands, Germany, and England using MRI as a method of screening and surveillance in women determined to be at high risk for breast cancer by family history or genetic testing. With demonstrated sensitivity to breast cancer approaching 100%, there is increasing demand to use MRI as a screening tool in high risk women with dense breast tissue, a population poorly served by mammographic screening. Nonetheless, few data exist regarding the feasibility of MRI in this application. MRI techniques have not yet been optimized for screening, the appropriate screening interval is not known, standards for interpreting and reporting are not developed and the clinical management of 'lesions' seen on MRI is problematic, particularly in view of its low specificity and lack of integrated biopsy capabilities.

MRI for the diagnosis of mammographic and palpable abnormalities

Mammographic abnormalities are frequently biopsied and frequently found to be benign. There is a fair amount of variability in biopsy rates at significant cost, both emotional and financial (Esserman *et al*. 2000*a*, Burnside *et al*. 2001). Biopsies are recommended for women who are given a classification of BIRADS 4 or 5. BIRADS is a standardized system of reporting the results of mammographic examinations and providing specific recommendations for subsequent management. For example, BIRADS 1 indicates a negative study. BIRADS 4 is suspicious, and BIRADS 5 is highly suggestive of malignancy. However, the BIRADS 4 classification is quite broad, including lesions that have as little as a 5% chance of malignancy (either DCIS or invasive cancer) or as much as 70% chance of malignancy. To investigate the added value of MRI as a definitive diagnostic test

for women with mammographic findings that are suspicious for cancer, the International Breast MRI Consortium is conducting a multi-institutional study to assess the sensitivity and specificity of MRI for women who will undergo a definitive biopsy either by core biopsy or surgical excision. Results are expected in 2004.

MRI as a tool to evaluate the response to neoadjuvant chemotherapy

The American College of Radiology Investigators Network, in collaboration with the Specialized Program of Research Excellence and the Cancer and Leukemia Group B will be opening a multisite study to evaluate the role of MRI in predicting response to therapy. In this study, a staging technique will be used. The initial imaging types, as well as the tumor size and volume change, will be evaluated as predictors of recurrence and survival. The imaging parameters will be compared with molecular markers to determine if either or both can be used early on in the course of therapy to help guide the choice of therapeutic agents in the future.

Technical improvements

Some ongoing areas of investigation include (1) ongoing efforts to standardize MR interpretation, (2) development of MR-guided biopsy equipment and procedures, (3) evaluation of axillary lymph node metastasis, (4) MRI guidance for tumor ablation, (5) integration of MRI into breast imaging clinics through the development of dedicated breast MRI scanners, and (6) development of new contrast agents to improve specificity and labeled therapeutic agents for non-invasive evaluation of response. These are described briefly below.

Ongoing efforts to standardize interpretation, lexicon, and imaging platforms

Clinical implementation of breast MRI has been hindered by the lack of standardization and guidelines for imaging methods and interpretation. In a technical report of the Office on Women's Health 'International Working Group in Breast MRI', the findings and recommendations for clinical implementation of breast MRI were presented. One outcome of the working group was a breast MR image interpretation lexicon, analogous to the mammographic BIRADS reporting system. The breast MRI lexicon provides a common language for describing architectural features, time-course of contrast enhancement and disease extent. The lexicon continues to be tested and refined and it is anticipated that a final version will soon be issued by the American College of Radiology.

MR-guided biopsy

Incidental enhancing lesions on MRI that were not detected clinically or mammographically are a common occurrence and present a clinical management dilemma because of the low specificity of breast MRI. MR-guided biopsy techniques are essential to prevent an increase in biopsy rate and escalation of surgical strategies from breast conservation to mastectomy. A current barrier to the use of breast MRI is the lack of widespread ability to perform lesion localization using MR-guided needle and wire placement procedures. There have been several studies reporting MR-guided procedures for MRI-visible breast lesions; however, biopsy capabilities are not yet sufficiently developed for reliable use. Integrated MR-guided biopsy will require significant involvement on the part of manufacturers to equip MR scanners with apparatus and scan techniques needed to stabilize and scan the breast, provide needle guidance, and verify needle positioning. These procedures must be performed efficiently within 5–10 min of contrast injection when enhancement is present. MR-compatible core biopsy needles are under development.

MRI as a tool to evaluate lymph node metastases

Evaluation of lymph nodes is a critical element of cancer staging. However, surgical dissection of the lymph nodes is associated with complications and efforts to avoid it have led to the introduction of techniques to reduce the morbidity associated with axillary surgery. Full axillary dissection in women with clinically normal nodes is being replaced by sentinel lymph node dissection. Several multicenter cooperative group studies are underway to assess the long term impact of the sentinel node technique. It would, however, be preferable to avoid a surgical procedure altogether by non-invasively evaluating the axilla. No imaging modality is able to accurately identify nodes and determine the presence of tumor spread. Large nodes that are replaced by tumor can be seen on both mammography and MR scans, but usually these nodes are obvious clinically. Several contrast agents have been developed to differentiate benign from malignant nodes with limited success (Harms *et al.* 1993). Ponder *et al.* (2000) have developed a non-contrast technique to scan the breast and axilla in order to evaluate the presence of tumor in lymph nodes via comparison with the index cancer in the breast. The accuracy of this technique to identify the prevalence of tumor is currently under investigation in a phase II multisite study.

MRI as a tool for tumor ablation

A number of investigators are developing MR-compatible tumor ablation techniques, and these techniques are currently under study (Harms *et al.* 1993). The value of MRI- over

ultrasound-guided ablation is that the extent of disease is often much better delineated with MRI. However, the difficulty arises in the creation of MR-compatible tools and the use of them in the scanner, prolonging the time that a woman would remain in the machine. Ultrasound-guided procedures are far easier to arrange and much more comfortable for women. The combination of MR and ultrasound may prove to be the best solution. There are no studies to date that demonstrate the long term safety of ablation which enable the elimination of surgical excision, but it is an area of active research.

Development of dedicated breast MRI systems

In a 1997 consensus meeting conducted by the Department of Health and Human Services Office on Women's Health, in addition to the lack of MR-guided biopsy, integration into breast imaging centers was identified as one of the major impediments to the dissemination and clinical implementation of breast MRI. One approach to integration is the development of dedicated breast MRI systems. The potential advantages of dedicated systems include close physical proximity, flexible scheduling, faster turnaround of results, direct involvement of the breast imager in examination supervision and interpretation, ability to integrate mammographic, ultrasound, and MRI evaluations with FNA and core biopsy procedures, better patient acceptance, and lower cost.

New contrast agents and gadolinium-labeled therapeutic agents

A major limitation of breast MRI is the rapid equilibration of enhancement of the contrast agent gadolinium. Differential enhancement between malignant and benign tissue diminishes after a few minutes of injection. Contrast agents now under development may remain intravascular longer, allowing better differentiation between benign and malignant breast tissue. New therapeutic agents also under development could be combined from the vascular spaces of malignant and some benign breast tissue. Combining gadolinium with novel drug delivery compounds may enable not only a better picture of the tumor, but the measurement of the biodistribution of these compounds. Hybrid therapeutics and imaging compounds may facilitate clinical testing by enabling the measurement and monitoring of the biodistribution of the agents over the course of treatment.

Conclusion

MRI of the breast is rapidly becoming an important tool for breast cancer research and management. Table 1 summarizes our recommendations for the use of MRI as a clinical and research tool. There are data to support the use of MRI in the clinical management of breast cancer, but there has not been sufficient data to support the use of MRI outside of a clinical study. Breast MRI should be considered as one of the tools to guide clinical management in the following situations where MRI has been shown to improve local staging and better define the extent of disease.

(1) Known breast cancer in young women or women with very dense breasts.
(2) Strong suspicion of lobular cancer.
(3) Scattered calcifications suggestive of extensive DCIS or extensive intraductal cancer (EIC).
(4) A patient with bloody nipple discharge who has a normal or abnormal ductogram.
(5) Axillary adenocarcinoma without evidence of breast primary on mammogram.
(6) Suspicion of a local recurrence in a setting of scar and or radiation change in a patient who has undergone breast conserving therapy.

MRI has promise in several other areas and ongoing studies will help to define its role better. Whenever possible, referral to a center where a clinical trial is in process would be very advantageous. These trials are described in more detail earlier in this paper.

(1) Screening trials for women considered to be at very high risk for breast cancer (e.g. BRCA 1/2 mutation carriers).
(2) Trials to determine the presence of synchronous contralateral breast cancer in women with a known diagnosis of breast cancer.
(3) Trials for women with stage 2 or 3 breast cancer who will be undergoing neoadjuvant therapy.

Table 1 MRI indications.

Clinically indicated uses for MRI	Study indications for MRI
Staging in young women, dense breasts	Screening high risk women
Staging for lobular carcinoma	Screening contralateral breast, known Ca
Known DCIS, EIC, suspicion that cancer extends beyond mammographic findings	Staging, response to therapy in patients undergoing neoadjuvant therapy
Axillary carcinoma, unknown primary	Diagnostic tool after abnormal mammogram
Bloody nipple discharge, suspicion of DCIS	Evaluation, staging of axillary lymph nodes
Suspected local recurrence in setting of scar	

EIC, extensive intraductal cancer

(4) International Breast MRI Consortium Trial to assess the value of MRI in determining whether mammographic abnormalities are malignant.
(5) Evaluation of lymph nodes for malignancy.

A note of caution. All MRI scans are not equivalent. It is essential to use experienced imagers where there is significant breast MRI experience and relatively high volume of cases. A poor quality MRI examination is worse than foregoing MRI even where there is a strong indication.

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