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Converting evidence to practice: A guide for the clinical application of MRI for the screening and management of breast cancer

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ABSTRACT

Introduction: Magnetic resonance imaging (MRI) has been increasingly utilized to screen and manage breast care. As the literature demonstrating its benefit expands, so do the potential clinical indications. However, routine review of the literature is merited to re-evaluate the appropriate and cost-effective use of MRI and guide clinicians in the areas of controversy.

Methods: A literature review was performed to evaluate the current evidence for the use of MRI.

Results: Evidence supports MRI screening for genetic mutation carriers and for those with an equivalent lifetime risk (>50%). Regarding staging and management, MRI is indicated for monitoring tumour response to neoadjuvant therapy. MRI should also be considered for patients with invasive lobular carcinoma, mammographically occult breast cancer and Paget's disease.

Discussion: Though MRI is limited by moderate specificity and high cost, it can be a valuable, sensitive and cost-effective tool with thoughtful and judicious patient selection.

1. Introduction

Magnetic resonance imaging (MRI) has become an increasingly accepted breast cancer screening and management tool. The first report of breast cancer showing contrast enhancement on MRI was over two decades ago.[1] Since then, many studies have reported that contrast-MRI has sensitivity in the range of 88–100% for the detection of breast cancers as small as a few millimetres in size.[2–6] MRI currently has the greatest sensitivity of all breast imaging modalities; however, the technology is limited by moderate specificity (37–70%)[7–11] and cost. The potential indications for MRI have rapidly expanded, surpassing the concrete data demonstrating its benefit. Some of these uses are appropriate and some are less so.

In this review, we will compare the most commonly used breast imaging modalities, discuss each one's strengths and weaknesses, and examine those situations where MRI adds value. Finally, we will review the available data for and against the use of MRI and make recommendations to guide MRI's appropriate clinical application.

2. Background

It is important to understand when conventional imaging is sufficient and when MRI would add value. Perhaps the best place to begin is to review how the image of an MRI is generated in comparison to other breast imaging modalities. Each imaging tool uses different technologies to create an image

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of breast tissue. Therefore, in varied clinical situations, each modality will have different indications for optimal use.

Mammographic images of breasts are generated by sending ionising radiation through the compressed breast and onto a film plate. As the X-ray beam penetrates the breast tissue, it encounters the various densities created by fat, fibroglandular tissue, calcifications and/or neoplasms, all of which variably attenuate the X-ray beam. Low density tissues, such as fat, appear radiolucent (black), whereas high density tissues, such as calcifications, appear radiodense (white). A tumour on mammography can present as a spiculated mass, focal asymmetry, architectural distortion or a cluster of ductal calcifications. The success of mammography for tumour detection relies on the contrast between the tumour and the surrounding tissue from which it arises.

Ultrasound images of the breast are formed by transmitting high frequency sound waves into the breast tissue and measuring the waves that are reflected back. The image created is based on a computation of the speed of sound travelling through and returning from the various tissues and fluids within the breast. Because of the large difference in sound wave reflection between solids and liquids, ultrasound is particularly useful for distinguishing cystic from solid lesions. Though it has not been shown useful as an independent screening tool, it can improve cancer detection when used as a targeted adjunct to clinical breast exam or mammography.[12] Ultrasound-guided biopsy is efficient and comfortable for the patient when compared to stereotactic or MRI-guided procedures. Therefore, it is the preferred biopsy method when a lesion is appreciable on either initial ultrasound or second-look ultrasound following MRI.

Conventional imaging modalities are not without controversy and limitation. The capability for cancer detection by mammography and ultrasound is diminished when both the surrounding breast tissue and malignancy have similar densities. Both mammography and ultrasound fall short in cases where low density lesions such as ductal carcinoma *in situ*, invasive lobular cancer or small multi-focal cancers are present.

In contrast to the conventional tools described above, MR images are generated by the interaction between a magnetic field and the hydrogen atoms in the breast tissue. The resultant signal is then reconstructed into a three-dimensional representation providing high anatomic detail. Gadolinium contrast is injected to demonstrate the blood vessels in the area of the body being studied. The presence of tumour angiogenesis combined with the kinetics of contrast uptake and washout allows for consistent breast tumour enhancement on MRI. Therefore, in situations where conventional imaging is unable to effectively detect the presence or extent of a malignancy, MRI can often successfully visualise breast cancer.

Concerns about MRI's moderate specificity and high cost are merited and should be considered prior to utilising MRI in a clinical setting. The relatively high false positive rate of MRI is likely to decrease with continued improvements in the technology. For instance, the sensitivity and specificity of breast MRI are greatly affected by the temporal and spatial parameters set by the examiner. It has been shown that a combination of low temporal (kinetic) resolution and moderate spatial (anatomic) resolution can achieve high sensitivity and moderate specificity for breast cancer. As MRI's spatial resolution improves, so does the level of anatomic detail. Therefore many institutions have adopted high spatial resolution integrated with a kinetic analysis such as signal enhancement ratio. Advances in MRI have also allowed for the transition from unilateral to simultaneous bilateral exams without a decrease in image quality. Despite these improvements, MRI continues to be expensive; current costs range from US$1000 to 4000. These limitations should temper the routine use of breast MRI for the screening and management of breast cancer. However, with thoughtful and judicious patient selection MRI can be a valuable, sensitive and cost-effective tool.

3. Screening

Mammography is the only screening modality proven to detect early stage breast cancer and to reduce overall mortality.[13–20] Screening programmes currently exist in 27 countries. Although level one evidence supports its use in screening, there are clearly women whose cancers go undetected by mammography. The younger the patient the less sensitive mammography is for the detection of invasive cancer; sensitivities for women aged 70–84, 60–69, 50–59 and 40–49 are 82.7%, 75.9%, 72.2% and 66.9%, respectively.[21] The efficacy of mammography is limited in extremely dense breasts where sensitivity to detect cancer may be as low as 60–70%.[22] Additionally, women at high risk for developing lobular cancers are potentially being screened ineffectively with mammography. It is for these women that MRI as a supplemental screening modality may be of value.

While there are no data to support MRI screening for women in the general population, there is level two evidence to support annual MRI screening for women at highest risk for developing breast cancer.[23] Warner et al. compared the sensitivity of clinical breast exam, mammography, ultrasound and MRI for screening in BRCA mutation carriers.[24] Physical exam alone was the least sensitive screening tool (9%), mammography combined with physical exam found only 45% of cancers, and ultrasound did not improve performance (33% sensitivity). MRI sensitivity was superior over all other modalities (77%), however, optimal performance was found when a combination of mammography and MRI was used (95%). In the second large cohort, Kriege et al. screened 1909 women with a genetic or familial predisposition for breast cancer using clinical breast exam every 6 months and a combination of mammography and MRI every 12 months.[25] Forty-five cancers were detected overall; 32 were detected by MRI (22 of these were mammographically occult) and 18 were detected by mammography (8 were occult on MRI, 5 of which were DCIS). It is important to note that high resolution techniques were not used in this study and may account for the DCIS lesions that were missed. This study also found that MRI detected cancers earlier than mammography alone in BRCA mutation carriers (63% versus 47% lymph node negative cancers) suggesting that this population is developing high-grade, rapidly growing cancers in the midst of annual screening. These studies support the addition of MRI

to the annual screening regimen for BRCA mutation carriers. On the basis of these data, the American Cancer Society (ACS) has endorsed annual MRI screening for women with p53 mutations, PTEN mutations, and their untested first-degree relatives. Reducing the screening interval to 6 months by alternating annual mammography and MRI would potentially detect earlier stage cancers in these very high risk women.[23]

There are no data supporting the use of annual MRI screening for women that have a moderate lifetime risk for breast cancer (15–20%). Kriege et al. stratified breast cancer detection rates according to lifetime risk.[25] Very high risk women (e.g. those with a BRCA mutation or an estimated >50% lifetime risk of breast cancer) had a cancer detection rate of 26.5 per 1000 patients. The high risk (30–49% lifetime risk) and moderate risk (15–29% lifetime risk) women had cancer detection rates that were much lower, 5.4 and 7.8 per 1000, respectively. In these high and moderate risk women, MRI offers little value beyond traditional screening methods.

Precursor lesions such as lobular carcinoma *in situ* (LCIS), atypical lobular hyperplasia (ALH) and atypical ductal hyperplasia (ADH) have variable risk depending on age. Women with lobular neoplasias have a 6- to 10-fold risk of developing ipsilateral or contralateral lobular cancer.[26] Similarly, women with ADH or ALH have a 4-fold risk of developing breast cancer,[26,27] which doubles if the woman has an associated family history.[28] In women less than 45 years of age with atypia of any kind, the risk of developing breast cancer is up to 7-fold higher than the average risk.[29] Mammographic density is also a strong independent risk factor for breast cancer development.[30,31] Women with BIRADS 4 breast density may have up to a 4- to 6-fold increased risk for developing breast cancer.[32] Furthermore, tumours are more likely to arise in the areas of greatest density.[33] These are challenging clinical situations where screening MRI may be beneficial; however, the current guidelines do not clearly define an effective screening strategy in these areas of controversy.

One potential way to address the dilemma of screening high and moderate risk women is to use a quantitative risk estimate that combines the Gail score with mammographic density. The Gail model is a well-accepted breast cancer risk assessment tool that calculates a woman's 5-year and lifetime risk based upon age, age at menarche, age at first live birth, family history of breast cancer and number of breast biopsies.[34] Tice and colleagues have since demonstrated that measurement of breast density estimates breast cancer risk as accurately as the Gail model.[35] Furthermore, when the Gail score was adjusted for breast density, overall predictive accuracy improved and was superior to each risk assessment tool independently. The density-modified Gail risk is calculated by multiplying the lifetime Gail risk by 0.59, 1.00, 1.41 or 1.94 for a BIRADS of 1, 2, 3 or 4, respectively. Those with a lifetime risk of >50% as calculated by the density-modified Gail model are recommended for MRI screening. Consideration can be given to women with a 35–49% lifetime risk using this tool, though there is no current evidence to support the addition of annual MRI screening.

Fig. 1 shows the screening breast MRI of a woman categorised as very high risk according to her density-modified Gail score. MRI was performed on this 45-year-old woman with extremely dense breasts and a history of LCIS. Her lifetime risk of developing breast cancer using the Gail model and the density-modified Gail model was 28% and 54%, respectively. Her age and history of LCIS, combined with her high breast density, supported the use of MRI screening. MRI performed on this woman detected a 1.8 cm lobular carcinoma not seen on mammography and not appreciated on physical exam despite its peripheral location. This illustrates how a quantitative risk measurement can be helpful when there is a question regarding the benefit of MRI. Though family history, precursor lesions or breast density alone may not meet criteria to prompt annual screening with MRI, the summation of two or more of these independent variables may identify women with risk sufficient to warrant annual MRI screening.

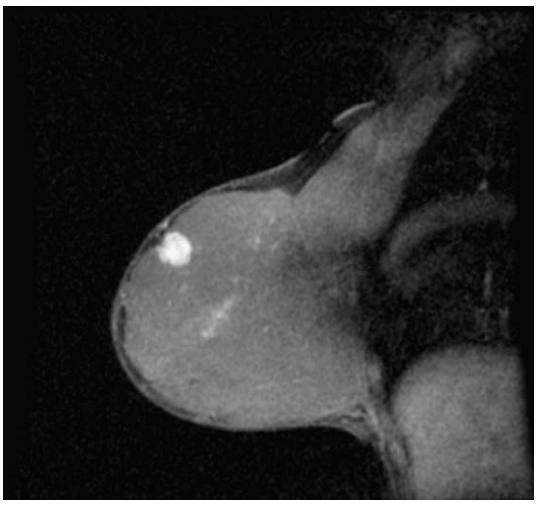

Fig. 1 – Screening breast magnetic resonance imaging (MRI) of a woman with BIRADS 4 breast density and lobular carcinoma in situ (LCIS). A 1.8 cm mammographically occult invasive lobular carcinoma was identified. This tumour was not palpable, even retrospectively.

An important consideration in instituting MRI screening is its cost. MRI is an expensive test and even further costs are generated when evaluating MRI findings, many of which turn out to be benign. Thus, it is important to be judicious in the use of MRI. In the population where screening mammography is recommended (women age 50–70), the detection rate is 5–7 cancers per 1000 patients; in women 40–49, the detection rate is 1–2 cancers per 1000 patients. MRI is at least 10 times more expensive and, thus, it is more reasonable to consider MRI when cancer rates approach 20 per 1000 patients. Plevritis et al. studied the costs of adding MRI to annual mammography screening and noted that multiple factors influenced cost-effectiveness including the patient's prior probability of breast cancer, the effectiveness of mammography, the cost of MRI, and the quality of life gains from MRI.[36] This study found that the cost per quality adjusted life year (QALY) saved for annual MRI plus mammography relative to annual mammography alone was determined to vary with age as well as with BRCA mutation carrier status.[50] For women aged 35–54 years of age, the estimated cost per QALY was US$55,420 for BRCA1 mutation carriers and US$130,695 for BRCA2 mutation carriers. Broadening the age range for annual screening from 25 to 69 years of age increased the cost per QALY to US$88,651

and US$188,034 for BRCA1 and BRCA2 mutation carriers respectively. This increase in cost is likely attributable to the lower incidence of breast cancer in younger women (aged 25–34) and the declining quality of life and competing risk of death from other causes in older women (>55 years). The single most important variable influencing the cost-effectiveness of MRI screening, however, was the prior probability of breast cancer. There are no data on the cost-effectiveness of MRI screening for women with mammographically dense breasts, previous history of chest irradiation (e.g. Hodgkins disease), atypia or previous breast cancer. However, all available evidence and expert opinion suggest that screening with MRI is more cost-effective as the risk of breast cancer increases, mammography performance decreases, quality of life gains increase and the cost of MRI decreases.[23]

In summary, evidence supports annual MRI screening for women with an estimated lifetime risk $\geqslant$50%, which largely includes women with a BRCA1 or 2 genetic mutation. The American Cancer Society (ACS) expert consensus panel also recommends annual MRI screening for women with a lifetime risk 20–25% as calculated by risk assessment models based on family history, such as BRCAPRO.[23] This translates to an MRI screening recommendation for those women who have not had genetic testing but are predicted to have at least a 20–25% risk of being a genetic mutation carrier or a 20–25% lifetime risk based on the Claus model. The ACS does not recommend MRI screening for women with lifetime risk of 20–25% based on the Gail model. In the United States (US), the most frequently used tool to estimate a woman's lifetime risk for breast cancer is the Gail model, which combines family history with additional risk factors, such as reproductive history. When adjusted for breast density, this model's predictive accuracy improves. We feel that a lifetime risk $\geqslant$50% as calculated by the density-modified Gail model fits the risk category for which there is evidence demonstrating the efficacy of MRI screening. It targets a high risk population for whom mammography is least sensitive. A limitation of the Gail model is that it only includes first-degree maternal relatives, and may underestimate risk from paternal or extended family members. Thus, women considered very high risk based on family history alone (BRCAPRO or Claus model) may also meet criteria. Clinical discretion should be used in these cases and ultimately, MRI screening should be recommended only to those patients who would benefit most (see Table 1).[23,36] There is sufficient evidence to recommend annual MRI screening for very high risk women, such as genetic mutation carriers, by alternating MRI and mammography every 6 months. Consideration for annual screening MRI should be given to women who have a lifetime risk of >50% based on a density-modified Gail score and untested women with a strong family history.

Table 1 – Evidence to support the use of (magnetic resonance imaging) MRI for screening

Annual MRI recommended (level 2 evidence)
BRCA mutation carriers
First-degree relative of BRCA carrier, but not tested
Annual MRI recommended (level 3 and 4 evidence)
History of radiation to chest between age 10 and 30[A]
Patients with Li Fraumeni syndrome and first-degree relatives[A]
Lifetime risk $\geqslant$20–25% based on BRCAPRO or Claus model
Lifetime risk $\geqslant$50% based on density-modified Gail model[A]
Lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH) and atypical ductal hyperplasia (ADH) in women <45 years of age[A]
Annual MRI can be considered
Lifetime risk 35–49% based on density-modified Gail model
LCIS in women >45 years of age[a]
Personal history of invasive lobular cancer[a]
No current evidence to support annual MRI
Secondary screen for abnormal mammogram
Lifetime risk 15–20% based on family history
Personal history of breast cancer
ALH or ADH alone
BIRADS 4 breast density
History of mammographically occult cancer in the absence of other risk factors (young age, dense breasts, etc.)

This table provides a summary of indications for annual screening MRI and the level of evidence to support its use. Although the ACS recommends annual screening MRI for women with a lifetime risk 20–25% or greater based on family history, we have not found this supported in the literature.

A Recommendation for annual MRI screening based upon the estimated lifetime risk >50%; however, these specific conditions have not been tested in a cohort study using MRI screening.

a Consideration for annual MRI screening based on the difficulty in detecting lobular cancer with conventional imaging. Additional risks factors and breast density should also be taken into consideration before recommending annual MRI screening.

4. Diagnosis

Currently, breast cancer diagnoses are prompted by a palpable mass or a lesion found on screening imaging. Detection of a suspicious lesion is then followed by a biopsy for confirmation of diagnosis. Obtaining tissue is necessary not only to distinguish *in situ* from invasive disease but also to provide valuable tumour marker information. If neoadjuvant chemotherapy is being considered, tumour markers should be assessed prior to initiating treatment.

Diagnostic characterisation of lesions by MRI is improving, but it is not sufficiently specific to substitute a biopsy. The performance of MRI as a diagnostic procedure was evaluated by the International Breast MRI Consortium (IBMC) study 6883. This study found that high spatial resolution scans were as sensitive and specific as kinetic sequences that did not yield anatomic detail. This study also demonstrated that MRI had a significantly higher yield of incidental lesions which proved to be cancer when compared to mammography (0.18 versus 0.072).[37] However, MRI also shows enhancement of a variety of benign lesions, such as fibroadenoma and sclerosing adenosis. Of the 78 women who had additional suspicious MRI lesions and underwent biopsy, 56 (73%) had cancer, and 22 (27%) did not. While the majority of suspicious lesions were cancer, a sizeable fraction were not. Therefore, surgeons should not proceed with an oncologic procedure, especially nodal staging or mastectomy, for an MRI enhancing lesion without a tissue diagnosis. A recent study suggests that DCIS can potentially be diagnosed prospectively using MRI.[38]

However, validation in a multi-centre setting is needed before MRI can be considered a reliable diagnostic tool.

With respect to cost, MRI competes with the less expensive mammogram and core needle biopsy (CNB). One study compared CNB, MRI, and excisional biopsy in the work-up of suspicious breast lesions.[39] The authors concluded that both MRI and CNB were cost-effective alternatives to excisional biopsy but that in most instances, CNB was the least costly diagnostic option. MRI does not eliminate the need for a biopsy, therefore, we do not recommend the routine use of MRI as a diagnostic tool. One potential use for diagnostic MRI could be the localisation of a lesion seen only on one mammographic view and not visualised with ultrasound.

There is no role for MRI in the diagnosis of breast cancer unless suspicious mammographic findings cannot be evaluated or localised.

5. Staging and management

Once a cancer is diagnosed, staging is the next step in guiding the treatment plan. Currently, physicians use physical exam with the aid of imaging to estimate clinical stage. This assessment prompts important decisions, such as the need for neoadjuvant versus adjuvant chemotherapy, or mastectomy versus breast conservation. The accuracy of estimating disease extent by mammogram or clinical exam is reduced when the breast tissue is dense or the cancer does not form a discrete mass. In these circumstances, MRI can be of great benefit, justifying its cost. Although the data on the cost-effectiveness of MRI as a staging tool are limited, at least one prior study has proposed that the estimated costs avoided by the use of pre-operative staging MRI (e.g. cost of re-excising positive margins, emotional cost to the patient) justifies the cost of MRI up to $2000 per scan.[40]

The following is a discussion of the clinical scenarios where improved sensitivity for breast cancer detection and characterisation would improve clinical management and in which MRI should be considered. A summary of these recommendations can be found in Table 2.

Table 2 – Evidence to support the use of MRI for staging and evaluation

Strong evidence (level 2 evidence)
Determining extent of disease after neoadjuvant chemotherapy
MRI should be considered (level 3 or 4 evidence)
Mammographically occult breast cancer
Defining the extent of invasive lobular cancer
Screening for synchronous contralateral breast cancer
Paget's disease
Multi-focal/multi-centric disease
Patient selection for total skin-sparing mastectomy
Differentiating recurrence from scar
Positive margins after partial mastectomy
Investigational
Monitoring response to neoadjuvant therapy
Defining the extent of DCIS

This table provides a summary of indications for MRI in patients diagnosed with breast cancer and the level of evidence to support its use.

5.1. *Invasive lobular carcinoma*

Though invasive lobular carcinoma (ILC) is the second most common invasive breast cancer, it only represents 5–10% of all breast cancers. It has an increased propensity to be multi-focal, multi-centric and/or bilateral in comparison to other histologic types. Due to its insidious nature, ILC is more difficult to detect and, once detected, the extent of disease is difficult to determine.

A recent study correlated mammographic and MRI tumour size to pathologic size for 67 patients with invasive lobular carcinoma. MRI was significantly more accurate in estimating tumour size (51/67) while mammography was found to frequently underestimate tumour size (29/67). MRI overestimated tumour size in seven patients, however, these patients had concurrent DCIS or LCIS accounting for the size discrepancy.[41] Another study evaluated ILC tumour size as estimated by physical examination, mammography, sonography and MRI and compared them to pathologic size. MRI was again demonstrated to be superior over conventional imaging and clinical assessment.[42] When used in the pre-operative setting, MRI may be helpful for reducing the number of operations needed to achieve clear margins in women pursuing breast conservation therapy (BCT). It may also identify those patients for whom mastectomy is more appropriate.

Evidence supports the use of MRI for determining the extent of disease in patients with invasive lobular carcinoma.

5.2. *Ductal carcinoma in situ*

DCIS is widely acknowledged to be a non-obligate precursor lesion for invasive breast cancer. Regardless, there is still agreement that DCIS, especially high-grade DCIS, should be treated to avoid progression to or occurrence of invasive cancer. The challenge posed by DCIS is that it can often be multi-focal or associated with occult invasive disease. By implementing strict criteria specific for DCIS, MRI has been shown to be more accurate than mammography in detecting DCIS and estimating the extent of disease, specifically high-grade DCIS.[38,43] MRI also appears to be particularly strong at identifying multi-focality, occult invasion, and residual disease following neoadjuvant hormonal therapy.[44] Imaging features correlate well with pathologic and biologic features, such as nuclear grade, which suggests that MRI captures the heterogeneity of the disease. Despite the fact that MRI may improve upon conventional imaging for the evaluation of DCIS, limited data exist to support the routine use of MRI in these patients. Neoadjuvant hormonal therapy for DCIS is being prospectively studied in an ongoing trial, in which serial MRI is being used to monitor response to therapy and identify areas suspicious for invasive disease.[44]

There is no evidence to support the routine use of MRI to evaluate DCIS. However, MRI may be useful when DCIS is suspected to be extensive, multi-focal, or when consider-

ing the use of neoadjuvant hormonal therapy on a study protocol.

5.3. *Axillary nodal metastasis with unknown primary*

The presentation of isolated axillary metastasis without clinical or mammographic evidence of a breast primary is rare and often treated with a modified radical mastectomy (MRM). However, many of these patients do not have evidence of microscopic disease within their mastectomy specimen.[45,46] MRI is now a common adjunct in the radiographic evaluation of these patients due to its increased sensitivity. MRI can often identify a primary lesion when one is present as well as determine whether the lesion is discrete or multi-focal. This information can be useful in determining a patient's candidacy for BCT.

The largest prospective study to date evaluated 40 patients presenting with axillary cancer without an apparent breast cancer.[47] All patients underwent MRI, which identified the primary lesion in 28 (70%) patients. Of the 22 patients who underwent surgical excision, cancer was identified by MRI in 21 cases (95%). Overall, 47% of the patients successfully preserved their breast (partial mastectomy, axillary lymph node dissection and radiation therapy in MRI-positive patients; axillary lymph node dissection with radiation therapy in MRI-negative patients). They reported that no local recurrences had occurred at the time of publication with a median follow-up of 19 months. In the 18 patients who underwent mastectomy, all MRI-positive patients were pathologically confirmed to have cancer. Of the five women with a negative MRI, one patient had tumour in her surgical specimen. In this single false negative, the authors stated that the patient was obese and that the tumour was located in an area deep in the breast that was inadequately visualised on the MRI.[47] The performance of MRI was excellent in this study, but careful patient selection is important and the surgeon should be certain that an adequate MRI study has been performed before offering BCT.

Some studies have reported high local failure rates in occult breast cancer patients treated with radiation therapy alone; however, these patients were treated prior to the MRI era. Theoretically, if their tumours were detectable by MRI, these patients may have had the advantage of surgical excision, which would have likely decreased the reported local recurrence rates. Though a modified radical mastectomy may provide effective local control, carefully selected BCT patients have demonstrated an equivalent short-term survival outcome. Further follow-up is needed for those who had a negative MRI and elected for BCT. Patients could potentially avoid breast surgery entirely if no tumour is found on mammography or MRI.

MRI is indicated to identify the presence of a primary lesion in a patient presenting with axillary nodal metastases and mammographically occult cancers.

5.4. *Paget's disease*

Paget's disease represents an estimated 2–3% of breast cancers. Paget's disease is associated with underlying DCIS or invasive cancer in up to 98.6% of cases, which often goes undetected or underestimated by mammography. A review of 70 patients demonstrated that women with Paget's disease were likely to have high-grade tumours, multi-focal disease, over-expression of c-erb B2, and have an overall poorer prognosis.[48] For these reasons, women with Paget's have historically undergone a mastectomy with axillary lymph node dissection. More recently, however, BCT has been proven as a safe alternative.[49]

Given the superior sensitivity of MRI for high-grade DCIS, multi-focal disease, and mammographically occult disease, it is logical to conclude that MRI is the best tool to evaluate Paget's disease. Though the data are very limited, the available evidence is encouraging. In a series of 9 cases, 8 had underlying DCIS or invasive cancer. All 8 of these lesions (100%) were visualised on MRI while only 25% were appreciated on mammogram.[50] Larger studies are needed but the available data are a compelling argument in support of MRI to evaluate Paget's disease of the breast.

MRI is recommended in all patients newly diagnosed with Paget's disease to evaluate the presence and extent of underlying disease, particularly in patients pursuing BCT.

5.5. *Screening for synchronous contralateral breast cancer*

The presence of a synchronous contralateral breast cancer would greatly change the surgical management of a newly diagnosed patient. We currently rely on mammography to screen the contralateral breast at the time of diagnosis. While several studies have been published about the use of MRI to screen the contralateral breast, the concerns of high cost, moderate specificity and unnecessary biopsies have also surfaced. Though MRI has been shown to detect contralateral disease in only 3.1% of breast cancer patients, the chance of a biopsy is 12.5%.[51] The anxiety prompted by MRI detected lesions in the contralateral breast is of genuine concern. Despite the fact that the majority of women recommended for biopsy will not have a synchronous cancer, many patients may opt for bilateral mastectomy due to their anxiety.

Though MRI is not indicated to evaluate the contralateral breast in all women with newly diagnosed breast cancer, there is likely a select patient population for whom MRI may be beneficial. Memorial Sloan-Kettering Cancer Center (MSKCC) evaluated screening MRI's performed on the asymptomatic, mammographically normal, contralateral breast in patients with newly diagnosed breast cancer. Synchronous contralateral breast cancer detection rates were higher for those with a history of breast cancer in a first-degree relative as compared to those without (13% versus 3%). Patients with invasive lobular carcinoma also had higher cancer detection rates as compared to other histologic diagnoses (13% versus 4%).[52] Though the data are limited, these characteristics should prompt consideration for MRI screening of the contralateral breast. MRI should also be considered for women planning to undergo a unilateral mastectomy with TRAM reconstruction as a TRAM on one side precludes the ability to perform a TRAM on the contralateral side should cancer be detected in the future. In general, the clinician can rely

on the recommendations for MRI screening already discussed when considering whether to screen the contralateral breast of a woman who presents with breast cancer.

> MRI should be used to screen women for contralateral and ipsilateral synchronous cancers when they have invasive lobular carcinoma or a very high risk for breast cancer. MRI is also indicated when planning for unilateral TRAM reconstruction.

5.6. *Neoadjuvant chemotherapy*

Neoadjuvant chemotherapy is increasingly being used in the treatment of locally advanced breast cancer as it potentially offers these women the option of BCT. In this setting, there is a need for a non-invasive tool to accurately assess the tumour before and after the neoadjuvant treatment period. Clinical exam, mammography and ultrasound have traditionally been used to monitor progress, however these methods have only modest capability for predicting residual tumour size in the neoadjuvant setting.[53,54] Chagpar et al. found that when residual pathologic tumour size was compared with projected tumour sizes generated from physical exam, mammography and ultrasonography, correlation coefficients were 0.42, 0.41 and 0.42, respectively.[54] Furthermore, mammography is particularly inaccurate at predicting residual tumour size in the setting of calcifications as tumour associated microcalcifications typically remain unchanged after neoadjuvant chemotherapy.[53,55]

MRI has repeatedly demonstrated the capability to accurately reflect tumour response to therapy as well as residual tumour.[53,56–58] Fig. 2 illustrates MRI's ability to accurately represent tumour response to neoadjuvant chemotherapy. Pre-treatment and post-treatment MR images of three patients are shown, demonstrating the range of responses from complete response to progressive disease. Many investigators have shown that MRI represents the extent of residual cancer found by pathologic examination of the surgical specimen after neoadjuvant chemotherapy.[53,55,56] In a study at the University of California, San Francisco (UCSF), MRI correctly identified residual or primary cancer in 55 of 58 cases and defined the extent of cancer in 54 of 58 cases.[40]

MRI holds promise as an early predictor of response. We reported that MRI assessment of tumour volume early in the neoadjuvant treatment period can predict final response to neoadjuvant chemotherapy.[59] A significant change in MRI tumour volume after one cycle of neoadjuvant chemotherapy was found to correlate with final MRI volume ($p = 0.0005$). Fig. 3 shows serial MR images from the same patient throughout her neoadjuvant treatment. This patient underwent successful BCT and remains free of recurrence after 6 years. The performance of MRI volume change is being tested in a prospective multi-centre study, the I-SPY TRIAL.[70]

Pre-treatment MRI tumour pattern has also been found to be predictive of BCT eligibility.[60] Tumours that were well circumscribed on initial MRI underwent more circumferential tumour shrinkage in response to neoadjuvant chemotherapy, as compared to those with a more diffuse pattern, and thus were more likely to achieve BCT.

The information provided by MRI to clinicians and locally advanced breast cancer (LABC) patients in the neoadjuvant setting can be useful for determining which patients would have successful breast conservation versus which patients would be better served with a mastectomy.

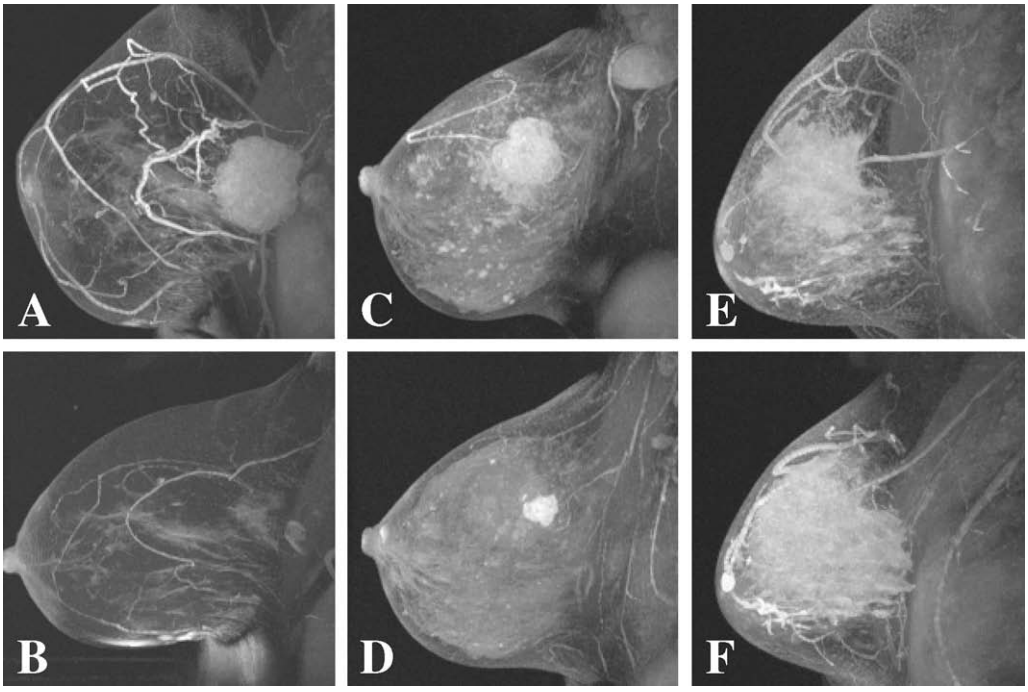

Fig. 2 – Monitoring response to neoadjuvant chemotherapy with MRI. (A) and (B) represent the pre-treatment and post-treatment MR images of a patient who had a complete response. (C) and (D) represent pre-treatment and post-treatment images from a patient whose tumour underwent a partial response. (E) and (F) demonstrate progressive disease despite neoadjuvant chemotherapy.

There is sufficient evidence to recommend the use of MRI to monitor tumour response to neoadjuvant chemotherapy and to assess BCT eligibility after treatment.

5.7. *Patient selection for total skin-sparing mastectomy*

For a select group of patients undergoing mastectomy, total skin-sparing mastectomy (TSSM) is a viable option with superior cosmetic results. This technique preserves the entire skin envelope including the skin of the nipple-areolar complex (NAC). Incisional approaches and reconstruction options that optimise outcome and safety in the setting of TSSM have been described; however, patient selection for this procedure has not been standardised.[61,62] Although most clinicians use a combination of clinical exam and imaging parameters to assess patient candidacy for TSSM, some use only clinical evaluation. When patient selection is based solely on clinical parameters, serial sectioning of the nipple core on final pathology reveals disease in 45.5% (54/112) of attempted total skin-sparing mastectomies.[63] The addition of imaging criteria to the selection process improves operative success; using ultrasound or mammography to exclude patients with tumours located within 1–2 cm of the NAC reduces the number of selected patients with nipple involvement to 6.9% (4/58) and 10% (14/137), respectively.[64,65] When MRI is the principal imaging tool used to evaluate for disease absence within 2 cm of the NAC, only 3.1% (4/129) of cases demonstrate disease involvement on final pathologic examination. These findings were confirmed in a recent study citing a 97% success

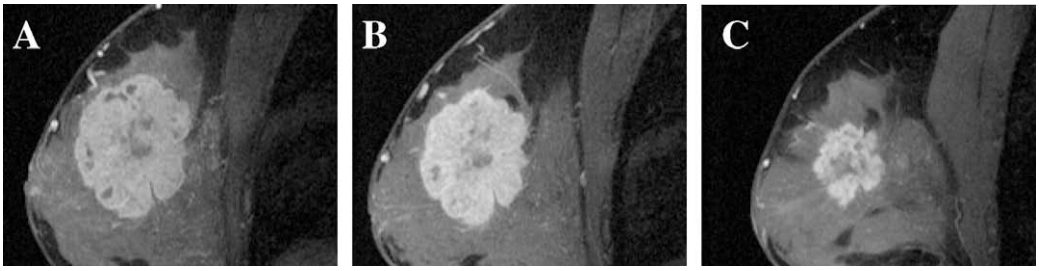

Fig. 3 – Tumour volume reduction seen throughout neoadjuvant treatment. Serial MR images demonstrate tumour volume shrinkage from 65 cm^3 on pre-treatment image (A) to 42 cm^3 after 1 cycle of AC (B) to 4 cm^3 after 4 cycles of AC (C).

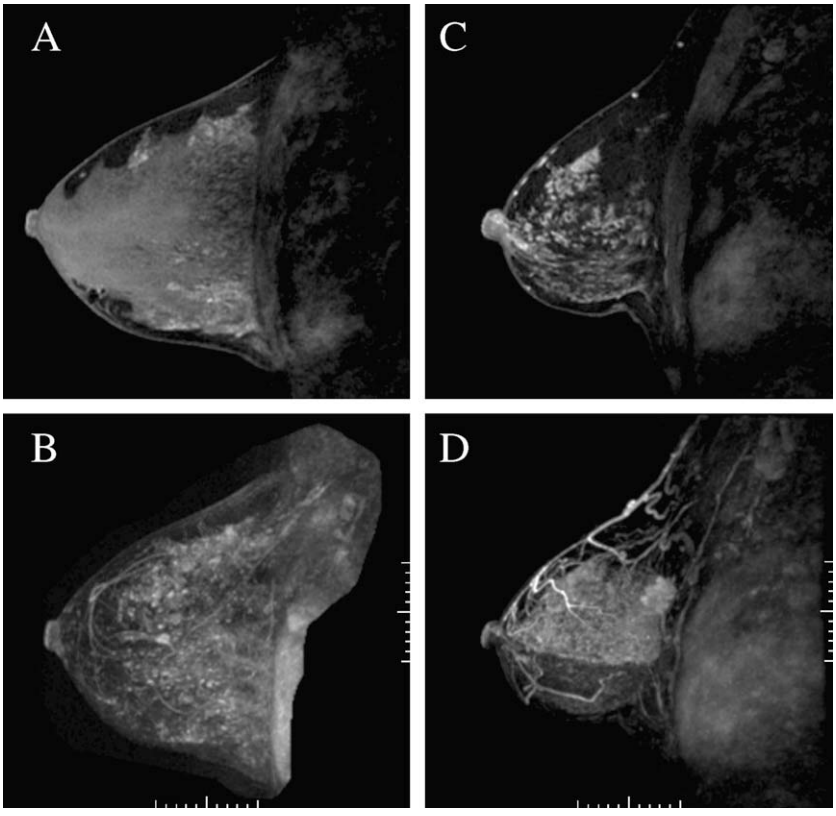

Fig. 4 – Pre-operative MRI is used to guide patient selection for total skin-sparing mastectomy. (A, B) A selected patient that has no evidence of contrast enhancement near the nipple areolar complex with a corresponding maximum intensity projection image. (C, D) An excluded patient with enhancement involving the nipple areolar complex with a corresponding maximum intensity projection image.

rate when using MRI to exclude nipple involvement.[61] Fig. 4 demonstrates MRI's ability to accurately demonstrate nipple involvement.

MRI is helpful in excluding tumour involvement of the retro-areolar ducts, thus assisting in the selection of candidates for total skin-sparing mastectomy.

6. Concerns

6.1. *Low specificity and lack of standardisation*

Though MRI has been repeatedly proven to detect invasive breast cancers with a high sensitivity, MR imaging is not without pitfalls.[2,3,11] One of the largest drawbacks to MRI is the moderate specificity reported by several studies.[66–68] Harms et al. reported a specificity of 37% and found that, of the false positive lesions detected on MRI, only 53% of them consisted of lesions associated with an increased risk of malignancy (e.g. LCIS, atypical hyperplasia).[11] MRI cannot distinguish cancer from the various other causes of vascular enhancement such as inflammation, sclerosing adenosis, or papilloma. These so-called false positives have increased rates of proliferating macrophages and CD34 endothelial cells relative to benign lesions.[69] MRI's lower specificity leads to unnecessary interventions to evaluate enhancing lesions that are often found to be benign.

Perhaps contributing to the variable specificity reported for MRI is the lack of a standard imaging protocol. The large number of variables that can be modified in an MRI examination can lead to inconsistencies between MRI studies performed at different institutions as well as serial images performed at the same institution. Heywang et al. investigated parameters for various contrast enhanced dynamic MRI protocols as well as various exam interpretation schema and found that, depending on the settings, MRI sensitivity could fluctuate anywhere between 70% and 98% while specificity could change inversely between 30% and 96%.[66] Because of the emphasis on identifying subclinical disease and characterising the extent of disease, we have prioritised high spatial resolution as the preferred technique at UCSF and are validating this technique in a multi-centre study in the setting of neoadjuvant therapy.[70] This technique maximises the information obtained and includes a three-point kinetic analysis to provide additional characterisation of tumours. Achieving widely available and reproducible MRI standards will help improve MRI's ability to accurately distinguish between benign and malignant lesions. Standardisation will also enable data from different institutions to be comparable and for a broader group to rapidly apply improvements in technique.

7. Conclusions

MRI is an instrumental tool for the screening and management of breast cancer in select patients. Its strengths lie where current imaging tools are limited, such as the evaluation of high risk women with dense breast tissue and assessment of disease extent for mammographically subtle cancers. In addition, MRI holds promise as a non-invasive tool for monitoring response to neoadjuvant chemotherapy, evaluating residual disease for surgical planning and measuring in vivo tumour response to investigational agents. This should only be done in the context of a clinical trial. As our understanding of MRI's benefits and limitations improves, so will our ability to discern when its application is beneficial or harmful. Improvements in technique and standardisation will allow a broader implementation and better define its clinical utility. The application of MRI in clinical practice should be guided by the general principle that MRI is beneficial in high risk patients where increased sensitivity for detection and characterisation is needed. It is of little or negative value when risk is low and the increased sensitivity would largely generate false positives.

Conflict of interest statement

None declared.

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