MINI-REVIEW

Breast Magnetic Resonance Imaging Indications in Current Practice

Sawsan Abdulkareem Taif

Abstract

Although mammography is the primary imaging modality for the breast, it has its limitations especially with dense breast parenchyma. Breast magnetic resonance imaging (MRI) has evolved into an important adjunctive tool as it is currently the most sensitive technique for breast cancer detection. Despite this high sensitivity, overlap in the appearances of some benign and malignant breast lesions results in additional unnecessary intervention with negative results. These false positives, in addition to high cost and limited availability, necessitate establishing proper indications for breast MRI. The literature was here reviewed for recent clinical trials, meta-analyses and review papers which have studied this important subject. PubMed; the US national library of medicine, was utilized to review the literature in the last twenty years. Using the obtained information, current uses of breast MRI are discussed in this paper to determine the indications which are relevant to clinical practice.

Keywords: MRI - indications - applications

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Introduction

In the last few years, magnetic resonance imaging (MRI) has emerged as an adjunctive tool to mammography in the assessment of various breast conditions. The high sensitivity for cancer detection allows it to be used in evaluating several aspects of breast cancer diagnosis and treatment. The American Cancer Society (ACS) and the American College of Radiology (ACR) have discussed this issue and suggested several scenarios in which breast MRI can be used for both diagnostic and screening purposes (Saslow et al., 2007; Argus and Mahoney, 2010; ACR, 2013). However; controversy is still present regarding which of these indications proved to be useful.

In this paper; PubMed, the US national library of medicine, was utilized to review the literature in the last twenty years. Medline was reviewed for recent clinical trials, meta-analyses and review papers which have studied this important subject. Using the obtained information, current uses of breast MRI are discussed to determine the indications which are relevant to clinical practice.

Worldwide; MRI is increasingly performed in different clinical situations. The sensitivity, specificity as well as the commonest clinical scenarios for breast MRI will be reviewed in the next section to identify indications with the potential to improve patient care making them most applicable to clinical practice.

MRI sensitivity and specificity

MRI is highly sensitive but not so specific; sensitivity for breast cancer is ranging from 85% to 100% (Heywang-Kobrunner et al., 1997). In contrast, specificity is much more variable, reported from 37% up to 100% (Lee, 2004; Enriquez and Listinsky, 2009).

The use of dynamic contrast has increased both the sensitivity and specificity of breast cancer detection. Nevertheless; common causes of false-positive (Figure 1) and rarer causes of false-negative diagnoses still occur. False positive results can be minimized by confirming that the enhancement is genuine and not an artifact; as well as differentiating it from normal enhancing breast structures. Analyzing the enhancing lesions according to the American College of Radiology breast imaging reporting and data system (BI-RADS) lexicon was also found to be an important factor in reducing false positive results.

The few false negatives occasionally result from lack of breast cancer enhancement; or from overlooked or misinterpreted enhancing lesions (Millet et al., 2012).

A recent study done by Mahoney et al has reported the positive predictive value (PPV) for cancer of MRI suspicious lesions to be 27.8%. The PPV for BIRADS 4 lesion was comparable to mammography (20.5%) while PPV for BIRADS 5 lesion was 71.4% which is much lower than BIRADS 5 mammograms (81-95%).

For masses, irregular shape, irregular or spiculated margins, and marked internal enhancement were most predictive of malignancy (Figure 2). For non-mass like enhancement; ductal, clumped, and reticular or dendritic enhancement were the features frequently seen with malignancy. Kinetic enhancement features were less predictive of malignancy than were morphologic features

*Department Radiology, Khoula Hospital, Muscat, Oman *For correspondence: sawsantaif@gmail.com*

(Mahoney et al., 2012).

MRI technique

MR breast examination is done in the prone position using a standard breast coil.

Field strength of 1.5 Tesla and more is required for imaging the breast. The morphological sequences which include T1, T2 and a fat suppression sequence help to evaluate breast tissue density and to assess the condition of the skin, axillae, and the edge of the pectoral muscle. In addition; standard breast MRI protocol requires the use of dynamic contrast enhancement, with subtraction technique which facilitates visualization of contrast uptake of breast lesions. The time/intensity curves for contrast uptake are then created to show pattern of enhancement.

The contrast agent used in MRI is gadolinium (Gd). Various types of Gd are used in different centers. Pediconi etal studied the effect of using two different types and found that lesion detection and characterization is significantly better with 0.1 mmol/ kg gadobenate dimeglumine than same dose of gadopentetate dimeglumine (Pediconi et al., 2008).

Clinical Scenarios for Breast MRI

Axillary lymph node metastasis from an occult breast cancer

Previous studies believed that patients presenting with metastatic adenocarcinoma involving the axillary lymph nodes with no evidence of breast cancer on conventional studies should be considered to have an occult ipsilateral breast cancer; an entity which is forming less than1% of all breast cancer cases (Orel et al., 1999).

A patient presented with an isolated axillary lymphadenopathy should be subjected to mammography and physical examination. However; if primary tumor could not be identified, fine needle aspiration (FNA) or histological examination from the enlarged lymph node has to be done.

Bilateral breast MRI to look for an occult breast cancer is strongly indicated if histology reveals an adenocarcinoma or undifferentiated carcinoma.

Studies using MRI have reported detection rates for an occult breast cancer ranging from 62% to 86% in these patients (Orel et al., 1999; Buchanan et al., 2005).Often the identified primary tumors are smaller than 2 cm (Mumataz et al., 1997).

In addition, performing breast MRI in these patients helps to plan further management as identification of the occult cancer allows breast conserving surgery (Orel et al., 1999; Vlastos et al., 2001; Argus and Mahoney, 2010). Moreover; targeted hormonal and chemotherapies may be offered when histology of the primary tumor was obtained.

Occasionally, the primary is not identified even by MRI; a situation which is more difficult to treat. The typical treatment is by modified radical mastectomy and axillary clearance assuming that the patient has an occult ipsilateral cancer although tumor is identified in only two thirds of mastectomy specimens. Prognosis for these cases is generally favorable and found to be comparable to stage 2 breast cancers.

Few studies have claimed that mastectomy in women with negative breast MRI is not mandatory; rather these patients may be treated by radiotherapy and axillary dissection. Other authors offered only clinical observation and follow up for these cases (Olsen et al., 2000; Moy and Mercado, 2008). However; follow up without local treatment in not accepted by many authors, who thought that a high percentage of women who were treated with axillary lymph node dissection without breast intervention subsequently developed ipsilateral breast cancer (Argus and Mahoney, 2010; Lu and Liu, 2011).

In this challenging diagnostic and therapeutic problem, management is better to be discussed in a multidisciplinary team to determine the most appropriate treatment in every single patient (Orel et al., 1999; Buchanan et al., 2005; Argus and Mahoney, 2010).

Can MRI differentiate benign from malignant lymph node?

Presence of lymph node involvement affects the way of management. It means that a sentinel lymph node biopsy is not needed and patient has to undergo full axillary dissection. Breast MRI has limited sensitivity (63-90%), for detecting metastatic lymph nodes and was not found of value in differentiating benign from malignant lymph node. Certain imaging criteria were reported for malignant lymph nodes but neither morphological nor enhancement characteristic is sensitive enough to obviate the need for biopsy. Therefore; When abnormal axillary lymph node morphology is identified by MRI, ultrasound guided tissue sampling should be performed; positive results will spare the patient from sentinel lymph node biopsy (Figure 3). However; if axillary lymph nodes are not enlarged or tissue sampling yield negative results, we should proceed to sentinel node biopsy (Figure 2). Positive results will be followed by extensive axillary dissection. Nodal involvement is not a contraindication to breast conservation surgery (Mumataz et al., 1997; Moy and Mercado, 2008; Argus and Mahoney, 2010).

Preoperative evaluation

This field is the one subjected to most argument. Breast-conserving therapy, consisting of lumpectomy and adjuvant radiotherapy, is considered standard treatment for early-stage breast cancer. Breast conservation surgery has been proved to be a safe treatment option in the last three decades (Fisher et al., 2002). It is increasingly performed nowadays as it has the advantage of improving psychosocial health in relation to body image and sexuality. Although results have shown that it is associated with a slightly higher local recurrence rate; this risk is significantly decreased in patients who receive radiotherapy giving an equivalent long term survival to mastectomy. Adjuvant radiotherapy plays the key role in achieving a local control in those women; providing 70% proportional reduction in cancer recurrence. Following this procedure, the ten year recurrence rate was ranging from 5%-10% in different studies.

This evolving practice of breast conserving treatment has increased the need of preoperative staging of breast cancer. This staging is useful in predicting patient's prognosis as well as determining the treatment options

(Argus and Mahoney, 2010).

Breast MRI was found to be the most accurate imaging technique for local staging in women recently diagnosed with breast cancer; its sensitivity approaches 99% when combined with mammography and clinical examination (Berg et al., 2004; Argus and Mahoney, 2010). It is superior to conventional techniques in determining the size of the primary tumor as well as in identifying additional sites of occult malignancy (Boetes et al., 1995; VanGoethem et al., 2004; Dillon et al., 2006). MRI is particularly useful in mammographically dense breasts, patients with invasive lobular carcinoma or extensive ductal carcinoma in situ (DCIS), large tumors and posteriorly located tumors (Figure 4). In all these cases, mammography tends to underestimate extent of the disease. Unlike mammography, sensitivity of MRI is not affected by breast density making it superior in evaluating these conditions (Berg et al., 1995; Hwang et al., 2003; Mann et al., 2008; Moy and Mercado, 2008).

Occasionally the findings identified by preoperative MRI will change the plan of management. For example, MRI finding of tumor extension into the areola is considered a contraindication to breast conservation surgery. Tumor extension into the chest wall is another important prognostic factor that will influence treatment plan. It indicates a locally advanced tumor which carries worse prognosis and is regarded a contraindication to immediate surgery. Those patients are offered neoadjuvant chemotherapy (NAC) and radiation to reduce the size of the tumor, followed by breast conserving surgery if possible.

Tumor extending to involve only the pectoralis muscle is not a contraindication to breast conservation because part of the muscle can be removed, however; if large portion is involved, radical mastectomy may be performed. The only finding which reliably indicates tumor invasion on breast MRI is muscle enhancement (Figure 4). Loss of the fat plane between the tumor and certain structure is not by itself an indication of invasion (Figure 5) (Morris et al., 2000; Moy and Mercado, 2008).

Furthermore; MRI has the advantage of accurately identifying multifocal or multicentric disease which occurs more often with invasive lobular carcinoma (Figure5). Multifocal disease means that tumors are contained in only one quadrant of the breast while in multicentric disease the tumors are located in separate quadrants. Studies have shown that MRI detects additional ipsilateral tumors in 10-27% of patients (Liberman et al., 2003). Moreover; it detects unsuspected contralateral tumors in 3-10% (Lehman et al., 2007; Moy and Mercado, 2008).

Presence of a multifocal disease is not considered an absolute contraindication to surgery as wider local excision may be performed in some of the cases.

MRI is also advised in all patients with DCIS who are considered for partial breast irradiation. Irradiation of the tumor cavity following breast conserving surgery as an alternative to whole breast irradiation will reduce its toxic effect. MRI finding of a more extensive disease will alter the recommendation for partial irradiation in 20% of patients (Kowalchik et al., 2012).

In general, when MRI is performed for preoperative staging, the expected potential benefit is a reduction in the number of surgeries required to obtain negative surgical margins and to decrease recurrence rate. However, researches are still controversial and did not show strong evidence that preoperative MRI will improve the overall outcome or prognosis. Studies have observed that use of MRI tend to change the surgical management, usually from breast conservation to more radical surgeries; either a wider local excision or mastectomy (Houssami and Hayes, 2009; Solin, 2010; Painter et al., 2011). In recent study performed by Duygulu et al on candidates for breast conserving treatment, they concluded that preoperative MR changes the surgical plan in 20% of patients by increasing the mastectomy rate. This fact led to an important concern that MRI may be causing overtreatment and unnecessary mastectomies (Duygulu et al., 2012).

The additional unrecognized cancers detected by MRI may be in fact clinically irrelevant to the patient who will undergo breast irradiation after surgery. Another concern is that MRI is associated with high false-positive results, which may necessitate further imaging or needle biopsy. The true-positive to false positive MRI estimate was found to be 1.9:1. These unnecessary biopsies cause even more intervention and anxiety to the patient (Kuhl et al., 2007; Houssami and Hayes, 2009).

Several studies have shown different results in respect to the effect of preoperative MRI on the surgical management and the re-excision rate. In a recent retrospective study performed by Obdeijn et al, they showed substantial reduction in the rate of positive surgical margins and reoperations in breast cancer patients who underwent preoperative MRI. Similar results were also obtained by Lim and Mann (Lim et al., 2010; Mann et al., 2010; Obdeijn et al., 2013).

Two recent randomized controlled trials by Turnbull et al and Peters et al showed different results. They found that the addition of preoperative MRI in patients considered for breast conserving surgery did not result in a reduction in reoperation rates and its use is not cost effective in this setting (Turnbull et al., 2010; Peters et al., 2011). However; to best of author knowledge, no randomized controlled trial was done yet to study the effect of performing MRI on the patient outcome and overall survival. Few previous studies in this respect are either retrospective or prospective but non-randomized. Results from these papers are controversial regarding weather MRI has any effect on patient outcome. In his retrospective study, Fischer reported a lower recurrence rate in women with preoperative MRI than women who had no MRI staging (Fischer et al., 2004), while other studies like Solin and Kuhl showed that MRI was not associated with any difference neither in the recurrence rate nor the overall survival (Kuhl et al., 2007; Solin et al, 2008).

Houssami meta-analysis concluded that preoperative MRI is of little benefit for the average woman with early stage breast cancer as he found no clear impact on clinical outcome. On other hand, Duygulu believed that MRI should be performed in all patients prior to beast conserving surgery particularly those exhibiting dense

breast parenchyma as it significantly changes the surgical plan (Houssami and Hayes, 2009; Duygulu et al., 2012).

In conclusion, preoperative MRI has not yet proved its value in improving the prognosis in women with breast cancer as no prospective study supports the routine use of preoperative MRI. Nevertheless; breast MRI can still be used in preoperative evaluation prior to breast conserving surgery in certain specific conditions like large or posterior tumors, dense breasts and invasive lobular carcinoma. Management should always be discussed by a multidisciplinary team including the radiologist, the pathologist, the surgeon and the oncologist. Further randomized controlled trials are needed to assess the impact of preoperative MRI on patient outcome. (Schnall et al., 2005; Houssami and Hayes, 2009; Argus and Mahoney, 2010).

Post breast conservation, positive surgical margins

One of the most important prognostic factors of local cancer recurrence is the presence of positive surgical margins following lumpectomy. Patients are usually offered one additional attempt for excision before proceeding to mastectomy.

Breast MRI can help to assess the extent of residual tumor in cases when histological examination reveals positive surgical margin. This is useful to plan further surgical management and to identify patients requiring mastectomy rather than re-excision only.

Some authors believe that the best time to perform postoperative MRI is between 35 and 42 days following surgery. Others recommend MRI to be done as early as possible in the postoperative period as the presence of seroma cavity facilitates visualization of any enhancing lesion. Sensitivities ranging from 61% to 86% for detecting residual disease have been reported. Patient with positive margins and negative MRI still require surgery because microscopic residual disease is already found by histological examination (Orel et al., 1997; Frei et al., 2000; Lee et al., 2004; Argus and Mahoney,2010).

Monitoring response to neoadjuvant chemotherapy

Neoadjuvant chemotherapy (NAC) is defined as the administration of chemotherapy to treat invasive breast cancer before any local treatment, such as surgery. NAC is often recommended in patients with locally advanced cancer to shrink tumor before surgery. Breast MRI is currently considered the most accurate method for evaluating the response in breast cancer patients receiving NAC with several studies have shown MRI being superior to conventional imaging (Figure 5 and 6). Authors recommend pretreatment MRI with compatible markers placed prior to NAC to indicate the location of the tumor (ACR,2013). Sequences which are used are dynamic enhanced MRI, diffusion weighted imaging (DWI) and MR spectroscopy. Changes which are observed include tumor size, morphology, enhancement and metabolism.

Many parameters have been proposed for early response monitoring of NAC by MRI. Of these parameters, tumor size and volume, and apparent diffusion coefficients (ADC) values of DWI are the most important with the greatest advantage observed with the use of volumetric measurement of tumor response early in treatment (Hylton et al., 2012; Lobbes et al., 2012; ACR, 2013).

It is ideal to perform MRI after the first cycle of chemotherapy has been completed to monitor if there are signs of early response to the primary treatment. Theoretically, this allows the oncologist to change the type of neoadjuvant drug in the middle of treatment. However, this is not supported by some authors.

Early response monitoring can be used for the distinction between good and partial responders. When good response is observed, the selected regimen could be continued. Patients that showed only partial response may benefit from a more prolonged chemotherapy treatment. In non-responders, the non-useful toxic agents should be discontinued and earlier surgical intervention can be considered.

The rare over and underestimation of residual disease have been reported by using MRI, but in general, correlation with pathology specimens is good (71-90%).The accuracy of breast MRI to predict pathologic complete response has a moderate sensitivity, but high specificity. However; pathologic complete response occurs in minority of patients rendering MR assessment of the residual disease more important. Even if residual disease is not evident by MRI, surgical resection is advised due to the potential underestimation of residual disease (Hylton et al., 2012; Lobbes et al., 2012; Tejerina et al., 2012).

Postoperative follow up, differentiating recurrence from scar

MRI is highly sensitive in the differentiation between developing scar and recurrent cancer or residual disease after breast conservation surgery. This is a very important problem in which mammography and US sensitivity is poor. The absence of enhancing lesion on MRI has a high negative predictive value (NPV) for cancer (Figure7). However, the reverse is not true. Enhancing areas do not necessarily represent cancer as they can normally be visualized in the site of surgery and radiotherapy up to 3months, after which it does not usually interfere with diagnosing a tumor.

Tumor recurrence is uncommon during the first 18 months following treatment and, in most cases it appears at the surgical bed in the first 5 years. Therefore; MRI is better performed after the first 12–18 months of treatment to avoid false positives resulting from inflammatory changes, fat necrosis and a developing scar (Tejerina et al., 2012).

Screening women with increased risk of breast cancer

Mammography is the only imaging modality that has proved to be useful in screening the general population. Previous studies have shown reduction in breast cancer mortality following mammography screening programs. MRI is more sensitive than mammography for screening high risk women who have increased lifetime risk of breast cancer (Sardanelli et al., 2011). Multiple studies reported MRI sensitivities from 79% to 98%.

ACS recommends annual screening breast MRI as an adjunct to mammography for women with very high risk for breast cancer. These include patients with known

BRCA1 and BRCA2 mutations and their untested first-degree relatives; women with a lifetime risk for breast cancer of 20–25% or greater, women with prior irradiation to the chest between the ages of 10 and 30 years, patients with cancer predisposition syndromes, or may have one of these syndromes based on a history in a first-degree relative.

MRI screening has the advantage of detection of nodal free small cancer in these high risk women. However, MRI is not appropriate for screening the general population due to its limited specificity and high cost.

Results from literature are controversial regarding women with intermediate risk (15-20%) of breast cancer. These cases include women with prior history of breast cancer, lobular carcinoma in situ, atypical ductal hyperplasia, atypical lobular hyperplasia and dense breasts on mammography. MRI screening is less cost-effective and associated with higher false positive results in these women, therefore; the decision for screening MRI should be made on a case by case basis. MRI is not recommended for screening women at average risk (less than 15%) (Saslow et al., 2007; Argus and Mahoney 2010; ACR,2013).

Evaluation of women with breast implants

Cosmetic breast implants have become increasingly popular throughout the world. MRI is used in these patients for two reasons; first is the assessment of implant integrity and second is searching for a breast cancer. Unlike saline implant rupture, which is apparent on physical examination, silicone implant rupture can be difficult to identify. MRI is regarded the imaging modality of choice for detecting silicone implant rupture. Following implant placement in the breast, the silicone will be surrounded by a fibrous capsule formed by the body itself.

Most of ruptures in the implants are intracapsular which mean that the silicone remains contained within the fibrous capsule. Extracapsular rupture is rare and has both the silicone envelope and fibrous capsule ruptured and the silicone released free in the breast.

MRI sensitivity for the detection of implant rupture ranges from 78% to 100%versus 28% for mammography and 59% for ultrasound. The specificity of MRI ranges from 63% to 91%.

Unenhanced MRI using silicone-hyperintense inversion recovery sequence is the best technique for assessment of breast implant. MRI signs of intracapsular rupture include the linguine sign if rupture is complete; forming dark curvilinear lines in the implant due to floating collapsed silicone shell and the keyhole sign in partial rupture (Cherr et al., 2001; Giovanni et al., 2008; Argus and Mahoney,2010).

Equivocal mammographic finding (lesion characterization)

The use of breast MRI as a problem solving tool for equivocal mammographic findings is controversial.

MRI can be used as an adjunctive modality for further evaluation of an equivocal finding seen on mammography; its value is to determine whether an abnormality seen on mammography is real and to locate it prior to biopsy. Examples of these equivocal findings are differentiating scar from cancer (Figure7), focal asymmetry (Figure8) and architectural distortion. In this context, MRI should be used after full imaging work up including mammography and US.

Moy et al performed a study to evaluate the usefulness of MRI in cases in which mammography and US findings are inconclusive. They found 100% sensitivity, 91.7% specificity and 92% overall accuracy. They found MRI to be useful for a mammographic finding that is shown only in one view; as a negative MRI in this setting will increase confidence in performing short-term mammography follow up rather than stereotactic biopsy (Figure8).

On the other hand, MRI may reveal a true lesion and ascertain its location, allowing confident biopsy. Second look US can also be done in these cases to look for an US correlate (Moy et al., 2009).

As the negative predictive value (NPV) of MRI is only 85.4%, it is not high enough to obviate the need for biopsy for lesions having suspicious or indeterminate features on conventional imaging. If a mammographic abnormality is confirmed to be a true lesion, proceeding directly to biopsy is more appropriate and cost effective.

Furthermore, MRI is not found to be helpful in evaluating microcalcifications. Biopsy has to be decided on mammographic findings in these cases. However; when histology revealed DCIS, MRI can be useful to show the tumor extent.

In conclusion, strict selection criteria should be followed in using MRI to evaluate an equivocal mammographic finding; it should be performed following full imaging workup by mammography and US (Argus and Mahoney, 2010; Moy and Mercado, 2008; Moy et al., 2009).

Conclusion

From the review of previous literature, we conclude that MRI is a highly sensitive but less specific imaging modality which is frequently indicated in various breast conditions. It has been proved to be useful in certain conditions like metastatic axillary adenopathy from occult breast cancer, screening the high risk women, monitoring response to NAC, postoperative differentiation of tumor recurrence from scar, evaluation of breast implant and in certain equivocal mammographic findings.

However; in other situations, as the preoperative staging prior to breast conserving treatment, the role of MRI is still controversial. Randomized controlled trials are needed to clearly define its role and the impact on patient outcome to guide future practice.

Studies have shown that MRI has no value in other conditions like precluding needle biopsy in indeterminate breast lesions and microcalcifications, screening the general population and in differentiating benign from malignant lymph nodes.

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