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REVIEW ARTICLE

Expanding the indications for MRI in the diagnosis and treatment of breast cancer: what is best practice?

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Abstract

Breast magnetic resonance imaging (MRI) now has an accepted place in screening younger women at high risk of breast cancer, and is increasingly used in a number of other settings including assessment of response to neo-adjuvant therapy and local staging of cancer. Although the evidence for its general use in these settings is very limited, in highly selected patients, especially where discordance with conventional measurements occurs, MRI can have a place in assessing extent of disease, both whether operable and how operable, and guiding surgery. These scenarios and future indications and alternative technologies are explored in this paper.

Introduction

It has been 36 years since Damadian first described the use of nuclear magnetic resonance imaging (MRI) of the breast.[1] Initial images were disappointing, but intravenous contrast[2] and faster sequences have changed this. MRI is now standard for screening women at high risk of breast cancer (BC).[3] However other indications remain controversial and in many countries, including Australia, are not funded by government or health insurers. Key to the developing use of MRI has been the development of MRI-guided biopsy techniques.[4]

The American College of Radiology Breast Imaging and Reporting Data System (BI-RADS)[5] provides a standardised approach to nomenclature and interpretation of breast MRI. The American College of Radiology Imaging Network (ACRIN) 6667 Trial[6] and European Society of Breast Imaging[7] provide standards for breast MRI equipment, protocols and reading.

The false mantra 'breast MRI has high sensitivity but low specificity'[8] is now challenged with sensitivity over 90% and specificity 97%.[9] A 2012 systematic review[10] evaluated the diagnostic accuracy of MRI in detecting additional lesions found a positive predictive value of 67% as did Houssami et al.[11]

In Australia breast MRI is currently used in screening young women at high risk of developing BC, and widely for other non-Medicare rebatable indications. This paper will explore these indications and provide cautions to help limit inappropriate use.

MRI as a Screening Tool

In 2009, the Australian Government-funded breast MRI *in the diagnosis of breast cancer in asymptomatic women with a high risk of developing breast cancer when used as part of an organised surveillance program*. The criteria for

screening provide for an annual MRI for women under 50 with a known mutation predisposing to BC or 'National Breast and Ovarian Cancer Centre (NBOCC) Category 3' risk (>20% lifetime risk), plus 6 month follow-up MRI if indicated or MR-guided biopsy.

However, we have sparse data on MRI screening sensitivity, specificity, positive or negative predictive values, recall rates and interval cancer rates. Information from international studies (not from real life screening programs) suggest these parameters are at least comparable to population screening programmes of women >50 years, and although there is some evidence for down staging of tumours at presentation, any improvement in BC-specific survival data is yet to be seen.[12–17]

But how should we define 'high risk'? NBOCC Category 3 includes women in whose family breast or ovarian cancer (OC) occurred in at least three relatives on one side of the family, or breast or OC in at least two relatives including one with bilateral BC, BC <40 years, OC<50 years, BC and OC in one individual, a relative with BC<45 years plus a sarcoma <45 years, male BC or if the family have Ashkenazi Jewish heritage.

Throughout the world, criteria for inclusion in MRI screening programmes[18] vary depending on both model of risk used and the population it is used in. Ozanne et al.[19] showed using three common models there was only 5% agreement on who was at high risk! Thus we need to develop modern validated models of risk to decide who may benefit most from MRI.

Still to be determined is also the best programme of screening within a multidisciplinary high-risk management programme – most guidelines recommend starting at 25–30 years or 10 years before the youngest relative developed BC. Current provisions only rebate MRI in women under 50, but clearly for some this arbitrary age limit may not be applicable. Some clinics suggest alternate 6 monthly MRI with mammogram.[20,21]

A group that merits special mention is women treated with chest irradiation at a young age. Current guidelines recommend breast MRI beginning 8–10 years after treatment, and combined with mammography has a sensitivity of 94%.[22]

It is also recognised that women with a prior history of some benign lesions have a significant increased BC risk – for lobular carcinoma in situ (LCIS) similar in magnitude to gene carriers. It is not known if the addition of MRI to mammographic and/or ultrasound (US) screening improves outcomes for these women, or in a selected group who are very young and with mammographically dense breasts.

MRI in Assessing Disease Extent and Guiding Surgery

Breast-conserving surgery is now offered to over 70% of Australian women (www.breastsurganz.com), however, in about 25% of cases conventional assessment (usually mammogram, US and clinical examination) underestimates the extent of the cancer and if further surgery is necessary.[23] We have recently shown (H. Ballal, D. Taylor, A. Bourke, B. Latham, P. Riley, J. Bourke, D. Dissanyake and C. Saunders C, under review) that this is more common in the presence of extensive ductal carcinoma in situ (DCIS) and multifocal disease.

There is clearly a need for more accurate techniques for defining the extent of malignancy, guiding surgery to achieve clear margins in one operation and optimising cosmetic outcome. It is unclear if MRI can improve this.[24] There is little evidence pre-operative MRI reduces the risk of reoperation but it may increase unnecessary biopsies or additional imaging, and increase the likelihood of mastectomy, at least as an initial operation, although final mastectomy rate is not increased.[25] MRI may also increase the likelihood of contralateral mastectomy, although this is unclear as the population of women who choose contralateral mastectomy is often similar to those who wish to have or are recommended an MRI. There is a small risk MRI may delay surgery, and increase patient anxiety, but, most importantly, there is little evidence it reduces local BC recurrence. The reasons for this are unclear, perhaps the complexity of translating a 2D image acquired prone to a 3D surgical field; or perhaps MRI just finds microscopic disease that is adequately treated with radiotherapy and systemic therapy.

More plausible perhaps is that the randomised studies to date have taken fairly unselected populations of women scheduled for breast-conserving surgery (BCS) and looked at outcomes in those having additional MRI to those not. The comparative effectiveness of MRI in BC (COMICE) trial[26] and MONET trial[27] are the largest of these.

COMICE concluded addition of MRI to conventional triple assessment did not reduce reoperation rate, (odds ratio 0.96, 95% CI 0.75–1.24; $P = 0.77$) MONET demonstrated a higher re-excision rate in the MRI group (18/53, 34%), versus the control group (6/50, 12%), $P = 0.008$, although the rate of conversion to mastectomy did not differ significantly. This is difficult to explain, given that baseline characteristics were comparable between groups, as was the rate of primary BCS. But median volumes of excised tissue were lower in the MRI group and the authors postulated the higher rate of re-excision was due to surgeons being inappropriately reassured by small lesion size on MRI. This suggests that

the sensitivity of MRI in showing extent of in situ disease is less than standard imaging, in contrast to others[28,29] where MRI better depicted the extent of than mammography.

A more recent randomised controlled trial (RCT) of 440 women, selected by young age alone[25] found the MRI group had higher BCS planned and a change to mastectomy occurred in 15%, but a lower overall re-operation rate in the MRI group (5% vs. 15%) ($P < 0.0001$). There was no difference in overall mastectomy rate despite initial higher mastectomy rate in the MRI group.

Non-randomised studies report mixed results – one recent study of patients planned for BCS having pre-operative MRI, compared to 119 controls with no MRI 1 year earlier, found MRI changed the surgical plan to more extensive surgery in 34%. However, significantly fewer MRI patients had positive resection margins (15.8% vs. 29.3%; $P < 0.01$) and patients in the study group underwent significantly fewer reoperations compared with the historical control group (18.9% vs. 37.4%; $P < 0.01$).[30]

Another retrospective series at Memorial Sloan Kettering[31] suggests, compared to matched controls, patients having MRI had identical rates of final negative margins although fewer in the MRI group needed re-excision (29% vs. 45%; $P = 0.02$). There was no significant difference in locoregional recurrence ($P = 0.33$) or disease-free survival ($P = 0.73$), however, those referred for MRI were more likely to have extremely dense breasts (28% vs. 6%; $P < 0.0001$) and mammographically occult cancer (24% vs. 9%; $P = 0.0003$) – perhaps making this a more 'real life' study.

A local unpublished study in Western Australia attempted to assess if the conventional assessment criteria for BCS would be altered by pre-operative MRI. In 50 women (61 cancers) apparently suitable for breast conservation on conventional assessment, MRI was undertaken with the surgeon blind to the results, and both compared to final histopathology. MRI would have correctly predicted 11 of 13 cases requiring mastectomy, 2 of 3 cases requiring re-excision and identified two contralateral cancers not seen on conventional imaging. Moreover MRI would have identified 15 of 18 patients who required more extensive surgery than predicted by conventional assessment. MRI proved most accurate in younger women and those with lobular cancer.

Evidence for MRI Effectiveness with Discrepancy in Conventional Imaging – Selected Patients

There is considerable non-randomised evidence that pre-operative MRI can be more useful in selected groups of patients. Weinstein showed in invasive lobular cancer that MRI shows disease extent more accurately than mammography (85% vs. 32%)[32] and MRI changes management in up to 50% of patients.[33] Mann showed MRI may decrease re-excision rate of lobular cancers (27% vs. 9%; $P = 0.010$), and lower final mastectomy rate (48 vs. 59%; $P = 0.098$).[34]

Very dense breasts often prove challenging, however, evidence that MRI performs better than conventional imaging in not only better defining cancers but leading to better outcomes is sparse.[31]

Another situation where MRI often proves useful is occult malignancy. A meta-analysis showed a 74% breast lesion detection rate for MRI with 90% sensitivity but 31% specificity.[35] This may allow identification of small lesions and BCS for women who would otherwise undergo mastectomy.

Some studies suggest MRI is probably most accurate in high-grade tumours, performs better than mammography, and is thus complementary, in younger women.[36,37] One author nicely describes MRI as a 'problem solving tool'.[38]

Onco-Plastic Surgery

A recent but rapidly growing trend is for onco-plastic surgery, safely removing the tumour with optimisation of cosmetic outcomes. Accurately defining the size and geographical distribution of the cancer greatly assists this surgery, and although this is usually adequately done by mammogram and US, MRI may prove useful for surgical planning.

Is MRI Best for Assessing Response to Chemotherapy?

Imaging is used both during neo-adjuvant chemotherapy (NAC) to predict response and possibly allow change of therapy, and after NAC to assess if BCS is possible. International guidelines recommend MRI for these purposes, and most clinical trials mandate MRI at least twice during neo-adjuvant treatment.

Evidence suggests MRI performs better than mammography[39–41] but there are no direct studies comparing it to US – which may be almost as good.[42] Our own experience suggests MRI may overestimate residual tumour size due to rim enhancement, scattered nodules or fibrosis. US is not good at measuring residual DCIS which needs to be assessed carefully. MRI technology such as diffusion-weighted imaging MRI, which gives information on cell membrane integrity, may improve accuracy.[43]

Determining suitability for breast radiotherapy

For women with low-risk BC, partial breast irradiation provides similar local control and possibly better survival than whole breast irradiation after BCS.[44] However studies to date have not mandated MRI to assess suitability for BCS.[45] Using MRI as a guide for whom radiotherapy may be safely omitted is the subject of the PROSPECT trial (https://www.anzbctg.org/clinical-trials/anz1002/prospect).

Breast MRI in Pregnancy and Lactation

There are[46] a lack of data demonstrating efficacy of MRI during pregnancy and safety concerns about gadolinium, plus difficulty positioning the pregnant patient prone. In lactating patients contrast-enhanced MRI may be performed safely, but increased background enhancement make it difficult to differentiate lactational changes from suspicious findings.[47]

Given that only a minute percentage of gadolinium-based contrast medium that is excreted into breast milk is absorbed by the infant's gut, available data suggest it is safe for the mother and infant to continue breast-feeding after receiving such an agent.[48]

Other Potential Indications

In our practice up to 30% of patients have close margins at initial BCS. MRI may prove useful to assess extent of residual disease post-op allowing mapping for further BCS. No evidence exists to compare this with careful post-operative US.

Breast MRI has been used to assess the contralateral breast for occult malignancy, in particular those with a high risk of having a genetic mutation.

The role for follow-up after BC using MRI remains unclear – for detecting local recurrence or new lesions. It seems intuitive that in women whose first cancer was occult on conventional imaging it may be a useful tool but evidence is anecdotal to date. However, in young women with a strong family history, or those who have a proven gene mutation, it would seem a reasonable follow-up option.

Use of MRI in Clinical Practice

There are no data in Australian practice about the use of MRI in local staging of cancer. A United States survey of breast surgeons[49] queried routine MRI use in specific clinical scenarios and reported higher rates of MRI use in high-volume and specialised surgeons, and private practice. There was greater routine MRI use in the setting of extreme mammographic density (87.9%), strong family history of BC (73.4%), and invasive lobular carcinoma (69.4%).

More than 40% of American women will have an MRI at time of diagnosis of BC. In Australia it appears that pre-operative MRI is mostly used in the context of multidisciplinary breast teams on a case-by-case basis, to assess disease extent or response to NAC. But there is no rebate for this, thus it is either performed in public hospitals or the cost is passed on to the patient.

But there is the potential for using MRI to improve clinical outcomes for selected women diagnosed with BC. The challenge will be to prove its utility in a carefully designed clinical trial. Meanwhile we continue to accrue experience and low-level evidence (Figure 1).

Where to From Here?

A recent application to the Australian Medical Services Advisory Committee for MRI follow-up screening for women <50 with prior cancer was not supported. However, another application for MRI to be used to stage local cancers with discrepancy in conventional staging and to assess response to NAC is still awaiting an outcome.

Advances in Breast MRI and Development of Newer and Possibly Better Technologies

Future advances in diffusion-weighted and diffusion tensor imaging, MRI spectroscopy and Quantitative Perfusion Imaging[50–53] may mean breast MRI can be performed without IV contrast injection,[54] and with improved specificity and accuracy.

MRI may prove important in predicting prognosis[52] and response to neo-adjuvant treatment. Contrast enhanced spectral mammography (CESM) is able to show areas of tumour neoangiogenesis. Sensitivity and specificity are significantly better than standard

When should we NOT recommend pre-operative MRI ?

- For routine use
- **Just** because breasts are dense
- **Just** because patient is young
- **Just** because of a non-significant family history
- **Just** because of a lobular cancer
- Because there are many other complex breast benign lesions eg papillomas
- During pregnancy or lactation

Figure 1. Who does not need magnetic resonance imaging (MRI).

mammography with or without US[55] and while CESM is not as sensitive as MRI, studies have shown better specificity[56] and with lower cost, higher accessibility, shorter examination and reading times, fewer contra-indications and better patient tolerance than MRI.[57]

Conclusions

In highly selected patients, MRI as part of a multi-disciplinary work-up by an experienced team can have a place in assessing extent of disease, whether operable and how operable, and guiding surgery. This should be considered if discordance with conventional measurements occurs, perhaps especially in younger women with lobular cancer and/or increased breast density. MRI can be useful in the diagnosis of occult malignancy, in assessing response to neo-adjuvant therapy and in follow-up of very high-risk women. CESM may be an alternative, particularly for those women who cannot tolerate MRI.

Conflict of Interest

The authors declare no conflict of interest.

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