Magnetic resonance imaging: The evolution of breast imaging
Sylvia H. Heywang-Köbrunner*, Astrid Hacker*, Stefan Sedlacek
Ntl. Reference Centre Mammography Munich, Sonnenstr. 29, D 80331 Munich, Germany

Keywords: Breast MRI; Imaging; Evidence; Indications; Review

Abstract

Introduction and aims: To provide an overview of the principle of current breast MRI, the available evidence concerning its indications and optimum use and future potentials.

Methods and results: To date sensitivities of 90–91% have been achieved with a specificity of 72–75%. MRI is the most sensitive method for detecting invasive carcinoma and comparable to mammography concerning detection of DCIS. The achievable specificity, false positive and biopsy rates, however, are much lower than for screening mammography thus do not allow its use for screening of the general population.

Indications with proven advantages concern screening of women at high risk and special diagnostic problems that cannot be solved by conventional imaging and percutaneous biopsy: search for primary tumour in CUP syndrome, differentiation of nipple retraction, differentiation of scarring versus recurrence and selected difficult cases. There is no proven benefit for its general use for preoperative staging.

One major problem may concern the imperfect interface between imaging and surgery. Further research is also needed for the use of MRI in women at intermediate risk. In women at low risk MRI screening is not recommended. Novel possibilities of MRI concern diffusion weighted imaging as well as MR spectroscopy. Their value for improved lesion differentiation is not yet fully established. Their main potential appears to concern an improved and earlier prediction of response to neoadjuvant therapy. Future developments might address development of more specific contrast agents, replacement of vascular enhancing agents by special MR techniques, testing of sodium MRI or image fusion with other imaging modalities.

Discussion/conclusion: MRI allows new patho-physiological information and thus can complement the information available by conventional methods. Present research should concentrate on improving specificity, improving the interface of imaging and surgery and has to include outcome analyses. Due to issues of specificity the responsible use of MRI should be limited to appropriate indications.

© 2013 Published by Elsevier Ltd.

Introduction

Breast MRI is the latest method which has become available for breast imaging.

The main information gained by MRI relies on evaluation of MR contrast-enhancement.

To date, more than 25 years after its inauguration [1], national and international guidelines recommending reliable techniques, evaluation methods and indications have become available [2–4].

A large body of data is meanwhile available and allows assessing its accuracy and its use for various indications.

Parallel to MRI potentials other methods such as digital mammography or high resolution breast ultrasound have constantly been improved and new technologies such as tomosynthesis are developing. Percutaneous breast biopsy meanwhile allows solve diagnostic questions without the need for multiple imaging tests.

In this context a continuous check of the value of each method, here MRI, is needed to optimally use each method or combinations of methods. Apart from sensitivity and specificity data outcome analyses are becoming available, which help us check benefits and potential harms associated with each modality in different clinical settings.

While such data are becoming available MR techniques have been improved and novel supplementary techniques are becoming available.

In this article we will give an overview of the basic principles of breast MRI, as used today, about available data concerning its accuracy and the value of MRI for certain indications based on the available evidence. Potentials of upcoming MR technologies and future developments are included.

* Corresponding authors.
E-mail addresses: Sylvia.heywang@referenzzentrum-muenchen.de (S.H. Heywang-Köbrunner), Astrid.hacker@referenzzentrum-muenchen.de (A. Hacker).
Methods

This review is based on a PubMed search (breast, MRI and meta-analysis or systematic review or proton spectroscopy or diffusion-weighted imaging) including the past 5 years. Former literature is included where needed. It is not a systematic review, but considers the available literature and information weighted by the existing level of evidence, variance among the published data and their value in the diagnostic and clinical context based on the author’s experience.

Results

History of breast MRI and its principle

Plain MRI (without the use of contrast agent) has proven insufficient for detection or exclusion of breast cancer. To date only limited information from plain MRI is used to compliment the information of contrast enhancement concerning detection and exclusion of malignancy. The most important information provided is gained from evaluation of the morphology, amount and dynamics of contrast enhancement.

Since inauguration of contrast-enhanced breast MRI imaging technology has been refined. To date high spatial and temporal resolution has become available allowing to assess the information provided by MRI. The pathophysiological information not available from mammography and ultrasound is based on evaluation of contrast enhancement. Contrast enhancement in malignant tumours correlates with visualisation of increased vascularity, vascular permeability and interstitial space in tumour vessels. Their growth is initiated by angiogenic factors that are produced by invasive tumours and probably also by part of the DCIS. The washout phenomenon, which occurs in about 50% of invasive breast cancers, describes the fact that in these tumours the contrast agent accumulates faster and is washed out faster than in many normal or benign tissues. Another part of the malignant tumours exhibit fast enhancement without early washout (so-called plateau-type enhancement). This type of enhancement is also observed in many benign tumours (the latter being even more frequent in women than malignant tumours) and some other benign conditions. Persistent enhancement means that contrast agent propagates slowly in the tissue and continues to increase with time during the first 5–10 min post injection. This type of enhancement or absent is seen in less than 10% of invasive malignancies. Certain morphological features are typical of malignancy (spiculated or irregular margins of a lesion, increased enhancement of lesion periphery), others may indicate malignancy in a variable part of the cases (segmental, ductal or regional enhancement patterns) or may be observed mostly in benign and infrequently in malignant cases (well-circumscribed round or oval enhancement or diffuse enhancement). Absence of enhancement correlates well with absence of invasive breast cancer (NPV > 95%) [5].

Thus in a number of cases highly suggestive or specific presentations exist. This may contribute to better detection of early malignancy in breast tissue that is difficult to assess by conventional imaging (mammography and ultrasound) or to improved differentiation of certain benign from malignant changes.

However, as mentioned above, significant overlap of the presentation of certain benign and malignant lesions also exists, which in general can be explained by similar pathophysiology.

Thus MRI offers additional information. But, in spite of improvements of imaging technology, and better evaluation tools, its limits lie in the pathophysiology of contrast enhancement with the available contrast agents, which to date are contrast agents which distribute in vessels and interstitial space.

Accuracy of breast MRI

To date ample data with histologic proof exist concerning the sensitivity and specificity of MRI. According to 2 meta-analyses sensitivity of MRI for malignancy ranges around 90%, specificity around 75% [6,7]. These data show that most invasive cancers (90–95%) enhance with contrast agent, while only part of the DCIS enhance. Overall MRI proves the most sensitive method for the detection of invasive malignancy. Reports concerning the exact part of DCIS detectable by MRI vary significantly, depending on the chosen algorithm for evaluating MRI imaging, on patient selection, and probably the detail of histopathological correlation and verification. Since a significant part of the DCIS does not exhibit the enhancement dynamics or morphology typical of invasive malignancy, algorithms that target for a high detection rate of DCIS will have a lower specificity and vice versa. Even though a correlation between stronger and earlier enhancement and higher grade of DCIS or presence of invasion certainly exists as reported by Kuhl [8], according to our experience this is a moderate correlation and several exceptions with strong and early enhancement among grade 1 DCIS and low enhancement in some of the high grade DCIS exist [9]. In a publication that compared preoperative MRI and mammography with thin slice histopathology mastectomy specimens the detection rate of DCIS (including also small foci) was reported to be just 40% for both mammography and MRI [10]. The information of MRI and mammography partly overlapped and partly was complimentary. In most other publications (where imaging was correlated with standard histopathology) the sensitivity of MRI for DCIS was reported to range between 60 and 80% [11].

Accordingly MRI and mammography are complimentary concerning the detection DCIS in general and of high grade DCIS. The less desirable detection of low grade DCIS occurs with both methods. The amount of low grade DCIS detected by mammography or by MRI also depends on the algorithms chosen for either method.

Another systematic review of the literature compared accuracy of different breast imaging methods [12]. It confirmed a sensitivity of 92% for the detection of malignancy and a specificity of 77.5%. In this review the diagnostic accuracy of MRI exceeds that of PET (83%, 74%) and scintimammography. Concerning the clinical use it should, however, be remembered that PET and scintimammography are associated with a significantly higher radiation doses than mammography [13], since the contrast agent of these methods distributes in the whole body.

Using the so-called Bayes theorem the authors of this systematic review concluded that MRI could only be used for exclusion of malignancy in patients with a pre-MRI suspicion of malignancy of 12% or less. They assumed that such patients could barely be selected clinically. For a “clinical” selection this may be true. However, according to our own experience, patients with this pretest probability can quite well be selected based on their individual risk, their exact diagnostic question and based the outcome of the preceding tests (mammography and ultrasound).

Since quality assured percutaneous breast biopsy in general has a higher negative predictive value than any imaging, MRI should not replace percutaneous breast biopsy in cases with sufficient suspicion, where a lesion can be targeted. However, MRI may be quite helpful for solving selected diagnostic problems, which cannot be solved by standard imaging and percutaneous breast biopsy (see indications, below).
Indications discussed for breast MRI

When indicating or using MRI the following may need to be considered:

- MRI has the highest sensitivity for invasive malignancy. In all comparative studies it exceeds that of other imaging tests. However, no imaging method detects all breast cancers.
- The negative predictive value of MRI is high (ranging around 90–95%), but lower than that of percutaneous breast biopsy.
- The specificity of MRI is significantly lower than that of screening mammography, but comparable to that of mammography combined with ultrasound. (Due to the lower detection rate of mammography and ultrasound, as shown in numerous intra-individual studies, mostly both methods need to be used in cases with a suspicion.)
- MRI is the most expensive breast imaging method and targeting of lesions detected by MRI requires a specialized team, specialized equipment [14], which so far is not widely available. It also causes additional costs.

The following subchapters summarize the existing evidence concerning indications presently discussed for breast MRI.

MRI in patients at increased risk

Women at high risk are defined as women with a lifetime risk of breast cancer >30% (most European programs), or >20% (USA). This includes carriers of BRCA1 or 2 gene mutations, other rare gene mutations as well as women, in whom no gene mutation was found but whose calculated lifetime risk exceeds the above thresholds. Women who underwent radiation therapy of the chest wall or mediastinum before age 30 also belong to the high risk group. Their risk starts around 10 years after radiotherapy.

According to 2 systematic reviews [15,16] comprising more than 4000 patients and about 9000 examinations, the sensitivity of MRI alone ranged around 71–100%, for mammography 25–50%, for mammography combined with ultrasound 48–67%; and for all methods around 80–100%. The specificity (concerning recommendation for biopsy) ranged around 93–98% for MRI alone, 95–99% for mammography alone, 89–98% for mammography and ultrasound, 91–98% for all methods. When using the three methods in women at high risk approximately 33% of the malignancies are detected by MRI alone, 11% by mammography alone and just 3% by ultrasound alone [17].

As demonstrated by Kriege [18] and Schmutzler [19] cancers detected by intensified screening (using at least annual mammography and MR, or combined with ultrasound) are detected at significantly earlier stages than in women of the same age group outside these programs. Kriege reported detection at stage T1 for 75% of the cancers detected within the program and for 51% in the chosen control group, lymph node involvement in 33% of the women within the program and in 48% of the control group. Schmutzler reported detection at stage T1 for 75% of the cancers detected within the program and for 51% in the chosen control group, lymph node involvement in 33% of the women within the program and in 48% of the control group. These studies are complemented by a recent report on long-term follow-up of BRCA-positive patients, which pointed out a very high disease-free survival among patients with breast cancer diagnosed by MRI [20]. These data suggest a positive impact on prognosis. However, more data will be needed for exact calculation of a mortality reduction. The latter will, however, be difficult based on the existing (single arm) studies. While significant mortality reduction is proven for prophylactic mastectomy, the exact impact on mortality of intensified surveillance thus remains uncertain. In the individual case timely detection cannot be warranted. Furthermore imaging is associated with an important rate of false positive results and the need for image-guided biopsy.

In patients who opt against prophylactic mastectomy intensified surveillance is indicated. That is, imaging should start at early age (MRI beginning at age 25, mammography at age 30 or 5–10 years before the age of the youngest family member affected2). It should at least include mammography and MRI at 12 month intervals, optimally interleaved every 6 months [3,21,22].

Women at intermediate risk constitute a much larger and quite inhomogeneous group. So far limited data exist. They concern “MR screening” of the contralateral breast (of women with a personal history of breast cancer) and of women with previously proven ADH or LCIS.

Data on MR screening of the contralateral breast are comprised in one single-armed prospective multicentre study on 969 patients and in a meta-analysis which included this study and published data from further 21 studies [23,24]. These data confirm that the incremental cancer detection rate (over conventional imaging) ranges around 4%. Since recruitment was only partly consecutive, a selection bias might exist. This result was achieved by approximately 5% [23] or 10% [24] additional biopsy recommendations (often MR-guided) on eventually benign changes. All studies showed that the contralateral breast cancers were detected at very early stages. However, considering the stages of the primary cancers and the concomitant treatment and surveillance the prognostic value of this earlier detection is yet unknown. One very recent publication reported an increase of synchronous cancers followed by a significant decrease of metachronous cancers in those women who had undergone one single preoperative MRI study as compared to those who had not [25]. If this desired effect can be confirmed by other publications, this might indeed be an important proof for the positive effect of imaging surveillance.

For women at intermediate risk due to histologically proven LCIS only retrospective evaluations from single institutions are available. The latest available studies concern 133 patients with 307 examinations [26] and 220 patients with 670 examinations [27] of this fairly rare entity. They report an incremental detection of malignancy by MRI in up to 2% of the examinations. This was achieved by additional biopsy recommendations in 8.8 or 10.6% of the examinations, respectively.

Based on the existing data the ACR concludes that MRI may be justified in some women at intermediate risk (15–20%) [20], whereas the latest recommendation of the EUSOMA working group of 2010 based on the preceding literature data stated that insufficient data still exist and further evidence is needed for the intermediate risk group [3].

As to MR screening of women at low risk no data exist. Considering the low yearly incidence of <3/1000 in the normal population, the too low specificity of MRI, which would annually or biannually cause unnecessary further histopathological assessment or short-term follow-up in a significant proportion of the screened population (increased by a factor of 3–5 compared to screening mammography) and the higher costs of MRI, MR screening of the normal population does not appear a sensible option.

---

1 In some publications specificity is calculated with respect to any recommendation for additional imaging or biopsy, in other publications specificity calculations only refer to the recommendation of biopsy.

2 Some programs also include ultrasound.
Thus all existing guidelines and recommendations dissuade from MRI screening in women at low risk.

MRI for preoperative staging

Ample data exist from various studies on this topic. Furthermore 3 meta-analyses and one sufficiently powered randomized study exist [28]. The meta-analyses comprised more than 3000 [29,30] or 10,000 examinations [31], respectively. They prove that MRI is the most sensitive method which correctly detects additional malignancy not shown by conventional imaging in 12–13% of the cases. Also biopsy rates, which for this indication on average yielded a rate of >60% malignancy, are quite acceptable.

Unfortunately, however, both the meta-analyses and the randomized studies fail to prove a significant benefit of outcome. While MRI increased the overall rate of mastectomies from 18.2% to 25.5% and the rate of wider excisions, the rate of incomplete margins did not change significantly from 11.6% to 11.4% [30]. While the results from meta-analyses may be influenced by a selection bias (more difficult cases in the MR group), the randomized study also yields similar results with no significant change of re-excision rates (18.8% vs. 19.3%), as proven on (816 patients with primary breast cancer with and 807 without MRI) [28]. The main criticism of this randomized study, which, however, very probably will also apply to most of the studies underlying the meta-analyses, concerned the lack of MR-guidance. This could, in fact, be an explanation for some of the disappointing and puzzling results. However, this certainly also reflects the available state-of-the-art in most countries and institutions.

Whether or to which degree systematic exact MR-guided biopsy and marking could contribute to a better outcome or which role MR occult disease might play is yet unknown. As may be expected from the results concerning margins status, no statistical difference concerning early recurrence has been detected in the above mentioned randomized study, either.

In summary, today no proof exists that a general recommendation for preoperative MRI could improve patient outcome. Future research will have to concentrate on improving the interface between MR imaging and surgery.

Based on the existing data the EUSOMA Working group has stated that no general recommendation can be given for preoperative MRI. Research is recommended to investigate the value of preoperative MRI in defined subgroups of patients [2].

Monitoring of neoadjuvant chemotherapy

The use of MRI for monitoring of neoadjuvant chemotherapy is not yet standard, but is being investigated. MRI can be used 1–2 weeks after the second or third cycle of chemotherapy or before surgery.

According to two systematic reviews [32,33] the positive predictive value for predicting pCR ranges around 47–73% and the negative predictive value around 71–100%. These results are better than for clinical examination, ultrasound or mammography. However, over- and underestimates occur. MRI is least reliable in cases with diffusely growing cancers. However, absence of enhancement, early concentric shrinkage of the tumour volume after neoadjuvant chemotherapy or early change of the dynamic enhancement curve correlate well with pCR. Further information may be expected from novel MRI techniques such as diffusion-weighted imaging or proton spectroscopy (see below).

Problem solving

Based on its excellent sensitivity and a specificity which is comparable to the combination of mammography and ultrasound MRI may be quite helpful for solving problems that cannot be solved by conventional imaging and percutaneous breast biopsy. Such problems include search for primary tumour, exclusion of malignancy in severe scarring after breast conservation, in patients with implants, with other causes of severe scarring and some selected problems.

In patients with axillary malignant lymphadenopathy of unknown origin MRI has proven quite helpful and allowed detection of the primary in about 70–80% of the cases where conventional imaging failed [34,35]. Also several single institution series of patients have been published demonstrating the value of contrast-enhanced MRI for detection or exclusion of malignancy within difficult-to-assess scar tissue after breast conservation or silicon implant [36–39]. Rare special problems may include differentiation of very subtle changes that cannot be reliably reproduced (mammographic abnormalities seen on one view only, questionable changes within scarred tissue or very close to the chest wall) or clinical changes without correlating focal lesion on conventional imaging (nipple retraction, Paget’s disease without mammographic or sonographic abnormalities).

Ongoing research and future perspectives

Today new MR technologies have become available and are being tested. These concern diffusion-weighted imaging and proton spectroscopy.

Diffusion weighted imaging (DWI) is a new functional MR technique which provides information about the random motion of protons in tissues. Restricted diffusion of water molecules is observed in tissue with increased cellular density or increased fibrosis, as this often occurs in malignant tumours. It is visualized as hyperintense signal on diffusion-weighted images or as low signal on calculated images of the apparent diffusion coefficients (ADC). First studies have shown higher ADC values in benign lesions and normal fibro-glandular breast tissue than in most malignancies.

Based on the available data sensitivity and specificity of diffusion-weighted imaging (DWI) [40] both range around 84%. Therefore the value of DWI for differentiation may be limited. However, its use for monitoring and prediction of response to neoadjuvant treatment appears promising. Both evaluation of ADC values before treatment and change during treatment may be more accurate than monitoring of tumour diameter or tumour volume [41,42]. According to a meta-analysis [43] a sensitivity of 93% and a specificity of 82% have been described for the definition of responders based on ADC measurements.

Proton spectroscopy is another novel method which promises additional interesting information. Proton spectroscopy uses the fact that precession frequency of protons differs slightly depending on their molecular bindings. Spectroscopic imaging allows identifying certain groups of molecules contained in the imaged voxel. The group of molecules which are considered of most interest for identification of malignancy presently are phosphocholines. Since a major part but not all breast cancers and some benign lesions contain phosphocholines [44] both the sensitivity and specificity of choline spectroscopy performed with variable techniques range around 80% according to a meta-analysis [45]. Recent publications with sophisticated technology but still low numbers reported higher sensitivities and specificities [46,47].

Whereas the role of spectroscopy for lesion differentiation requires further testing, promising results have been reported concerning prediction of patient outcome based on monitoring of the choline and lactate concentrations during neoadjuvant chemotherapy [48].

Other fields of future research concern electron spin labelling. This is a method which allows magnetic labelling of flowing blood,
a technique that might in the future be of interest for avoiding contrast injection. Whether contrast agents with more specific binding can be developed remains to be seen. In the far future, sodium imaging may become available and may be of interest, since it is expected to produce different signal in malignant tumours.

Discussion/conclusion

Contrast-enhanced MRI has become a reliable and reproducible additional tool for breast imaging. Based on ample data it proves to have the highest sensitivity among the imaging methods combined with a specificity that is comparable to that of mammography combined with ultrasound. The evolution of MRI included development and propagation of a standardized technique, optimization of diagnostic algorithms and evaluation of its optimum use in the clinical context.

The presently available state-of-the-art yields reproducible images with high resolution. The combined evaluation of lesion morphology, enhancement dynamics and information from other imaging tests allows achieving at least the above mentioned sensitivities and specificities.

It must be known that the sensitivity of MRI is not perfect. So it should not replace histopathological assessment where sufficient suspicion exists and particularly where percutaneous breast biopsy is possible. Based on the yet achievable specificity MRI is moderately appropriate for screening. In the high risk group MR screening is justified by its significantly better specificity for the special spectrum of tumours seen in these patients and for evaluation of this younger age group of patients who present with very dense and sometimes difficult to assess breast tissue. Also present results for this indication suggest a positive impact on prognosis. However data allowing calculate its effect on mortality reduction are not (yet) available. Based on the design of the existing studies they will also be difficult to obtain. However, due to the high difference of sensitivity and the suspected impact on prognosis randomized studies do no more appear feasible or ethically appropriate for these patients. Because of the unavoidable bias caused by participation rates and cross over in randomized studies and the very long time span between the diagnostic test and the endpoint (death), the best suited study type for solving the remaining questions of diagnostic tests may also need to be further debated.

To date MRI is indicated in combination with at least mammography in those patients at high risk who do not opt for prophylactic mastectomy. First encouraging results have been reported for women at intermediate risk. However, specificity issues and the need for MR-guided histopathological assessment need to be considered. For women at low risk a recommendation must be given against MR screening.

To date no benefit in outcome could be proven for the use of preoperative MRI. It correctly detects more and sometimes subtle malignancy. This, however, appears to increase the rate of mastectomies without decreasing the rate of incomplete margins or the recurrence rate. Further research might be essential for a better link between imaging and image-guided surgery. However, even if this can be achieved, diligent testing (optimally in randomized studies) will still be needed to assure a benefit in preoperative patients. Facts, which could counteract a benefit from more sophisticated imaging and subsequent more aggressive surgery might be presence of further malignancy that is occult to imaging anyway or the detection of very subtle malignancy that would be sufficiently treated by irradiation and adjuvant therapy already.

As a diagnostic method MRI is quite valuable for those cases, where conventional imaging and percutaneous breast biopsy cannot solve the diagnostic question (in severe scarring or other special situations). The use of MRI for monitoring neoadjuvant chemotherapy is presently evolving and being tested. Novel techniques like diffusion weighted imaging or MR spectroscopy may gain importance for this indication.

To date the problems which are still associated with MRI concern issues of specificity, the availability and optimization of MR-guided biopsy or surgery, and the most appropriate use of MRI. Specificity can be optimized by use of optimum technique and appropriate interpretation criteria, by diligent combination of MR interpretation with the obtained information from conventional imaging, by appropriate timing of MRI with respect to the menstrual cycle (the optimum time for MRI is the second week of the menstrual cycle), by withdrawal of gestagen component of hormonal replacement therapy where possible and by correct selection of appropriate indications.

Clinical studies are continuously needed to compare the diagnostic value of MRI with that of other newly developing or further optimized techniques such as digital mammography, tomosynthesis or high resolution ultrasound. Appropriate study designs will be needed to furthermore countercheck the effect of additional imaging on patient outcome.

Novel techniques are continuously evolving and by use of additional molecular information MRI promises further valuable information which to date has not yet been exploited.

Conflicts of Interest Statement

Sylvia Heywang-Kobrunner’s private institution receives research funding from Siemens.

References

Sung JS, Malak SF, Bajaj P, Alis R, Dershaw DD, Morris EA. Screening breast MR imaging.


Lieberman S, Sella T, Maly B, Sosina J, Uziely B, Sklair-Levy M. Breast magnetic resonance imaging characteristics in women with occult primary breast carcinoma.


