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Breast Magnetic Resonance Imaging as a Problem-Solving Modality?

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Summary

Mammography is the primary imaging modality for the early detection of breast cancer. Because of the low predictive value of mammography, a large majority of patient referred for biopsy have benign disease. The question is whether magnetic resonance imaging (MRI) is a diagnostic alternative to biopsy for women with inconclusive findings at mammography or mammographic (Breast Imaging Reporting And Data System (BIRADS) 3 lesions. In this article the breast MRI and indications will be described. An overview will be given of MRI as a problem-solving modality in mammographic BIRADS 3 lesions and inconclusive mammographic findings with and without microcalcifications. The negative predictive value of breast MRI must be sufficiently high to definitively indicate a lack of need for biopsy and thus to be an effective addition to the work-up of mammographic BIRADS 3 lesions or inconclusive findings on mammography. Therefore, breast MRI should only be used for cases with proven diagnostic value.

Introduction

The worldwide incidence of breast cancer is higher than other malignancies among women. In the Netherlands, breast cancer incidence has increased to a high level and approximately one out of eight women will develop breast cancer during life (1). Although the incidence has increased, the mortality has decreased during the last two decades and at the moment the risk of dying of breast cancer is 1 in 26 (2). Five to ten per cent of all breast cancers are hereditary (3). Mammography is the primary imaging modality for the early detection of breast cancer. Despite advances in mammographic techniques (digital), mammography still has its limitations with regard to both sensitivity (85.5%) and specificity (87.7%) (4). A diagnostic mammographic examination usually consists of craniocaudal and mediolateral oblique views in accordance with the National Breast Cancer Consultation in the Netherlands (NABON) and the American College of Radiology (ACR) standards (5, 6). Mammograms are coded using the ordered categories of the ACR breast imaging reporting a data system (Breast Imaging Reporting And Data System – BIRADS) lexicon: category 1, negative; 2, benign finding; 3, probably benign; 4, suspicious finding; 5, highly suggestive of malignancy (5).

The diagnostic work-up of breast lesions depends on the BIRADS classification of the breast lesions. The guideline for non-invasive diagnostic tests for breast abnormalities of the Agency for Health Care Research and Quality in the United States (AHRQ) and the guideline of the NABON state that breast lesions classified as BIRADS 1 and 2 require no further work-up or follow-up other than routinely required. The probability of a BIRADS 3 lesion being cancer is considered to be less than 2%. The work-up of a BIRADS 3 lesion should be a biopsy or follow-up mammography after 6 months. In practice, the work-up of BIRADS 3 lesions is decided by the possibilities for biopsy procedures, but also the wish of the patient and the preference of the radiologist. The additional value of breast magnetic resonance imaging (MRI) in BIRADS 3 lesions is not yet clear (6, 7). The chance of malignancy for a BIRADS 4 lesion varies from 2% to 95% and for a BIRADS 5 lesion the chance of malignancy is higher than 95%. Therefore, the work-up for these categories requires a biopsy procedure. This biopsy procedure cannot be replaced by breast MRI, because histology is obligatory in these cases (6, 7).

Because of the low predictive value of both physical examination and mammography, a large majority of patients referred for biopsy have benign disease (8, 9). The question is whether MRI is a diagnostic alternative to biopsy for women with inconclusive findings at mammography or mammographic BIRADS 3 lesions.

MRI

Breast MRI is emerging as a clinically useful additional diagnostic tool (7, 10). MRI scans are also coded using the

ordered categories of the ACR breast imaging reporting a data system (BIRADS) lexicon (5). Image analysis is based on the enhancement pattern of lesions in dynamic breast MRI and on morphological changes (11–13). With these two criteria, breast MRI has an excellent sensitivity for detecting breast cancer, which usually exceeds 90% (11, 14, 15). Furthermore, breast MRI has the ability to depict cancers which are occult on mammography, ultrasound and clinical breast examination. However, an overlap between benign and malignant lesions still exists and the overall specificity of MRI has been variable ranging from 37% to 97% (16, 17). The diagnostic accuracy of breast MRI varies on the expertise of the radiologist and the particular patient population studied. Accordingly, MRI false positives will vary based on the clinical setting in which breast MRI is performed. It is important that breast MRI is used for those indications for which there is evidence of proven diagnostic accuracy.

As first-line imaging modality, breast MRI is performed by screening women at increased risk of breast cancer (10, 18–21). As second-line modality, breast MRI can be used for the following indications: inconclusive findings in conventional imaging, preoperative staging, axillary node malignancy and unknown site of primary breast cancer, the evaluation of therapy response in the neoadjuvant chemotherapy setting (10, 18–21), imaging of the breast after breast-conserving therapy, prosthesis imaging (10, 20), nipple discharge (10, 21), MRI in drug development and discovery (10), MR-guided biopsy and lesion localization prior to surgical excision (20).

Scientific evidence supports the use of breast MRI for specific clinical indications, although data are lacking to support the use of MRI for clinical scenarios (18, 19). It is not yet common practice to use breast MRI as a problem-solving modality, because sparse data are yet available to support its use for challenging or inconclusive mammographic findings (14, 22–27). In general, MRI can be used as a problem-solving modality when the findings of conventional imaging are inconclusive, because the sensitivity of breast MRI for the detection of cancer is the highest of all imaging techniques (14, 28, 29) and in most of the cases a negative breast MRI excludes malignancy (30–32).

MRI as a problem-solving modality in mammographic BIRADS 3 lesions or inconclusive mammographic findings

Kuhl (10) described two reasons indicating that the evidence for the effectiveness of breast MRI is relatively weak in helping to solve mammographic problems. The first reason is that ultrasonography (US)- or mammography-guided core or vacuum biopsy can obtain histological proof of equivocal lesions. The variety of minimally invasive procedures is widely available, relatively safe, inexpensive and giving diagnosis without surgical intervention. Furthermore, breast MRI has its limitations which include higher costs, longer examination time and lower availability when compared with mammography and ultrasound (10, 18).

Secondly, an imaging modality with high negative predictive value (NPV) is required to settle a diagnostic problem. In single-centre studies the NPVs of breast MRI have been reported to be as high as 98% (30–32). However, in a multicentre trial of Bluemke et al. the NPV is not high enough to exclude malignancy with sufficient confidence in case of an equivocal or suspicious lesion seen at conventional imaging (14). The diagnostic accuracy of MRI was studied in 821 patients with a suspicious (BIRADS 4 or 5) mammographic finding (85%) or a suspicious clinical finding with a negative or benign conventional work-up (15%) prior to biopsy (14). MRI had an NPV of 85% with cancer missed in 48 of 329 negative MRI examinations. This NPV was not high enough to avoid biopsy of suspicious imaging (BIRADS 4 or 5) or clinical findings based on the absence of a suspicious MRI correlate (14).

Nevertheless, there are clinical situations in which the NPV of breast MRI is high enough to be used for problem solving: (i) in patients who are being followed up after breast-conserving surgery, because it may be difficult to distinguish a developing scar from recurrent cancer (33, 34); (ii) to discriminate between, complicated cysts and solid tumours, particularly in young BRCA 1 mutation carriers (31, 35–37); (iii) to draw up the differential diagnosis of mammographic focal or global asymmetries without suspicious calcifications (10); (iv) the work-up of mammographic abnormality which is only depicted on one view and not seen on ultrasound (10); and (v) to analyse multiple round smooth masses which are equivocal at mammography and US (10).

Mammographic BIRADS 3 lesions. Gokalp and Topal (24) investigated the role of MRI in the evaluation of probably benign lesions (BIRADS 3) in mammography. MRI was performed in 56 lesions assessed as probably benign by mammography in 43 patients. The distribution of these 56 mammographic BIRADS 3 lesions was non-calcified regular shaped lesions (64.3%), focal asymmetric densities (21.4%), generalized microcalcifications (12.6%) and a cluster of tiny calcifications (1.7%). The sensitivity, specificity, accuracy, positive predictive values (PPVs) and NPVs of MR in the determination of malignancy in BIRADS category 3 were calculated as 100%, 96.4%, 96.4%, 33.3% and 100% respectively. Gokalp and Topal concluded that MRI did not provide additional information in comparison with mammography in the evaluation of category 3 lesions because it had a low PPV similar to that of short interval follow-up. However, MRI may be helpful in the evaluation of focal asymmetric densities. Nine of the 12 mammographic focal asymmetric densities were confirmed as breast tissue and the other three as masses with MRI. Nevertheless, this should be further investigated in larger groups (24).

Inconclusive mammographic findings without microcalcifications. In the article of Moy et al. (27) the usefulness of breast MRI in cases of inconclusive mammographic or sonographic findings was evaluated. In this study, 115 breast MRIs were used as adjunctive tool and the findings were correlated with pathology. Forty-eight of the 115 patients (41.8%) were at high risk. The equivocal mammographic findings for which MRI was performed were asymmetry without associated microcalcifications (85.2%), architectural distortion (10.4%) and change in the appearance of the site of a previous benign biopsy finding (4.3%). The findings at mammography were BIRADS category 0 in 78 cases (67.8%), category 3 in 15 cases (13%) and category 4 in 22 cases (19.2%). MRI had a sensitivity of 100% and compared with mammography had significantly high specificity (91.7% vs. 80.7%, $P = 0.029$), PPV (40% vs. 8.7%, $P = 0.032$) and overall accuracy (92.2% vs. 78.3%, $P = 0.00052$). Moy et al. concluded that breast MRI can be a useful adjunctive tool when equivocal findings at conventional mammography are asymmetry or architectural distortion (27).

Inconclusive mammographic findings with mircocalcifications. There is one diagnostic criterion in which the NPV of breast MRI is known to be insufficient which involves patients with suspicious mammographic calcifications. Three studies (22, 23, 25) evaluated the role of MRI in patients with microcalcifications. They include different BIRADS categories: Uematsu et al. (25) and Cilotti et al. (23) included category 3–5 microcalcifications and Bazzocchi et al. (22) included category 5 microcalcifications.

In the article of Uematsu et al. (25), breast MRI was performed in 100 screening-mammographic detected microcalcifications in 96 patients. These patients also underwent a stereotactic vacuum-assisted breast biopsy (SVAB) as gold standard. PPVs and NPVs were calculated on the basis of a BIRADS category and the absence or presence of contrast uptake in the area of microcalcifications. With MRI three out of four malignancies with BIRADS mammography category 3 were diagnosed as true positive; therefore, the PPV of BIRADS 3 mammography category 3 added MRI was 1.8%. NPV of BIRADS mammography 3 was 93% vs. 97% NPV of MRI ($P = 0.167$). The PPV of contrast uptake of MRI was 86%, which is significantly higher than the 67% PPV of BIRADS mammography 4 and 5 ($P = 0.033$). Uematsu et al. concluded that the imperfect PPV and NPV of the MRI in the evaluation of screening-detected microcalcifications lesions cannot replace SVAB. However, MRI provides additional information with high PPV and NPV and may therefore offer an alternative to SVAB for women who do not want to undergo SVAB with equivocal mammographic findings (25).

Also Cilotti et al. (23) concluded that the PPV and NPV of MRI in the characterization of microcalcifications are not high. In their study, 55 patients with mammographic calcifications classified as BIRADS categories 3, 4 or 5 underwent MRI and biopsy with stereotactic vacuum-assisted biopsy (SVAB). MRI BIRADS category 1, 2 and 3 were considered as benign and 4 and 5 as malignant. The sensitivity, specificity, PPV, NPV and diagnostic accuracy were 73%, 76%, 73%, 76% and 74.5% respectively. Their conclusion is that mammography and stereotactic biopsy remain the only techniques for characterizing microcalcifications. MRI cannot be considered a diagnostic tool for evaluating microcalcifications (23).

This is also the conclusion of Bazzocchi et al. (22). In their study they concluded that MRI cannot be used in the assessment of mammographically detected microcalcifications due to low sensitivity (87%) in 112 category 5 microcalcifications. The decision to perform biopsy should be based only on mammographic findings, because one is unable to exclude cancer sufficiently with MRI (22).

Akita et al. (26) concluded that additional bilateral breast MRI compared with mammography alone significantly improved the rate of diagnosis of malignancy in breast lesions which were detected as suspicious microcalcifications at mammography. In this study 50 patients with mammographic microcalcifications (9 category 3 and 41 category 4) were included. These patients underwent MRI before SVAB. Mammography had a sensitivity of 100%, a specificity of 24% and an accuracy of 44%, whereas mammography plus MRI had a sensitivity of 85%, a specificity of 100% and an accuracy of 96%. They also concluded that performing additional bilateral breast MRI with mammography may alter the indications for and implementation of SVAB. However, further research is needed to establish the clinical value of bilateral breast MRI for the management of patients showing positive findings on mammography (26).

Nevertheless, MRI can be useful in patients with calcifications. It can help demonstrate or exclude underlying invasive cancer, because MRI has a high NPV for invasive cancer. Secondly, an important application of MRI in patients with ductal carcinoma *in situ* (DC15) associated with suspicious microcalcifications could be to evaluate disease extension (10).

Conclusion

Breast mammography still is the primary imaging modality for early detection of breast lesions in almost all patients. The diagnostic work-up of these lesions depends on the BIRADS classification. The work-up of BIRADS 4 or 5 lesions is a biopsy procedure. For BIRADS 3 lesions or inconclusive mammographic findings the work-up should be a biopsy or follow-up imaging modality after 6 months. To be an effective addition to the work-up of an inconclusive finding on mammography, the NPV of breast MRI must be sufficiently high to definitively indicate a lack of need for biopsy. Although there are sparse published data to support utilization of breast MRI for problem solving, specific clinical situations should be identified in which it is

known that the NPV is high enough and others for which is not attainable because the NPV is not high enough, rather than compare overall NPVs of imaging modalities. It is clear that MRI cannot be used for the assessment of mammographically detected microcalcifications, but it can help to demonstrate or exclude underlying invasive cancer. As only two studies have been published in which mammographic BIRADS 3 lesions or inconclusive mammographic findings are discussed, a firm conclusion cannot yet be drawn. Therefore, further research should be performed to decide whether MRI can be used as a problem-solving modality in mammographic BIRADS 3 lesions and inconclusive mammographic findings not consisting of microcalcifications. Meanwhile, breast MRI should only be used for cases with proven diagnostic value.

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