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PICTORIAL ESSAY

Magnetic Resonance Imaging of Invasive Ductal Carcinoma and Ductal Carcinoma in Situ in Detecting Multifocal/Multicentric and Bilateral Breast Disease: A Pictorial Essay

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BACKGROUND

In accordance with the standard protocol in place, all patients with biopsy-proven breast malignancy (either by ultrasound-guided or stereotactic biopsy), with histology of invasive ductal carcinoma (IDC) and/or ductal carcinoma in situ (DCIS), subsequently undergo preoperative magnetic resonance imaging (MRI) of both breasts to rule out multifocal/multicentric and bilateral disease before considering breast-conserving therapy (BCT). Some of the patients are referred from the surgical department to the radiology department for MRI if they do not opt for private imaging. Unlike invasive lobular carcinoma (ILC) which is characteristically associated with multifocal/multicentric or bilateral disease,[1] primary IDC and DCIS are not known to be linked to a high rate of such involvement, and patients may proceed directly to BCT without preoperative MRI in our locality. This pictorial essay reviews our experience in detecting multifocal/multicentric and bilateral disease in patients with primary IDC and DCIS using MRI and illustrates the associated MRI features.

MAGNETIC RESONANCE IMAGING FEATURES

Most primary breast carcinomas present as a palpable mass. By definition, a 'mass' is a three-dimensional lesion that occupies space. Mammography remains the cornerstone of breast cancer screening and is often the first imaging modality used. Ultrasound is useful in characterising palpable masses, especially in dense breast tissue, providing real-time assessment of lesion morphology and vascularity. MRI is generally reserved for problem-solving, preoperative staging, or screening high-risk populations. Any enhancing lesion measuring less than 5 mm on MRI is termed a 'focus', which is too small to characterise. Evaluation of a mass is based on its shape, margins, T1- and T2-weighted signals, and its enhancement pattern.[2] MRI provides valuable functional information regarding masses, including kinetic curves and diffusion restriction, which will be discussed in a subsequent section. MRI often reveals multifocal/multicentric and bilateral disease in IDC and DCIS that is occult on mammography or ultrasound, commonly presenting as non-mass enhancement (NME).

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Non-Mass Enhancement

NME refers to an area of enhancement without an associated mass and is the most common MRI finding in multifocal/multicentric and bilateral disease.[2-4]

Various distribution patterns of NME on breast MRI include focal, linear, ductal, segmental, regional, multiple regions, and diffuse.[5] Focal NME is defined as a single, small, confined area of abnormal enhancement occupying less than 25% of the breast. Linear NME appears as a line not conforming to a ductal pattern (Figure 1), while ductal NME may be linear or linear branching corresponding to one or more ducts, usually radiating towards the nipple (Figure 2). A mixed pattern of linear and ductal enhancement is commonly seen. Ductal enhancement is considered suspicious for malignancy, with a positive predictive value ranging from 26% to 58.5%.[2,5] Segmental enhancement (Figure 3) is triangular or cone-shaped, representing involvement of a single branching ductal system. Such enhancement has a high positive predictive value for carcinoma, ranging from 67% to 100%.[2,6,7] Regional enhancement involves a larger area not conforming to a ductal distribution and may appear geographic or patchy, potentially representing background parenchymal enhancement or benign lesions such as fibrocystic changes.[4] Multiple regions of NME are defined as at least two large volumes of tissue not conforming to ductal distribution and separated by normal tissue or fat. Diffuse NME refers to widely scattered, evenly distributed enhancement throughout

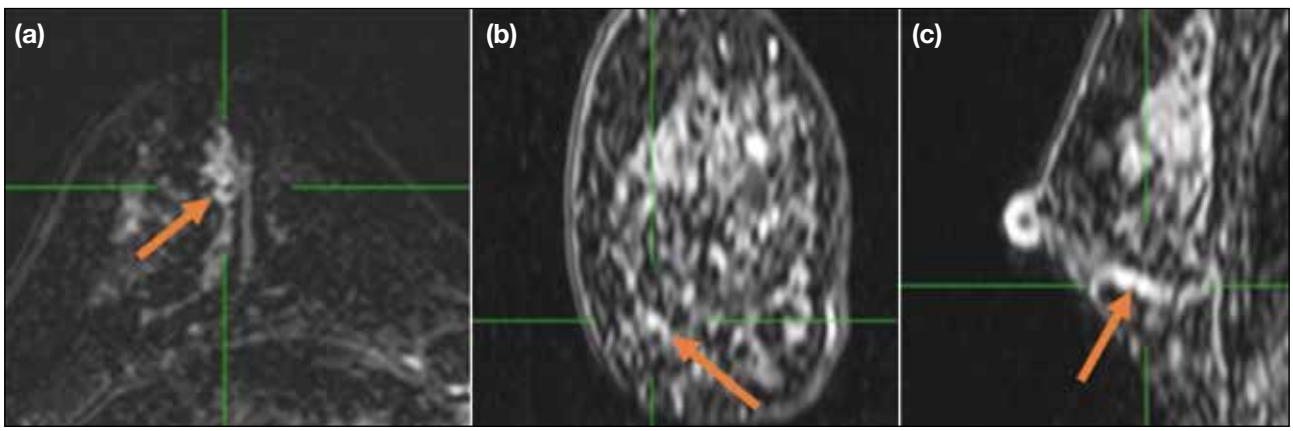

Figure 1. A 52-year-old woman with left breast carcinoma. Incidental note of linear non-mass enhancement (NME) in the right inferior breast on magnetic resonance imaging (arrows); biopsy on second-look ultrasound revealed usual ductal hyperplasia and intraductal papilloma and patient subsequently had left breast-conserving therapy. Reformatted axial (a), coronal (b) and sagittal (c) post-contrast T1-weighted images with subtraction show linear NME in the right inferior breast.

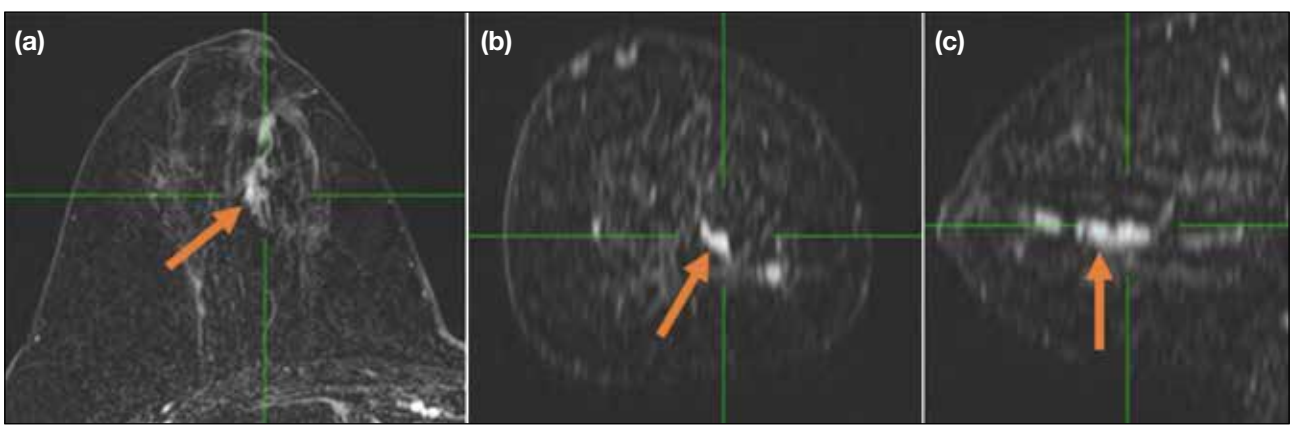

Figure 2. A 41-year-old woman with biopsy-proven right-sided ductal carcinoma in situ (DCIS) undergoing preoperative magnetic resonance imaging. (a) Reformatted axial post-contrast T1-weighted image with subtraction shows the DCIS as central ductal non-mass enhancement extending towards the nipple (arrow). Reformatted coronal (b) and sagittal (c) post-contrast T1-weighted images with subtraction (arrows).

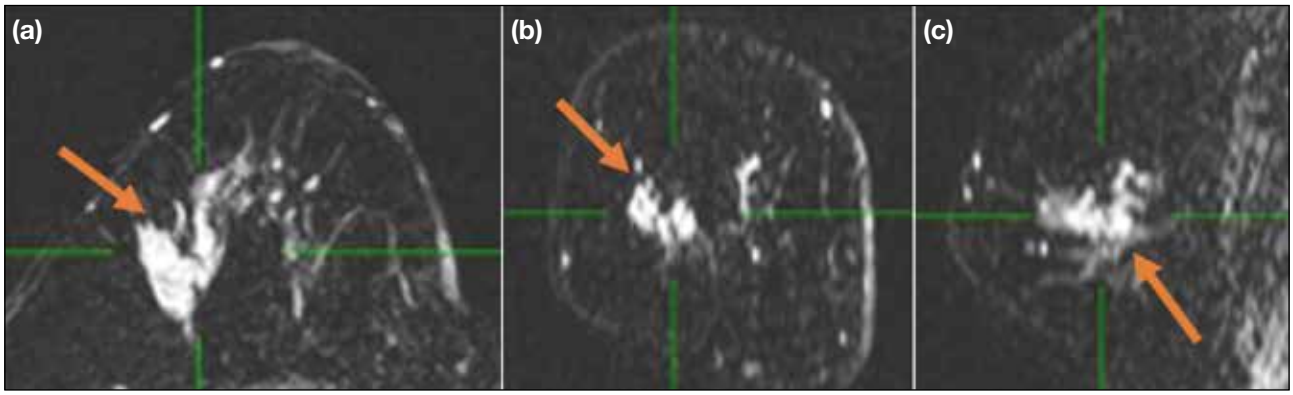

Figure 3. A 60-year-old woman with biopsy-proven high-grade ductal carcinoma in situ in the right breast, manifesting as clumped non-mass enhancement in a segmental distribution on magnetic resonance imaging (arrows). (a) Axial post-contrast T1-weighted image with subtraction. Reformatted coronal (b) and sagittal (c) post-contrast T1-weighted images with subtraction.

the breast. Multiple-region and diffuse enhancement are more characteristic of benign proliferative changes.[4]

The internal characteristics of NME include homogeneous, heterogeneous, stippled/punctate, and clumped patterns. Homogeneous enhancement refers to confluent, uniform enhancement while heterogeneous enhancement is non-uniform and appears in a random pattern. Stippled/punctate enhancement describes multiple, tiny (1-2 mm), dot-like, similar-appearing enhancing foci that do not conform to a ductal distribution. Clumped enhancement refers to an aggregate of enhancing masses or foci in a cobblestone pattern. Among non–mass-like enhancement patterns, stippled enhancement is less likely to be malignant, with a 25% incidence of malignancy, whereas homogenous, heterogeneous and clumped enhancement patterns are associated with higher likelihoods of malignancy at 67%, 53%-69% and 60%-88%, respectively.[2,7,8]

Kinetic Curves

Kinetic curve is derived from the time-signal intensity curve through dynamic contrast-enhanced MRI, reflecting the haemodynamic features of a specific lesion. It can be interpreted in terms of early and delayed phases. During the early phase (typically within 1-2 minutes after contrast injection), the initial rise of the enhancement curve can be classified as slow, medium, and rapid. An initial peak signal intensity achieved within 90 seconds and exceeding 90% is defined as rapid enhancement, which is highly suggestive of malignancy. In the delayed phase (after 2 minutes), three types of kinetic contrast enhancement are observed: persistent (type I), plateau (type II) and washout (type III).[2] These patterns are further illustrated in Figure 4.

Restricted Diffusion

The presence of restricted diffusion on diffusion-weighted imaging indicates a higher probability of malignancy due to increased cellularity. In equivocal cases, the apparent diffusion coefficient (ADC) value can be measured. An ADC value of less than 1.25 is considered to indicate the presence of restricted diffusion, while a value of 1.25 or greater suggests its absence. The recommended mean (± standard deviation) threshold ADC value as $1.25 \pm 0.17 \times 10^{-3}$ mm^2/s, based on studies on the differential diagnosis of breast tumours, in which an ADC value below this threshold indicated a malignant lesion.[9,10] The interpretation is illustrated in Figure 5.

OUR EXPERIENCE

We retrospectively reviewed 115 patients with IDC and DCIS (Figure 6). Initially, 70 patients presented with left breast carcinoma and 45 with right breast carcinoma. Multifocal/multicentric or bilateral disease was identified in 22 patients, giving an incidence of 19.1%. Among those with left breast carcinoma, 10 had ipsilateral multifocal/multicentric disease and two had contralateral disease, thus classified as bilateral (Figure 7). Among patients with right breast carcinoma, eight had ipsilateral multifocal/multicentric disease and two had contralateral disease, also classified as bilateral. A total of 61 patients underwent unilateral BCT while 54 underwent mastectomy, including four who had bilateral mastectomy. In total, 22 patients were converted from

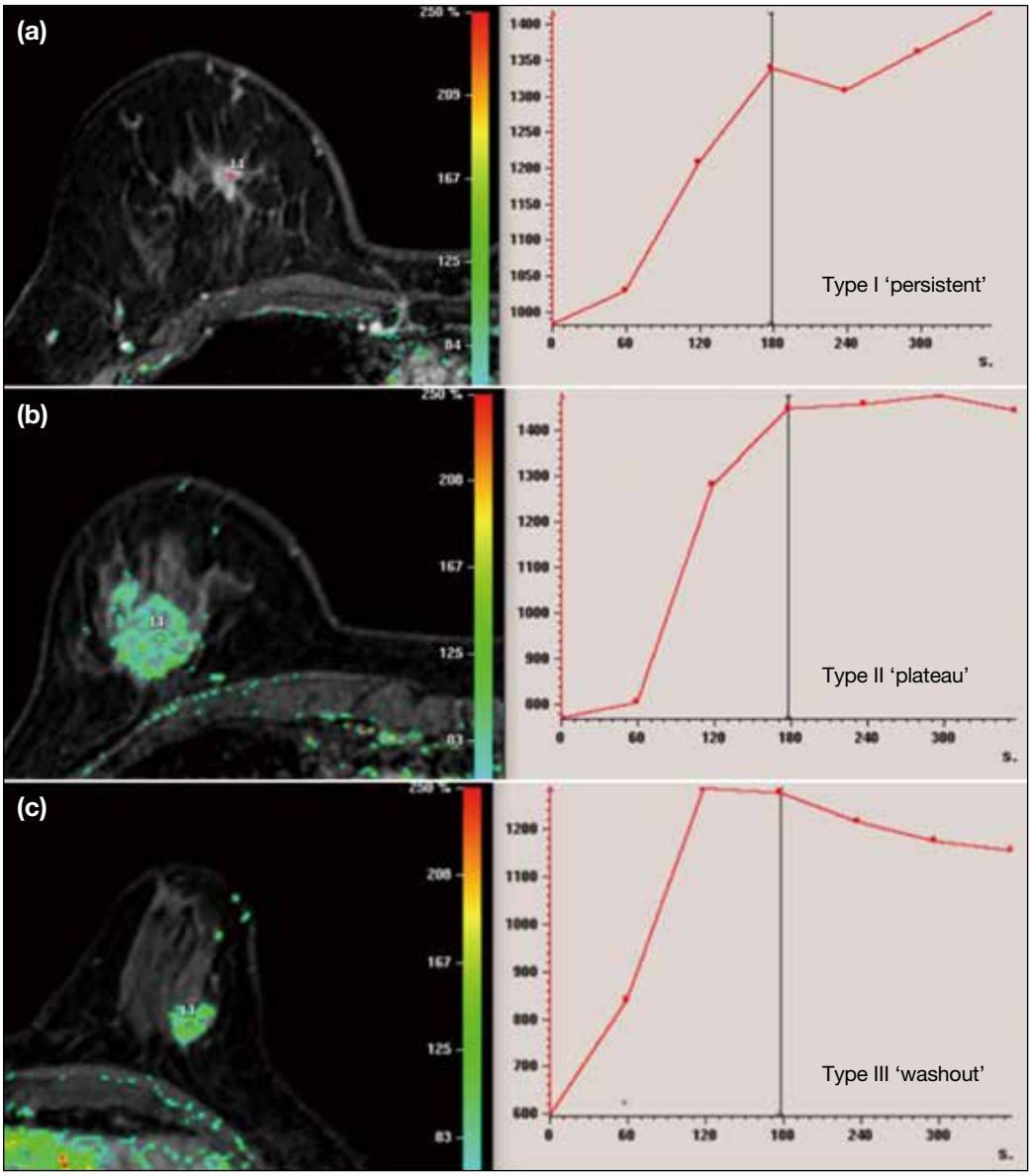

Figure 4. (a) Type I curve demonstrates slow and continued rise of enhancement with time (6% risk of malignancy[2]). (b) Type II curve shows a slow or rapid initial rise followed by a plateau in the delayed phase, which allows a variance of 10% up or down (6-29% risk of malignancy[2]). (c) Type III curve shows rapid initial rise followed by a drop-off with time (washout) in the delayed phase (29%-77% risk of malignancy[2]).

BCT to mastectomy. Some patients with a single ipsilateral tumour opted for mastectomy during follow-up due to individual factors, such as fear of incomplete excision, older age, or lack of cosmesis concern.

MRI scans are reported according to the BI-RADS (Breast Imaging Reporting and Data System) 5th Edition from the American College of Radiology.[11] The primary tumour is defined as the palpable mass or the most suspicious lesion with biopsy-proven DCIS or IDC, presenting as an enhancing mass or NME on MRI. Suspicious lesions (predominantly NME) other than the primary tumour, with a BI-RADS category 4 or higher, located in the ipsilateral or contralateral breast, are classified as multifocal/multicentric or bilateral disease. The need for second-look ultrasound is determined on a case-by-case basis, influenced by patient-related factors (e.g., breast density, family history of breast cancer) or the preferences of the reporting radiologist and/or breast surgeon. For example,

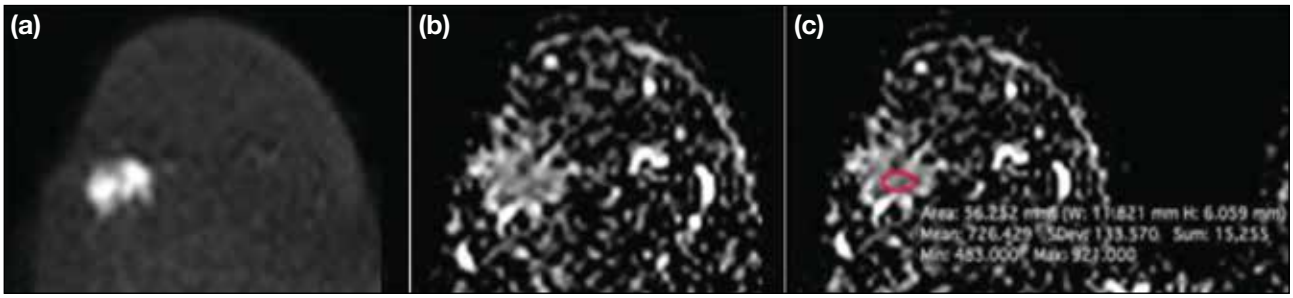

Figure 5. A 61-year-old woman with invasive ductal carcinoma in the right breast. (a) Diffusion-weighted imaging shows high signal intensity of the tumour. (b) Apparent diffusion coefficient (ADC) map demonstrates corresponding low signal intensity, suggestive of restricted diffusion. (c) The ADC value, measured directly on OsiriX DICOM viewer (Pixmeo SARL, Bernex, Switzerland), is 0.726 × 10^{-3} mm^2/s (the mean value was displayed by the software in the form of 10^{-6} mm^2/s).

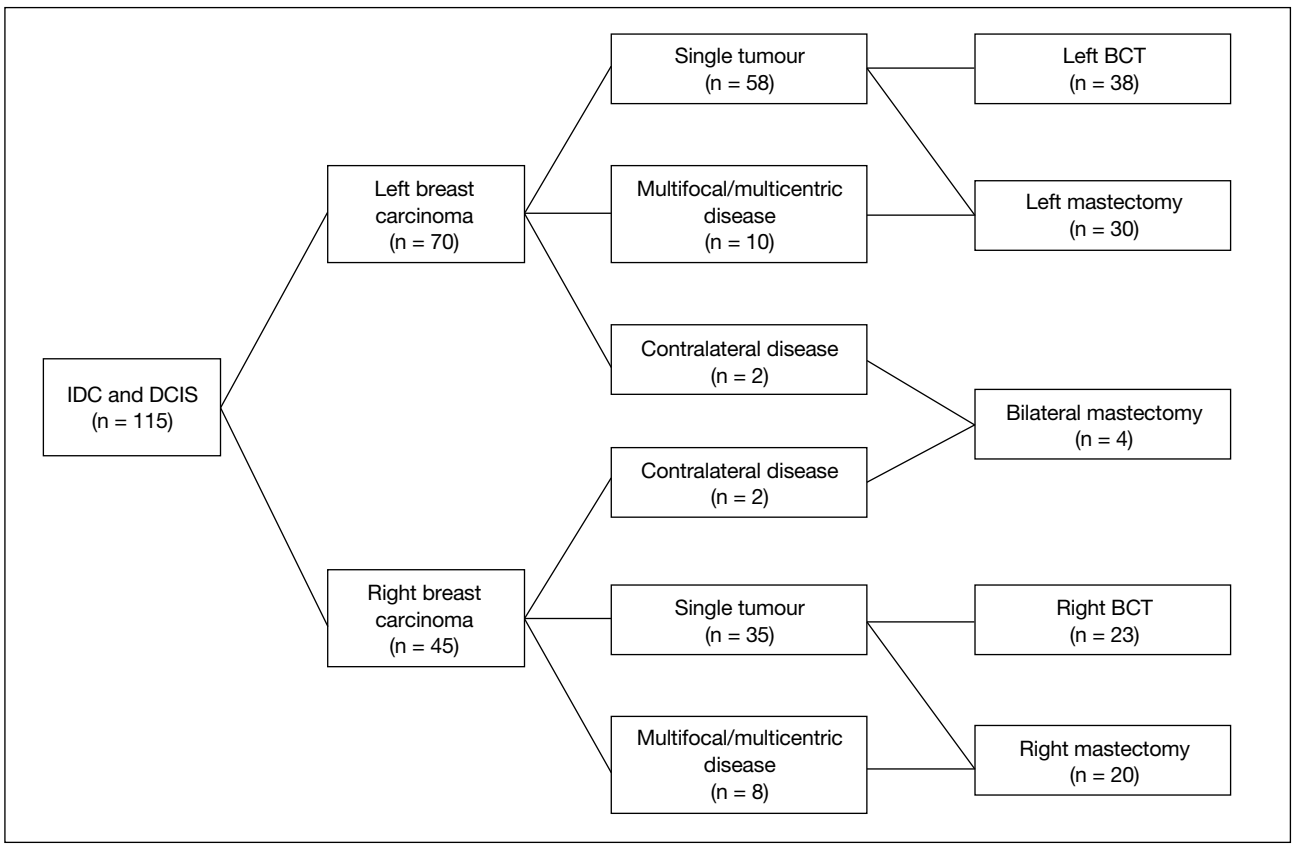

Figure 6. Disease patterns and management of the selected patients.
Abbreviations: BCT = breast-conserving therapy; DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma.

if contralateral breast disease is identified (which greatly affects treatment plan), or if the patient strongly desires BCT, ultrasound is performed to guide biopsy and inform subsequent management. If the lesion is not visible on second-look ultrasound, particularly in cases of equivocal NME patterns such as focal or linear distribution, MRI-guided biopsy would be considered when clinically necessary due to required alterations in the treatment options. If the suspected multifocal/multicentric disease in the same breast is deemed highly suspicious, such as clumped areas of NME in a segmental distribution, second-look ultrasound would not be performed, and the patient would be advised to undergo mastectomy.

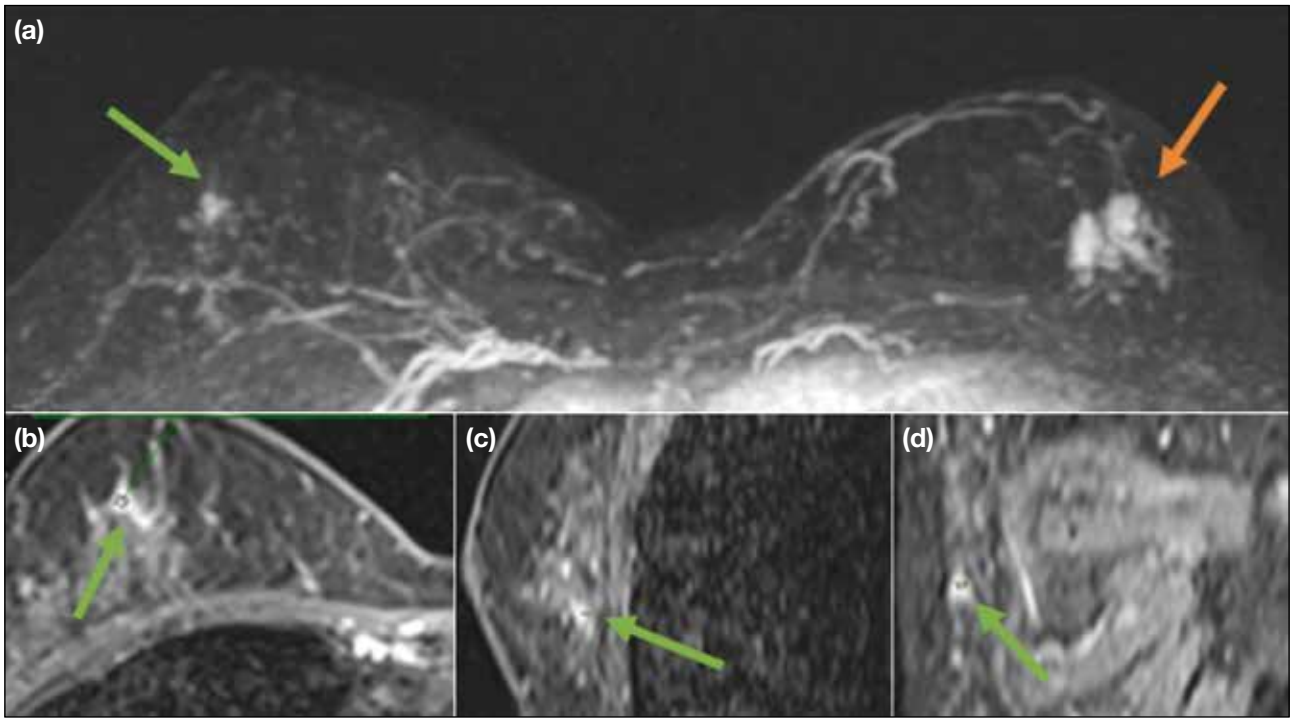

Figure 7. A 63-year-old woman with bilateral breast carcinoma detected by preoperative magnetic resonance imaging, prior to bilateral mastectomy. (a) T1-weighted three-dimensional reconstructed subtraction axial image shows the primary tumour (invasive ductal carcinoma) as an enhancing lobulated mass in the left breast (orange arrow) and an incidental finding of focal non-mass enhancement (NME) in the right breast (green arrow). (b) Reformatted T1-weighted post-contrast image of the right breast shows focal NME (green arrow), which was confirmed to be ductal carcinoma in situ by ultrasound-guided biopsy. Reformatted sagittal (c) and coronal (d) post-contrast T1-weighted images with subtraction (green arrows).

Following surgical excision, the histology report is reviewed to assess the presence of multifocal/multicentric and/or bilateral disease. Multifocal disease refers to foci located in the same quadrant as the primary tumour, separated by more than 2 cm, whereas multicentric disease indicates involvement of different quadrants within the same breast. A background of DCIS, multiple foci of DCIS, or IDC or DCIS in another quadrant is defined as multifocal or multicentric disease. The presence of DCIS or IDC in tissue specimens from both breasts is classified as bilateral disease. Among the 115 cases, 17 were true positives, five were false negatives, 91 were true negatives and two were false positives. The sensitivity and specificity of MRI in detecting multifocal/multicentric and bilateral disease were calculated to be 77.3% and 97.8%, respectively.

Among the five MRI false-negative cases, one of them could be detected by mammogram, which showed extensive grouped microcalcifications spanning more than 3 cm and crossing two quadrants. MRI was performed to rule out bilateral disease even though mammogram and ultrasound were negative for the contralateral breast, as the patient was young (37 years old at the time of diagnosis). The patient subsequently underwent mastectomy due to multicentric involvement demonstrated in the mammogram. The remaining four cases were negative on mammography and ultrasound, and they eventually had mastectomy due to patient preference or small breast size relative to the primary tumour.

In both false-positive cases, MRI showed focal NME suspicious for multicentric involvement. Histological diagnoses of the corresponding sites revealed atypical apocrine adenosis (Figure 8) and fibroadenoma (Figure 9). Both patients opted for mastectomy due to previous chest wall irradiation for contralateral breast carcinoma, which increased the risk of toxicity with possible re-irradiation, and because of a large tumour size that made preservation of the nipple-areolar complex impossible. In both cases, MRI findings alone did not alter the management.

There are no well-established data in the literature regarding the incidence of multifocal/multicentric and bilateral disease with the histology of IDC and DCIS. A previous study instead investigated the incidence of such disease based on the immunohistochemical features, including oestrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2.[12] ILC is more frequently found to be multifocal/multicentric or bilateral compared to DCIS and IDC, with reported incidences commonly ranging from 10% to 20%.[13,14] A retrospective observational study reported the incidence of multifocal/multicentric ILC to be 18.9%,[15] which is similar to the rate of DCIS and IDC observed in our study. DCIS can occur independently and act as a precursor to IDC, although the mechanism of progression from DCIS to IDC remains poorly understood. Currently there are no definitive imaging features that can reliably predict which forms of DCIS are more likely to progress to invasive cancer. The most common manifestation of DCIS is calcification (approximately 80%), while concomitant DCIS is found in 60% of invasive cancers yet calcifications are only seen in 30% of those cases. Consequently, it is not uncommon for IDC to coexist with multifocal/multicentric DCIS, which may seem defying to our usual knowledge about IDC. Preoperative MRI, as the most sensitive imaging tool, plays an important role in patients with DCIS or IDC who are planning BCT, to rule out multifocal/multicentric disease.[16,17] Some

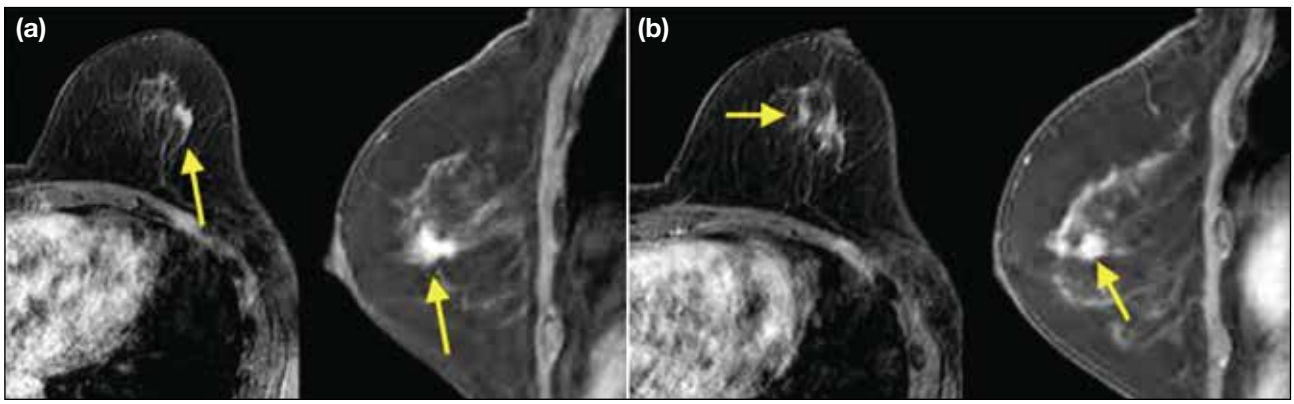

Figure 8. One of the false-positive cases in which the suspected multicentric lesions were found to be atypical apocrine adenosis on final pathology following mastectomy. (a) Post-contrast T1-weighted images: axial (left) and sagittal (right) views show the primary tumour (intermediate-grade ductal carcinoma in situ [DCIS]) as focal clumped non-mass enhancement (NME) [arrows]. (b) Post-contrast T1-weighted images: axial (left) and sagittal (right) views of the multicentric foci show focal nodular NME at L10H, mid-depth of the breast (i.e., near the back of the left breast at the 10 o'clock position) [arrows]. The imaging features of DCIS and atypical apocrine adenosis on magnetic resonance imaging are similar, making them difficult to distinguish. Common benign NME lesions include fibrocystic change, apocrine metaplasia, pseudoangiomatous stromal hyperplasia, and post-irradiation changes.

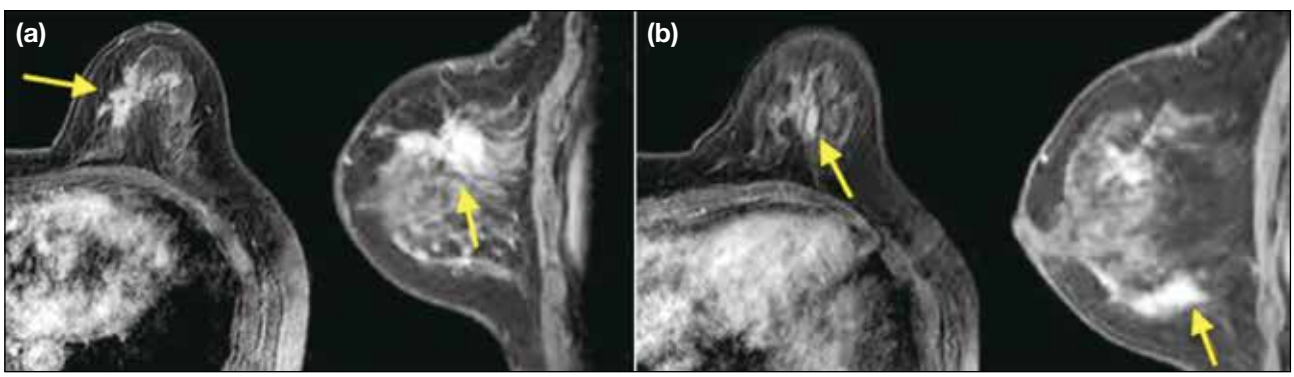

Figure 9. One of the false-positive cases in which the suspected multicentric lesion was found to be fibroadenoma on final pathology following mastectomy. (a) Post-contrast axial (left) and sagittal (right) T1-weighted images of the primary tumour (high-grade ductal carcinoma in situ) show clumped non-mass enhancement (NME) in a segmental distribution with associated architectural distortion of the surrounding parenchyma (arrows). (b) Post-contrast axial (left) and sagittal (right) T1-weighted images of the multicentric focus (fibroadenoma) demonstrate focal nodular and linear-like NME with no definite ductal or segmental distribution (arrows).

lesions may be pure IDC or DCIS while others may be DCIS progressing to IDC. The heterogeneity of this disease thus does not exhibit any unifying or statistically significant MRI feature. Further study regarding the association of the immunohistochemical profile of the tumour with its likelihood of multifocal/multicentric and bilateral disease may be worthwhile.

Among the five false-negative cases, all involved multifocal and multicentric low-to-intermediate-grade DCIS in the same breast, which is known to be less readily detected by MRI. The sensitivity of MRI for detecting low-grade DCIS is 74.0%, and 84.1% for intermediate-grade DCIS,[18] figures that are comparable to our study. While DCIS most commonly presents as NME on MRI, its detection may still be challenging in some cases. As all patients initially underwent mammography, which remains the gold standard for detecting calcifications, a common feature of DCIS, the suboptimal sensitivity of MRI in identifying low-to-intermediate-grade DCIS could be mitigated by the complementary conventional mammography. In our study, one case of multicentric DCIS was detected by mammography but not by MRI, highlighting the crucial and complementary role of mammography in comprehensive assessment of disease extent.[19-24]

CONCLUSION

Based on our experience, there is a considerable incidence of multifocal/multicentric and bilateral disease in IDC and DCIS, for which MRI is an effective tool for preoperative evaluation. With better knowledge of the associated MRI features, multifocal/multicentric and bilateral disease may be more readily detected, enabling appropriate subsequent patient management.

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