Imaging

The Use of Imaging in Breast Cancer Diagnosis and Triple Assessment

Imaging section is edited by Dr Tom Lynch

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Breast cancer is the most prevalent cancer amongst women and is estimated to affect one in nine women in their lifetime. Recent statistics indicate that the incidence of breast cancer has increased annually, likely due to increased public awareness and the introduction of screening programmes. Over the last few decades there has been a real drive to diagnose breast cancer as early as possible in an attempt to improve survival rates. This means the vast majority of women are diagnosed with early stage disease. Surgery remains the main treatment modality but improvements in adjuvant systemic treatments mean that most women can be treated with the aim of cure.

The majority of patients diagnosed with breast cancer are symptomatic and the most common finding is of a lump. All patients are assessed using the triple assessment of clinical examination, imaging and pathological biopsy. Thus radiological imaging plays a major role in preoperative assessment and diagnosis of breast cancer and aids decision making regarding the type of surgical procedure that is considered.

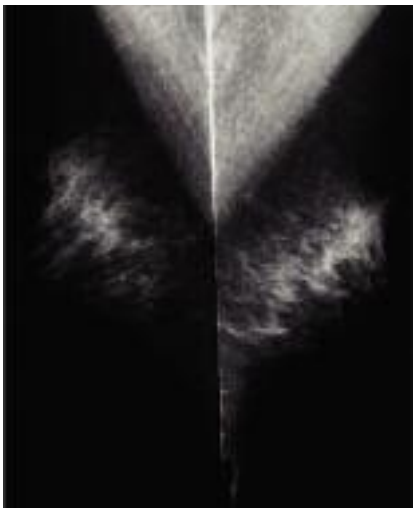
A number of different imaging techniques are useful in the assessment of breast cancer including mammography, ultrasonography and magnetic resonance imaging (MRI). The purpose of this review is to focus on these three imaging modalities to describe the common radiological features of malignancy and also the use of these techniques in screening.

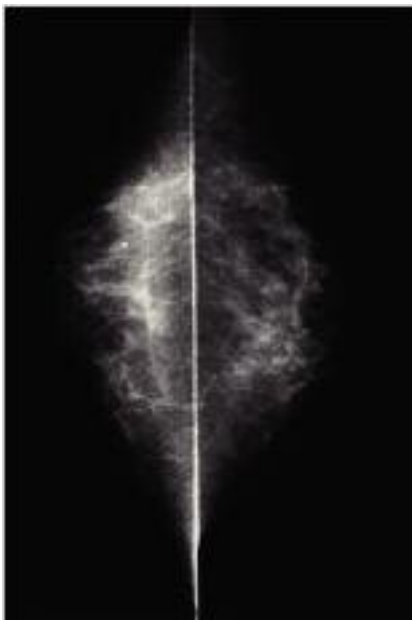
Mammography

Mammography was first used routinely in the investigation of breast abnormalities in 1960 but it was not until 1976 when it was used as a screening modality. The technique uses low energy x-rays to create detailed images of the breast and accuracy can be enhanced by compressing the breast to maximise the amount of tissue that can be imaged and reduce x-ray scatter. Two mammographic views are routinely obtained including cranio-caudal (CC) and medio-lateral-oblique (MLO) views (Figures 1a and b). Further supplemental views such as latero-medial (LM), medio-lateral (ML), exaggerated CC, magnification and spot compression views may be used to improve the diagnostic procedure. Abnormalities are described and located to a quadrant or ascribed a clock face position while the depth of the lesion is assigned to the anterior, middle or posterior third of the breast.

The most common feature of a malignant lesion on mammography is a dense spiculated mass. Other features suggestive of malignancy should also be assessed including associated clusters of pleomorphic microcalcification (different sizes and shapes), asymmetric density or distortion, skin thickening, puckering, nipple retraction and axillary lymphadenopathy. These features may be present separately or variably together (Figure 1c). A few notable exceptions to this are inflammatory and lobular carcinomas which may present as subtle asymmetry or distortion or be occult on mammography.

Mammography is a very accurate technique depending on patient age and density of the breast. Carney et al concluded that the adjusted sensitivity increased with age from 68.6% in women 40 to 44 years of age to 75.4% in women 50-54 years and up to 83.3% in women 80 to 89 years of age. Adjusted specificity increased from 89.1% in women with extremely dense breasts to 96.9% in women with almost entirely fatty breasts [2]. Ultimately, it may not be possible to determine if lesions seen in the mammogram represent a malignancy and





Figures 1a and b (top and middle): Normal mammogram medio-lateral oblique and craniocaudal views.

Figure 1c (bottom): Right medio-lateral oblique mammographic view showing a dense spiculated mass typical for a carcinoma.

Table 1: BIRADS and the RCRBG classification for breast imaging.

Category	*BI-RADS*	*RCRGB*
0	Assessment incomplete. Need to review prior studies and/or complete additional imaging	Normal/no significant abnormality. There is no significant imaging abnormality.
1	Negative. Continue routine screening.	
2	Benign finding. Continue routine screening.	Benign findings. The imaging findings are benign.
3	Probably benign finding. (<2% chance of malignancy) Short-term follow-up mammogram at 6 months, then every 6- 12 months for 1- 2 years	Indeterminate/probably benign findings. There is a small risk of malignancy. Further investigation is indicated.
4	Suspicious abnormality. Perform biopsy, preferably needle biopsy	Findings suspicious of malignancy. There is a moderate risk of malignancy. Further investigation is indicated.
5	Highly suspicious of malignancy: appropriate action should be be taken. Biopsy and treatment, as necessary.	Findings highly suspicious of malignancy. There is a high risk of malignancy. Further investigation is indicated.
6.	Known biopsy-proven malignancy, treatment pending.	

BI-RADS, American College of Radiology Breast Imaging Reporting and Data System; RCRBG, Royal College of Radiologists Breast Group.

Adapted from Maxwell AJ, Ridley NT, Rubin C, Wallis MG, Gilberte FJ, Michell MJ. The Royal College of Radiologists Breast Group breast imaging classification. Clinical Radiology 2009;(64):624-7.

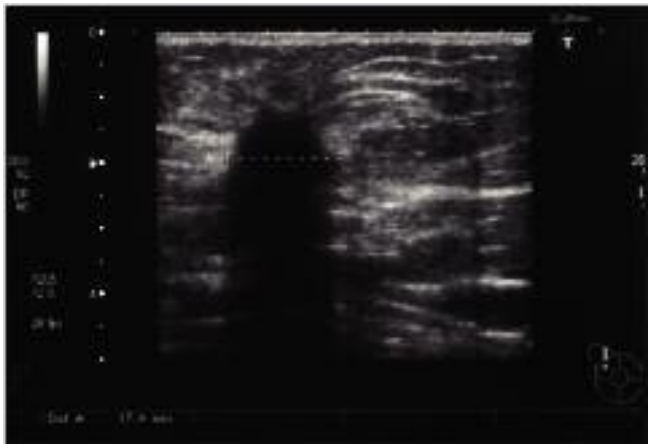


Figure 2: Ultrasound image showing an irregular hypoechoic mass, taller than long, crossing tissue planes, with distal acoustic shadowing typical for carcinoma.

benign lesions may initially have an indeterminate or suspicious appearance on mammography. Moreover, the Royal College of Radiologists Breast Group UK have adapted the breast imaging reporting data systems (BI-RADS) classification to determine if there is a requirement to further evaluate breast lesions (Table 1). Thus mammography is commonly the first line investigation for patients over the age of 35 with breast symptoms and is often followed by further investigation such as ultrasonography and biopsy for definitive diagnosis.

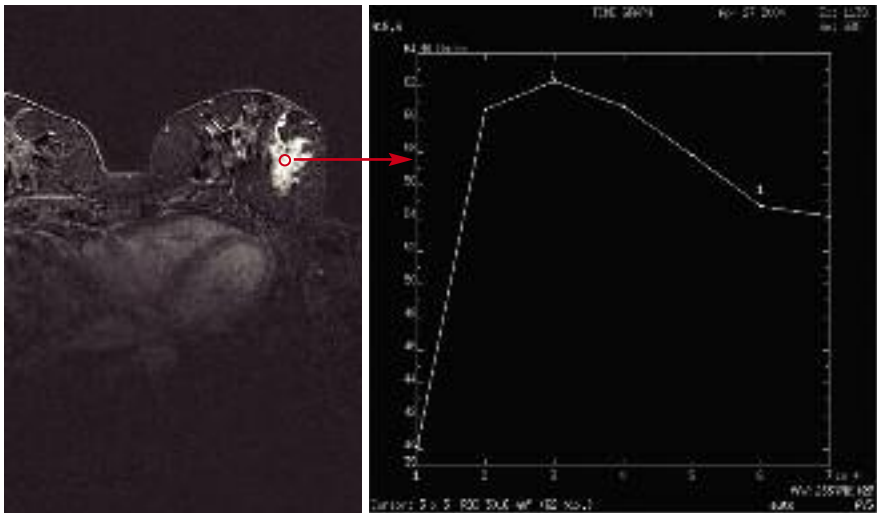
Given success in the investigation of symptomatic breast lumps, mammography was subsequently introduced to screen asymptomatic women for breast abnormalities. The aim of this strategy is to diagnose cancers at the earliest possible stage in order to maximise chances of cure. In support of this, a meta-analysis of seven multinational randomised controlled trials demonstrated that breast cancer screening with mammography reduced breast cancer mortality by 20-30% in women above the age of 50 years [3]. Similar findings were presented to the Milan Global Summit on mammographic screening [4]. The National Health Service Breast Screening Programme (NHSBSP) invites women aged 50-70 years of age for mammography every three years and over 2.2 million women were invited for screening in England between 2007 and 2008, an increase of 5% from the year before and 52.5% over 1997 [1]. This programme was responsible for the detection of 14,110 cases of breast cancer out of 1.7 million women screened above the age of 45 years between 2007 and 2008, double the number detected between 1997 and 1998 [1]. However, part of this increase could also be due to extension in the age for screening from 64 to 70 years.

Recent advances in mammography including digital images and computer-aided detection have been investigated to determine their role in improving success of screening. The digital mammography imaging screening trial (DMIST) conducted by the American college of radiology imaging network (ACRIN) over a two year period involving 49,528 women revealed that digital mammography is more sensitive than conventional plain film mammography in patients under the age of 50 years and in those with radiographically denser breasts [5-7]. Digital mammography provides easier access, storage and retrieval of images and makes teleradiology possible. More importantly, there will be improved diagnostic accuracy by means of transmission and manipulation of images.

Screening mammograms in the UK are typically read by two radiologists, or non radiologist screen readers. The sensitivity is increased by 5-15% in detecting malignant lesions when reviewed in this way.[8-10] However, this approach requires increased resources and recent age extension in breast screening has increased workload and provides a challenging task. Computer-aided detection (CAD) may represent a solution to these challenges. CAD systems use computer algorithms to analyse digital mammographic images by identifying and marking suspicious areas to the reader. In support of this, several studies have been performed in the UK and US regarding the sensitivity and specificity of CAD systems. Cancer Research UK invited 28,000 women to have their mammograms read both by the conventional two radiologist reader method and via computer-aided detection using only a single radiologist. The outcomes were presented at the National Cancer Research Institute's conference in Birmingham in October 2008. Single reading with CAD was found to be as sensitive as the conventional method. A similar study, computer-aided detection trial (CADET) II involved over 30,000 women in England to determine if the performance of a single reader using computer-aided detection system would match the performance achieved by two radiologist readers [11]. The conclusion was similar to Cancer Research UK. Based on current evidence, there may be a role for CAD in breast screening reporting. However, the implementation of this new technology will take time due to the cost involved. There is also a known increased rate of false positive results, recall and biopsy procedures with CAD [12-15]. This will directly increase the requirement for further investigations and increase patient anxiety. It has also been suggested that single reading with CAD doubles the reading time therefore making it no more time efficient.

Ultrasound

Ultrasonography of the breast is the second most common imaging modality used in the investigation of breast lumps. It is a relatively simple, straightforward and inexpensive imaging technique that does



Figures 3a: Contrast enhanced MRI showing an enhancing irregular mass with a spiculated margin in the outer left breast with a corresponding type 3 dynamic enhancement curve typical of a carcinoma.

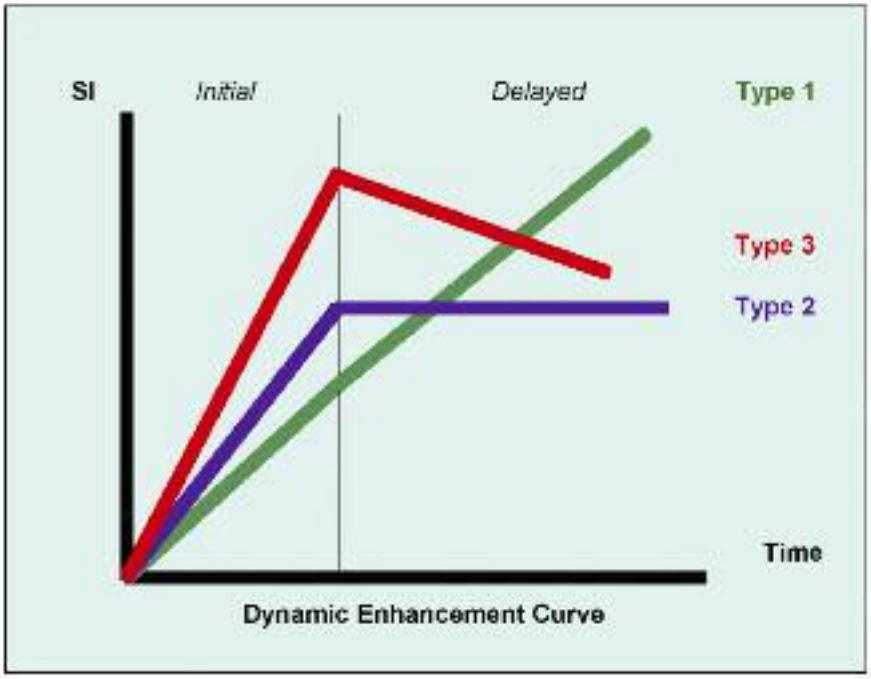


Figure 3B: Examples of normal, benign and malignant appearances in the dynamic enhancement curves.
Type 1: Steady enhancement - persistent gradual increase in signal intensity, typically seen with normal and benign entities.
Type 2: Plateau - early increased enhancement with maximum signal intensity achieved after two minutes which plateaus and remains constant, typically seen in fibroadenomas (benign), but can be seen in some carcinomas (malignant).
Type 3: Washout - early increased enhancement with maximum signal by two minutes which washes out and decreases over time, typically seen in malignant lesions.
Adapted from E.A. Morris and L. Lieberman. Breast MRI - Diagnosis and Intervention. 2005 ISBN 0-387-21997-8.

not involve ionising radiation. However, the major drawback is that it is operator dependent and should only be performed by experienced radiologists and sonographers familiar with breast imaging and intervention. It is more commonly used as an adjunct to mammography in the evaluation of focal masses and to determine solid or cystic characteristics. It is also particularly valuable in guidance of interventional procedures and has been shown to be a safe and accurate means of guiding fine needle aspiration and core biopsy to obtain cytohistopathology.

The ultrasound criteria for characterising solid breast masses were established in 1995. Using specific criteria solid lesions can be broadly categorised into malignant, indeterminate and benign categories. The features suggestive of a malignant lesion include spiculated margin, posterior acoustic shadowing, microcalcifications, duct extension, microlobulation, angular margins, marked hypoechogenicity and taller-than-long (not parallel) orientation (Figure 2a) [16].

Ultrasound can be particularly useful as a first line investigation tool and is a preferred imaging modality to evaluate palpable masses or nodularity in women under the age of 35 years, who commonly have denser breast tissues and benign breast lesions that make interpretation of mammograms difficult. It can also be used in evaluating the post mastectomy scar site to assess palpable lesions suspicious of recurrence. Often these are due simply to fibrous scarring but to exclude local recurrence, an ultrasound guided biopsy is frequently required for a definitive diagnosis.

Further applications of this modality have evolved since the emergence of sentinel lymph node biopsy as an increasingly accepted standard of care for treatment of the ipsilateral axilla during surgery for breast cancer. This has resulted in increased use of ultrasound assessment of the axilla as part of the pre-surgical work up of breast cancer. Fine needle aspiration and/or core biopsy of any detectable axillary lymph nodes is performed at the time of diagnosis and involvement precludes a sentinel lymph node procedure. The typical appearances of a malignant lymph node are thickened or eccentrically bulging cortex and a diminished or absent fatty hilum. There is a wide range of sensitivity and specificity in ultrasound of the axilla ranging from 57-92% and 44-100% due to the use of different morphology, sonographic criteria and subjectivity in the interpretation of the images [18-22]. BI-RADS category 5 lesions have an overall sensitivity and specificity of 94% and 89%, respectively, with a positive predictive value of 97% and negative predictive value of 80% [18].

The major limitation of ultrasound is that unfortunately it is not sensitive in detecting the microcalcifications of early cancer and ductal carcinoma in situ (DCIS) therefore it is not appropriate as a widespread screening technique.

Magnetic resonance imaging (MRI)

MRI is a noninvasive imaging modality which uses a powerful magnetic field and radio frequency pulses to produce detailed images of the breast. The major benefit of this technique involves the use of intravenous contrast agents such as gadolinium due to the fact that invasive breast cancers have increased vascularity and permeability resulting in early uptake and early washout of contrast agents (Figure 3a and 3b). MRI also images the breast in multiple planes with delineation of soft tissues allowing detection of small cancers.

A number of potential applications of MRI scanning in the detection and management of breast cancer have been suggested. For example, MRI may be potentially useful in the pre-operative assessment by accurately delineating disease and identifying multifocal lesions. This question was prospectively examined in the COMICE trial that randomised 1623 patients with biopsy proven primary breast cancer, scheduled for wide local excision following triple assessment between December 2001 and January 2007 [23]. The aim of this study was to determine

if MRI with triple assessment reduced the rate of reoperation within six months or rate of avoidance of mastectomy at initial surgery. Patients were randomised to receive additional imaging by the means of MRI and triple assessment or triple assessment only. The results revealed that the addition of MRI to prior to surgery did not significantly alter patient management and reoperation rates were similar in both groups.

A further potential application of MRI scanning is to improve screening detection rates especially in patients at high risk of breast cancer (e.g. a positive gene test or strong family history). Previous systematic reviews of the relevant literature have summarised data from 11 prospective studies and conclude that screening high risk women for breast cancer with both MRI and mammography is more effective than mammography alone [24,25]. Sensitivities were quoted to range from 80-100% for the combination examination and 25-59% for mammography alone [24,25]. One of the largest studies in this area is the multicentre MARIBS (MAgnetic Resonance Imaging for Breast Screening) that compared standard mammographic screening with MRI in 649 high risk women between the ages of 35-49 years. In this study, mammography successfully identified only 40% of the tumours compared to 77% detected by MRI. The sensitivity of MRI was even higher in BRCA1 mutation carriers at 92% compared to 23% with mammography [26]. The authors of this study concluded that MRI is superior to mammography in this population of high risk patients. This and other studies have resulted in a number of national societies developing guidelines for use of MRI in screening for breast cancer such as the American Cancer Society (ACS) and National Comprehensive Cancer Network (NCCN) and NICE. The ACS and NCCN recommend use of MRI as an adjunct to mammography for patients with documented BRCA mutation, untested women with first degree relative with BRCA mutation, women with lifetime risk of developing cancer >20-25% (calculated from family and personal history) and women who previously received radiation to chest between the ages of 10-30 years. In the UK, NICE recommends offering MRI screening to women according to their age and risk.

In addition to primary screening of a high risk group, MRI has also been evaluated in follow-up screening of patients. The American College of Radiology Imaging Network (ACRIN) conducted a study of 969 patients with a previous diagnosis of unilateral breast cancer and no abnormalities on either mammogram or clinical examination of the contralateral breast. Lesions requiring biopsy were detected in 121 of women of which 30 of these being positive for cancer. Eighteen were invasive carcinoma, whilst the remaining 12 were ductal carcinoma in situ. The authors concluded that MRI could detect cancers in the contralateral breast that were missed by mammography and clinical examination [27].

Taken together, these results suggest that the place of MRI in breast cancer screening has yet to be fully defined. MRI has demonstrated value in detecting some cancers not apparent by clinical examination and mammography especially in high risk patients but it should also be noted that MRI may not detect some lesions that are detected via mammography and as yet none of the studies have demonstrated any mortality reduction from MRI screening. Thus in current practice mammography remains the first line imaging investigation in the search for breast cancer.

Conclusion

Breast imaging plays a crucial role in the management of breast cancer. The gold standard is mammography but other modalities such as ultrasound, MRI and nuclear medicine are useful or potential adjuncts to diagnosis. In the future other modalities including computerised tomography and nuclear medicine could provide support in staging and determining response to treatment. Therefore, it is important that clinicians are fully aware of the benefits and limitations of each imaging modality. ■

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