Diagnostic and interventional imaging techniques in breast cancer

Simon Lowes
Alice Leaver
Alan Redman

Abstract

Imaging plays a critical role in the diagnosis and management of breast cancer. Two-view mammography and ultrasound form the mainstay of breast imaging and are essential components of the triple assessment. Digital mammography is rapidly replacing analogue mammography, and recent advances such as digital tomosynthesis add a third dimension to conventional 2D mammographic images. The versatility of ultrasound allows assessment of the breast and axilla as well as accurately targeted interventions, from the simple diagnostic core biopsy to preoperative tumour localization. It also guides large volume biopsies and excision of certain benign lesions, which in some cases can obviate surgical excision. Newer ultrasound techniques being applied to the breast and axilla include elastography and the use of intradermal microbubbles to guide the radiologist to the sentinel axillary node. Breast MRI is a powerful modality in assessing breast cancer. It can provide accurate information on size and multifocality of lesions, particularly those that are mammographically challenging such as lobular cancers, and it is also used to assess response to neoadjuvant chemotherapy and guide surgical management. CT scans, and in selected cases Positron Emission Tomography, play important roles in the assessment of metastatic disease.

Keywords Breast biopsy; breast imaging; breast MRI; mammography; tomosynthesis; ultrasound

Introduction

Imaging plays a central role at each stage of the breast cancer pathway. Breast screening by definition relies on mammographic imaging to detect asymptomatic cancers. On the other hand, patients with breast symptoms presenting to one-stop clinics will have immediate imaging to investigate their problem. From there any significant abnormality will be biopsied under image guidance to allow tissue diagnosis. Patients may then have staging using cross-sectional imaging modalities, and MRI can be used to monitor response to neoadjuvant chemotherapy or to aid surgical planning. Prior to surgical excision of breast cancers, radiologists may be required to localize the lesion using ultrasound or stereotactic (mammographic) guidance to assist the surgeon in accurate tumour removal with satisfactory margins. Imaging is also key in follow-up assessment and detecting recurrence.

These established diagnostic and interventional imaging techniques continue to evolve, and there is a constant drive to develop new approaches to help achieve the best possible outcomes for the patient. Some of the more promising new developments are discussed below.

Optimizing patient care also depends upon radiologists and surgeons maintaining a strong working relationship, and as such it is important for us to have a reasonable understanding of one another's roles. This article aims to give the surgeon an overview of the role of imaging techniques and radiological interventions in the diagnosis and management of breast cancer.

Mammography

Two-view mammography (low-dose x-rays of each breast compressed in two different planes: craniocaudal [CC] and mediolateral oblique [MLO]) is the most fundamental and frequently employed imaging modality in breast imaging. In recent years digital mammography has largely replaced analogue (film) and is now used throughout the NHS Breast Screening Programme (NHSBSP). The technology is partly a spin-off from NASA and their development of light detectors used on the Hubble Space Telescope! Digital receptors and computers are used to analyse the X-rays, and the resulting mammograms are viewed on very high-resolution monitors.

In the NHSBSP two trained film readers (radiologists or film reader mammographers) read each set of mammograms, and a third reader may be required to 'arbitrate' if there is disagreement between the first two readers. In some screening programmes computer-aided detection (CAD, see below) is used as a second reader in place of a human being. Film readers analyse the pattern on each mammogram and compare them with previous examinations, looking for abnormal patterns that may represent breast cancer (Figure 1). Any densities are analysed for signs which have a high predictive value for the presence of malignancy (such as ill-defined or spiculate margins, or architectural deformity of the tissue), and for features more reassuring of benignity (such as well-defined margins). Any calcification within the breasts is also appraised. Macrocalcifications of various different patterns — for example, parallel vascular calcification, 'popcorn' (fibroadenoma) calcification, duct ectasia type calcification and cystic 'tea cupping'— are relatively straightforward to classify as benign on mammogram with no further investigation required. Diffuse bilateral microcalcification is also benign. Clustered or segmental microcalcification, however, can be a sign of pre-invasive or invasive carcinoma. Clusters may have signs suggestive of malignancy, such as a branching or 'sharp' appearance, but most malignant microcalcification will actually have no specific suspicious signs and therefore radiologists tend to maintain a low threshold for further investigation even in the absence of

Simon Lowes *BSc (Hons) MB BS (Hons) MA PhD FRCR is a Consultant Breast Radiologist at Queen Elizabeth Hospital, Gateshead, UK, and Honorary Clinical Senior Lecturer, Newcastle University, UK. Conflicts of interest: none declared.*

Alice Leaver *MB ChB BSc (Hons) MPhil FRCR is a Consultant Breast Radiologist at Queen Elizabeth Hospital, Gateshead, UK. Conflicts of interest: none declared.*

Alan Redman *BSc MB BS FRCR is a Consultant Breast Radiologist at Queen Elizabeth Hospital, Gateshead, UK. Conflicts of interest: none declared.*

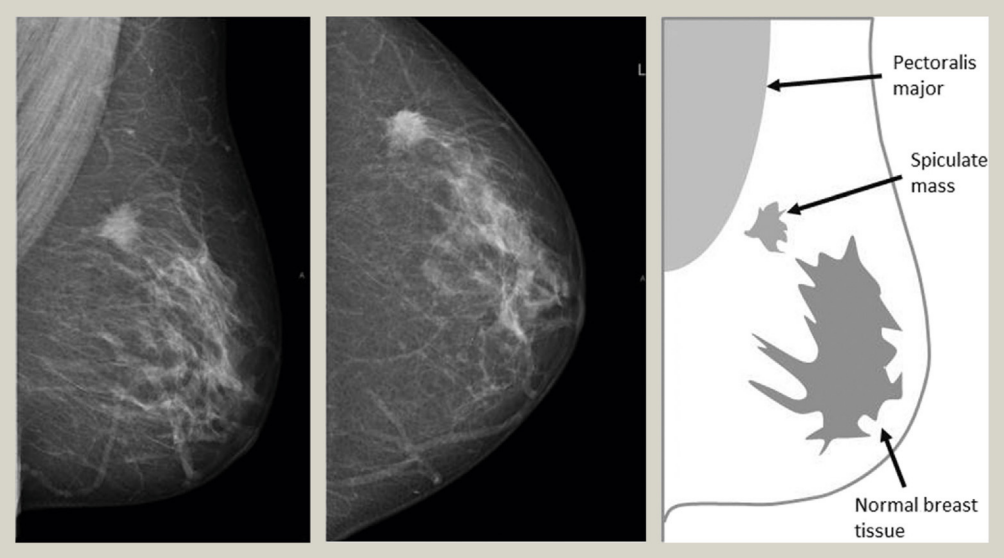

Figure 1 Digital mammogram mediolateral oblique view (left image) and craniocaudal view (middle image) demonstrating a spiculate mass in the upper outer quadrant. This is grade M5 (malignant). The line diagram (right image) illustrates the mass on the mediolateral oblique view.

suspicious features. Densities or microcalcifications that are judged to have a risk of malignancy are recalled to an assessment clinic for further assessment. In the NHSBSP approximately 1 in 20 screening mammograms lead to a recall. Recalled mammographic abnormalities undergo further imaging that may lead to needle biopsy. The threshold for recall is deliberately set low as the programme needs to detect small cancers in order to potentially make a difference to population mortality, and because of this low threshold for recall the majority of cases recalled to assessment clinic will prove to be benign.

In a symptomatic setting such as a one-stop clinic, mammogram is the first-line imaging investigation for almost all abnormalities in patients aged 40 or above. Mammography is also first line for clinically suspicious or clinically malignant lesions in those aged 35–39 years.[1] Under the age of 35 the density of the breast tissue reduces the sensitivity of mammography, the risk to benefit ratio in relation to the radiation dose is more uncertain, and therefore ultrasound is the primary imaging modality. When mammograms are performed, the radiologist assesses the mammogram in much the same way as in the screening setting, looking for features that may guide further investigation. When reporting the mammogram it is good practice for the radiologist to include a grade to indicate the likelihood of malignancy, ranging from M1 (normal) to M5 (malignant).

Mammography is also used after surgical treatment of primary breast cancer. The technique for surveillance is the same as for screening: an MLO and a CC view on each breast (no mammography on mastectomy side or mastectomy with reconstruction). A surveillance regimen containing mammography is important for detecting recurrence and second cancers, and confers a survival advantage when compared to surveillance without imaging. There is no clear evidence for the optimum frequency of imaging, or optimum duration of mammographic surveillance. Recurrence can occur many years post treatment and late detection of recurrence is expensive. Taggart[2] showed that patients with a history of breast cancer also have an increased risk of developing a second primary breast cancer which is maintained for at least 20 years, that ipsilateral breast cancer recurrences are mainly detected either by the patient or by mammography, and that these recurrences are associated with improved survival when compared to those found by physical examination by a clinician. Also, non-attendance for mammographic follow-up is associated with poorer survival versus attendance.

Ipsilateral breast cancer recurrence is often similar in mammographic appearance to the original breast cancer— for example, a patient with a mass containing microcalcification will frequently demonstrate microcalcification in tumour recurrence. Where the primary breast cancer is mammographically occult there is an increased rate of mammographically occult recurrence (e.g. 32% versus 12% in a study by Yang et al.[3]). Some centres therefore have follow-up guidelines for these patients that include either surveillance ultrasound or MRI. Mammographically dense breasts are also associated with an increased risk of primary and recurrent breast cancers, and of delay in detection of these cancers when using mammography. Mammography, however, is a cheap, quick and easy examination to perform. Moreover, mammograms are easily compared with previous films and have a low false positive rate when compared with MRI and ultrasound.

National Institute for Health and Care Excellence (NICE) guidelines[4] recommend annual mammography if diagnosed with primary breast cancer up to 50 years old, and for a minimum of 5 years if diagnosed after 50 years of age. This is common, although not universal, practice in UK breast units. The Cancer Reform Strategy[5] recommended a personalized risk-adjusted follow-up to meet individual patient needs, and ideally mammographic frequency should be determined by the lead time achievable for a patient's specific characteristics (young age, for example) and tumour biology. The MAMMO-50 trial is currently recruiting patients over the age of 50 years, aiming to establish whether certain patient and/or tumour characteristics are better served by a regimen of less frequent mammographic surveillance but over a longer period of time. Ideally we should tailor all

imaging, including the interval between mammograms and the duration of surveillance, to each patient's needs.

Computer-aided detection (CAD)

Computer-aided detection (CAD) has been developed to increase cancer detection rates in screening mammography. The process uses computer algorithms to analyse digital mammograms and bring any suspected abnormalities to the film reader's attention. The aim is to reduce the number of false negatives caused by readers' observational 'misses', which may be caused by a variety of factors including subtle abnormalities, complex tissue architecture, reader distraction, or inexperience.

The current standard practice of double-reading screening mammograms is based on the established observation that two readers have a higher sensitivity for cancer detection than a single reader. The UK-based CADET II trial, which compared the cancer detection rates achieved by double-reading against those with a single reader using CAD found that the two methods were equivalent.[6] CAD therefore offers potential to maintain the sensitivity of doubling-reporting but with the advantage of requiring only a single reader.

Although CAD is used in many countries for reading mammograms, its use is not commonplace in the NHS Breast Screening Programme as it is not currently deemed to be cost effective.[6]

Digital breast tomosynthesis (DBT)

Each image in conventional two dimensional mammography represents a superimposition of all features of the breast, resulting in difficulties such as composite densities (superimposition of normal glandular tissue from different parts of the breast, simulating a mass) and the masking of pathology by overlying normal glandular tissue. DBT has been developed to overcome these problems. There are different designs of DBT machine, but the principle is that they acquire multiple images at different angles to the compressed breast and then reconstruct images to create a stack of 'slices' that may be scrolled through at a workstation. This allows radiologists to 'unpick' composite densities and to unmask and further assess the mammographic morphology of different pathologies. Potential disadvantages of the system are increased patient radiation dose, increased radiologist time to read the images (compared with mammogram alone) and large data files with associated storage and retrieval problems and delays. A DBT system has been approved for use in the NHS BSP. Early studies suggest that DBT plus conventional mammography can reduce recall rate (increased confidence in the nature of benign lesions and ability to unpick composite densities) and can improve cancer detection rate. Ongoing developments include the technology to synthesize 2D mammogram images from the DBT data set, contrast-enhanced DBT, and CAD for use on DBT.

Contrast enhancement for mammography and DBT

For many years we have used contrast-enhanced MRI to further evaluate breast pathology, but MRI is a time consuming, expensive and limited resource. It is also contraindicated in certain patients. Iodinated intravenous contrast may now be used in association with DBT to demonstrate both functional information (lesion enhancement) and lesion morphology as a fused study —similar to MRI but at reduced cost. There is also ongoing research interest in the potential for iodinated contrast to improve the accuracy of conventional mammography.

Breast ultrasound

Ultrasound plays a pivotal role in the diagnostic work up of many breast patients.

In understanding the role of ultrasound in breast diagnosis, it is important to appreciate that ultrasound is generally considered to be at its most effective when used as a targeted examination focussed to evaluating a specific area of interest. This can be an area which is of radiological interest because of a potential abnormality identified on another imaging modality (such as a density seen on mammography), or an area which is of clinical interest because of signs and/or symptoms at that site. It is, therefore, extremely important in a symptomatic setting to ensure robust communication between the clinician and the radiologist in order that ultrasound can be correctly targeted to any area of clinical interest.

Best practice diagnostic guidelines for patients presenting with breast symptoms[1] indicate that ultrasound is the imaging method of choice for the majority of women aged under 40 years. Over 40 years of age ultrasound is used as an adjunct to mammography when there are focal clinical or mammographic signs. Focal abnormalities identified on ultrasound are assessed for signs that favour malignancy (irregular shape, ill-defined margin, solid hypoechogenicity, posterior acoustic shadowing, tissue distortion) and for signs that favour benignity (smooth shape, well-defined margin, hyperechogenicity, posterior acoustic enhancement). There is, however, significant cross-over of ultrasound features between benign and malignant groups (Figure 2) and therefore guided-needle biopsy is warranted in the vast majority of solid lesions regardless of the ultrasound findings. There are exceptions to this: in appropriate clinical scenarios patients with typical ultrasound features of fat necrosis, lipomas, hamartomas and, under 25 years of age, fibroadenomas can be safely diagnosed without recourse to a needle biopsy.[1]

Ultrasound may have a particular role to play in women of any age with dense breasts. Women with dense breasts have a significantly higher underlying risk of breast cancer than those with involuted (fatty) breasts, and mammography is significantly less sensitive for cancer detection in the dense breast. In the screening arena much work has been done in recent years looking at the value of adding ultrasound as an adjunct to mammography in women with dense breasts. Studies performed thus far do indicate that ultrasound in this population detects additional cancers, and these mammographically occult cancers tend to be small invasive lesions[7] whose detection could have a positive impact on breast cancer mortality within the screened population. There are, however, two important issues that must always be borne in mind when considering the utility of whole breast ultrasound. Firstly, a thorough screening ultrasound examination of both breasts is significantly more time consuming than the sort of targeted ultrasound often performed in the symptomatic setting. Secondly, whole breast ultrasound identifies additional abnormalities which lead to a high false positive rate. The time and cost issues can to some extent be mitigated by utilising automated whole breast ultrasound. This system generates a 3D volume dataset which is

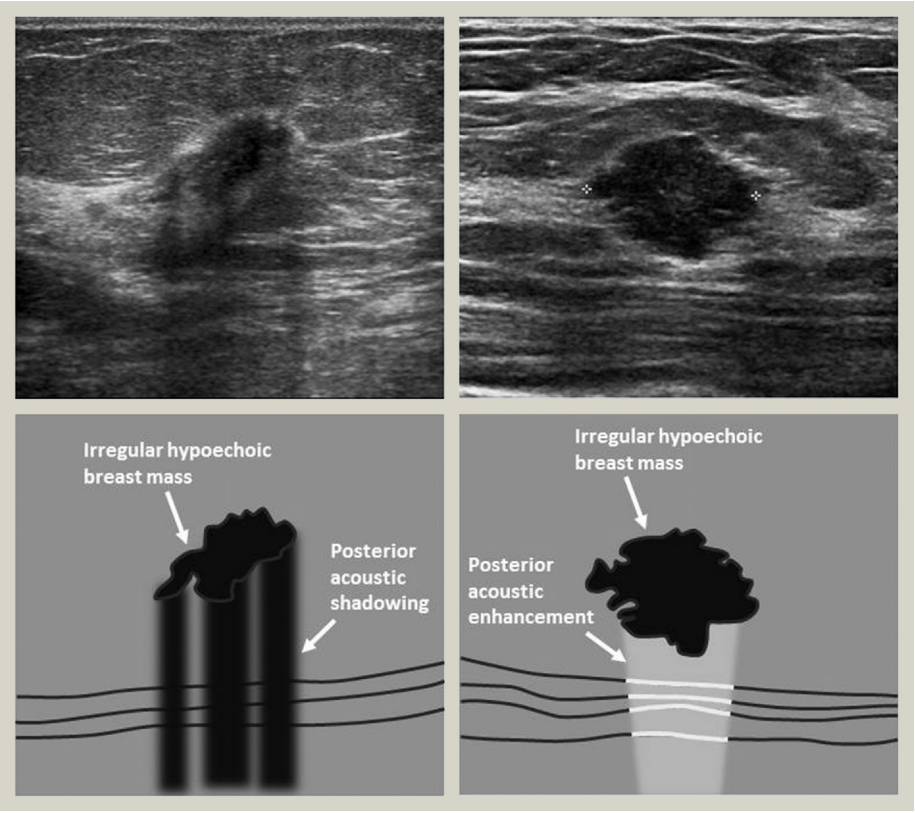

Figure 2 Two examples of hypoechoic masses on ultrasound. The irregular margins suggest malignancy. The image on the left shows the typical posterior acoustic shadowing (darkness deep to the mass) seen in malignant lesions. The image on the right in contrast shows posterior acoustic enhancement (brightness deep to the mass), which is a feature more typically seen in benign lesions. In both cases core biopsy confirmed grade 3 invasive ductal carcinoma.

subsequently analysed by a radiologist, and this more cost effective technique has been gaining popularity in screening programmes in the USA particularly for women with dense breasts. Whether whole breast ultrasound is performed hand-held or automated, the high false positive rate does lead to additional (unnecessary) biopsies.

In the UK, the role that ultrasound plays in the imaging algorithm is very much a greyscale assessment looking for a discrete abnormality. Cysts are easily identified and dismissed and then, apart from the specific exceptions described above, solid focal abnormalities are assessed for the likelihood of malignancy with the benign or malignant diagnosis being confirmed by a guided needle biopsy. Given the high false positive rate of ultrasound, and the high rate of benign biopsy, there has long been interest in developing new ultrasound technologies that might increase diagnostic certainty to a level at which benign biopsies could be avoided. Doppler ultrasound has the potential to differentiate the neo-angiogenesis seen in malignant lesions from the lower vascularity more commonly present in benign lesions, and this distinction can be enhanced by the use of contrast agents. The diagnostic accuracy of Doppler, however, has thus far not proved robust enough for this technique to be widely adopted. More recently, there has been growing interest in the potential for elastography to more reliably predict benignity. Elastography uses a compression source to apply force to the breast tissue and the imaging system then measures the resultant tissue displacement. Elastography has the potential to generate qualitative and quantitative data regarding the elasticity of the tissues in the breast. Normal tissues and benign lesions tend to be relatively elastic whereas malignant lesions tend to be stiffer with higher elasticity values. This is a relatively new technology, many ultrasound machines do not yet have the capability to perform the test, and there is as yet no standardization across the industry in terms of the quantitative data that is generated. Nonetheless, there is a growing body of evidence suggesting that the addition of elastography as an adjunct to greyscale ultrasound can increase the specificity of the ultrasound examination and decrease the rate of unnecessary biopsies.[8]

Ultrasound is accepted as an effective imaging tool for assessment of abnormalities in patients with implants in augmented or reconstructed breasts. Ultrasound can differentiate breast lesions from implant complications, and it is recommended as the first-line imaging tool in suspected implant ruptures.[1] Ultrasound is also the appropriate first line imaging tool for chest wall lesions and suspected recurrence at mastectomy sites.

Ultrasound of the axilla

Axillary assessment using ultrasound may be performed to investigate patient symptoms, an abnormal appearance of the axilla on screening mammography, or to stage ipsilateral axillary lymph nodes in breast cancer patients. The most common causes of enlarged axillary lymph nodes seen in UK breast units are localized infection, breast cancer metastases, lymphoma and leakage from silicone implants.

The presence of breast cancer metastases within axillary lymph nodes is the most important prognostic factor in a patient with breast cancer (Figure 3). When a patient is diagnosed with breast cancer or extensive DCIS in the UK, usual practice is to assess the ipsilateral axilla preoperatively with physical examination and ultrasound. This is in line with NICE guidelines.[4] The aim is to identify possible lymph node metastases and guide the multidisciplinary team decision as to the most patient-appropriate lymph node surgery for each patient: surgical sentinel lymph node biopsy or surgical axillary node clearance. Lymph nodes are found by ultrasound and are then classified morphologically as benign, suspicious or malignant. Units use different classification systems but most systems rely on assessment of cortical thickening (diffuse or focal), ratio of cortex to hilum, or mass-like appearance.[9] Ultrasound-guided biopsy is performed on any lymph nodes which surpass the chosen threshold. Overall sensitivity of the ultrasound and biopsy process does vary widely with patient population (increased sensitivity in the symptomatic population and patients with more advanced disease) and reported rates range from less than 10% to over 60%. Overall sensitivity is low due to the inherent inability to identify which node is the sentinel node, and also due to the fact that the node selected for biopsy is only partially sampled by the FNA or core biopsy and hence there is a risk of geographical miss of metastatic deposits. A Maidstone team have pioneered the use of an intradermal microbubble injection (Sonovue: sodium hexafluoride) as an ultrasound contrast agent to identify the sentinel lymph node (Figure 4). This allows improved sonographic assessment and biopsy of the sentinel node.[10] Failure of preoperative radiological assessment of the axilla can result in a need for further treatment after SLNB: surgical axillary node clearance or axillary radiotherapy. This may result in increased patient morbidity, delayed further treatment (radiotherapy, chemotherapy) and increased cost, and this motivates the ongoing research to find ways to maximize the accuracy of preoperative radiological axillary assessment.

Silicone within axillary lymph nodes is much less of a diagnostic challenge for a sonographer. The characteristic snowstorm appearance on ultrasound has a positive predictive value very close to 100% and hence an ultrasound-guided biopsy is rarely required. In terms of interpreting the significance of the finding, any history of previous implant rupture should be borne in mind if the current implant looks intact. Where uncertainty exists regarding the status of the current implant there should be a low threshold for recourse to MRI.

Breast MRI

Breast MRI is an expensive test, with limited availability, but it has the highest sensitivity for cancer of any of the breast imaging techniques, and it has the potential to provide accurate diagnostic information across a wide range of clinical applications.

The MRI examination requires the patient to lie prone, with breasts immobilized in a breast 'coil' which can generate high

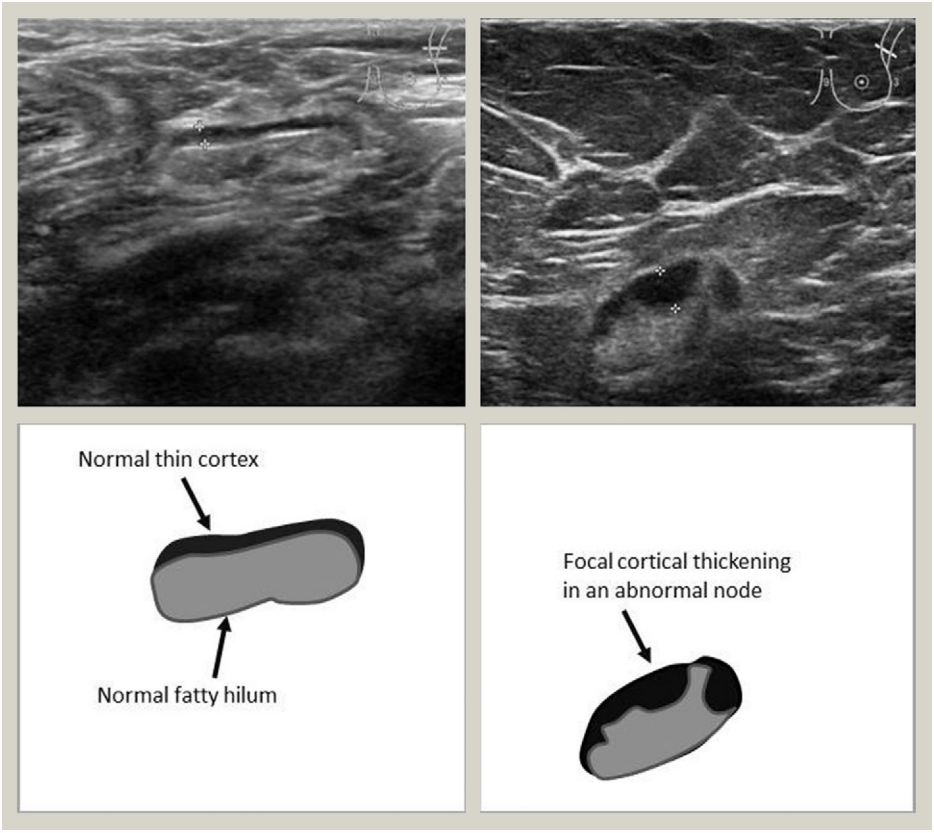

Figure 3 Ultrasound images. Two cases with breast cancers presenting to one-stop clinics. The left image shows a normal lymph node; cortical thickness is less than 1.8 mm which would not reach threshold for a biopsy. The right image shows a lymph node with 3.6 mm of focal cortical thickening. In our unit we would grade this LN4 (suspicious). A core biopsy targeted to this thickened cortex confirmed metastasis.

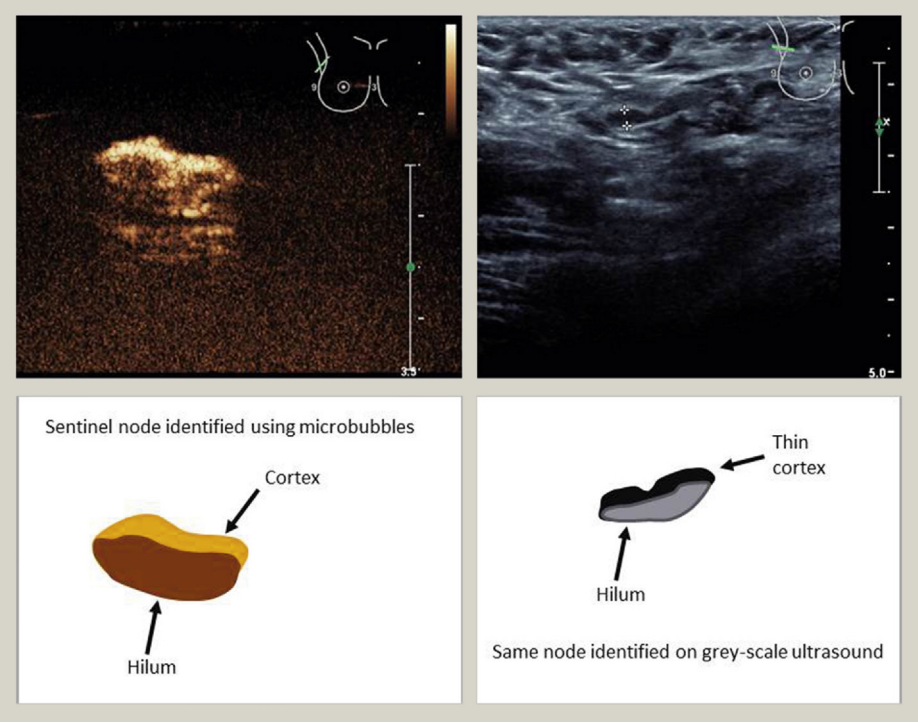

Figure 4 A 56-year-old woman with a screen detected 15 mm malignant mass in the right breast. Initial ultrasound of the right axilla was normal. The left ultrasound image, performed post periareolar injection of Sonovue, shows a lymph node which is lit with microbubbles indicating this to be the sentinel node. The right ultrasound image shows the same node on usual grey-scale view, there are no features on grey-scale assessment which would ordinarily have triggered a biopsy. Having identified this sentinel node due to the microbubble enhancement, a core biopsy was performed which yielded a macrometastasis.

resolution images in multiple planes. The minimum requirements for a breast cancer detection study are a bilateral unenhanced high tissue contrast sequence and a bilateral dynamic post-gadolinium sequence. These sequences ideally yield both high spatial and high temporal resolution because breast lesions detected on MRI are assessed in two ways: lesion morphology and lesion enhancement pattern.

Morphologic analysis involves assessment of both the shape of a mass and the margin. As with mammograms and ultrasound, lobulated or irregular shapes are more suspicious of malignancy than round or oval, and irregular or spiculated margins are more suspicious than smooth.

Enhancement analysis involves assessment of both the pattern of enhancement and the dynamic enhancement curve. Heterogeneous patterns of enhancement, particularly if there is rim enhancement, are more suggestive of malignancy than homogenous enhancement. The dynamic enhancement curve is generated by plotting the lesion's signal intensity change over time. Signal intensity increases as the gadolinium, which has been injected intravenously, leaks out into the extracellular space. This leakage of contrast tends to happen more quickly in cancerous tissue because of the tumour angiogenesis which produces vessels with increased permeability. Hence, in malignant tissue the early part of the signal intensity curve tends to show a rapid rise. Following this, contrast leaks back into the permeable tumour vessels relatively quickly and therefore a signal intensity curve with a rapid rise followed by an early plateau or early decrease is more suspicious of malignancy than a continually increasing curve (Figure 5).

As well as demonstrating enhancing masses, MRI may show foci of non-mass-like enhancement. A common pattern of non-mass-like enhancement is the finding of multiple small scattered foci of enhancement; this appearance can be dismissed as background benign breast change. Large areas of non-mass-like enhancement can be assessed for patterns which are suspicious for malignancy, such as segmental or clumped enhancement. These patterns can be seen in DCIS, though it is important to note that breast MRI is significantly less sensitive for in situ disease than it is for invasive cancer.

In terms of enhancing foci, the most difficult diagnostic challenge is the finding of small (5–10mm diameter) individual foci of enhancement. Such foci of enhancement are not uncommon, and while they can be due to malignancy, the vast majority are due to benign proliferative breast lesions. It is these enhancing foci which are the prime cause of the high false positive rate of breast MRI.

When enhancing foci are found on MRI they will often trigger a recommendation for 'second-look' ultrasound. Second-look ultrasound examinations are targeted to the sites of interest identified on the MRI, and in the majority of cases lesions will be located by ultrasound and can be subjected to core biopsy. Where MRI demonstrates an enhancing focus, but second-look ultrasound finds no corresponding lesion, there are two principal management options. The MRI abnormality can be biopsied under MRI guidance or, in cases with a low suspicion of malignancy, a recommendation can be made for interval follow-up MRI. Where MRI guided biopsy is deemed necessary, this may necessitate referral to one of the relatively low number of units in

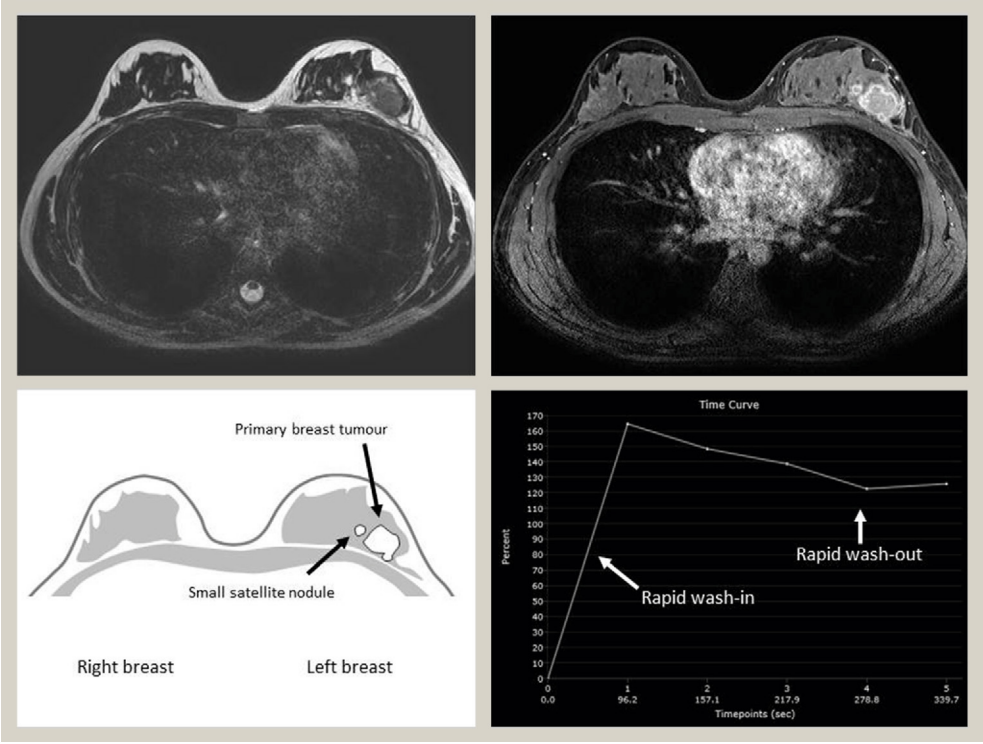

Figure 5 MRI Breast examination. Top left image: T2-weighted sequence showing an irregular mass in the left outer half. Top right image: Post contrast image showing the main mass and an adjacent satellite nodule which are both rim enhancing. Bottom left image: Line drawing identifying the primary breast tumour and the small satellite nodule. Bottom right image: Signal intensity plotted against time shows a rapid increase in contrast uptake followed by a rapid 'washout'. The morphology and enhancement characteristics of this mass are consistent with malignancy.

the UK who have the equipment and expertise to perform this procedure.

Despite the high false positive rate of breast MRI, the high degree of sensitivity for invasive cancer detection and the ability to provide high-resolution soft tissue detail in multiple planes make breast MRI a potentially very useful tool in a range of clinical scenarios.

The high sensitivity of MRI for cancer detection can be utilized in preoperative assessment, and in many UK breast cancer units this is now the most common application for breast MRI. Several studies have shown that MRI is more accurate than mammography and ultrasound at depicting multifocal and multicentric disease and has a higher correlation with histological size. Further, a number of studies have shown that these MRI advantages are more pronounced in dense breasts and in invasive lobular cancer. Current NICE recommendations[4] are that preoperative MRI should be offered to patients who meet any one of the following conditions: invasive lobular cancer being considered for breast conservation; breast density which precludes accurate mammographic measurement; or discrepancy in disease extent between clinical examination, mammography and ultrasound. It should be borne in mind, however, that debate continues as to whether preoperative MRI does lead to improved patient outcome. Several studies have cast doubt on this, not least the UK COMICE trial[11] which found that preoperative MRI did not lead to a reduction in reoperation rates in patients with small breast tumours. Furthermore, an important issue to consider in respect of MRI staging arises from the high false positive rate: when MRI findings are potentially leading to a change in the surgical management plan, such as conversion to mastectomy, the additional suspicious abnormalities identified on MRI should always be confirmed pathologically.

Other potential roles for breast MRI are summarized in the 2010 European Society of Breast Cancer Specialists (EUSOMA) guidelines.[12] Of these, the principal applications utilized in the UK are: monitoring of response to neoadjuvant chemotherapy, detection of occult primary tumours in women presenting with adenocarcinoma in axillary lymph nodes, and MRI screening in young women at genetically high risk. MRI is also employed as a problem-solving tool when conventional imaging has failed to resolve an issue. In this regard MRI not infrequently has a role to play in differentiating scar tissue from recurrence, in assessing lesions in augmented and reconstructed breasts, and in searching for underlying breast cancer in non-resolving mastitis.

There is considerable ongoing interest in the potential for adjunct MR imaging methods to improve the specificity of the breast MRI examination. Functional MRI techniques such as MR spectroscopy, MR elastography and MR diffusion weighted imaging rely on surrogate biomarkers of malignancy. Of these, diffusion weighted imaging, which relies on the restricted water diffusion caused by the higher cellularity seen in malignant tissue, has thus far shown the most promise.

Breast intervention

In both screening and symptomatic settings, breast examination and imaging are used to triage patients to no further action, interval review (rarely) or pathological evaluation (cytology and/

or histology). A range of interventional devices may be utilized (Figure 6). Biopsies are generally performed as outpatient procedures under local anaesthetic. These interventions can be X-ray guided (using stereotactic localization), but most interventions taking place in a breast unit are ultrasound-guided core biopsies of breast lesions or axillary lymph nodes. Ultrasound allows real-time visualization of the needle, and hence use of ultrasound to guide breast intervention decreases the risk of geographical miss, haematoma and pneumothorax.

Ultrasound-guided fine needle aspiration (FNA) may be performed with or without local anaesthetic, and can provide rapid diagnostic information within the hour if there is pathology provision, though the availability of this rapid turnaround service in the UK is diminishing. Ultrasound-guided core biopsy provides a greater volume of tissue and more information, but takes longer for pathologists to process and report. The majority of breast and axillary biopsies performed are ultrasound-guided 14G core biopsies, with two to three biopsies per lesion; approximately 20 mg of tissue is obtained.

Larger bore diagnostic core biopsies are also widely performed within breast units. This is usually vacuum assisted (VACB) for pathological assessment of indeterminate breast microcalcification. This procedure is most often stereotactic (X-ray guided) but can be ultrasound-guided if the microcalcification is visible on ultrasound. Tissue acquisition is piecemeal, either specifically directed or around the clock-face, often 6 or 12 cores with a needle between 7G and 13G. If microcalcification is the target, cores are X-rayed to check for calcium while the patient remains in position. If the cores do not contain sufficient representative microcalcification then the targeting and biopsy process may be immediately repeated. Stereotactic VACB may also be used for biopsy of mammographic soft tissue densities that are sonographically invisible. It is usual to site a clip after stereotactic biopsy, followed by post-clip mammograms, to confirm the site of biopsy and clip.

Radiologists are often required to localize impalpable lesions, to aid surgeons with their surgical excisions. This is usually performed using guide wires inserted through an introducer needle under local anaesthetic, guided either by ultrasound or stereotaxis. Some biopsy marker clips are visible on ultrasound, and post biopsy haematomas are often visible such that guidewire localization of a proven ultrasonically invisible DCIS may be performed using ultrasound to guide the wire through the post-VACB haematoma cavity (Figure 7). Whichever targeting method is used, the aim is to insert the wire via the shortest possible route. The wire introducer (needle) must transfix the lesion with the tip of the needle ideally lying immediately beyond the lesion. The introducer is then withdrawn to enable some type of hook to deploy, anchoring the wire within the tissue. Mammograms are then performed to double check adequate position of the guidewire pre theatre. If the check mammogram demonstrates that the guidewire and hook have been left short of the lesion then the lesion is not adequately localized and the risk of failure of surgical excision is significantly increased. In this scenario the guidewire should be repositioned, to ensure adequate transfixing of the lesion, before the patient is sent to theatre. Guidewire-facilitated surgical specimens must be X-rayed intra operatively immediately after excision, and surgeons need to be immediately informed if the target lesion/marker clip is not in the specimen with apparently adequate margins — this information gives the surgeon the opportunity to perform further surgery while the patient is still under anaesthetic.

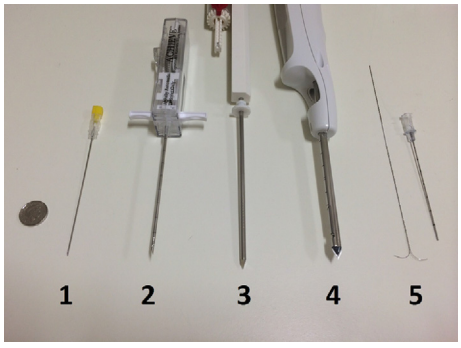

Figure 6 (1) 20G FNA; (2) 14G core biopsy; (3) 10G cordless VACB; (4) 7G VACB; (5) guidewire with introducer.

Some early research is being performed with detectable markers which could potentially replace guidewires as a method of localization. The main attraction of detectable markers over guidewires is that they can be inserted several days prior to surgery thereby improving operating theatre efficiency on the day of surgery. They also avoid the downsides of guidewires such as the risk of a wire being dislodged prior to surgery, the risk of wire fracture, and the distress and discomfort caused to the patient by having a wire protruding from the skin. Magnetic markers are being trialled in both the UK and the USA, but some of the most promising results thus far have been with radioactive iodine seed insertion. The radioactive iodine seed localization (RSL) technique involves 'seeds' which are made of titanium containing ^{125}I. Each seed measures 4.5 × 0.8 mm. As with guidewire localization, the seeds are preloaded into needles and inserted under direct ultrasound guidance or using stereotactic mammographic guidance. Because the seed is metallic it is seen easily both on ultrasound and mammograms. Once in theatre, the seed, and hence the lesion, is localized by the surgeon using a gamma probe. This technique is still being evaluated in the UK and so very few centres are using it at present, but studies have suggested that RSL is at least as effective as guidewire localization in achieving satisfactory surgical margins.[13] If this early promise is maintained, RSL may well be adopted much more widely in the near future.

Other fairly common interventional procedures include ultrasound-guided drainage of fluid collections such as seromas, abscesses and haematomas (early or liquefied). Local anaesthetic is used and a needle thickness appropriate to the thickness of the fluid. Most of these aspirations are performed through 19G needles, but large-bore VACB should always be borne in mind as a potential option for drainage of troublesome, persistent, multiloculated collections. Peri-implant fluid collections can be safely aspirated with careful ultrasound guidance. Ultrasound can also prove very useful for locating the port of an expander implant when surgeons have difficulty, enabling insertion or aspiration of fluid as required.

A less common interventional procedure in the UK is breast lesion removal using the Breast Lesion Excision System (BLES, Intact Medical, Framingham, USA). This device has been widely employed in the USA, having been introduced in 2001, and has

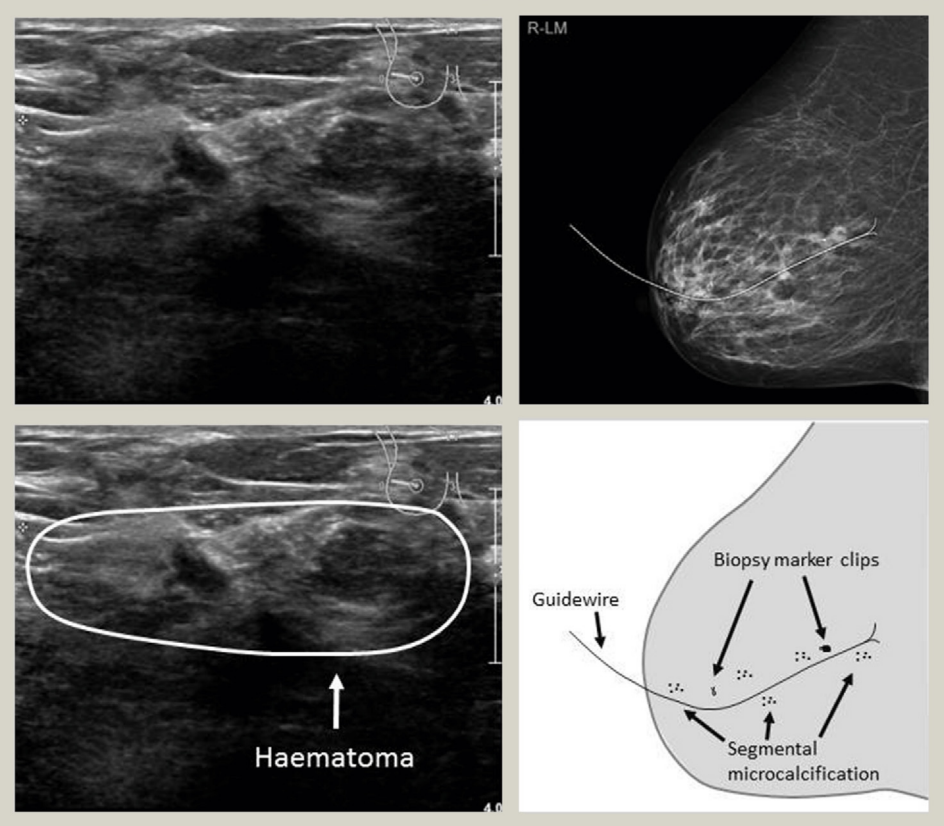

Figure 7 Large segmental area of DCIS microcalcification confirmed on VACB at two sites. The microcalcium was invisible, but post VACB there was sufficient haematoma for the guidewire to be placed through the biopsy haematoma under ultrasound control (left-hand images). Post wire insertion check mammogram (right-hand image) shows guidewire successfully transfixing the microcalcification with the hook lying just beyond.

been well validated as a safe and efficacious procedure. The BLES biopsy procedure was approved in the UK by the National Institute for Health and Care Excellence (NICE) in 2009. The device consists of a 'wand' which is inserted into the breast under local anaesthesia via a 6–8 mm incision. A wire basket emerges from the end of the wand and utilizes radio-frequency cautery to excise a single complete sample of tissue (Figure 8). The wand is withdrawn, bringing the basket and specimen with it. The unique feature of the BLES is that it removes a single complete specimen with intact architecture and intact surgical margins, as compared to VACB excision biopsies which remove lesions piecemeal with disrupted architecture and no potential for margin assessment. Published literature suggests that the procedure is well tolerated with low complication rates, and has the potential to yield benefits in terms of reduced underestimation and reduced false negative rates compared to VACB, and reduced complication rates and reduced cost compared to surgical excisions. Disadvantages compared to VACB include larger skin incisions, a greater degree of technical challenge particularly in terms of accurate wand positioning prior to basket deployment, and limited applicability to larger lesions and lesions close to chest wall or skin. Currently the largest basket available in the UK is 20 mm, but a 30 mm basket is in development. Uptake of the BLES in the UK has been very slow, but the unique ability to remove intact lesions with clear margins may yet lead to a much more prominent role in the diagnostic/therapeutic pathway.

Computed tomography (CT)

The principal role for CT in breast malignancy is as a whole body staging investigation. CT body scans are used to assess metastatic spread in staging of primary breast cancer, to monitor therapeutic response and to assess potential recurrence. Modern multi-detector CT scans are very sensitive for both visceral and bony metastases. In recent years several studies have suggested that a CT of chest abdomen and pelvis, potentially extended to include the weight-bearing upper femora, can obviate the need for a bone scan in the staging algorithm, and this potential is reflected in the current Royal College of Radiologists Breast Guidelines.[14]

Dedicated breast CT scanners have been developed which can generate 3-dimensional images of the breasts for a similar radiation dose to conventional mammography. Early research has shown promising results, however the machines are expensive and have not been introduced to the NHS.

Positron emission tomography (PET)

PET is a functional imaging modality producing 3D maps of radionuclide uptake in the body using positron-emitting tracers following intravenous injection. In clinical practice it is standard to use radioactive fluorine incorporated into a biologically active glucose analogue in the form of ^{18}F-fluoro-deoxyglucose (^{18}F-FDG). The principle behind this is that tissues with increased metabolic activity, such as cancer cells, consume more

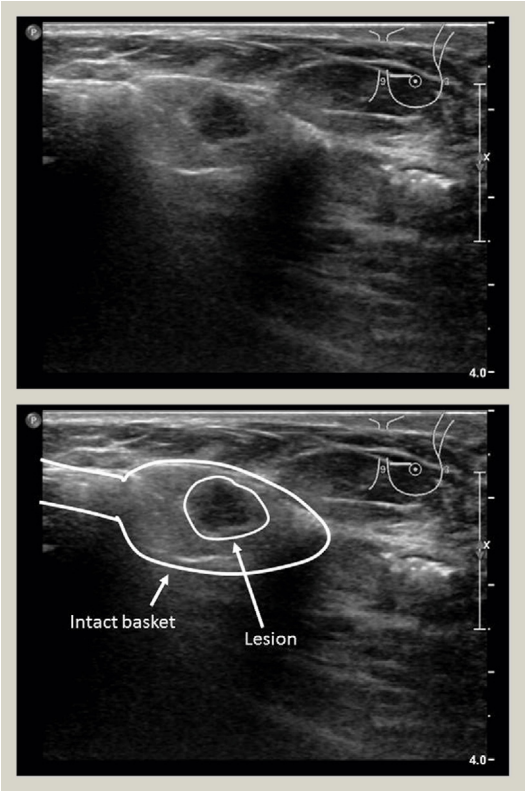

Figure 8 Ultrasound image showing a 20 mm Intact wand with the basket deployed. The basket has surrounded the 10 mm papillary lesion and the wand can be withdrawn removing the single intact specimen with it.

glucose and therefore will take up the radiolabelled glucose analogue more avidly than the surrounding tissues. These tissues will correspondingly be represented as areas of increased uptake on the PET images.

PET scanners are a form a gamma camera that have a similar outward appearance to a CT scanner comprising a table on which the patient lies, which passes through a circular gantry. Although PET images give a broad anatomic map of ^{18}F-FDG uptake, they lack the superior anatomic clarity of CT. As a result, PET studies are now commonly combined with CT, and the two studies are carried out in the same session using a dedicated PET-CT scanner. Once the two sets of images are superimposed, the resultant PET-CT images provide functional information with precise anatomic localization giving powerful information on disease extent and response to treatment.

PET-CT is used widely in the imaging of many types of cancer but its role in imaging breast cancer is still evolving. PET-CT is not recommended for the initial assessment of stage I breast cancer because of its low sensitivity in detecting small (<1 cm) and low-grade breast lesions; however, it has a role in the staging of clinical stage IIB and primary operable stage IIIA breast carcinoma, and it is also useful for restaging of cancer in patients with known breast cancer recurrence or in those suspected of having recurrence.[15]

Although PET allows detection of extra-axillary lymph nodes and distant metastases, its spatial resolution is not sufficient to allow the detection of early axillary node involvement and micrometastases.[15]

Problems with spatial resolution will hopefully be overcome with the recent development of positron emission mammography (PEM), a dedicated breast PET scanner designed to improve the sensitivity for detecting small breast lesions.

Another potential role for CT-PET is in assessing response to neoadjuvant chemotherapy. Whereas MRI has the advantage of excellent soft tissue discrimination, dynamic enhancement characteristics, and avoids the use of ionizing radiation, traditional MRI sequences lack the functional information that PET might offer. Indeed, assessing radiological response to chemotherapy with MRI using size and enhancement properties does not always predict pathological response, and therefore further information on metabolic activity provided by PET (or PEM) may be a useful adjunct.

Scintimammography

Scintimammography is another radionuclide-based imaging technique and uses the tracer ^{99}Tc-sestamibi, which is known to be taken up in a variety of tumours, including breast. A definitive role for scintimammography in breast cancer imaging is not yet fully established and it is not in widespread use in the UK at present. It is not deemed suitable for determining primary diagnosis or for routine screening; although it shows good sensitivity and specificity for palpable breast lesions, it has been shown that it is not able to provide reliable detection of non-palpable, small breast tumours. Some studies suggest it may be helpful in assessing response to chemotherapy, assessment for recurrence, and adjunctive screening in women with dense breasts.

Breast screening programmes

Different breast screening programmes (BSP) are in operation throughout the developed world. In the UK, the NHS BSP invites women aged between 50 and 70 years to attend two view digital mammography every 3 years. In some regions this is being extended to include women between the ages of 47 and 73 years. Women over the age of 70 may self-refer for screening mammograms by requesting an appointment from their local screening service every 3 years.

The benefits and risks of screening are a matter of constant debate. The fundamental problem is that some of the cancers diagnosed may never have caused those patients a problem in their lifetime so could be termed 'over-diagnosed' or 'over-treated', but science has not yet advanced to the stage that we can differentiate between those cancers that need treatment from those that do not. In what has been considered in some quarters to be an extreme response to this debate, the Swiss Medical Board recommended in 2014 that the country's mammography screening programme be suspended on the basis that the unnecessary interventions triggered by screening yielded a burden which outweighed the lives saved. An extensive review of the NHS Breast Screening Programme was performed in 2012.[16] The review estimated that the NHS BSP confers a 20% reduction in breast cancer mortality, preventing approximately 1300 breast cancer deaths each year but that approximately 19% of cancers represent 'over-diagnosis' and would not have affected that woman during her lifetime. The NHS BSP is constantly and extensively audited for quality assurance, with emphasis upon

retaining a low patient recall rate to keep unnecessary investigations to a minimum.

In the UK, patients with a family history of breast cancer are potentially eligible for additional mammographic screening. NICE have published guidelines for screening in patients with a family history which includes imaging strategies individualized to different levels of risk. Most of the imaging strategies are based on mammogram and/or MRI, and in the younger age groups annual screening is recommended due to the shorter lead time of breast cancer in this population.

Conclusion

Key diagnostic information on breast pathology can be achieved with mammography and ultrasound, either on their own or in combination. Both are readily accessible in any breast imaging department and are quick and cheap to perform. Combined with image-guided biopsy they often provide enough information to formulate a definitive management plan, either to proceed to surgery in the case of malignant lesions, or to discharge patients with benign lesions. In some cases further imaging and biopsies are necessary, a decision usually made by the multidisciplinary team.

MRI is increasingly utilized to assess disease extent and monitor response to chemotherapy, and adding PET-CT or even PEM to the imaging repertoire may provide further strength to our diagnostic and prognostic capabilities. Recent advances in ultrasound techniques such as elastography show good promise in helping to select breast lesions for biopsy, and the potential role for microbubble guided preoperative sentinel node biopsy is being evaluated.

Outpatient image-guided excision of non-malignant lesions has been shown to be safe and efficacious, and this can both avoid a general anaesthetic and free up theatre time for other procedures. One day it may be possible to extend this technique to excising small malignant lesions, meaning that a one-stop surgical excision and sentinel node biopsy could all be done under local anaesthetic under ultrasound guidance.

Even the humble mammogram continues to evolve. Newer techniques such as digital breast tomosynthesis can enhance the diagnostic utility of mammograms, and if in the future it is incorporated into the NHS BSP it may help to reduce unnecessary recalls. CAD could increase the sensitivity of screening mammography and reduce the number of readers required, if the hurdles of cost-effectiveness can be overcome.

As imaging techniques evolve the working relationship of the radiologist and surgeon becomes closer. The goal of both specialties is to provide the best outcome for patients with breast cancer, and if imaging can be optimized to provide the best information to guide the surgeon then this is a step closer to achieving that goal. ◆

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