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ARTICLE

Breast imaging in the new era

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Abstract

In the last decade, there have been huge advances in the field of breast imaging. Full field digital mammography systems optimise lesion to background contrast with resultant improvement in the sensitivity of the technique for cancer detection, facilitated by computer-aided detection. Though mammography remains the only established modality for population-based screening, preliminary results from several large studies indicate that magnetic resonance imaging (MRI) has a role in high-risk patients. On the other hand, advances in ultrasound, MRI and nuclear medicine have the potential to greatly improve the specificity of breast imaging with regard to cancer detection and lesion characterisation. A number of new and experimental techniques are being developed which may have great impact in this area and these will be discussed.

Though MRI now has an established place in the diagnosis of breast cancer, it is becoming clear that it can directly affect surgical and medical management by enabling assessment of response to chemotherapy and endocrine therapy, and facilitating choice of the most appropriate surgery. Just as the role of MRI has evolved, so too the place of nuclear medicine, particularly positron emission tomography and radio-immunoscintigraphy should become clearer in the next few years.

Keywords: *Breast cancer; mammography; computer-aided detection; ultrasound; magnetic resonance imaging; positron emission tomography.*

Introduction

Numerous imaging modalities are now available to the breast radiologist and recently there have been exciting new developments which show great promise for the future, though their precise place in the breast imaging armamentarium remains to be defined. This article will highlight the more interesting of these new modalities as well as improvements and developments in established techniques. Whilst some of the advances facilitate lesion detection, such as full field digital mammography (FFDM) and computer-aided detection (CAD), others are aimed more at lesion characterisation and increasing the specificity of the examination with regard to the diagnosis of breast cancer, for example in ultrasound, magnetic resonance imaging (MRI) and nuclear medicine. In addition, a number have an increasingly important role to play in directing and evaluating patient management, for example, in the choice of surgery and assessment of response to chemotherapy. Despite all of these advances, it is still the case that no single imaging modality is capable of identifying and characterising all breast abnormalities and a combined modality approach will continue to be necessary.

FFDM

One of the greatest challenges in screening mammography is the need to balance high sensitivity for abnormalities which could prove to be malignant with an acceptably low recall rate for assessment. Though film–screen mammography remains the only proven method of population-based screening, the specificity is poor, with only

5%–40% of lesions recommended for excision biopsy proving to be malignant[1–3]. In addition, 10%–20% of palpable cancers are not visible on conventional film–screen mammograms, chiefly because of insufficient lesion–background contrast. With digital mammograms, each component of the imaging chain (image acquisition, display and storage) can be optimised. Contrast can be manipulated to increase lesion conspicuity[4]. The very wide latitude of the system compared to film–screen combinations means that adequate images can be obtained even with suboptimal exposure factors, virtually eliminating the need for repeat examinations secondary to technical inadequacy. This has important implications for minimisation of radiation exposure. A recent study found more consistent image quality with better contrast, fewer artefacts, fewer technically inadequate films and slightly better lesion characterisation when conventional and digital mammograms of the same breasts were compared[5] (Fig. 1). 'Add-on' digital units, which use special high-resolution charge-coupled devices (CCDs) for stereotactic fine needle aspiration and biopsy, have been in use for some time, but full field digital systems have only recently become commercially available. There are various technologies in use, including multiple tiled CCDs, single-piece flat panel detectors, slot scan CCDs and solid-state amorphous silicon. All of these are coupled to caesium iodide detectors, hence the production of an electrical signal which can then be digitised and stored. Hard copies can be produced but more importantly, soft copy images can be manipulated on high-resolution monitors. Though none of these technologies can reproduce the spatial resolution of film–screen mammography (up to 16 line pairs per millimetre), this is more than compensated for by the vastly superior contrast resolution for all areas of the breast, as demonstrated in phantom studies and clinical situations[6,7]. The newer 'Selenia' system marketed by LoRad utilises amorphous selenium to generate an electrical signal directly, so that theoretically the spatial resolution should be even better. There is also a new system under development that uses silicon wafers to increase spatial resolution and potentially reduce radiation dose significantly. With all of these systems, focal areas can be magnified on screen directly, obviating the need for formal magnification views and reducing radiation exposure[8]. A monitor can replace a multipanel viewer and eradicate the need for manual loading of mammograms.

Other advantages of digital imaging include faster image acquisition with easier image storage and retrieval[9,10]. This facilitates efficient organisation of double reading. The potential for telemammography is extremely important, given the current shortage of breast radiologists. Film costs can be virtually eradicated. Finally, digital mammography enables the use of CAD (see below).

There are disadvantages to digital mammography, including the expense of equipment—currently around three to five times that of conventional systems. Image resolution and sharpness have been problematic, but it appears that it is unnecessary to achieve a pixel size lower than 50 μm, to give a resolution comparable to that of film–screen systems. In addition, monitors must adequately display high-resolution images, and those capable of 10 lp/mm resolution are extremely expensive. Finally, a large amount of data is required (approximately 30 MB for a single mammographic image compared to 0.5–1 MB for one CT or MR image) so there are potential problems with data storage and transfer, with high costs for telemammographic transmission.

CAD

Mammographic screening is a highly demanding task requiring the reader to perform a detailed search for subtle signs of abnormality occurring infrequently. Interpretative accuracy remains victim to the limitations of human perception and subtle signs may in retrospect be visible on previous mammograms in as many as 70% of breast cancers[11,12]. Double reading has been shown to be the most accurate method of reading screening films[13–15] but this obviously increases manpower requirements substantially. Generally, two readers will detect an equal number of abnormalities but each will find some that were missed by the other, so that the cancer detection rate can be improved by 5%–15%[16]. CAD may offer an alternative to double reading by improving perception. All CAD systems work by producing marks on digitised mammograms (prompts) that could represent calcifications or masses. The reader makes an initial unprompted search of the original mammogram, then reviews the prompted areas to determine whether they require further investigation. Thus, CAD functions as a 'second observer' rather than a true 'second reader', since the radiologist must interpret the CAD marks[16], most of which will be dismissed as insignificant. The radiologist still makes the final interpretation of the mammogram. If the system is sufficiently sensitive and specific the process should improve reader performance[17], though possibly less than independent double reading[18]. In a study involving The Netherlands screening program, the performance of the radiologists using computer output was found to be similar to that of double reading by two radiologists[19]. There has been greatest success in detecting microcalcifications[20,21] and the systems perform least well for asymmetric densities. CAD can undoubtedly enhance the radiologist's performance, not least because it functions consistently and is not susceptible to fatigue or distraction[22]. It can also improve the detection rate of small breast abnormalities. In one large study the proportion of early malignancies detected was increased from 73% to 78% and the number of cancers detected was increased by 19.5%[23]. However, there is some evidence to show that performance does depend on breast density, with sensitivity diminishing in extremely dense breasts[24].

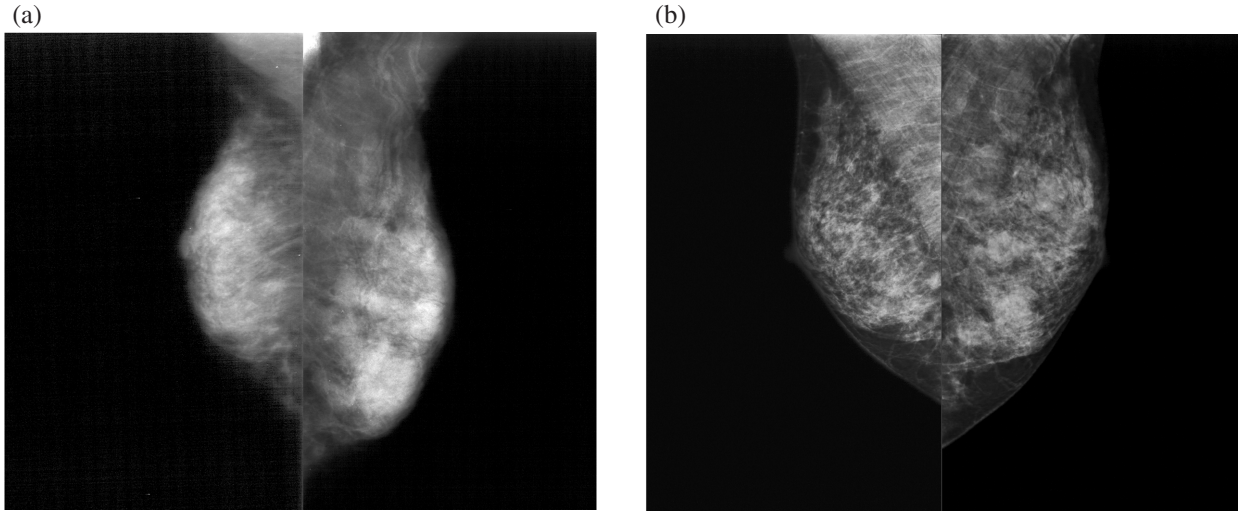

Figure 1 **Conventional film–screen (a) and digital (b) mammograms of the same patient, taken on the same day. Note much improved contrast detail within the glandular parenchyma with simultaneous visualisation of the skin on the digital image.**

The first commercially available CAD system was introduced in 1998. Three systems now have FDA approval. Currently the most popular system is the R2 Image Checker, which will detect potential masses and microcalcifications and has an additional symbol for lesions with a high probability of malignancy.

Limitations include the time and effort to digitise films; this will be eliminated with digital mammography systems, for which CAD has been shown to work equally well in preliminary studies[25]. Unfortunately, in order optimise sensitivity, CAD currently marks a significant number of normal areas on mammograms, so the vast majority of prompts will be false positive (97.4% of all marks were dismissed by the radiologist in one study). This can potentially draw attention away from genuinely abnormal regions and could lead to an increased rate of additional unnecessary investigations. If the algorithm is too sensitive the reader may become over-reliant and miss cancers that the system overlooks. Recall rates will inevitably be increased slightly—in one study from 6.5% to 7.7%[23].

Ultrasound

After mammography, sonography is the most important breast imaging modality. Its main role is in the diagnosis of cysts, the characterisation of mammographically indeterminate masses and palpable masses, and in guidance for percutaneous biopsy[26]. Its role in screening has been studied but is yet to be established[27,28]. However, it can be used as a screening tool, for example in women with normal mammograms and dense breasts[29].

Recent advances in breast ultrasound technology include the development of transducers with higher centre frequencies (up to 15 MHz), an increased number of transducer elements for higher lateral resolution, broadband transducers, and increasingly sophisticated signal processing, resulting in lower noise and higher contrast. Extended field of view imaging (e.g. ScieScape^{TM}; Siemens) provides panoramic high-resolution images of the entire breast. Tissue harmonic imaging has the potential to improve lesion–background contrast and proximal resolution both for breast lesions and in particular the axilla, resulting in an improvement in overall image quality despite some problems with posterior acoustic shadowing[30]. It can improve operator confidence in the nature of a lesion by reducing near-field noise.

Doppler ultrasound with microbubble contrast agents

Doppler ultrasound imaging is underpinned by the assumption that neoangiogenesis within a malignant mass may enable differentiation of a malignant from a benign mass. Power Doppler confers advantages over conventional colour Doppler in the demonstration of intralesional blood flow, as it is more sensitive to low velocity blood flow, without the problems of angle dependency and aliasing. The use of microbubble contrast agents further improves the detection of this intralesional blood flow by enhancing signal strength in small vessels by up to 20 dB ('Doppler rescue')[31]. More than 15 different contrast agents are now marketed but their mechanism of action is the same. Encapsulated gas-filled bubbles in the 5–7 micron range produce an increase in backscatter, so that flowing blood is more easily visualised and tissue enhancement occurs. The microbubbles break when exposed to a higher power ultrasound to allow the detection of contrast agents in tissue when the gray-scale does not clearly show the

agent, stimulated acoustic emission[32,33]. It has been shown that the use of microbubble contrast agents with Doppler ultrasound can improve diagnostic accuracy for both palpable and impalpable breast masses as well as lymph nodes[34–36]. In addition to improving depiction of vascular anatomy, contrast agents allow functional imaging with assessment of perfusion kinetics and calculation of bolus transit time (Fig. 2). Both of these can facilitate differentiation of benign and malignant masses[37]. Other potential applications include monitoring of response to neoadjuvant chemotherapy and differentiation of scarring from local recurrence[38].

Disadvantages of contrast agents include the additional cost and the need for an intravenous injection.

Ultrasonic spiral CT and compound imaging

Ultrasonic spiral CT provides volumetric coverage of the area of interest with an efficient scan technique. Theoretically, there may be advantages over conventional two-dimensional imaging, since the viewer can move through the breast in a virtual fashion and locate lesions. The three-dimensional display can facilitate appropriate surgical planning and tumour volume can be assessed more accurately[39]. The technique lends itself to computer-aided diagnosis using feature extraction and neural networks[40].

Real time compound spatial imaging reduces edge artefacts, shadowing and speckle, making lesion borders and internal echotexture more readily assessable. However, compound and volumetric ultrasound cannot be used as substitutes for conventional ultrasound, since loss of information on posterior acoustic enhancement removes an important diagnostic feature[41].

Vibrational Doppler imaging or sonoelastography

This is an outgrowth of the fremitus technique where the patient is asked to hum a pitch while colour or power Doppler is used to image the breast. Softer areas will vibrate more while cancers and firm masses vibrate less and can be seen as an area of reduced colour. In sonoelastography, a separate external transducer which is vibrated at different frequencies supplies vibration, and the amount of tissue vibration at each frequency can be quantitatively assessed. Cancers tend to vibrate less and show much less variation as the frequency of vibration is altered.

Elastography assesses the elastic properties of tissues by applying a slight compressional force. Data are collected to allow calculation of the amount of displacement of breast tissue and a strain image or elastogram is produced. Benign lesions are poorly visualised on an elastogram while cancers, being much harder than surrounding breast tissue, stand out. Elastography may be particularly useful in distinguishing fibrosis of the breast from cancer, though malignant masses may appear larger on elastograms than on conventional imaging because of the surrounding desmoplastic reaction. This technique may potentially be able to reduce the benign biopsy rate. Ultrasound velocity correlates with tissue elasticity, and so methods such as ultrasound CT and clinical amplitude/velocity reconstructive imaging (CARI) sonography, which are purely experimental at present, provide an indirect measure of elasticity. In CARI sonography, based upon B mode imaging of the compressed breast, a so-called reflexogen line is displayed under the breast tissue and the height of the line indicates ultrasound velocity[42].

MRI

There has been dramatic progress in the field of breast MRI over the last decade and MRI can now be used as a complementary tool in the diagnosis and management of breast disease. MRI has exceptional sensitivity for the detection of breast cancer and can depict cancers that are entirely occult on conventional imaging. Reported sensitivities for invasive cancers using dynamic intravenous gadolinium-based contrast agents are consistently greater than 90%[43–45], but since enhancement depends on, amongst other things, the degree of neoangiogenesis induced by the tumour, sensitivity for ductal carcinoma *in situ* (DCIS) is lower, at around 40%–70% depending upon the precise technique used[46]. A relative lack of neoangiogenesis also explains the occasional false negative examination with mucinous and lobular carcinomas. In the last decade there has been a large amount of work on the refinement of pulse sequences, coil technology, and methods of evaluating contrast enhancement and washout, with the aim of not only maximising sensitivity, but more importantly, improving specificity. Any active area of the breast can enhance false positive studies occurring with benign breast change, fibroadenomata, papillomas, ductal and lobular atypias. Thus, reported specificities for breast MRI have varied from 37% to 97%, depending upon whether the entire breast is scanned or only the region of interest, and on the particular pulse sequence used[47,48]. The degree of overlap between benign and malignant lesions is such that unnecessary additional biopsies may result[43]. It has been established that diagnostic accuracy can be optimised by combining analysis of morphological features with time-intensity curves[49]. The presence of rim or centripetal enhancement and rapid early enhancement with washout has a very high positive predictive value for malignancy. Washout is rare with benign lesions, though it may occasionally be seen in myxoid fibroadenomata and in this situation, the T2 signal characteristics and $T2^*$ signal after first pass perfusion imaging may be helpful[50]. Diffusion/perfusion imaging may also improve specificity of

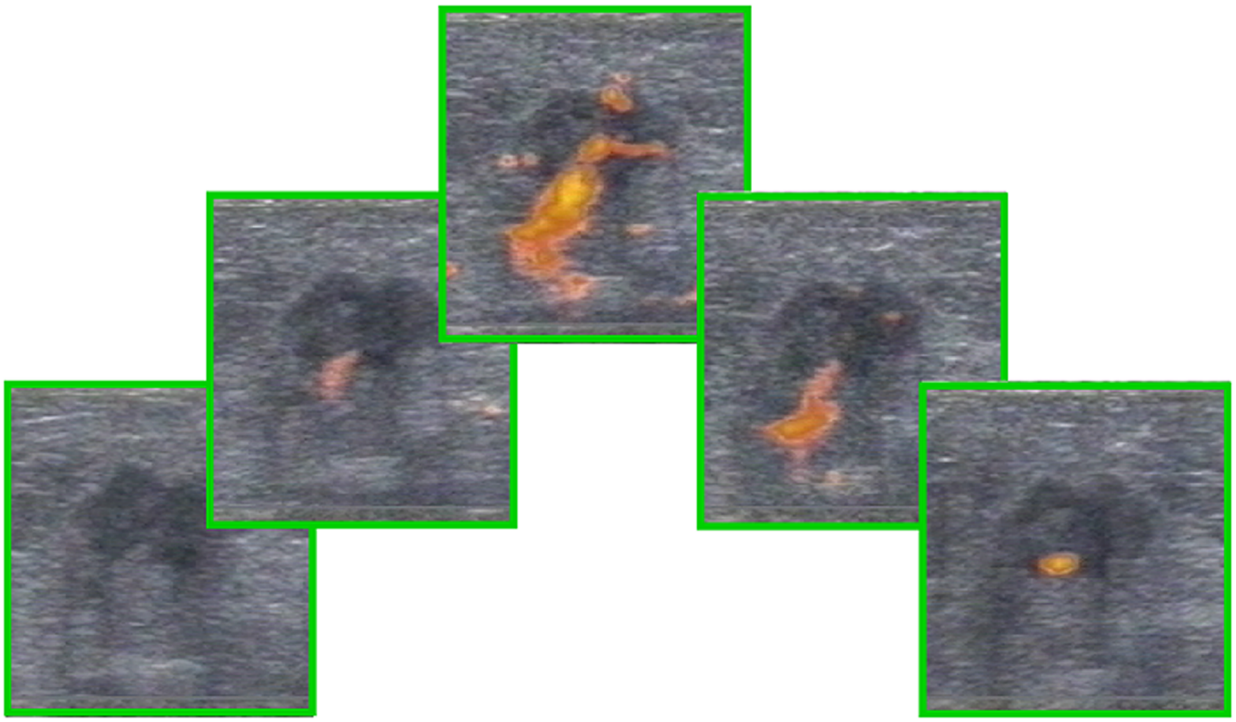

Figure 2 **Sequential ultrasonographic images with power Doppler interrogation depicting the arrival of a bolus of microbubble contrast agent at a malignant tumour (figure courtesy of Dr E Moskovic, Royal Marsden Hospital). Note typical malignant tumour vascularisation.**

the MR examination (see below) and there are some data to suggest that short-term anti-oestrogen pre-medication can diminish confounding non-specific enhancement of normal glandular parenchyma.

MRI has become the method of choice in the evaluation of the augmented breast, since it is highly accurate in assessment of implant integrity and in cancer detection[51].

It appears to be more accurate than conventional methods in local staging of known breast malignancy, particularly with regard to the presence of multifocal or multicentric disease, an extensive intraduct component or chest wall disease, all of which would preclude breast-conserving surgery (Fig. 3). This is particularly the case in women with dense breasts and large tumours[43]. Furthermore, unsuspected synchronous contralateral carcinomas can be picked up[42,43,52–54] and it can help in the planning of treatment for lobular carcinoma, which is difficult to stage locally with conventional methods[55]. However, the clinical significance of small subclinical foci of cancer detected by MR preoperatively is as yet unknown, and the UK based prospective randomised COMICE trial, which has just commenced, should answer this.

MRI is probably the current method of choice for the detection of local recurrence following breast conservation therapy[56]. More recently, it has been shown that breast MRI can often quantify the amount of residual malignancy in the breast after wide local excision, where pathological examination has shown incomplete tumour excision[57,58] (Fig. 4).

There has been interest in whether MRI can be used to stage the axilla preoperatively in patients with breast cancer. Pre-contrast studies alone are insufficiently sensitive for lymph nodes that are small or minimally enlarged, but early data suggest that both dynamic contrast enhanced studies and more importantly ultra-small superparamagnetic iron oxide enhancement may increase overall accuracy[59–61].

MRI has an increasingly important role in the assessment of response to neoadjuvant chemotherapy where it has been shown that MRI correlates more closely than mammography or ultrasound with final pathological tumour size, as it can differentiate between residual tumour and desmoplastic reaction to chemotherapy[62,63]. This facilitates planning of surgery, particularly with regard to the appropriateness of breast-conserving surgery.

Another area where breast MRI shows promise for the future is in the screening of high-risk women, where mammography may be ineffective and yet pose a radiation hazard. Women who carry the BRCA 1 or 2 gene have an up to 85% risk of developing breast cancer over their lifetime, and a number of studies underway in the States and Europe suggest that in this group of women, MRI may be a useful screening tool[64]. Larger studies are currently underway.

(a) (b)

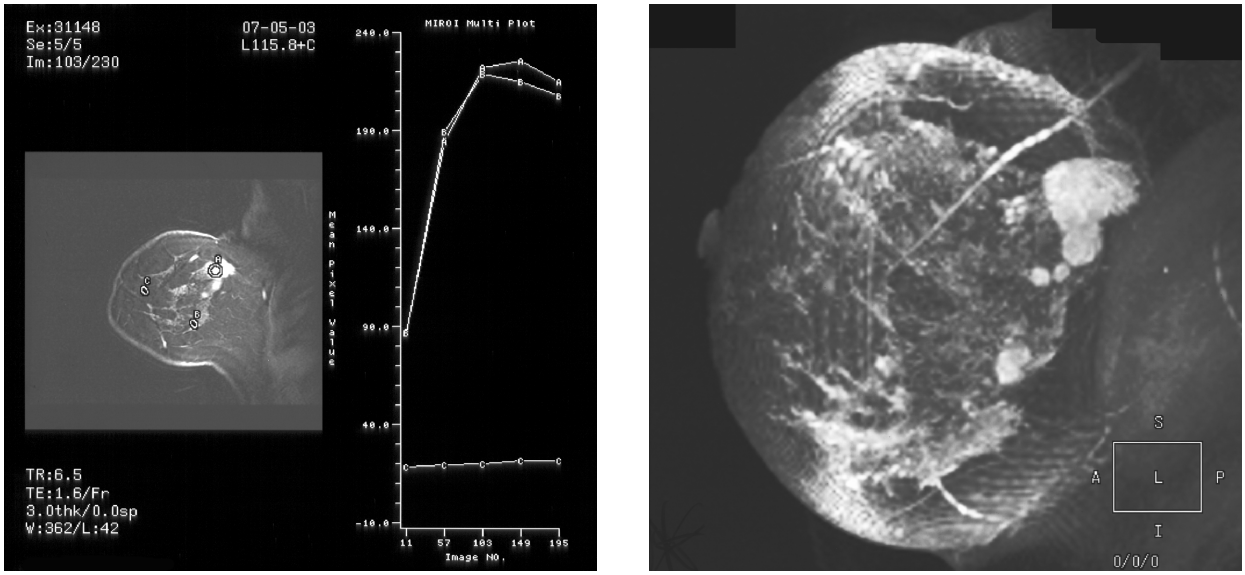

Figure 3 **(a, b) Staging MRI scans from a patient with suspected multifocal breast cancer. There is a type III time-intensity curve typical of malignancy (a). Note the presence of satellite nodules adjacent to the main tumour mass, well shown on the MIP image (b).**

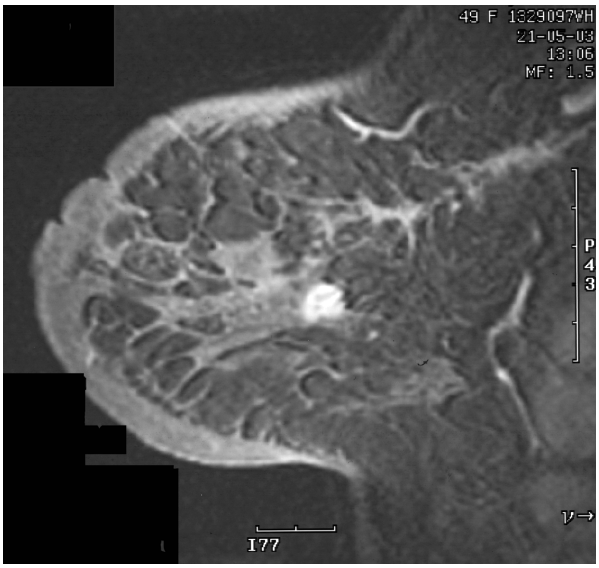

Figure 4 **3D T1W gradient-echo MRI scan, with fat suppression, from a patient with a screen-detected cancer which was missed at excision. This post-contrast sagittal image clearly demonstrates an irregular enhancing malignant mass some distance from the linear enhancement seen in the surgical scar.**

Perfusion and diffusion imaging

Both of these techniques have only recently been applied to breast imaging, but preliminary results suggest that they may help differentiate between benign and malignant masses. The apparent diffusion coefficient (ADC), a marker of cellularity, is lower in invasive malignancies[65,66]. Malignant tumours appear to have higher relative blood volumes (rTBV) than normal breast tissue and benign tumours, so perfusion imaging may provide yet another non-invasive means of tissue characterisation. Changes in tissue permeability in patients receiving chemotherapy can be used to predict tumour response early on in treatment.

MR elastography

This novel technique takes advantage of differing elasticity between benign and malignant tissues. A mechanical wave is applied to the breast during MR imaging and the resultant tissue shifts are imaged using motion-sensitive phase-contrast or spin-echo sequences[67]. Early work indicates that it is feasible to detect the higher elasticity and stiffness of malignant breast tissue and benign masses or normal parenchyma, though clearly some overlap between stiff glandular parenchyma and soft malignancies would be expected[68,69].

MR spectroscopy

Both phosphor spectroscopy and proton spectroscopy have been studied in breast disease. Using the former, changes in a number of compounds have been identified in breast cancers, including phosphomonoesters (phosphocholine and phosphoethanolamine), phosphodiesters, total phosphate and total nucleoside triphosphates[70]. Phosphor spectroscopy is limited by the rather large

voxel size and by variable overlap of changes in benign and malignant disease, whereas proton spectroscopy has the potential advantage of smaller voxel size (down to 1 cm^2). Phosphocholine is detectable with proton spectroscopy and occurs more frequently in breast cancers than benign entities, so it may have some role in lesion differentiation, though at present, there are insufficient data in the literature[71,72]. A recent study demonstrated reasonable sensitivity and excellent specificity for invasive ductal cancer; most of the false negative cases were pure DCIS[73].

The disadvantages of MRI include its considerable cost implications and the fact that MRI-guided biopsy is technically difficult and time consuming, given that many lesions may only be evident on MRI. However, improved techniques for MR-guided biopsy and intervention have been developed in the last few years[74,75]. Finally, there will of course always be a small group of patients who have contraindications to breast MRI or are unable to tolerate it.

Electrical impedance scanning

This technique exploits the changes in local electrical properties shown by malignant cells. Malignant breast tissue has increased capacitance and conductivity compared with normal breast tissue, resulting in decreased electrical impedance. This can be measured by application of a very small electrical current to the breast, to produce electrical impedance tomograms or electrical impedance maps. The Transscan TS 2000, marketed by Siemens, utilises a small probe applied to the skin in much the same way as an ultrasound probe. Impedance values are shown on a display monitor with malignant areas showing as white spots. In one study using the high-resolution 'targeted' mode, sensitivity was 93%, but with a significant number of false positives. Unfortunately, overlap of benign and malignant changes has been shown, especially in perimenopausal women[76–79]. Recent software developments have concentrated on refining the technique by using a number of small electrodes applied to the breast in a manner similar to that of ECG leads, to produce a functional map of impedance rather than an image. It is hoped that this will improve its diagnostic accuracy.

Computerised infrared imaging

This modality is non-invasive and detects physiologic tissue response rather than anatomical features. A proportion of the heat leaving the body is in the form of infrared radiation and this is increased in malignancies because of increased blood flow and the release of vasoactive mediators[80]. A camera is used that is highly sensitive to infrared radiation in the appropriate spectrum and the computerised system differentiates benign from malignant tissue on the basis of the strength of the infrared signal. It may be useful in assessment of indeterminate lesions found at mammography, which are of low to moderate suspicion, as it appears to have a high negative predictive value of over 90% for masses[80]. Malignancies with a negative infrared result were mainly DCIS manifest as microcalcifications alone. Infrared imaging may help determine whether or not biopsy is warranted, potentially reducing benign biopsy rates[80].

Nuclear medicine

Nuclear medicine provides a means of functional imaging, based on biochemical and physiological characteristics of the breast tissue. Thus, unlike mammography, it is not adversely affected by breast density. Recently, the role of nuclear medicine techniques in characterisation of indeterminate mammographic lesions has been intensively studied. Single photon emission computed tomography (SPECT) results in improved sensitivity in the detection of various radiolabeled tracers within the breast compared to standard planar techniques[81]. New tracers, including monoclonal antibodies, perfusion agents, receptor binding hormones and ligands are also under evaluation. In addition, there is now substantial research into the diagnostic impact of positron emission tomography (PET), particularly with fluorodeoxyglucose (^{18}FDG), but also ^{11}C-methionine and fluoro-17-beta-oestradiol (FES), a measure of oestrogen receptor expression[82].

Radioimmunoscintigraphy (RIS)

RIS has been used to target tumour-associated antigens. The ^{99m}Tc label is now accepted as a better choice than previously used agents such as ^{131}I or ^{111}In. The technique requires expression or overexpression of antigen on tumour cells relative to normal tissues. Various antigens have been found in breast cancer and antibodies against these have been developed for use in RIS. These include carcinoembryonic antigen (CEA), polymorphic breast epithelial mucin antigen, and TAG 72 antigen. Perfusion agents can also be utilised such as Thallium-201, ^{99m}Tc Sestamibi, ^{99m}Tc-Tetrofosmin, ^{99m}Tc-Methylene-diphosphonate (^{99m}Tc-MDP) and ^{99m}Tc-DTPA. Receptor agents such as somatostatin receptor have also been used and oestrogen and progesterone receptors are being developed[82]. The clinical role of these techniques in the primary diagnosis of breast cancer is uncertain, but they could have a role in the non-operative assessment of the axilla[83] (Fig. 5). No matter which radiopharmaceutical is considered, it is clear that SPECT offers considerable diagnostic advantage over planar scintigraphic techniques, though it is unclear as yet whether the use of SPECT and newer high-resolution cameras will result in the required

sensitivity for reliable identification of tumours under 1 cm in size[84].

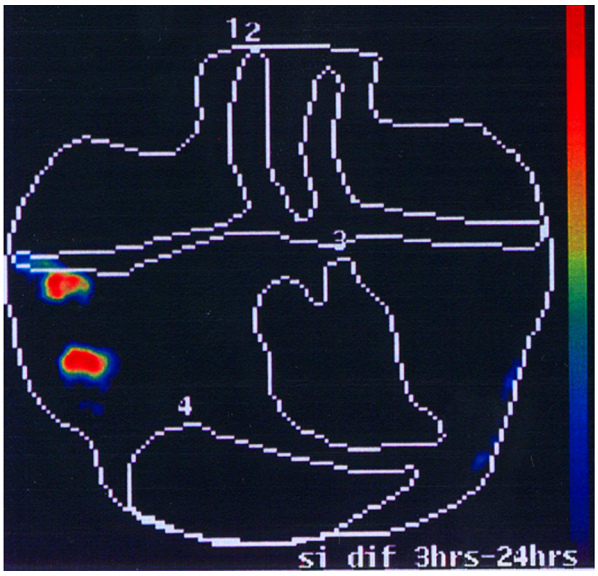

Figure 5 **Tc99m hHMFG-1 radioimmunoscintigraphy. Positive right axillary nodes and breast cancer (figure courtesy of Professor K E Britton, St Bartholomew's Hospital; reproduced by permission from: Br J Cancer 2002; 86: 870–8).**

Sestamibi scintimammography

The radiopharmaceutical technetium 99m methoisobutyl isonitryl has been known to be a tumour-seeking agent since 1987, when uptake into a metastatic thyroid lesion was observed. ^{99m}Tc Sestamibi is sequestered in the cytoplasm and mitochondria because of the strong electrostatic attraction between the positively charged lipophilic ^{99m}Tc-MIBI molecule and the negatively charged mitochondria. Selective uptake by cancer cells depends on cellular perfusion, mitochondrial uptake and transmembrane electronegativity[85].

The technique involves the injection of 20–25 mCi of ^{99m}Tc Sestamibi into the contralateral arm or into the foot if bilateral tumours are suspected, with the patient being imaged at 5 min and 1 h in the prone position. Focal areas of uptake in the breasts are considered positive[86]. Slow growing tumours often do not demonstrate significant tracer uptake, which can potentially result in false negative studies. False positive focal uptake can result from benign entities such as infection, inflammation and benign tumours such as papillomas or fibroadenomas. Thus, it cannot always obviate the need for biopsy.

Overall, the sensitivity is said to be 85%, specificity 89%, positive predictive value 89%, negative predictive value 84% and accuracy 86%[86]. However, scintigraphic detection of palpable cancers is much better than that of non-palpable cancers, the sensitivity for lesions greater than 12 mm being 92% and for lesions of 7–11 mm only 50%[87]. The smallest detectable lesion in one study was 5 mm[88] but generally sensitivity is poor for small or medially located lesions and for DCIS. Because of this, Sestamibi scintimammography is not currently a candidate for a screening tool, though it may have a role in the evaluation of mammographically indeterminate lesions and dense breasts. In this situation, it may be more specific than ultrasound[89]. Some studies report similar accuracies for ^{99m}Tc Sestamibi and MRI in diagnosing breast cancer in the mammographically indeterminate lesion[88,90]. However, ultrasound-guided biopsy is generally cheap, accurate and safe and the extra cost for these investigations is not justified in most cases.

It may have some role in the assessment of axillary nodal metastatic spread, with sensitivities of up to 84% quoted, and even higher specificities[91–93].

Tc99m tetrofosmin scintigraphy has also been evaluated in the diagnosis of breast cancer but comparative studies have shown little advantage over sestamibi. Tetrofosmin SPECT scintigraphy may have a role in the diagnosis of local recurrence, one recent study suggesting greater overall accuracy than for conventional imaging procedures[94].

Of more interest is the potential role of scintimammography in the identification of multidrug resistance in tumours. Sestamibi is used as a substrate for the multidrug resistant P-glycoprotein system (P-gp). The P-gp system transports sestamibi out of tumour cells, thus the efflux in patients with untreated breast cancer can be used as an indicator of multidrug resistance. High washout or a negative scan predict multidrug resistance and lack of response[95–98].

Disadvantages include the expense, the length of the examination and patient exposure to ionising radiation (a breast dosage of 2.5 mGy and gonadal dosage of 6–9 mGy).

PET

The glucose analogue 2-^{18}fluoro-2-deoxy D-glucose (^{18}FDG) is used in PET imaging to yield physiological information with rapidly dividing neoplastic cells displaying higher metabolism of glucose compared with normal tissues, and therefore increased uptake of FDG[99]. FDG uptake is correlated with proliferative fraction, though seemingly not with other prognostic factors[100]. Breast density, previous surgery or radiotherapy do not affect the results of FDG–PET and unlike MRI, benign breast disease will be negative on FDG–PET. Limitations include poor detection rates for tumours less than 1 cm due to limitations in spatial resolution, inability to detect non-invasive tumours (DCIS), lobular carcinomas and multicentric tumours[82,101]. There is also a significant radiation dose. Thus, as with scintimammography, it has no real role in the primary diagnosis of breast cancer. FDG–PET may be useful in identifying involved axillary nodes and distant metastases. Axillary

nodal status is an important prognostic indicator in breast cancer patients[102] and surgical nodal dissection carries with it significant costs and patient morbidity. FDG–PET has shown itself to be more accurate than clinical examination and although FDG–PET alone cannot be used to obviate surgical nodal dissection, it may allow the selection of women likely to benefit from the procedure, and allow evaluation of more distant nodal groups[103]. However, reported sensitivities are variable, from 90% to less than 50% in some series[104–106]. FDG–PET positivity in the axilla is a function of axillary tumour load and FDG avidity of the primary tumour[107].

It has been shown that additional information regarding unsuspected distant metastases was provided by PET in 29% of patients[108], and it is more sensitive in the detection of bone metastases than technetium bone scans, particularly when they are osteolytic. On a patient basis, it is more accurate than conventional imaging when clinical suspicion of recurrence is high.

As with scintimammography, FDG–PET is able to assess tumour response to primary hormonal and chemotherapy early on after commencement of treatment[109–111]. A fall in the standardised uptake value (SUV) occurs early on in patients who are responding, so that final response can be predicted after only one to two courses. Thus, therapy can be changed in non-responders before avoidable toxicity has occurred. FDG–PET is better able to distinguish fibrosis from residual tumour, unlike clinical examination and mammography, though the presence of a large *in situ* component of disease can cause persistent elevation of the SUV when there is little residual macroscopic disease[109]. In the setting of a very good clinical response, however, FDG–PET can miss residual invasive disease[112]. Early FDG–PET findings also seem to predict long-term outcome[110].

One new technique under evaluation is the combination of mammography with functional imaging from FDG–PET, positron emission mammography. This could potentially have a role in the evaluation of high-risk patients with mammographically difficult breasts[113].

Conclusion

Breast imaging is in an exciting phase of development with many new strategies being investigated and implemented. It remains to be seen how many of these techniques will show themselves to be robust and reliable enough to introduce into the routine screening and evaluation of patients with breast problems.

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