Eur J Cancer Clin Oncol, Vol. 24, No. 1, pp. 61–68, 1988.
Printed in Great Britain

0277–5379/88$3.00+0.00
Pergamon Journals Ltd.

Imaging Techniques in Breast Cancer. What is New? What is Useful? — a Review

MICHAEL N. MAISEY

Division of Radiological Sciences, United Medical and Dental Schools of Guy's and St. Thomas's Hospitals, Guy's Hospital, London SE1 9RT, U.K.

DURING the last decade there has been an explosive increase in diagnostic imaging techniques which are available to clinicians managing patients with breast cancer. The application of these new methods has largely been randomly employed on a trial and error basis with little regard for the effect they might have on management or clinical outcome. In many instances a comment made by a leader writer in the *British Medical Journal* writing on the subject of 'Taming High Technology' is only too true—'Any Doctor with pretensions to being a scientist must be ashamed of the way clinicians have responded to technical innovations, the frequent result has been that all innovators have made the same mistake, patients have suffered and only later has a consensus emerged'—this consensus is often not based on scientific data [1]. The purpose of this review is to examine some of these new imaging techniques; attempt to indicate their role in patient management; and highlight those which show promise for the future. A case will also be made for a more systematic approach to future work which should be aimed at evaluating the efficacy and effectiveness of diagnostic imaging techniques in the management of breast cancer.

The important imaging technologies to be considered are the following:

- *X-Rays*—radiology, computed tomography, digital angiography.
- *Radionuclides*—single photon and positron emission tomography.
- *Ultrasound.*
- *Magnetic resonance*—imaging and spectroscopy.
- *Thermography.*
- *Transillumination.*

Each of these imaging techniques displays the distribution of a different physical or biochemical characteristic of the tissue or organ which is being examined. Thus X-ray methods measure tissue density (or the electron density), the distribution of appropriately labelled radioactive compounds displays regional function and metabolism; ultrasound records tissue reflectance and reflecting surfaces; magnetic resonance imaging displays the concentration of protons and the local chemical environment (relaxation parameters) whereas magnetic resonance spectroscopy (usually with phosphorus-31 or protons) is capable of measuring the concentration of individual chemical compounds, e.g. ATP, and measuring tissue pH. Thermography measures the heat emission from the surface and transillumination records the absorption of light waves at the red and near infra-red portion of the electromagnetic radiation spectrum.

Rather than describe each imaging technique in any detail or to examine how each method can contribute to diagnosis and management, particular clinical problems in the treatment of breast cancer will be reviewed in order to assess the current and potential application of each technique. Before doing this it is worthwhile considering how a diagnostic investigation may be used to benefit patients with breast disease: (1) it may cause a change in management which will improve the final clinical outcome; (2) it may be used as an index of prognosis; (3) as an index of treatment response in the course of a clinical trial; (4) to monitor the progress of the disease as part of studies to further our understanding of the natural history of the disease process.

The following are some of the important clinical problems in breast disease facing clinicians to which modern imaging methods might be expected to make a significant contribution either now or in the future.

1. Diagnosis of breast cancer and screening for breast cancer.
2. The assessment of axillary node disease.
3. Pretreatment staging procedures.
4. The choice and the assessment of therapy.
5. The follow up of patients during the course of their disease.

1. DIAGNOSIS AND SCREENING

These may be considered as two separate clinical problems but are included together because the techniques which have been applied are the same, any differences are consequent upon the different disease prevalence in a screened population of normal women from that of patients presenting with symptomatic breast disease. It is now generally agreed that screening for pre-symptomatic breast cancer is worthwhile, both by detecting and treating early disease and also by improving the mortality from breast cancer [2–5]. The goal of imaging techniques both for diagnosis and for screening is (a) to detect all breast cancers in the screened or symptomatic population and (b) to separate the breast cancers detected as effectively as possible from the patients with benign breast disease not requiring surgical treatment.

Mammography has been shown to be highly effective as the first line investigation, both for screening and for the investigation of the symptomatic patient. This technique has an average sensitivity of 90% and a specificity of 94% [2], however the range of reported sensitivity and specificity may be wide (53–95% and 51–98%) [2, 6]. The positive predictive accuracy is approx. 8.6–14.3% [6, 7] for screened patients but of course much higher for symptomatic patients. These differences are because the sensitivity and specificity are constant for a test, whereas the positive predictive accuracy varies according to the prevalence of the disease in the population being examined. Mammography is not an ideal investigation. Its weaknesses lie in the use of radiation, even though it is an extremely low level and considered likely to be harmless. It is relatively difficult both to interpret and to standardize the interpretation. Technical variability is a further problem: quality control is absolutely critical to obtaining good results. Any technique which might be considered as an alternative to mammography would need to maintain the best possible results of sensitivity and specificity obtainable by mammography, and in addition be more technically robust, not require the use of ionizing radiation and permit easier standardization of image interpretation.

Techniques which can image the breast and demonstrate disease may be considered in three possible roles; these were well reviewed by Kopans *et al.* in 1984 [8]:

1. As a replacement for mammography as the prime screening investigation. At the present time no technique other than mammography has been shown to have similar efficacy or effectiveness in widespread studies.
2. As an adjunct to mammography, i.e. multimodality screening. There is no evidence that any other investigation can increase the sensitivity and specificity when used in this way. However, carefully controlled prospective studies comparing a combination of two investigations against only one investigation using Receiver Operated Characteristics (ROC) curve evaluation has never been undertaken. The need for an adjunct was discussed critically in an Editorial in *Radiology* in 1986 [9].
3. As an adjunct to mammography to increase the positive predictive accuracy. On average there is a 30% chance of cancer being present when the mammogram is positive. This varies in reported series from 10% to as high as 50% indicating that approx. 70% of patients undergoing surgical biopsy may be having an unnecessary surgical procedure. Any improvement in this positive predictive accuracy must be achieved with no loss of sensitivity. An adjunctive technique needs to be one which is capable of accurately diagnosing benign disease with a cut off point that permits no false negatives. At the present time no investigation has been shown to be effective in this respect, it is highly likely that an appropriate test will not be a morphological technique but one that measures a different biological or biomedical parameter and is capable of quantification.

Techniques for breast imaging will be reviewed in the light of these possible applications.

(a) *Ultrasonography (US)*

At the present time breast US is the only other imaging technique which has been accepted as having a role in the investigation of breast disease. In the best series a sensitivity of 73% and a specificity of 95% can equal that of mammography [10]. However, the current evidence is that to achieve these levels requires a degree of expertise and dedication on the part of the operators of an order that is not easily achievable in widespread use. The frequency of false negative lesions, mainly due to the misdiagnosis of fibroadenomas, makes it unlikely to perform well for accurate diagnosis of benign disease, with the exception of simple cysts which are easily assessed by aspiration. The following are generally accepted indications for ultrasound examinations in patients presenting with symptomatic breast lesions.

1. Mammographically negative palpable lesions.
2. Mammographically positive impalpable lesions.
3. Multiple masses which may be cystic.

4. Fear of ionizing radiation.
5. The investigation of high risk younger or lactating patients where the dense breast makes mammography technically difficult.
6. In some selected cases for US directed biopsy.

(b) *Transillumination*

The use of transillumination at the infra-red and near infra-red portion of the visible spectrum has been widely examined as a possible screening test particularly in view of its harmless nature. Results have been very variable but in general the sensitivity for the detection of malignant lesions in mixed population (screened and symptomatic) is generally low. For example, Monsees *et al.* [11, 12] and Geslien *et al.* [13] found 58% sensitivity, Gisuold *et al.* [14] 67%, although some others were higher, Wallberg *et al.* [15] 85% and Dowle *et al.* [16] as high as 88%, the higher figures are all symptomatic patients and usually associated with a lower specificity, e.g. 71% [16]. When asymptomatic screened patients are removed the sensitivity may drop to 52% [14]. The problems are observer variability, false positives due to variety of lesions, poor detectability of small lesions, variation of diagnostic criteria and no consistent features to make a positive diagnosis of benign disease with the exception of increased light transmissions with some cysts. The general consensus is that work should continue on the method to improve the technique but that no role has been shown for transillumination to be used either for screening or as an adjunct to mammography.

(c) *Thermography*

The recording of the increased heat emission from breast lesions has been used either as plate tomography [17] or telethermography [18], but the results of sensitivity and specificity make it quite unsuitable for either screening or a diagnostic adjunct [15, 20, 21]. The evidence is that to achieve even the results which have been reported requires the highest dedication to image quality and interpretation suggesting that the results would be even worse in widespread use.

Two investigations which are not in routine use, but are under investigation both have the two attributes of a potentially useful adjunct, i.e. measuring a different biological property and quantitative.

(d) *Magnetic resonance*

Magnetic resonance may be used in a variety of ways to assess the tissue under investigation. These include magnetic resonance proton imaging, the measurement of relaxation parameters, the use of para-magnetic material and *in vivo* spectroscopy.

Initial work with magnetic resonance imaging of the breast suggests a high sensitivity and specificity comparable to that of mammography [22, 23]. However, cost considerations, certainly for the foreseeable future, exclude it as a possible first line investigation. Magnetic resonance may be useful for deeply seated breast lesions, invasion of underlying muscle and for the identification of local lymph nodes [23]. The use of gadolinium DTPA which is a paramagnetic agent has been used to increase pathological contrast between normal and malignant tissue. In a small series of 20 patients Heywang *et al.* [24] were able to visualize all the carcinomas, three of which would have been missed by non-contrast enhanced imaging and two carcinomas, in dense breasts were not visible on mammography. These are encouraging results which deserve more widespread evaluation.

The original work of Damadian [25] suggested the possibility of distinguishing malignant from benign disease by using the T1 and T2 relaxation parameters. For various reasons, many of which may be technical difficulties in measuring these parameters *in vivo*, this separation has not been so clearcut in clinical practice. Weiner *et al.* [26] have shown that the use of T2 weighted imaging sequences improves the detectability of carcinomas over the T1 weighted which are essentially morphological images. They also showed that it is the prolonged T2 relaxation times of neoplastic cells which is the source of increased signal intensity in the T2 weighted spin echo imaging sequences thus providing some hope of benign/malignant separation on a quantitative basis in the future. Heywang *et al.* [23] on the other hand found that the T1 and T2 values of benign and malignant disease overlapped too much for them to have any clinical value in increased specificity, but suggested that there were technical reasons for their failure.

Magnetic resonance spectroscopy provides information about biochemical processes taking place within cells by measuring the concentrations of energy systems and metabolites. Most of this work has been *in vitro* but, although as yet in its infancy, *in vivo* spectroscopy using P31 is becoming a reality and has the potential to provide new unique information. Two recent studies illustrate some of the possibilities: Degani *et al.* [27] have studied post operative specimens of five benign and nine malignant breast tumours. They showed that the concentration of nucleoside triphosphates and phosphomonoesters are consistently higher than the benign lesions by a factor of three in the carcinomas and that chemical shift of the ATP signals also differed significantly. If these results were to be reproduced *in vivo* it would be possible to separate benign from malignant lesions with a high degree of confidence. In another study Cohen *et al.* [28] showed significant differences of phosphate metab-

olites between drug sensitive and drug resistant breast cancer cell lines; information which if reproduced *in vivo* could be critical in deciding patient management. There is a big gap between *in vitro* and *in vivo* studies but the initial results obtained are sufficiently encouraging for more effort to be directed to *in vivo* spectroscopy studies. These studies however are difficult, time consuming and expensive but until we know whether reliable reproducible results can be obtained we can only speculate on their potential impact in clinical medicine.

(e) *Digital angiography*

The use of digital radiography enables radiographic studies to be quantitative and permits the use of low concentrations of contrast media which can be used to assess the blood supply of breast lesions. Thus fulfilling the two criteria which may be important for the separation of malignant from benign breast lesions. Few studies have so far been reported using digital techniques. Watt *et al.* [29] studied 22 breast lesions and on the basis of retention of contrast material and abnormal vasculature were able to correctly categorize 19 of the 22 lesions into benign or malignant. This is an important study which warrants more widespread evaluation as digital radiology becomes more available.

2. IMAGING AXILLARY NODES

It has been shown that the involvement of axillary nodes by metastatic disease is a major prognostic factor in breast cancer [30] and this, rather than a therapeutic reason, is the major indication for surgical axillary node dissection to establish the presence or absence of disease at this site.

A technique which could either accurately predict the presence of disease or directly demonstrate disease in the axillary nodes non-invasively would be of major importance in the management of patients with breast cancer and could decrease the morbidity from surgical dissection. Cytochemical techniques are being developed which predict the likelihood of metastatic involvement and at the same time imaging techniques are being developed and evaluated which demonstrate the presence of disease within lymph nodes. Imaging methods capable of demonstrating axillary lymph nodes include computerized tomography, ultrasound, lymphoscintigraphy, magnetic resonance and immunoscintigraphy. In order to be useful clinically the technique must be capable of demonstrating lymph nodes involved with metastatic disease with as few false positive and false negatives as possible. The following section briefly reviews the techniques available for their potential to achieve this.

Computerized tomography (CT)

It is generally accepted that CT can often demonstrate abnormal lymph nodes [31], however, as with CT elsewhere in the body, it is limited to diagnosing enlargement only without being able to differentiate between those infiltrated by cancer from specific reactive hyperplastic glands.

Ultrasound

Like CT, ultrasound is capable of demonstrating abnormal axillary lymph nodes. Bruneton *et al.* [32] examined 60 patients with breast cancer undergoing axillary dissection, 22 patients had axillary node disease, ultrasound detected 17 of these and there was one false positive due to an inflammatory node. Although better than clinical examination US provides no alternative to axillary dissection for the majority of patients.

Lymphoscintigraphy

When ^{99m}Tc labelled colloid is injected subcutaneously into web spaces of the fingers functioning lymph nodes may be visualized by imaging the axilla after a few hours. McLean and Ege [33] studied 62 patients with axillary lymphoscintigraphy before axillary dissection. Sensitivity compared with axillary node dissection was 76% and specificity 67% which they concluded was as good but not better than clinical examination and could not therefore be used to replace axillary dissection. Problems with this technique include variability of normal anatomical node distribution, variations in diagnostic criteria, poor resolution and most importantly, that the technique is one which indicates disease by the absence of normal tissue uptake rather than demonstrating disease itself.

Magnetic resonance imaging

Magnetic resonance imaging like CT and US can demonstrate abnormal enlarged lymph nodes with the same limitations of these two methods. Some early work by Wiener *et al.* [26] has shown that lymph nodes involved with metastatic disease studied by MR after surgical dissection have significantly longer T2 relaxation times than hypoplastic lymph nodes. These results may be difficult to achieve pre-operatively *in vivo* but certainly provide an important potential requiring more work in the future.

Immunoscintigraphy

Imaging malignant tissue by the use of specific monoclonal antibodies labelled with radionuclides (usually ^{131}I, ^{111}In, ^{123}I) is the subject of enormous effort in all branches of cancer. Results in breast cancer have in general been less successful than in many other tumours. Labelled antibodies directed against breast cancer cell surface antigens will dem-

onstrate primary and metastatic breast cancer [34, 35]. By injecting the finger web spaces better targetting of the lymph nodes may be achieved and Thompson [36] using this technique has shown uptake in seven axillae with palpable nodes involved by tumour and in three with impalpable nodes involved by tumour.

Intravenous injection of antibody may also visualize involved lymph nodes but this is more variable [36]. These methods are encouraging because they are directed towards the demonstration of tumour itself. Present problems include relatively poor affinity antibodies, non-specific uptake and uptake by lymph nodes if the protein becomes aggregated and acts like a colloid in lymphoscintigraphy.

To summarize, there is at present no imaging technique which can replace axillary dissection for the demonstration of axillary nodes involved by metastatic disease. Ultrasound and lymphoscintigraphy may help in establishing the presence of nodes and thereby increase the yield from surgical dissection but the value of this in routine clinical management needs to be established.

3. STAGING PROCEDURES

There is disagreement about the role of staging procedures in breast cancer because of uncertainty about the frequency of metastatic disease in different stages of breast cancer, and because the management of patients with breast cancer varies. It is important however to know the facts about detectability of metastatic disease at different stages and only then to make decisions about how staging procedures should be used based on current management approaches. The subject has been reviewed recently by Feig [37].

Bone scanning, bone metastases

It is now generally agreed that bone scanning is the method of choice for the detection of bone metastases, being highly sensitive, simple, relatively inexpensive and generally available. It is, however, pathologically non-specific and X-rays, CT or biopsy may be necessary to establish a positive diagnosis of malignancy as a cause for a metabolically active focal bone lesion on the bone scan. There has been in the past considerable disagreement about the frequency of bone metastases in different stages of breast cancer. Recently McKillop [38] has reviewed the results of several modern series of bone scans in patients with various stages of breast cancer. The most frequent finding was that only one or two patients in all series with stage 1 breast cancer had bone metastases, the average in stage 2 was 7.2% and in stage 3 the average figure was 27.6%. These results have been confirmed in a recent much larger series of 1267 patients by Fogelman and Coleman [39]: stage 1 = 0%, stage 2 = 7%, stage 3 = 7% and stage 4 = 47% and similar results have been reported by Khansur *et al.* [40]. There is no general consensus about when bone scanning is used; in stage 1 it is generally agreed that there is no indication for routine pre-operative bone scanning unless the patient will have regular, e.g. annual, bone scans subsequently either for trial purposes or clinical reasons when the pre-operative bone scan is useful as a baseline. In stage 2 this will also apply but the higher yield makes routine pre-operative scanning more useful when therapy may be altered as a consequence of a positive study. Stage 3 probably always warrants bone scanning at the time of presentation. The role of regular follow up has also to be established. Wickerman *et al.* [41] concluded that only 0.6% of routine follow up bone scans in stage 2 carcinoma were efficacious in detecting asymptomatic metastases and recommended follow up only as indicated by symptoms. Similar conclusions were arrived at by Pauwels *et al.* [42] and Chaudary *et al.* [43] found that even for those asymptomatic patients found to have metastases on the bone scan the average 'lead time' before becoming symptomatic was 2–5 months. The value in the symptomatic patient on the other hand is undisputed [44] and is probably also a useful investigation in all patients with a recurrence in a site other than bone.

Imaging the bone marrow using ^{99m}Tc used for liver and spleen scanning have been suggested as a method for early detection of metastases which start in the bone marrow. The effect on the bone barrow may be generalized or focal replacement. A study by Lentle *et al.* [45] concluded that there was a high sensitivity but Gulenchyn and Papoff [46] found it to be very insensitive. More studies need to be performed to establish whether there is a role for this imaging modality.

Liver metastases

There is no role for liver imaging as a routine in breast cancer but it should only be used when there are biochemical or clinical suspicions of metastases. The most accurate technique is CT scanning; Alderson *et al.* [47] studied 189 patients with breast or colon cancer and found the best results with CT (sensitivity 93%, specificity 88%) the sensitivity of radionuclide scans was 86% and that of ultrasound 82%, however using ROC curve analysis they found that CT had a higher true positive ratio at every true negative level. It is widely felt that the initial study should be radionuclide scintigraphy for follow up because of the ease of comparison between studies. Radionuclide tomographic studies (SPECT) may increase the sensitivity of the radionuclide scan [48]. Magnetic resonance can also be used and may be as sensitive as CT [49], however

there can be no justification for using MR for routine liver imaging at the present time.

Brain

There is no indication for brain scanning in the asymptomatic patient with breast cancer. For the symptomatic patient CT is the imaging technique of choice. Radionuclide brain scanning is less sensitive but a reliable alternative in the absence of a CT scanning facility.

Magnetic resonance studies should be reserved for specific indications which include persistently negative CT scans when there is strong clinical evidence of metastases, posterior fossa lesions which are negative on CT scan, base of skull lesions particularly affecting cranial nerves and spinal cord lesions.

Radioimmunoscintigraphy by whole body imaging after injection of a specific monoclonal antibody labelled with indium-111, ^{123}I or ^{131}I is a theoretically attractive technique for the detection of all metastases irrespective of the site [34]. However, unlike some other malignancies, the quality of imaging and the specificity of the antibodies *in vivo* has not as yet reached a technical quality that would allow it to be considered for routine clinical practice.

4. CHOICE AND ASSESSMENT OF THERAPY

The choice of therapeutic regimes whether surgical, endocrine or chemotherapeutic has depended and continues to depend on careful clinical trials of selected methods and combinations of methods. Non-invasive imaging methods which would permit a more selected choice of treatment for the individual patient and very early assessment of response to enable a treatment regime to be changed more quickly than clinical and other markers than we have at the present time would be a great advantage. A number of techniques are emerging which may have a role in this more individual tailoring of treatment to the patient.

Any useful technique is likely to be one which measures a biochemical or biological parameter of the tumour and is capable of measuring changes quantitatively.

(a) *Magnetic resonance spectroscopy using* ^{31}P

Spectroscopic methods to measure the concentrations of phosphate compounds, principally ATP, phosphocreatine inorganic phosphate, phosphomonoesters and phosphodiesters, have been shown in experimental animal models of breast cancer to change rapidly in response to effective endocrine or drug treatment [50, 51]. There is a fall of the phosphomonoester peak and a rise in the phosphocreatine to inorganic phosphate ratios. This work holds out some promise of clinical application in the future, but technical difficulties with localization, reproducibility and the separation of tumour from normal tissue in the field of view, all require to be overcome before it can be expected to have a useful clinical application.

Magnetic resonance spectroscopy has also been applied to the measurement of drug concentrations within tumours using fluorine-19 spectroscopy of fluorinated cytotoxic drugs such as 5-fluorouracil [50]. As the concentration of chemotherapeutic agents within tumours is likely to be a major factor determining the therapeutic response, this technique could also have a role in tailoring drug regimes to the individual patient.

(b) *Radioisotope imaging techniques*

Radio-labelled oestrogens and progestogens have both been used to image and measure progestogen and oestrogen receptors *in vivo* [52, 53] and this could have a future role in the non invasive assessment of these receptors in patients with breast cancer.

CONCLUSION

This review has been wide ranging and has attempted to look at techniques which are available and the role they may have in clinical problems presenting during the management of patients with breast cancer. Some of the techniques have clinical application at the present time but some will require more technical development and evaluation to establish whether they will have any long term value in the management of patients with breast cancer. It is vital that before new diagnostic methods are introduced they are in the future subject to the rigorous evaluation for efficacy that currently applied to new therapeutic regimes. Without this we may never really know how and when to use the new technologies which are expensive and not without costs to the individual patient.

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