Breast cancer

New and emerging technologies for diagnosis and management

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Part six of this series discusses established and emerging technologies in breast cancer care, with an emphasis on technologies in diagnosis and treatment supported by evidence. These include percutaneous core biopsy techniques and breast imaging in diagnosis. From the surgical perspective, we discuss the emerging role of sentinel node biopsy as a potentially less invasive method of staging the axilla in women with breast cancer. We also review advances in radiotherapy techniques that have allowed delivery of radiotherapy with more precision and improved safety.

Detection and diagnosis

The early detection of breast cancer confers many benefits. It allows intervention at an earlier stage of cancer progression, resulting in improved long term survival for the patient. Advances in breast imaging have paved the way for the detection of very small breast cancers.

Core needle biopsy

In response to this shift toward detection of small, early breast cancers, an array of core biopsy methods has been developed to sample image detected lesions (*Table 1*). These methods allow a definitive histological diagnosis to be established. Core needle biopsy (CNB) histology provides a more accurate diagnosis than fine needle aspiration biopsy (FNAB)[1] and may assist in planning treatment before surgery in women with cancer by distinguishing between invasive and noninvasive (in situ) disease. Percutaneous CNB (PCNB) is used selectively in most breast services, and in the screening setting for sampling screen detected lesions. It is the standard method for sampling mammographically detected microcalcification. The decision to perform core biopsy (rather than FNAB) is influenced by a combination of factors such as the availability of technology, local expertise, and in particular the type of lesion seen on imaging. Therefore, such a decision is best made by the doctor responsible for making the diagnosis with the patient informed of biopsy options.

Breast ultrasound

The clinical application of ultrasound in breast diagnosis has developed substantially in recent years due to advances in ultrasound technology. Initially used as an adjunct to mammography, primarily to distinguish cystic from solid lesions, it is now considered the most accurate test for diagnosing breast cancer in young women.[3] Current ultrasound technology uses very high frequency probes (10–18 MHz). These have improved resolution, allowing detection of tiny lesions and differentiation between malignant and benign solid nodules.[4,5] However, it may also identify nonspecific and benign lesions that may require additional management. Ultrasound is generally the preferred method for image guided intervention, allowing

real time visualisation of needle or wire tip, and ongoing view of the sampling process. Although more sophisticated ultrasound technology (eg. three dimensional ultrasound) is under evaluation, its clinical contribution in breast diagnosis is not established.

Digital mammography

Digital mammography is a new type of mammography that uses a digital receptor instead of the conventional screen film method and produces computer generated images. It is used in screening services in several countries, but has only been recently introduced into Australia and is not yet widely available. It does not have major clinical advantages over conventional mammography in the diagnostic setting. However, in the screening setting it does detect additional cancers that are not visualised on conventional mammography.[6] The digital images can be manipulated on a computer screen, often allowing closer inspection of abnormal areas without the discomfort of additional images and additional radiation exposure.

Digital mammography has the potential to be used with computer software, generally known as 'computer aided detection' (CAD). It can 'read' the mammogram and identify areas of possible masses, distortion, and microcalcification, prompting the radiologist to examine these areas in detail. The CAD simply acts as a prompt, with final decision making as to the significance of the area identified resting with the radiologist. The CAD system may be used as a 'second read' in the screening setting, and in this context it has been shown (in trials) to identify a similar proportion of cancers as a film reader.[6] The use of CAD in screening is still under evaluation.

Table 1. Percutaneous core biopsy methods

- Conventional core biopsy
  - 14 gauge or 16 gauge core needles
  - automated biopsy device
  - provides thin strips of tissue for histological examination
- Large bore core biopsy
  - range of techniques to acquire increasingly larger samples of tissue
  - 11, 9 or 8 gauge core needles
  - some use a vacuum assisted core biopsy (VACB) device
  - allows a larger volume of tissue to be sampled for:
    - more accurate diagnosis
    - avoiding undersampling of the lesion (particularly important where there may be a spectrum of histological changes present)[2]
  - a localising clip may be placed at the site of the biopsy to aid in identifying the lesion for subsequent excision if most of it is removed at biopsy

Table 2. Advantages and disadvantages of axillary lymph node clearance surgery

Advantages	Disadvantages
Samples a large number of (or all) nodes and therefore accurately stages the axilla. Current 'gold standard'	Moderate to severe lymphoedema in 7% of patients (can be permanent and recurring)[12,13]
In most cases there is no need for further axillary treatment	Shoulder stiffness (usually temporary) Higher risk of side effects if combined with radiotherapy directly to the axilla
Allows radiotherapy to be limited to the breast	Neuralgia in distribution of intercostobrachial nerve or other sensory nerves (usually minor but can be severe)
Possible survival benefit (in node positive patients)	Possible injury to motor nerves during dissection (usually causes no physical disability)

Breast MRI

In the Australian context, dedicated breast magnetic resonance imaging (MRI) is not widely available. However, it is a useful imaging test in assessing the extent of disease in women with proven breast cancer. Studies have shown that breast MRI identifies additional sites of cancer (that are clinically and mammographically occult) in the same breast where a proven breast cancer has been diagnosed.[7] This is important as it can affect management of the

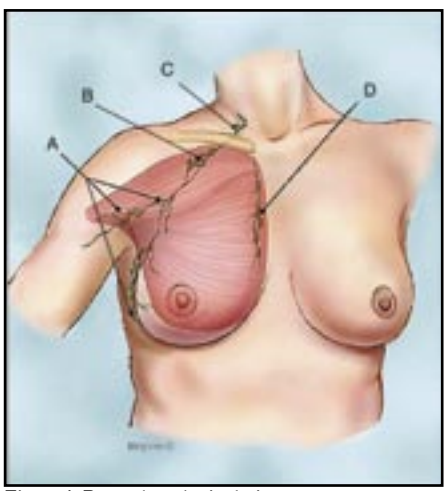

Figure 1. Breast lymphatic drainage
A. Axillary lymph nodes level I+II
B. Axillary lymph nodes level III (infra-clavicular)
C. Supraclavicular lymph nodes
D. Internal mammary chain (IMC) lymph nodes

patient. Breast MRI is also the imaging test of choice in women who require imaging to assess the integrity of their breast implants.

To date, several studies have shown that MRI is able to detect cancers not identified with mammography[6,8] in women with increased breast cancer risk on the basis of inherited gene mutations. This means that MRI has better sensitivity (though similar or lower specificity and may therefore cause additional false-positive results) than mammography in this group. However, it is unknown if this translates into benefit in the screening setting. Further studies are currently in progress to establish the role of MRI in surveillance of women with gene mutations. Magnetic resonance imaging is therefore not used in routine screening of women with gene mutations, and mammography remains the only standard screening test in all groups including those at increased risk.

The future

Although to date, advances in the detection and diagnosis of breast cancer have relied on conventional imaging and image based biopsy techniques, future technologies under different stages of development consist of a more varied approach. These include tumour biology based methods (such as identifying markers of cancer cells or the proteins that they secrete), ductal approaches (such as ductoscopy or ductal lavage), and functional imaging methods (which would have the advantage of identifying lesions that are likely to be clinically or biologically significant).

Surgical treatment

Axillary lymph node status is the most powerful predictor of a patient's prognosis and is important in determining adjuvant treatments. Removal of all (or most) of the axillary lymph nodes by axillary lymph node dissection (ALNDx) however, comes at a cost (*Table 2*), so techniques have been developed to allow accurate staging of axillary lymph nodes while minimising associated morbidity. There is minimal evidence so far that ALNDx has any survival benefit for node negative women. Some imaging techniques have been tested to determine their accuracy for the detection of nodal disease (eg. ultrasound and computerised tomography both have overall accuracies of <85%[10,11]) but none has proved reliable enough to allow treatment decisions to be made.

Table 3. Methods used to identify sentinel lymph nodes

Technique	Application
Lymphoscintography	Typically 20–40 MBq of technetium labelled colloid is injected peritumorally and the patient scanned for up to 3 hours. The radioactive material is trapped by draining lymph nodes resulting in 'hot spots'. These sites are then marked on the skin. Allows identification of extra-axillary sentinel lymph nodes, eg. internal mammary chain nodes (*Figure 1, 2*)
Intra-operative hand held gamma probe	Hand held gamma probe, eg. Navigator. Allows 'hot' nodes to be identified during dissection of the axilla or other anatomical sites (*Figure 3*)
Intra-operative blue dye (Patent blue V®)	Blue dye that is injected intra-operatively and taken up by lymphatic channels and nodes allowing their visual identification (*Figure 4*)

Sentinel lymph node biopsy

Sentinel lymph node biopsy (SLNBx) is a technique that has been used increasingly since its introduction 12 years ago. Although it is a technique that aims to accurately select patients who will benefit from ALNDx, its role in the staging and management of the axilla in women with breast cancer is still being defined. There are some controversial issues that remain unresolved, including patient selection, optimal mapping technique, and the management of micrometastatic disease. A number of randomised controlled trials investigating the role of SLNBx compared to ALNDx are being conducted around the world; the final results of which will not be available for another 5 years.

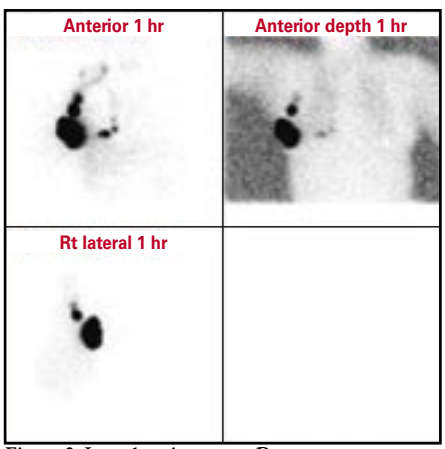

Figure 2. Lymphoscintogram. Demonstrates both axillary and internal mammary chain lymphatic drainage

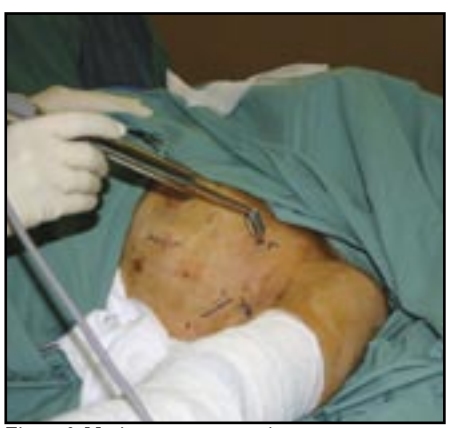

Figure 3. Navigator gamma probe

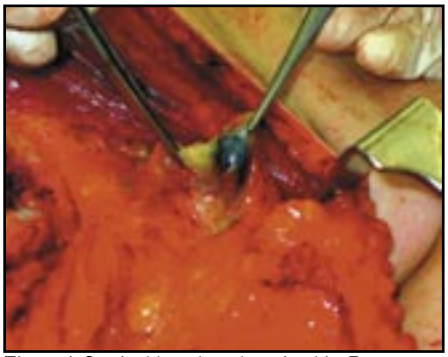

Figure 4. Sentinel lymph node stained by Patent blue V® dye

National Health and Medical Research Council guidelines recommend a level I/II ALNDx as the current standard treatment for the axilla in women with breast cancer.[9] Recently the breast section of the Royal Australasian College of Surgeons released a position statement saying that SLNBx can be offered to patients with unicentric tumours less than 3 cm in diameter following discussion of the implications of a false-negative result. Clearly management decisions on SLNBx should be made according to the individual clinical situation and with the woman fully informed by the surgeon providing care.

What is a sentinel node biopsy?

Sentinel node biopsy is a biopsy of the 'sentinel', or first draining ('guardian'), lymph node of a particular organ, in this case the breast. The technique works on the premise that the lymphatic drainage of the breast is reasonably constant, with the breast draining to axillary, supra- and infra-clavicular and internal mammary lymph nodes (*Figure 1*). When breast tumour cells escape into the breast lymphatics they will drain first to the sentinel node of the breast before spreading to other higher order nodes. Identification and examination of this sentinel node can determine its metastatic status, and this should accurately predict the status of the remaining axillary nodes.

To map the sentinel node, three different techniques are used. The combination of all three methods allows over 90% of sentinel nodes to be identified (*Table 3*). Once identified and removed, the sentinel node is subjected to a histopathological analysis that is more detailed than that of nodes retrieved from an axillary dissection specimen. This allows much smaller deposits of tumour (micrometastases – metastatic deposits <2 mm in diameter) to be identified than would be found on routine haematoxylin and eosin staining, therefore 'up staging' a proportion of patients. This clinical significance of micrometastases is uncertain.

False-negative results for SLNBx rates vary, but are typically in the 5–13% range.[14–18] A comparison of the advantages and disadvantages of SLNBx and ALNDx is shown in *Table 4*.

If a sentinel node is found to be involved with tumour, most surgeons would recommend complete axillary dissection either during the same operation or at a later stage. Patients with a 'negative' sentinel node enter a program of clinical observation of the axilla.

Table 4. Advantages and disadvantages of SLNBx compared with ALNDx

Advantages	Disadvantages
Low lymphoedema rate	False-negative rate 5–13% (fails to identify axillary metastatic disease)[14–18]
Less shoulder stiffness	Possible second operative procedure required if SLN is 'positive' for cancer
Shorter hospital stay	Allergic reaction to Patent blueV® dye (1–2% risk)
Allows detection of extra-axillary nodes not normally examined	Up to 13% of mapped sentinel nodes may not be identified at operation[16,17]

Radiotherapy

New technologies in breast radiotherapy have derived fundamentally from advances in computerisation. These advances have allowed increased sophistication, speed and accuracy in radiotherapy planning and treatment delivery. Most radiotherapy centres now plan breast radiotherapy by initially acquiring computerised tomography (CT) scan images of the breast with the patient in a reproducible treatment position. These images are transferred to a treatment planning computer, and allow the target volume (the breast) to be visualised in three dimensions. Radiotherapy beams are directed to the target, and the distribution of the radiotherapy dose within the breast calculated within minutes. Through a trial and error process of moving the angles of the beams and altering the weighting of radiation dose delivered by each beam, the optimal conformal plan is chosen.

Intensity modulated radiation therapy (IMRT) extends these principles, although it is still under evaluation for routine breast radiation treatment. It employs two main principles: inverse treatment planning, and changing the shape of the radiotherapy beam. Inverse treatment planning is when the radiation oncologist defines the target and the acceptable doses to surrounding structures, with the computer planning system then generating the optimal treatment plan. The shape of the radiotherapy beam may change during treatment by an individual field of radiation.

Both conformal radiotherapy and IMRT ensure the entire breast is uniformly irradiated to maximise the cosmetic outcome of the irradiated breast in the longer term. Local control may be improved as the target volume is more accurately defined. This is particularly so when additional radiotherapy is directed to the primary tumour bed (a 'boost'), as the surgical bed is generally clearly visualised on the CT scan. In addition,

radiation to the heart and lungs (dose limiting structures) can be either avoided or minimised. This has allowed radiotherapy to be delivered more safely, and may be a contributing factor to the survival advantage from postmastectomy radiotherapy seen in 'modern' randomised trials.

Another technological advance in the treatment of breast cancer has been the introduction of intra-operative radiation treatment.[19] This involves a single dose of radiation being given to the bed of the breast tumour at the time of initial resection. In principle, the radiation dose is targeted to the precise region of the breast at greatest risk of recurrence, and almost completely spares the surrounding heart and lung. This eliminates the need for a protracted course of daily outpatient radiotherapy and the associated disruption to a patient's life. Patients (and tumours) for whom this represents appropriate treatment remains to be clearly defined.

Conclusion

Breast cancer care has been enhanced by new technologies that have improved diagnosis, staging and therapy. The emerging trend is the incorporation of highly accurate and less invasive methods into diagnosis (core biopsy and dedicated breast ultrasound) and management options (sentinel node biopsy and conformal and intensity modulated radiation therapy). New technologies such as MRI in women with high risk continue to be evaluated in clinical research to identify their future role in breast practice.

Resources

Breast Cancer Institute website www.bci.org.au
A patient information sheet on sentinel node biopsy is available at www.bci.org.au/public/patientguides.htm
A short video of a sentinel node biopsy is available at www.bci.org.au/medical.htm (Quicktime 7 required)

Conflict of interest: none declared.

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