Management of early breast cancer

The current approach

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This seventh article in our series on breast disease will focus on what is new in the management of invasive primary breast cancer. Up-to-date information on the key aspects of breast cancer management is presented, including descriptions of the new technique of sentinel lymph node biopsy and the new hormone treatment, aromatase inhibitors. Current trends in surgery for breast cancer and the adjuvant treatments of chemotherapy and radiotherapy are also discussed.

While the incidence of breast cancer in Australia is increasing, mortality following breast cancer treatment is decreasing.[1] It is predicted that by 2006 there will be 12 500 patients with breast cancer diagnosed each year – or nearly 35 patients every day. We are therefore treating more breast cancer more successfully than ever before. This is due to the introduction of breast screening programs that have improved the early detection of breast cancer and advances in treatment.

Breast cancer – the definition

The term 'breast cancer' is used to describe invasive breast malignancy that has invaded beyond the basement membrane of the duct and therefore has the potential to spread to lymph nodes and other parts of the body.

Ductal carcinoma in situ (DCIS), or malignancy which is contained within the basement membrane of the duct, will be discussed in a future article in this series. It is thought that some, but not all, invasive carcinomas have progressed directly from DCIS (*Figure 1*).

Approach to the patient

Care of the patient with breast cancer has been influenced by the increasing trend toward patient centred holistic care. The woman newly diagnosed with breast cancer must be recognised as an individual, bringing her own ideas, experiences and needs to the crisis point of a breast cancer diagnosis. The patient and her family are encouraged to play an active role in making what are often difficult decisions. They are also encouraged to help plan treatment appropriate for the woman as an individual, rather than being passive participants receiving 'text book' treatment.

The specialist breast centre

Breast cancer is now recognised as a condition requiring a coordinated approach by a team of health professionals. Rather than being treated by a surgeon or oncologist alone, breast cancer is increasingly being treated by a multidisciplinary team, often consisting of a surgeon, radiation oncologist, medical oncologist, pathologist, breast physician, breast care nurse and allied health professionals. The team may also include a counsellor, psychologist, plastic and reconstructive surgeon, fertility specialist, and geneticist. The general practitioner plays a crucial role in supporting and educating the patient, and helping negotiate the health care system. The GP can also provide unique insight into the likely impact of the illness on the patient in the context of her individual medical and psychosocial situation.

Evidence has shown that patients who are treated by surgeons with a minimum caseload of 20 breast cancer patients each year have better survival than those who are treated by surgeons who see fewer cases. This evidence reinforces the specialised nature of breast surgery. Patients

treated by a specialist breast surgeon are more likely to have breast conserving surgery, and are more likely to receive adjuvant treatments such as radiotherapy.[2] There is also recent evidence suggesting that patients treated in rural areas are more likely to require further surgery after initial breast conserving surgery.[3]

This evidence suggests that an organised approach by a specialised team of clinicians who communicate well with each other benefits the patient.

The diagnosis and treatment of breast cancer is complex and involves balancing the needs of the patient, the options available based on the presenting stage of the disease, and considerations such as logistics, costs, complications of therapy and treatment outcomes. This article focusses on 'early' breast cancer, defined as stage I (localised to the breast and under 2 cm in size) or stage II (localised to the breast and between 2–5 cm) or a tumour (under 5 cm and with disease in the axilla. Locally advanced breast cancer and metastatic breast cancer will be covered in future articles in this series.

Treatment for breast cancer broadly involves three key components:

- Treatment of the breast:
  - breast conservation surgery + radiotherapy
  - vs. mastectomy +/- radiotherapy +/- breast reconstruction
- Assessment and treatment of regional lymph nodes, eg. the axilla:
  - axillary clearance vs. sentinel node biopsy vs. a combination of both techniques
  - in some older patients there may be options of observation or radiation, and
- Systemic treatment:
  - hormone therapy: tamoxifen, aromatase inhibitors, ovarian suppression
  - chemotherapy
  - new treatments such as monoclonal antibodies.

Almost all patients with breast cancer have treatment to the breast and axilla, and all should also routinely be considered for systemic treatment. The appropriateness of systemic treatment is determined by considering:

- patient factors (eg. age, menopausal status, general health, patient preference)
- features of the tumour (eg. pathological tumour size, nodal status, histologic grade, receptor status), and
- treatment factors (eg. proximity of facilities).

Treatment of the breast

Breast conservation surgery + radiotherapy

Breast conservation surgery (also referred to as lumpectomy or wide local excision) is the treatment preferred by most women, with approximately 70% with stage I or II disease being treated with conservation rather than mastectomy.[3,4]

Breast conservation surgery should be considered as the first step in a two-step treatment, almost always followed by radiotherapy to the breast. Numerous trials confirm that this combined treatment results in the same overall survival as total mastectomy. The breast is preserved, and with appropriate selection criteria, the risk of a recurrence of tumour in the breast is about 5% at 5 years and 10% at 10 years of follow up. The few patients who have a tumour recurrence in the breast undergo a 'salvage' mastectomy. The overall local control rates are identical for patients who choose mastectomy or breast conservation with equivalent survival rates. Patients treated with breast conservation surgery without radiotherapy have a local recurrence rate of at least 30% at 5 years, but this is lower (around 20%) for patients with smaller tumours with good clear margins.[5] Avoiding radiation may be associated with a lower survival due to the high risks of local recurrence.[6,7]

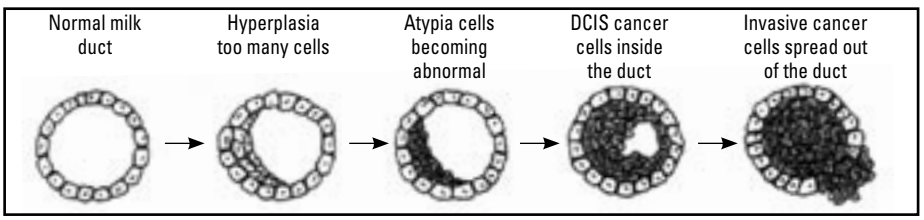

Figure 1. Progression from normal duct to DCIS to invasive carcinoma

Radiotherapy to the breast following surgery usually consists of daily treatment at a hospital for a period of up to 6–7 weeks. This may make it an impractical option for some patients, with some choosing mastectomy over breast conservation, even if they have a small tumour that would otherwise be suitable for conservation. Breast conservation is generally contraindicated for women who have:

- large tumours in relation to the size of the breast
- multicentric disease, or
- recurrent disease following previous radiotherapy.

It is also relatively contraindicated in women with severe collagen vascular disorders as radiotherapy may have a poorer cosmetic outcome in these patients.

Mastectomy (+/- radiotherapy/ breast reconstruction)

Mastectomy may be performed in cases where breast conservation is not possible or is not desirable (*Table 1.*) In patients with large or multicentric tumours, mastectomy may be the only option for local control. In addition, many women with early breast cancer who would be suitable for breast conservation also choose to undergo mastectomy. While mastectomy may have a greater negative impact on a woman's body image, patients who undergo mastectomy may have less anxiety about their cancer recurring than women who have breast conservation.[8]

Most patients who are treated with mastectomy could be offered breast reconstruction. Reconstruction may be performed as an immediate procedure at the time of the mastectomy, or as a delayed procedure. In New South Wales, the rate of breast reconstruction following mastectomy is 5%,[4] although the rate may be much higher in specialised breast units that routinely offer breast reconstruction to all patients undergoing mastectomy.

In general, women who undergo mastectomy for breast cancer treatment do not require postoperative radiotherapy.However, for women at high risk of recurrence, postmastectomy radiotherapy has been shown to reduce the risk

of local recurrence and improve overall survival.[9] Postmastectomy chest wall radiotherapy is usually recommended for patients with tumours greater than 5 cm (T3) or when four or more axillary lymph nodes are involved. There is also emerging evidence that postmastectomy radiotherapy may improve survival for some women with 1–3 involved nodes in the axilla.[10]

Assessment and treatment of the axilla

Assessment of the axilla is a critical part of breast cancer management as it provides valuable staging information. Axillary nodal status (ie. whether or not disease has spread to the axillary lymph nodes) is a critical prognostic feature as it is a powerful predictor of survival, independent of tumour size and grade.[11] Axillary status is also one of the major factors in determining whether systemic treatment such as chemotherapy is recommended. There is increasing evidence that maximising control of cancer locally (ie. in the breast and axilla) not only reduces the risk of local recurrence but also improves overall survival.[6]

There are several options for managing the axilla in patients with breast cancer:

- axillary lymph node dissection (ALNDx)
- sentinel lymph node biopsy (SLNBx)
- combination of ALNDx + SLNBx
- axillary radiotherapy (alone, or in combination with SLNBx or ALNDx)
- observation.

Axillary dissection

Axillary dissection (axillary clearance) is the traditional operation offered to manage the axilla in the patient with invasive breast cancer. Surgical techniques vary, however all aim to remove all or nearly all of the accessible axillary lymph nodes. This has two benefits:

- staging the axilla: NHMRC guidelines recommend a level I+II axillary node clearance.[12] In a level III axillary clearance an average of 25 lymph nodes are retrieved.[13] This large number of nodes obtained with axillary clearance provides a good sample size for assessing the extent of disease in the axilla, and
- treating the axilla: axillary clearance is often adequate treatment for the axilla even when lymph nodes are involved with tumour. A patient who has had a complete (level III) axillary clearance will often not require further local treatment to the axilla.

However, there remain a number of patients with node positive disease following axillary dissection that require radiotherapy to the axilla.

Axillary clearance, while being excellent for staging and treatment, has some disadvantages. Moderate to severe lymphoedema occurs in up to 7% of patients, and it may cause significant morbidity. A further 20–25% of patients will be troubled by mild to moderate lymphoedema. Other adverse effects include numbness in the distribution of the intercostobrachial nerve affecting the upper arm, and stiffness of the shoulder.[13]

Sentinel lymph node biopsy

Sentinel node biopsy is now considered the standard of care for women with a small early invasive breast cancer (see Part six of this series, August). The technique aims to identify and remove the first draining lymph node or nodes, and predict whether tumour involves lymph node basins away from the breast. It is assumed that patients who have a sentinel node clear of tumour will also have no tumour in the remaining axillary nodes, and that these remaining nodes will therefore not require removal. In this regard, SLNBx may be considered a test to assess whether or not a patient would further benefit from complete axillary dissection, thereby sparing the majority of women who are lymph node negative from the possible morbidity associated with full axillary clearance.

Axillary radiotherapy

Axillary radiotherapy may be used:

- alone: for patients who are poor candidates for surgery or who do not want surgery
- following a positive SLNBx: if a second operation (axillary clearance) is an undesirable option
- following ALNDx if there is extensive extra-nodal extension of disease in the axilla which cannot be completely removed with surgery alone.

Axillary radiotherapy has the adverse effects of lymphoedema and radiation to the adjacent lung field. The rate of lymphoedema following axillary radiotherapy alone is approximately the same as that following axillary clearance (~7%); the rate of lymphoedema following the combination of axillary clearance and axillary radiotherapy is much higher, approaching 30%.[14] Radiotherapy to the lung is associated with 'pneumonitis' in 1–2%, and this occurs 6 weeks to 6 months after treatment. Symptoms include shortness of breath, cough, and significant lethargy, which are helped with antibiotics and short term prednisone.

Table 1. Indications for mastectomy in patients with early breast cancer

- Patient preference: patient prefers a mastectomy over conservation and radiation therapy
- Large tumour relative to the size of the breast: tumour is too large to excise adequately and obtain reasonable cosmesis
- Multicentric tumour: two or more separate foci of cancer in different quadrants of the breast
- Recurrent cancer after previous breast conservation: previous radiation therapy treatment
- Pregnancy (first or second trimester): radiotherapy contraindicated
- Radiotherapy inaccessible

Observation of the axilla

Observing the axilla rather than sampling or treating it is an uncommon approach, usually reserved for cases of extremely small, early cancers in elderly patients with comorbidities that make surgery or radiotherapy difficult. Patients with DCIS do not require treatment of the lymph glands.

Systemic treatment

Despite excellent local therapy and the removal of all macroscopic disease, there remains a risk of distant relapse (metastatic disease) that is potentially treatable but ultimately fatal. The risk of relapse partly depends on identifiable tumour characteristics such as size and grade, and whether or not there were involved lymph nodes (*Table 2*).

In theory, administering drugs that can kill breast cancer cells after surgery should remove most or all of any remaining malignant cells (wherever they are) and thus prevent or delay such recurrence. There is now overwhelming evidence from 3 decades of randomised trials that this is the case. In summary:

- in women with either hormone receptor positive or negative disease, some months of chemotherapy will reduce the risk of recurrence and death
- in women with hormone receptor positive disease, some years of endocrine therapy will reduce the risk of recurrence and death
- in women with hormone receptor positive disease, better results are seen with a combination of chemotherapy and endocrine therapy than with either modality alone
- these advantages are still apparent after 20 years follow up.

Chemotherapy

Chemotherapy for breast cancer may be adjuvant (following surgery) or neo-adjuvant (before or instead of surgery.) In general, neo-adjuvant chemotherapy is reserved for cases of locally advanced or inflammatory breast cancer. In this article we will focus on adjuvant chemotherapy.

Chemotherapy is a toxic treatment, and is not appropriate for all patients. A balancing act is required, taking into consideration factors such as:

- the risk of relapse
- how much difference chemotherapy will make
- patient preference.

For example, if a woman has a cancer with many of the adverse features listed in *Table 2*, the chance of being alive and cancer free after 10 years is less than 50%. In women under the age of 50 years, chemotherapy will roughly halve the risk of relapse and therefore make a big difference to those at high risk.

However a small, low grade tumour with no involved nodes might be associated with a greater than 90% chance of remaining cancer free at 10 years, and chemotherapy would make such a small difference that it is probably not worthwhile.[15]

A number of chemotherapy combinations are known to be effective (*Table 3*). Cyclophosphamide, methotrexate, and fluorouracil (CMF) was the regimen first shown to be effective. It is now known that regimens containing anthracyclines (adriamycin or epirubicin) are on average a little better than CMF, although they cause more alopecia. The taxanes (paclitaxel and docetaxel) are active in metastatic disease and are being tested in the adjuvant setting. In general, the more drugs that are given, and the closer a patient is to 40 years of age, the higher the chance of early menopause and infertility.

All of these regimens cause reversible myelosuppression and alopecia. Nausea and vomiting are much less prominent side effects than they used to be because of improvements in anti-emetic therapy.

Endocrine therapy

Because it is very effective and reasonably nontoxic, endocrine therapy should be considered for all patients who have a tumour that expresses oestrogen or progesterone receptors (ie. ER or PR positive cancer). While a small proportion of women may have very low risk breast cancers not requiring any systemic therapy (eg. <10 mm in size and low grade), all others would be encouraged to have endocrine therapy either alone (moderate risk) or after some adjuvant chemotherapy (high risk). In younger women, oestrogen is mainly produced by the ovary, but in older women small amounts of oestrogen are produced by the adrenal glands, and in fat and muscle.

Endocrine therapy is aimed at reducing the oestrogen available to tumour cells (*Table 4*). This may be done by:

- giving an agent that blocks the oestrogen receptor (eg. tamoxifen for either premenopausal or postmenopausal women)
- reducing the level of oestrogen in the blood (ovarian suppression in premenopausal women, aromatase inhibitors in postmenopausal women).

Tamoxifen has been the standard hormonal treatment for breast cancer for many years and is known to be effective and safe. There is however, a slightly increased risk of endometrial cancer and venous thrombosis (both about 1 extra case per 1000 women treated per year). Much of the thrombosis risk can be avoided by stopping tamoxifen around the time of surgery or trauma.

Table 2. Features associated with higher risk of breast cancer relapse[15]

Axillary lymph node metastases
Large tumours (>2 cm)
High grade tumours
Young women (<35 years of age)
Hormone receptor status, eg. ER-ve/ PR-ve tumours
HER-2 receptor positive tumours

Aromatase inhibitors act by blocking aromatase (the enzyme that converts testosterone to oestrogen in peripheral tissues such as muscle and fat) and are effective only in postmenopausal women There are three medications in this class of drug:

- anastrazole (Arimidex®)
- letrozole (Femara®)
- exemestane (Aromasin®).

Recent trials show that aromatase inhibitors are more effective than tamoxifen in preventing breast cancer relapse. They also do not increase the risk of endometrial cancer or venous thrombosis, but do reduce bone mineral density, increasing the risk of fractures. It is not yet clear whether reduced relapse rates will translate into improved survival. The drugs are well tolerated and likely to become standard therapy in the future.[16]

Ovarian suppression is also an effective adjuvant hormonal therapy for women with hormone receptor positive breast cancer. On its own, it is about as effective as older style chemotherapies such as CMF. It is not yet clear whether it is as effective as newer chemotherapy combinations, especially when tamoxifen is added. For these reasons, ovarian suppression (eg. temporary suppression with drugs such as goserelin [Zoladex]) is not standard therapy and is not funded by the PBS for early breast cancer. However, laparoscopic removal of the ovaries is a useful treatment, particularly for women who are approaching menopause.

Table 3. Chemotherapy regimens commonly used in Australia

CMF	cyclophosphamide, methotrexate, fluorouracil
AC	doxorubicin, cyclophosphamide
AC then P	doxorubicin, cyclophosphamide followed by paclitaxel
FEC	fluorouracil, epirubicin, cyclophosphamide
FAC	fluorouracil, adriamycin, cyclophosphamide
CEF	cyclophosphamide (oral), epirubicin, fluorouracil

Table 4. Comparison of tamoxifen and aromatase inhibitors[16]

Tamoxifen	Aromatase inhibitors
Only works in tumours that are ER or PR positive	Only works in tumours that are ER or PR positive
Pre- and post-menopausal women	Postmenopausal women only
Increased risk of endometrial cancer	Reduced risk of endometrial cancer
Increased risk of DVT	Reduced risk of DVT
Hot flushes common	Hot flushes less common
Increased vaginal discharge	Increased vaginal dryness
Improves bone mineral density	Reduces bone mineral density

'Biological' therapies

Treatments that target receptors other than hormone receptors are in various stages of development. Trastuzumab (Herceptin), a monoclonal antibody directed at a cell surface receptor called HER-2 is active in breast cancer and is available in Australia for women with metastatic breast cancer. About 20% of breast cancers overexpress this receptor, and new studies suggest that for women with this subtype of breast cancer, the use of Herceptin in early breast cancer reduces cancer relapse over and above the effects of chemotherapy and endocrine therapy.[17] More information and decisions about funding are necessary to further investigate Herceptin therapy.

Conclusion

Clinicians managing breast cancer have an ever increasing armoury of treatments available to them. The main areas of change over recent years have been the development of sentinel node biopsy for managing the axilla, and the use of aromatase inhibitors as adjuvant hormonal treatment.

There is a trend toward treating patients in multidisciplinary treatment centres with a patient centred approach. This approach encourages women to be involved as an active member of the management team, helping to formulate an individualised treatment plan. The GP is often the crucial link between the patient, her family and the breast cancer treatment team.

Conflict of interest: none declared.

References

1. Australian Institute of Health and Welfare and Australasian Association of Cancer Registries. Cancer in Australia 2001. Canberra: AIHW, 2004.
2. Ingram DM, McEvoy SP, Byrne MJ, Fritschi L, Joseph DJ, Jamrozik K. Surgical caseload and outcomes for women with invasive breast cancer treated in Western Australia. Breast 2005;14:11–7.
3. Spilsbury K, Semmens, JB, Saunders CM. Subsequent surgery after initial breast conserving surgery: a population based study. Aust NZ J Surg 2005;75:260.
4. Boyages J, Jayasinghe U, Heard G, et al. The management of breast cancer in New South Wales in 1995. New South Wales Breast Cancer Institute: Sydney, 2004.
5. Fisher B, Anderson S, Bryant J, et al. Twenty year follow up of a randomised trial comparing total mastectomy, lumpectomy, and lumpectomy plus eradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–41.
6. Shukla HS, Melhuish J, Mansel MS, Hughes LE. Does local therapy affect survival rates in breast cancer? Ann Surg Oncol 1999;6:455–60.
7. Vinh-Hung V, Verschraegen C. Breast conserving surgery with or without radiotherapy: pooled analysis for risks of ipsilateral breast tumour recurrence and mortality. J Natl Cancer Inst 2004;96:115–21.
8. Fallowfield L, Hall A, Maguire GP, Baum M. Psychological outcomes in women with early breast cancer. BMJ 1990;301:1098.
9. Overgaard M, Hansen P, Overgaard J, et al. Postoperative radiotherapy in high risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med 1997;337:949–55.
10. Pierce LJ. The use of radiotherapy after mastectomy: a review of the literature. J Clin Oncol 2005;23:1706–17.
11. Fisher B, Bauer M, Wickerham DL, et al. Relation of the number of positive axillary nodes to the prognosis of patients with primary breast cancer. An NSABP update. Cancer 1983;52:1551–7.
12. National Breast Cancer Centre Early Breast Cancer Working Group. Clinical practice guidelines: management of early breast cancer. Canberra: 2001.
13. Silberman AW, McVay C, Cohen JS. Comparative morbidity of axillary lymph node dissection and the sentinel lymph node technique. Ann Surg 2004;240:1–6.
14. Boyages J, Barraclough B, Middledorp J, Gorman D, Langlands AO. Early breast cancer: cosmetic and functional results after treatment by conservative techniques. Aust NZ J Surg 1988;58:111–21.
15. EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15 year survival: an overview of the randomised trials. Lancet 2005;365:1687–717.
16. Winer EP, Hudis C, Burstein HJ, et al. American society of clinical oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor positive breast cancer: status report 2004. J Clin Oncol 2005;23:1–11.
17. American Society of Clinical Oncology. Conference Presentations, Orlando 2005.

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