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Early breast cancer

New developments in diagnosis and treatment

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Early (curable) breast cancer is the focus of this first article in a three-part series discussing important advances in the diagnosis and treatment of breast cancer. Subsequent articles will cover locally advanced and metastatic breast cancer, updated diagnostic tools, psychosocial care and risk factor modification.

Key points

- **The aim of treatment for early breast cancer is cure.**
- **Surgery is the mainstay of treatment, and adjuvant therapy may be added to reduce the risk of recurrence.**
- **Completion axillary dissection may not be required in all patients with one or two positive sentinel nodes but investigations are ongoing.**
- **Using intensity-modulated radiation therapy in whole breast radiotherapy improves the accuracy and homogeneity of radiation dose delivery.**
- **Molecular genetic profiling of breast cancer helps determine treatment, particularly chemotherapy in addition to hormone therapy.**
- **Trastuzumab, a monoclonal antibody to the HER2 receptor, is effective in women with HER2-positive breast cancer.**
- **Tolerance of treatment, particularly chemotherapy, is improving.**

In a recent overview, the Early Breast Cancer Trialists' Collaborative Group reported a halving of breast cancer mortality rates over the past 20 years.[1] This has been achieved through a series of progressive small gains, which add up to the substantial change in outcome despite increased prevalence due to the detection of more small, curable cancers through population screening.

This first article of a three-part series discussing important advances in the diagnosis and treatment of breast cancer will consider the management of early (curable) breast cancer. Subsequent articles will cover locally advanced and metastatic breast cancer, updated diagnostic tools, and psychosocial care and risk factor modification in the growing number of breast cancer survivors.

The aim of treatment in early breast cancer, defined as cancer that has not spread beyond the breast or axillary lymph nodes (stages I and II), is cure. This cure is achieved with a combination of surgery and adjuvant therapies. Adjuvant therapy may include chemotherapy, radiotherapy, hormone therapy and targeted, or biological, therapies and reduces the risk of recurrence by eliminating micrometastases. Neoadjuvant therapy, where the 'extra' treatments are given before surgery, is becoming increasingly popular worldwide, but in

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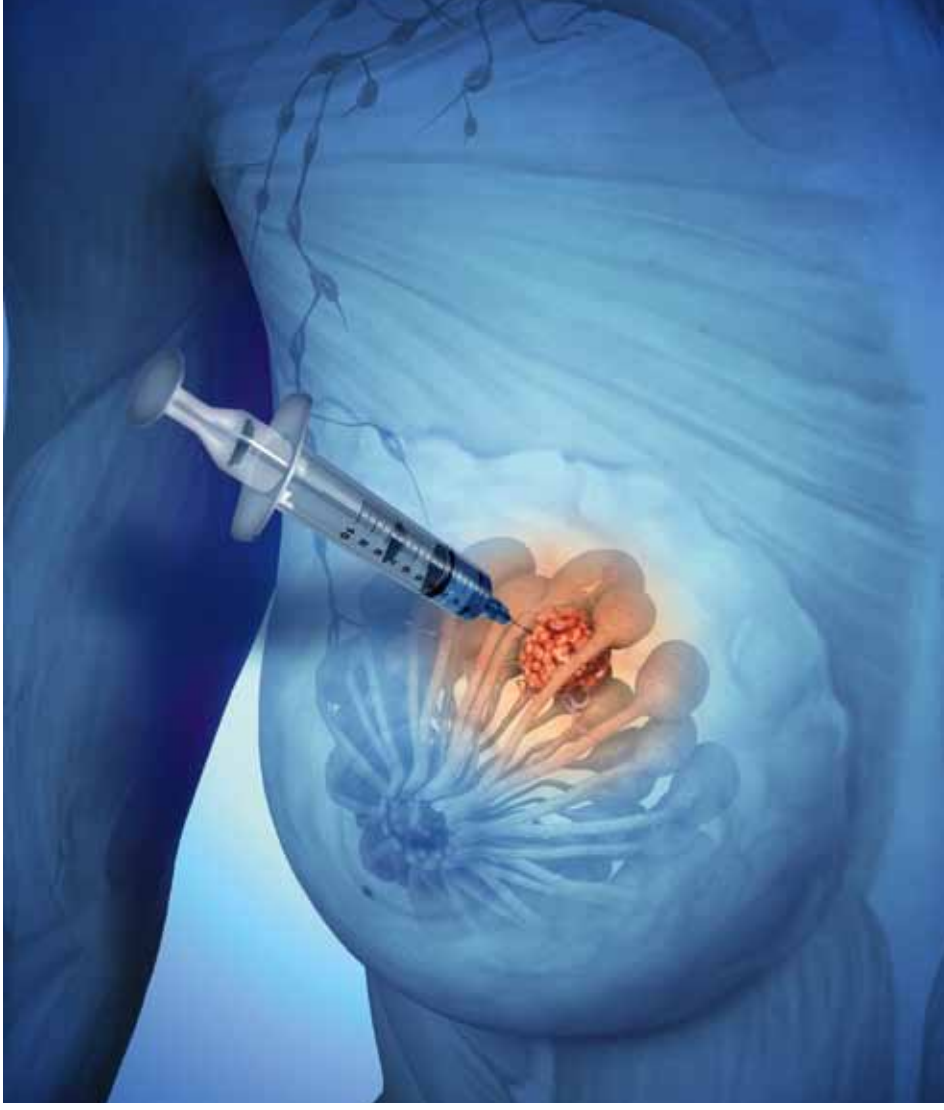

EARLY BREAST CANCER: ADVANCES IN DIAGNOSIS AND MANAGEMENT*

- Molecular genetic profiling and better understanding of the behaviour of breast cancer subtypes
- Improved risk assessment and tailoring of treatment
- Selective management of axillary lymph nodes
- Improvement in the accuracy and homogeneity of radiation dose delivery
- Monoclonal antibody to HER2 receptor (trastuzumab)
- Better tolerance of treatment, particularly chemotherapy

* Significant advances over the past decade; the order reflects the patient journey.

Australia is usually reserved for patients with locally advanced breast cancers.

Many consensus guidelines are available for management.[2,3] These recommend that all patients are discussed at a multidisciplinary meeting, where pathology results are reviewed and treatment recommendations are made by teams of medical, nursing and allied health experts. As with all cancers, management plans depend on both tumour and patient factors. Information for health professionals and for patients and carers is abundant, although access for non-English speaking patients and other groups such as Indigenous women still requires improvement. Men with breast cancer are treated similarly to women, although testing for the *BRCA* genes (the breast cancer susceptibility genes) should be considered in all such men.

Significant advances in the diagnosis and management of early breast cancer in the past 10 years are listed in the box on this page.

MOLECULAR PROFILING AND BREAST CANCER SUBTYPES

Molecular profiling of tumour samples has confirmed that breast cancer can no longer be considered and treated as a single disease entity. The receptor status of a breast cancer helps determine its targeted treatment: only endocrine-sensitive cancers can be effectively treated with hormone therapies such as tamoxifen and the aromatase inhibitors. Traditionally, the status of each receptor – the oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) – is determined separately by immunohistochemistry.

The recently developed technology of molecular profiling of tumour samples allows categorisation of breast cancers into molecular subtypes with distinct clinical outcomes, and is increasingly being used to determine treatment. Molecular profiles give gene expression data on many thousands of genes that cluster broadly into the five groups called luminal A, luminal B, claudin-low, HER2-enriched and basal-like (Table).[4] Modified profiles are available commercially (multigene assays) and increasingly used internationally, tailored towards examining genes that are predictive for benefit from adjuvant chemotherapy in addition to hormone therapy, and predicting patients who will derive little additional benefit from chemotherapy. Molecular profiling is increasingly being offered in Australia but is not yet government funded.

TABLE. MOLECULAR SUBTYPES OF BREAST CANCER[4]

Breast cancer molecular subtype	Immunohistochemistry staining		% of breast cancers	Prognosis
	ER	HER2		
Luminal A	Strong	Weak	40	Best
Luminal B	Weak	Moderate	20	Good
Claudin-low	Nil	Nil	12 to 14	Intermediate
HER2-enriched	Nil	Strong	10 to 15	Poor
Basal-like	Nil	Nil	15 to 20	Worst

ABBREVIATIONS: ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2.
Adapted from Prat et al. *Breast Cancer Res* 2010; 12: R68.[4]

BREAST SURGERY

Standard breast-conserving treatment for patients with invasive cancer involves excision of the primary cancer with negative histological margins, followed by adjuvant whole breast radiotherapy. The operation is called a wide local excision by some surgeons; others use the term partial mastectomy. It results in equivalent overall survival to a total mastectomy, and is therefore an option available to most patients unless the extent of disease, multifocality, size of breast or patient preference means that breast conservation is not possible or optimal.

There has been a trend over recent years, particularly in the USA, for increased mastectomy by choice and also contralateral prophylactic mastectomy. These mastectomies are not always justifiable on risk and sometimes the consequence of the patient being misinformed.

AXILLARY SURGERY

The surgical management of the axilla in patients with early breast cancer has been revolutionised over the past 20 years. The technique of lymphatic mapping and sentinel node biopsy uses tracers to identify and remove the first draining lymph node. Sentinel node biopsy is safe and effective in most patients with early breast cancer, with randomised trials demonstrating very low regional recurrence, no difference in overall survival and significantly reduced morbidity compared with full axillary dissection.[5-8] It has become standard of care for most patients whose lymph nodes are clinically negative (not palpable and not enlarged on imaging). The question of whether it is appropriate for very large and/or multifocal cancers is still the subject of clinical trials.

When the sentinel node is found to be involved with cancer, the standard treatment is to recommend completion axillary dissection. However, from observations that the sentinel node is very often the only involved lymph node, selective node dissection has been investigated. Results of a randomised trial have suggested that completion nodal dissection is not routinely required.[9,10] This is an area of continuing debate and investigation.

Other trial results that have challenged clinical practice include the following:

- micrometastases (2 mm or less in diameter) and isolated tumour cells (0.2 mm or less in diameter) in the sentinel node have minimal impact on outcome with modern adjuvant therapies[11]
- completion axillary dissection may not be required when the sentinel node involvement is limited to micrometastases[12]
- completion axillary dissection may not be required in all patients with one or two positive sentinel nodes but investigations are ongoing.[9,10]

Nomograms may be used to predict the likelihood of involvement of non-sentinel nodes.[13,14]

BREAST RECONSTRUCTION

The quality of life of many patients with breast cancer is enhanced by attention to the cosmetic outcome. Breast surgical techniques have been modified to improve this (so-called 'oncoplastic' breast cancer surgery), and reconstruction techniques have also advanced significantly.

Breast reconstruction after mastectomy can be performed either during the same anaesthetic (immediate breast reconstruction) or as a delayed procedure at any interval after all cancer treatments are complete (delayed reconstruction). For many years there has been a tendency for patients with higher risk breast cancer to avoid immediate reconstruction because of concerns that reconstruction might impair the ability to deliver adjuvant treatment. Although this remains controversial and appropriate patient selection is important, there is increasing evidence that immediate reconstruction is a reasonable option even when adjuvant therapy is required.

The range of reconstruction options, using either a prosthesis or autologous tissue, has increased. Skin can be removed

as part of the mastectomy or skin can be spared, and in some cases the nipple–areolar complex can also be safely spared. Prosthetic reconstruction usually involves placing a tissue expander after the mastectomy, and replacing it later with a silicone prosthesis. Autologous tissue uses fat, with or without skin and/or muscle, from another part of the body. The advantages and disadvantages of the various reconstructive options are summarised in the box on this page.

ADJUVANT THERAPY

Adjuvant therapy aims to add to definitive breast cancer treatment (surgery) to reduce the risk of both local recurrence (in the remaining breast or on the chest wall) and distant metastases in patients who have a high risk of occult disease (micrometastases). The rationale comes from many trials of various adjuvant therapies versus observation, showing a decrease in recurrence and/or death when the additional therapy is used.

Adjuvant therapies used in early breast cancer include:

- radiotherapy – mainly to reduce the risk of local recurrence
- hormone therapy – also known as endocrine therapy, and different to hormone replacement therapy
- chemotherapy and/or biologically targeted treatment – to reduce systemic recurrence and death.

Adjuvant radiotherapy

Radiotherapy after breast-conserving surgery

Randomised trials with follow-up periods of longer than 20 years have established the equivalence of breast-conserving surgery plus radiotherapy to mastectomy in terms of survival, and have confirmed a substantial decrease in the risk of local recurrence with radiotherapy. In addition, radiotherapy to the conserved breast halves the rate of any (i.e. local, regional or distant) disease recurrence and reduces the breast cancer death rate by one-sixth.[16] These proportional benefits from radiotherapy vary little between different patient subgroups. However, the absolute benefits for individual patients vary substantially according to their baseline recurrence risk without radiotherapy. Trials are ongoing to determine whether radiotherapy may be avoided in very low risk groups (for example, elderly patients with small cancers).

Whole breast radiotherapy has evolved from the use of two opposed tangential radiation fields to encompass the breast, to intensity-modulated radiation therapy, which improves the homogeneity of radiation doses delivered to the breast and decreases radiation exposure of the heart and lungs. Treatment planning using computed tomography is standard. These improvements will likely reduce the adverse effects, particularly the late effects of radiation.

Conventional whole breast radiotherapy is spread out (fractionated) over a five-week period, using a dose of 2 Gray per daily treatment (fraction) for five days of each week (fractionation schedule) to a total dose of 50 Gray. The regional lymph nodes may be included for higher risk patients (both after breast-conserving surgery and mastectomy).

Hypofractionated radiotherapy is characterised by delivery of fewer fractions of larger daily doses over a shorter overall duration, with a reduction in the total dose to avoid an increase in late toxicity. An accepted hypofractionated schedule for whole breast radiotherapy involves delivery of a total dose of 42.5 Gray in 16 daily fractions over 22 days. Reducing the number of treatments and time required improves patient convenience and potentially decreases treatment costs. Randomised trials with long-term follow up have shown similar rates of local recurrence, survival and cosmetic outcome for patients treated with hypofractionated radiotherapy and conventionally fractionated radiotherapy.[17-19] Thus, hypofractionated whole breast radiotherapy may be a suitable alternative to conventionally fractionated radiotherapy. It is likely to be more broadly adopted when additional supporting results from longer term follow-up of clinical trials are available.

Another change under investigation in breast radiotherapy is the use of partial breast irradiation targeting the tumour bed only, using a range of techniques.

Great interest and research efforts are being directed at defining patient subgroups who benefit or do not benefit significantly from radiotherapy, particularly using analysis of tumour genes and other molecular factors.

Radiotherapy after mastectomy

Postmastectomy radiotherapy is recommended in patients with four or more pathologically involved axillary lymph nodes or a primary tumour more than 5 cm in diameter, for substantial gains in local control and survival. Uncertainty

BREAST RECONSTRUCTIVE OPTIONS: ADVANTAGES AND DISADVANTAGES

Prosthesis

- Advantages
  - Quicker operation
  - Shorter hospital admission
  - Better results for smaller breasts
  - Option for patients with no significant abdominal fat
- Disadvantages
  - Rarely matches texture of normal breast
  - Contraction means revisional surgery may be required

Autologous tissue reconstruction

- Advantages
  - Good for patients with excess abdominal fat
  - Able to reconstruct larger breasts
  - Less distinguishable from normal breast
  - Often no revisional surgery required
- Disadvantages
  - Long and complex surgery
  - Longer hospital admission

EARLY BREAST CANCER: FACTORS IN ADJUVANT THERAPY DECISION-MAKING

Cancer factors
- Pathological size
- Grade
- Receptor status (ER, PR, HER2)
- Lymph node status
- Lymphovascular invasion
- Molecular genetic assay predicting recurrence
- Germline gene mutation (*BRCA1* and *BRCA2*)

Patient factors
- Age
- Comorbidities
- Fertility desires
- Social circumstance (geographical location, support)
- Access to clinical trial
- Long-term treatment toxicity
- Finances and drug access (for non-standard treatment)

ABBREVIATIONS: ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor.

remains about the benefits in patients at intermediate risk of recurrence (one to three involved nodes and primary tumour 2 to 5 cm in diameter, with additional risk factors such as high grade or presence of lymphovascular invasion).

Adjuvant systemic therapy

Hormone therapy

Hormone therapy is only effective for patients with oestrogen receptor-positive (ER+) and/or progesterone receptor-positive (PR+) cancers (i.e. endocrine-sensitive cancers), as determined by immunohistochemical testing. The benefit may vary with the degree of ER or PR staining in the tumour on testing, but it is known that even patients with minimal (but present) staining benefit.

Hormone therapy reduces the risks of recurrence of and death from the diagnosed cancer as well as reducing by 50% the chance of a future new ER+ breast cancer. The magnitude of the risk reduction using hormone therapy depends on the risk of cancer recurrence and needs to be weighed up against potential side effects. Because of fears that its effects on the cell cycle could reduce the efficacy of chemotherapeutic agents, hormone therapy is started after completion of any chemotherapy. However, it can be safely used concurrently with radiotherapy.

Clinical research in progress on adjuvant hormone therapy is directed at:
- how much premenopausal women benefit from ovarian ablation (using luteinising hormone-releasing hormone [LH-RH] analogues [reversible] or surgical oophorectomy) in addition to tamoxifen
- how long hormone therapy should be continued. Tamoxifen was traditionally stopped after five years of use because of the (very slightly increased) risk of uterine cancer, but this is not relevant to aromatase inhibitors. Recent trials confirm benefit in continuing hormone therapy beyond five years, but in any individual this needs to be weighed against the risk of adverse effects.

The available hormone therapies are the selective oestrogen receptor modulator tamoxifen and the aromatase inhibitors.

Tamoxifen. In the past tamoxifen was used for the treatment of breast cancer in both premenopausal and postmenopausal women, resulting in a 26% reduction in mortality and up to 47% reduction in local recurrence at 10 years.[20] It is still the only hormone therapy for premenopausal and perimenopausal women, in whom aromatase inhibitors are absolutely contraindicated (unless ovarian ablation is used; see the following section on aromatase inhibitors), and remains an option for postmenopausal women, particularly for those with low risk cancers or contraindications to or intolerance of aromatase inhibitors.

Tamoxifen, which acts directly on oestrogen receptors, with different activity in different tissues, is well tolerated by most patients. Its side effects include increased venous thromboembolic events, hot flushes and a risk of low-grade endometrial cancer (significant only after five years, which is why tamoxifen is stopped then), although it has a positive effect on bone mineral density.

In perimenopausal patients, tamoxifen is given for two to three years before a switch to an aromatase inhibitor after confirmation of postmenopausal status. There are also data supporting the addition of ovarian ablation (either chemically using an LH-RH agonist such as goserelin, or by surgical oophorectomy) to tamoxifen in high-risk premenopausal women, particularly when chemotherapy is not used.

Aromatase inhibitors. Aromatase inhibitors, which block the production of oestrogen via the aromatase enzyme present in fat, are the current first-line hormone therapy for breast cancer in postmenopausal women unless there is a relative contraindication (presence of established osteoporosis) or they are poorly tolerated. The adverse effects of these drugs are predominantly joint and muscle pain, exacerbation of hot flushes, dry vagina and persistent bone mineral loss.

The three drugs available in Australia, anastrozole, letrozole and exemestane, are of similar efficacy and each is taken once daily. Patients should have calcium and vitamin D levels checked, take daily calcium and vitamin D supplements and be monitored annually with a dual-energy x-ray absorptiometry (DXA) scan if osteopenic at initiation of therapy. Aromatase inhibitors should not be used in pre- or perimenopausal women, as they may paradoxically stimulate oestrogen production from even a small amount of functioning ovarian tissue.

Chemotherapy

Adjuvant chemotherapy improves both disease-free survival and overall survival in high-risk patients. The potential benefits need to be weighed against acute and long-term physical, psychological and

social morbidity, and are made on an individual patient basis. Decision-making involves assessment of multiple factors, including characteristics of the cancer and the patient influencing the likelihood of local and systemic cancer recurrence (see the box on page 22).

Recent developments have focused on more accurate ways to predict the risk of the cancer recurring, the risk of treatment toxicity and the benefit of the treatment (see the earlier section on molecular profiling). The aim is to improve cure rates, as once patients develop distant metastases, although they can be treated and longer-term disease control is possible, a cure is unlikely, meaning breast cancer will eventually kill the patient if they do not die of another cause.

The old paradigm of only treating node-positive patients with chemotherapy has been superseded, and selected high-risk node-negative patients are being offered treatment. Additionally, the paradigm has shifted towards assessing likely response to treatment (i.e. degree of risk reduction), rather than offering chemotherapy simply based on risk alone. Molecular profiling can identify patients who are likely to have a favourable outcome, and thereby reduces the proportion of patients requiring adjuvant chemotherapy. Furthermore, analysis using commercially available multigene expression tests (such as the Oncotype DX® assay) gives information in patients with ER+ breast cancer about the likelihood of benefit from chemotherapy over and above the benefit from hormone therapy.

Many different chemotherapy drugs are used in adjuvant treatment, which generally consists of four to six months of intravenous treatment. Anthracyclines (epirubicin and doxorubicin), taxanes (docetaxel and paclitaxel), cyclophosphamide, fluorouracil and methotrexate are used in patients with early breast cancer. Central venous access devices are often used to avoid repeated cannulation.

Antiemetic regimens have considerably improved tolerance, and the use of granulocyte colony stimulating growth factors (filgrastrim and pegfilgrastrim) has significantly reduced the incidence of febrile neutropenia. Lethargy remains a considerable problem, and all current chemotherapy regimens still cause alopecia.

Fertility options for premenopausal women have improved (these will be discussed in the last article of this three-part series, to be published in a future issue of *Medicine Today*).

Biological (targeted) therapy

Trastuzumab is a monoclonal antibody directed against HER2, a receptor tyrosine kinase involved in cell growth and proliferation. About 20% of breast cancers are HER2+, which confers a poorer prognosis. Large clinical trials have demonstrated that one year of adjuvant trastuzumab in patients with HER2+ cancers, used with chemotherapy, improves survival. The main side effect is cardiotoxicity requiring surveillance echocardiograms.

Newer anti-HER2 drugs, including oral agents, are being assessed, as are shorter and longer durations of treatment. At present there are no good data on adjuvant trastuzumab given without chemotherapy.

Studies of agents that work against other biological targets have had disappointing results.

SUMMARY

The aim of treatment for early breast cancer (presence of a breast lump, with or without axillary lymph node involvement, and no systemic metastases) is cure. Surgery is the mainstay of treatment, with selective management of axillary lymph nodes. Adjuvant therapy (radiotherapy, chemotherapy, hormone therapy and biological therapy) may be added to reduce the risk of recurrence by treating micrometastases.

Breast-conserving surgery followed by radiotherapy is an option in most patients with early breast cancer. Risk assessment for local and systemic recurrence guides advice about the use of further adjuvant therapy. Postmastectomy radiation is appropriate if there is a high risk of local recurrence, and systemic hormones or chemotherapy if there is a high risk of systemic recurrence.

Molecular genetic profiling of breast tumours is increasingly being used to identify those patients who will benefit from the various adjuvant therapies. Other recent advances include improved accuracy and homogeneity of radiation dose delivery, the use of the monoclonal antibody trastuzumab and improved tolerance to chemotherapy through the use of drugs to prevent nausea and neutropenia. MT

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References are included in the pdf version of this article available at www.medicinetoday.com.au.

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