Breast cancer

Eleri Lloyd Davies

Abstract

Breast cancer is the most common cancer to affect women, with a recent estimate of lifetime risk being one in eight. The number of women found to have breast cancer in the UK has risen to 52,250 in 2011 with the highest rise being in the 50–69-years age group. This is probably attributable to several lifestyle factors such as diet, alcohol consumption, lack of exercise and late pregnancies. Because of earlier diagnosis and major treatment advances, survival rates have gradually improved over the last 20 years, with 80% of patients with early breast cancer now surviving 10 years after diagnosis. Recent advances in surgical management include the use of oncoplastic techniques for breast conservation and also advances in breast reconstruction following mastectomy. One current controversial area is the management of women with positive axillary nodes at diagnosis. The majority of patients with breast cancer will be offered adjuvant treatment such as radiotherapy, hormones, chemotherapy and biological agents, which aim to reduce local recurrence and improve survival. Novel developments include the use of biological markers to predict outcome and response to chemotherapy. This overview discusses the up-to-date management of breast cancer and recent developments in this field.

Keywords Adjuvant therapy; biological markers; breast cancer; oncoplastic; sentinel node biopsy; trastuzumab

Terminology

Breast cancer is caused by the presence of malignant cells in the breast. Cancer cells are characterized by uncontrolled division, leading to abnormal growth (*in situ* carcinoma) and the ability to invade normal tissue locally (invasive cancer). Depending on whether the glandular or ductal units of the breast are involved enables pathologists to subclassify breast cancer into types. The primary tumour begins in the breast but, once it becomes invasive, may progress to the regional (axillary/internal mammary) lymph nodes and it then has the ability to metastasize. The commonest sites of systemic involvement are the lung, bones, liver, skin and soft tissue. The presence of and number of regional lymph nodes containing cancer remains the single best indicator of whether or not the cancer has metastasized.

Epidemiology

Each year, breast cancer is diagnosed in 1.3 million women worldwide and 465,000 deaths result from the disease. It occurs very infrequently in men (300/year in UK) compared with women.[1] The incidence increases with age, 80% occurring in women over the age of 50 years. It occurs less commonly in younger women, but they tend to display more aggressive disease (5-year survival rates: 81% <45 years, 86% >65 years). Other risk factors include early menarche, late menopause, parity, breastfeeding and prolonged use of exogenous hormones, obesity, lack of exercise and alcohol consumption. Fewer than 5% of breast cancers are genetic. Patients with proven gene mutations (*BRCA1/BRCA2*) have an estimated lifetime risk of developing breast cancer of 40–85%.

Breast cancer clearly poses a significant economic burden on an already struggling National Health Service (NHS). The cost of the NHS Breast Screening programme alone is £75 million (£37.50 per woman invited and £45.50 per woman screened). The cost of treating early breast cancer is poorly documented in the literature, but a recent publication estimated the total population cost of treating metastatic breast cancer at £26 million/year.[2] With new technologies and targeted therapies it is inevitable that these costs will increase, putting more pressure on the economy.

Pathology

The majority of breast cancers (70–80%) are ductal, with several special subtypes (medullary, papillary, tubular, mucinous). Lobular cancers account for the remaining 20%. The tumour/node/metastasis (TNM) classification looks at size, nodal status and distant metastasis. A simplified version is shown in Table 1. When considering nodal status, the presence of individual tumour cells is classed as node-negative, whereas micrometastasis (>0.2–2 mm) is classed as node-positive. The American Joint Committee on Cancer staging system provides a strategy for grouping patients with respect to prognosis (Table 2). Other variables that affect survival are oestrogen receptor (ER) and human epidermal growth receptor-2 (HER2) receptor status. The development of microarray-based gene expression profiling has shown breast cancer to be heterogeneous – it can be subclassified into five distinct subtypes: luminal A, luminal B, *HER2*-overexpressing, basal-like and normal-like. These subtypes have very different prognoses and responses to adjuvant therapies.[3]

Diagnosis

Patients present with symptoms or are detected through the NHS breast screening programme. National Institute for Health and Care Excellence (NICE) guidance[4] states that both symptomatic and screen-detected patients should be referred to a specialist breast clinic for triple assessment: clinical, radiological, pathological. These assessments are now being performed more frequently in one-stop clinics as shown in Figure 1. Clinical assessment includes a history and an examination by a specialist breast surgeon or clinician. All patients over the age of 35 years will have a two-view mammogram with or without tomosynthesis. Any areas of clinical or mammographic concern are then examined by ultrasound scanning. If there is a discrete lesion to biopsy, a core biopsy is performed. A scoring system is used, ranging from 1 (benign) to 5 (malignant) for each component of the triple assessment. All patients are finally discussed at multidisciplinary team meeting to confirm a diagnosis and treatment plan.

Investigations

- **Histological investigations** – as well as confirming the diagnosis (type, grade), these provide useful information

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Simplified tumour/node/metastasis (TNM) classification of breast cancer

Tumour stage		
T_1	Tumour <2 cm	
T_2	Tumour 2–5 cm	
T_3	Tumour 5 cm	
T_4	Tumour fixed chest wall/skin or inflammatory	
Nodal stage		
	Clinical	Pathological pN
N_0	No nodes	Negative of individual tumour cells (ITC)
N_1	Mobile regional nodes	1–3 micro- or macrometastasis
N_2	Fixed regional or internal mammary nodes	4–9 nodes
N_3	Supraclavicular nodes	>10 nodes, axillary and internal mammary or supraclavicular nodes
Distant metastasis		
M_0	No distant metastasis	
M_1	Distant metastasis	

Table 1

about oestrogen (ER), progesterone (progesterone receptor (PR)) and HER2 status.

- **Radiological staging:** computed tomography of the thorax, abdomen and pelvis, and bone scanning – are performed only if there is a high suspicion of metastasis (i.e. bone pain or locally advanced disease, lymph nodes discovered postoperatively or recurrent disease).
- **Magnetic resonance imaging** (MRI) is currently used in limited situations in breast cancer patients because a large multicentre trial (COMICE) demonstrated an increased incidence of overtreatment when MRI was used preoperatively in breast cancer.[5] The current indications are lobular breast cancer, multifocal disease, dense breast (where estimation of cancer size is an issue) and assessment of implant integrity. In lobular cancers there is a high incidence of bilateral disease and multifocality, and MRI has proved beneficial in surgical planning for these patients.[6] In addition, Figure 2 illustrates how MRI can be useful for accurate sizing of the cancer in very dense breasts.

AJCC staging system for breast cancer

Stage	TNM classification	5-year survival
I	$T_1N_0M_0$	90%
IIa	$T_1N_1M_0$ or $T_2N_0M_0$	80%
IIb	$T_2N_1M_0$ or $T_3N_0M_0$	65%
IIIa	$T_2N_2M_0$ or $T_3N_1M_0$ or $T_3N_2M_0$	45%
IIIb	$T_4N_0M_0$ or $T_4N_1M_0$ or $T_4N_2M_0$	40%
IIIc	Any TN_3M_0	30%
IV	Any T, ANY N, M_1	14%

AJCC, American Joint Committee on Cancer; TNM, tumour/node/metastasis.

Table 2

Management

Multidisciplinary team (MDT) meeting

Therapeutic decisions are made according to tumour size, lymph node status, ER, PR and HER2 status, general health of the patient and patient wishes. A number of tools (e.g. Adjuvant! Online, Predict and NICE guidelines) are used to aid decision-making. In addition, the use of commercially available kits (e.g. Oncotype DX®, MammaPrint™), which characterize expression of a subset of genes within the breast cancer tissue, are increasingly being employed to estimate the likelihood of disease recurrence and/or response to chemotherapy in certain breast cancer subtypes[7,8] (see *Cytotoxic Chemotherapy: Clinical Aspects* and *Adjuvant Therapy* on pages 25–29 and pages 39–41 respectively of this issue).

Surgery

Traditionally, the aim of surgery has been to completely remove the primary breast lesion and the axillary lymph nodes. Most patients were offered wide local excision (WLE) followed by postoperative radiotherapy or mastectomy. With increasing interest in oncoplastic breast surgery, a wide selection of breast-conserving approaches – therapeutic mammoplasty, circumareolar incisions with dermoglandular flaps and several mini-flaps – are now being offered, which achieve better cosmetic outcomes. In addition, in those 25–30% of patients who require a mastectomy, more women are being offered immediate or delayed reconstruction. Skin- and nipple-sparing mastectomy with reconstruction offers an excellent final cosmetic result for suitable patients.

There is an increased interest in the use of various tissue matrices (i.e. Strattice™ and AlloDerm®), as well as an increasing use of microvascular surgery to improve cosmetic results. Other advances include lipofilling/lipomodulation, which involves the use of autologous fat transplantation techniques to improve breast-volume defects following breast conservation or reconstruction.[9]

Historically, axillary surgery involved an axillary node clearance (ANC). With only 25–30% of patients being node-positive, the remaining node-negative patients were subjected to a risk of lymphoedema, shoulder stiffness and paraesthesia without benefit. Sentinel node biopsy (SNB) allows accurate staging of the axilla using a minimally invasive surgical procedure with reduced morbidity. The sentinel lymph node (SLN) is identified by using a combination of radioactive colloid suspension and blue dye (Figure 3) (see *Diagnostic and Therapeutic Imaging in Oncology* on pages 6–9 of this issue). If the SLN is negative on histological examination, the patient is classed as node-negative. However, the disadvantage of SNB is that women with positive nodes have traditionally required a second operation to complete axillary clearance. This has triggered an interest in intraoperative assessment of the SLN, followed by immediate axillary surgery if the node is positive. Several techniques have been introduced, including frozen section, touch imprint cytology and reverse transcription polymerase chain reaction.[10]

Recent publication of the Z11 clinical trial[11] comparing axillary dissection with no axillary treatment in women with