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Breast cancer

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ABSTRACT Breast cancer is now the most common cancer of women in the UK and incidence is increasing. Because of major treatment advances and earlier diagnosis over the past 40 years, survival rates have been improving gradually and women diagnosed with breast cancer today are almost twice as likely to survive for 10 years or longer as women 40 years ago. However, breast cancer remains a major contributor to cancer morbidity and mortality in the UK. The majority of patients present with potentially curative disease and surgery is the mainstay of treatment. Many patients receive adjuvant (post-operative) therapy, which reduces the risk of loco-regional and distant disease recurrence. Treatment options include radiotherapy, chemotherapy, endocrine therapy and biological agents, with treatment increasingly tailored to the individual tumour and patient, aiming to provide maximum survival benefit with minimum toxicity. Many patients participate in clinical trials of radiotherapy, new agents, drug combinations or novel dosing regimens. Patients with metastatic disease can rarely be offered curative treatment, but improved quality of life and prolonged survival may be achieved with palliative treatment, including hormones, chemotherapy, radiotherapy, trastuzumab and bisphosphonates. This overview aims to summarise current knowledge and recent developments in the management of breast cancer.

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EDUCATION

INTRODUCTION

Breast cancer accounts for more than 30% of cancer diagnoses in women in the UK but is rare in men. Worldwide, it is estimated that 1.38 million women are diagnosed with the disease each year, with 45,695 women diagnosed in the UK in 2007. The lifetime risk of a woman developing breast cancer in the UK is now estimated to be one in nine. Although eight out of ten people diagnosed with breast cancer survive more than five years, breast cancer is the third most common cause of cancer death in the UK.

BREAST CANCER RISK

The majority of breast cancer cases (81%) occur in women aged 50 years or older. Other risk factors include early age at menarche and/or late menopause, the prolonged use of hormone replacement therapy (HRT), lower parity, reduced rates of breastfeeding, a significant family history of breast cancer or a germ-line mutation in *BRCA1* or *BRCA2* genes. Although fewer than 5% of all breast cancers are known to have a demonstrable genetic basis, women with *BRCA1* or *BRCA2* mutations have an estimated lifetime risk of developing breast cancer of 40–85% and patients with a first-degree relative diagnosed with breast cancer have twice the risk of developing the disease. Patients with a suspicious family history (e.g. first-degree relative with breast cancer under the age of 40, first-degree and second-degree relative with breast cancer under the age of 50, first-degree relative with male breast cancer, first-degree and second-degree relative with breast or ovarian cancer, multiple unusual cancers in family) should be referred from their general practitioner to a specialist breast clinic and patients at increased risk are then referred to a specialist genetics service for further assessment.[1]

PRESENTATION

Patients may be symptomatic or diagnosed through screening. Symptoms or signs suggestive of a breast cancer diagnosis are variable but include a new, usually painless lump, new nipple inversion and *peau d'orange*. Erythema and swelling of the whole breast is often the presenting feature of inflammatory breast cancer and may be mistaken for infection. Approximately 10% of patients have metastatic disease at presentation.

NHS BREAST SCREENING PROGRAMME

The UK was one of the first countries in the world to establish a breast screening programme. In 2007–08, more than 2.5 million women were eligible for screening, almost 2 million women attended and 16,449 cancers were detected.[2] Currently, women aged 50–70 are invited to attend screening and, more recently, additional mammography views have been implemented at every screening assessment. Recent data have highlighted some of the difficulties associated with false-negative and false-positive results from screening. Approximately 9% of women are recalled because of a possible abnormality at initial breast

TABLE 1 Tumour, node, metastasis staging of breast cancer

Tumour stage	
T1	Tumour <2 cm diameter
T2	Tumour 2–5 cm diameter
T3	Tumour >5 cm diameter
T4	Tumour fixed to skin/chest wall or inflammatory cancer
Nodal stage	
N0	No regional lymph node metastasis
N1	Mobile regional lymph node metastasis
N2	Fixed regional lymph node metastasis or internal mammary lymph node metastasis
N3	Supraclavicular lymph node metastasis
Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

TABLE 2 Breast cancer staging

Stage	Tumour, node, metastasis (TNM)	5-year survival rate
Stage I	T1 N0 M0	90%
Stage IIa	T1 N1 M0 or T2 N0 M0	80%
Stage IIb	T2 N1 M0 or T3 N0 M0	65%
Stage IIIa	T2 N2 M0 or T3 N1 M0 or T3 N2 M0	45%
Stage IIIb	T4 N0 M0 or T4 N1 M0 or T4 N2 M0	40%
Stage IIIc	Any T N3 M0	30%
Stage IV	Any T, any N, M1	14%

cancer screening, but only a small proportion of these patients will subsequently be diagnosed with an in situ or an invasive cancer. However, recently published research estimated that 2–2.5 lives are saved for every over-diagnosed case.[3] These results highlight the crucial importance of patient education in any screening programme.

INVESTIGATIONS

National Institute for Health and Clinical Excellence (NICE) guidance states that patients should be referred to a specialist breast clinic for clinical assessment, mammography and ultrasound with core biopsy.[1] Those with high-risk disease usually undergo a computed tomography scan of the thorax, abdomen and pelvis and an isotope bone scan. The role of breast magnetic resonance imaging in management is an evolving one. It is often used in multifocal or lobular breast cancer (where disease may be more extensive than suggested by other imaging modalities), in younger patients and in inflammatory breast cancer. A management plan is agreed with the multidisciplinary team (surgeons, radiologists, pathologists, oncologists, nurse specialists, and palliative care physicians) and the patient.

SURGERY

The aim is to offer patients with early breast cancer curative treatment and the majority undergo surgery to remove the primary lesion and regional lymph nodes. Most patients are suitable for breast conservation, which needs to be followed by radiotherapy. However, this approach is not appropriate for approximately 25% of patients who require mastectomy, usually due to the extent of disease or for cosmesis.

An increasing number of patients who undergo mastectomy will proceed to immediate or delayed breast reconstruction and advances in oncoplastic procedures, such as breast reshaping and skin-sparing mastectomy, have led to improvements in cosmetic outcome for many patients. Historically, axillary surgery has taken the form of axillary lymph node dissection, which, although an effective treatment, carries a significant risk of lymphoedema, paraesthesia and pain. Many patients now undergo sentinel lymph node biopsy, a selective approach to the management of regional lymph nodes. This technique involves the injection of blue dye and/or radioisotope during the surgical procedure to identify the draining sentinel lymph node, which is then resected. If carried out in appropriate patients, results correlate with axillary status and the complication rate is significantly lower.

PATHOLOGY AND PROGNOSIS

Invasive ductal adenocarcinoma accounts for approximately 75% of all breast cancer diagnoses, but there is a range of less common types such as lobular, tubular and mucinous carcinoma. Pathological staging is according to the tumour, node, metastasis (TNM) classification of malignant diseases (see Tables 1 and 2).

These and other clinico-pathological factors, such as nuclear grade and oestrogen (ER), progesterone (PR) and Her2 receptor status, offer important prognostic information and have been incorporated into a number of tools to guide treatment decision making (e.g. Nottingham Prognostic Index, St Gallen criteria, Adjuvant! Online, National Institutes of Health consensus guidelines). Recently, microarray-based gene expression profiling has shown breast cancers to be biologically heterogeneous, with at least five distinct subtypes: luminal A, luminal B, Her2-overexpressing, basal-like and normal-like (see Table 3). These subtypes have very different prognoses and likelihood of response to endocrine therapy or chemotherapy. This remains an area of intensive research.[4]

ADJUVANT TREATMENT

Adjuvant treatment reduces the risk of loco-regional and distant recurrence. Despite apparently successful

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TABLE 3 Microarray-based breast cancer subtypes

Subtype	Phenotype	Gene expression and prognosis
Luminal A	ER+ and/ or PR+ and Her2-	• Express breast luminal epithelial markers • Respond to endocrine therapy • Good prognosis
Luminal B	ER+ and/ or PR+ and Her2+	• Less response to endocrine therapy • Poorer prognosis despite ER+
Her2-like	ER-/PR- and Her2+	• Express other genes located in Her2 amplicon • High response rate to chemotherapy • Poor prognosis
Basal	ER-/PR- and Her2-	• Express basal epithelial markers, e.g. cytokeratins • High response rate to chemotherapy • Poor prognosis
Normal-like	ER-/PR- and Her2-	• Express normal breast epithelial markers but gene expression not clearly defined • Better prognosis

surgery, microscopic tumour foci may remain in the residual breast/chest wall, regional lymph nodes or distant lymphatics or vasculature and the aim of adjuvant treatment is to eradicate this.

Radiotherapy

Loco-regional radiotherapy reduces the five-year breast cancer local recurrence rate from 26% to 7%.[5] Following breast conservation, all patients should be offered post-operative radiotherapy to the breast, as this has been shown to be equivalent to mastectomy at reducing the risk of local recurrence. Mastectomy patients at increased risk of local recurrence (T3–T4 tumours, lymphovascular invasion, ≥4 involved axillary lymph nodes) also benefit from chest wall radiotherapy and treatment of the ipsilateral supraclavicular fossa or axillary lymph nodes may also be offered to selected high-risk patients. Common early radiotherapy side effects include lethargy and skin reaction and later, rarer ones include telangiectasia, breast shrinkage, pulmonary fibrosis and late second malignancy. The international standard radiotherapy schedule administers 50 Gray in 25 fractions, but a recent trial investigated different radiotherapy schedules, concluding that 40 Gray in 15 fractions offered similar loco-regional control without increased toxicity.[6] Other trials are in progress, investigating novel radiotherapy techniques and partial breast radiation.

Endocrine therapy

Patients with ER-positive or PR-positive breast cancer (65% of patients) benefit from adjuvant hormonal treatment. Trials have confirmed that adjuvant endocrine therapy reduces the risk of breast cancer recurrence by 40% and death by 30%[7] and also reduces the risk of a second primary breast cancer. The selective oestrogen receptor modulator tamoxifen is a well-established treatment suitable for both pre- and post-menopausal women. More recently, studies of the aromatase inhibitors (AIs) anastrozole (Arimidex®), letrozole (Femara®) and exemestane (Aromasin®), given either alone or sequentially with tamoxifen, have shown this approach to be more effective than tamoxifen alone. Aromatase inhibitors are, however, only suitable for post-menopausal women and the optimal duration and combination of treatment are not yet clear. Many patients experience hot flushes with endocrine therapy and other side effects include venous thromboembolism and endometrial cancer (tamoxifen) and arthralgia and osteoporosis (AIs).

Chemotherapy

Adjuvant chemotherapy has been shown to reduce the risk of breast cancer recurrence by approximately 30% and death by about 20%.[7] The benefits increase significantly in younger, premenopausal women and those with higher risk disease (ER/PR-negative, Her2-overexpressing or heavily node-positive disease). Drugs are generally prescribed in combination regimens to maximise efficacy, overcome drug resistance and minimise side effects. General chemotherapy toxicity includes myelosuppression and risk of neutropenic sepsis, alopecia, nausea, diarrhoea and infertility and each drug has other specific toxicities (e.g. cardiac failure with anthracyclines).

Anthracycline-based regimens are considered the 'gold standard' treatment, but the emerging goal is one of more personalised treatment based on tumour biology, rather than a 'one size fits all' approach. Patients with one disease subtype may derive greater benefit from one form of chemotherapy than another (such as taxanes in Her2-overexpressing disease). Others (e.g. those with luminal A disease) may benefit less from adjuvant chemotherapy than previously thought. The aim is to offer treatment to those patients who require it and to avoid potentially toxic (and expensive) therapies in those who will not benefit.[4] This is being investigated in trials that allocate chemotherapy or endocrine treatment based on genetic profiling and clinico-pathological factors.[8,9]

Biological therapy and novel agents

The most successful novel biological therapy to date is the monoclonal antibody trastuzumab (Herceptin®), which has revolutionised treatment for patients with Her2-overexpressing breast cancer (15–20% of patients) and is now part of standard oncology practice. Trials have demonstrated that 12 months' trastuzumab plus chemotherapy reduce the risk of disease recurrence by about 50% and the risk of death by approximately 30%;[10] however, the optimum duration of treatment is uncertain and studies are ongoing to clarify this. Trastuzumab is given following, or with, chemotherapy and is generally

well tolerated. The main toxicity is a risk of cardiac failure and it is not, for this reason, given with anthracyclines. Other targeted therapies have not yet been accepted into standard practice in the UK. Evidence supporting their use is predominantly from trials in metastatic patients.

The oral tyrosine kinase inhibitor of Her1/Her2, lapatinib (Tyverb®), has demonstrated efficacy following trastuzumab failure, but it has not been approved for use by NICE or by the Scottish Medicines Consortium. Clinical trials using inhibitors of the nuclear enzyme polyADP ribose polymerase (PARP), whose function is in promoting DNA repair and apoptosis, have shown that PARP inhibition seems to be particularly effective in the treatment of patients with *BRCA* mutations and triple negative (ER/PR/Her2-negative) or basal-like breast cancer. Further targeted approaches include the use of anti-angiogenic drugs, such as the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (Avastin®). However, a huge challenge faced by the National Health Service is whether, and how, such expensive drugs can be funded.

NEOADJUVANT THERAPY

The use of pre-operative (neoadjuvant) chemotherapy or endocrine therapy is increasing. It may downstage locally advanced or inoperable tumours, potentially allowing curative surgery to take place. It also has an evolving place in selected patients who would otherwise require a mastectomy but may achieve conservation surgery following tumour shrinkage. In addition, neoadjuvant therapy allows the analysis of tumour tissue before and after systemic therapy. This means that response to different treatments can be correlated with cellular and genetic changes and with outcome. This should produce advances in our understanding of how drugs work and who will most benefit.

METASTATIC DISEASE

In 2008 approximately 12,000 women and 70 men died from breast cancer. It is, however, not known how many people are living with metastatic breast cancer. Treatment focuses on palliating symptoms, improving quality of life and extending life if possible, and is tailored to the individual patient's performance status, prior therapy and disease distribution. Many patients and families require significant support following a diagnosis of metastatic breast cancer. Treatment options include:

- Endocrine therapy, often with ovarian ablation in pre-menopausal patients. This is usually the first-line treatment of choice for patients with hormone-sensitive disease, unless the clinician believes that a more rapid response to therapy is required.
- Chemotherapy in patients with ER-negative disease and tumours that have become hormone-resistant. Various drugs may be useful (anthracyclines, taxanes, capecitabine, vinorelbine and others), but several factors influence the choice of treatment. There is ongoing debate about sequential versus combination therapy.
- Trastuzumab, which may benefit patients with Her2-positive disease, even if they have received it in the adjuvant setting. How best to treat patients following trastuzumab failure remains unclear.
- Radiotherapy, which has an important place in pain control, particularly painful bone metastases, and in emergency treatment of spinal cord compression, stridor or superior vena caval obstruction. Other indications include palliation of brain metastases or fungating chest wall disease.
- Bisphosphonates in patients with lytic bone metastases, to improve pain control, together with reducing the risk of pathological fracture and future skeletal events.

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SELF-ASSESSMENT QUESTIONS

1. A fit, pre-menopausal 33-year-old woman undergoing breast conservation with sentinel lymph node biopsy has been referred to you for adjuvant treatment. Pathology confirms a 30 mm grade 3 invasive ductal cancer which is oestrogen-receptor positive and Her2-overexpressing. Sentinel lymph node is negative. Which one of the following would be the most appropriate treatment?

A. Radiotherapy, trastuzumab and tamoxifen.
B. Radiotherapy and tamoxifen, followed by letrozole.
C. Trastuzumab and tamoxifen.
D. Chemotherapy, trastuzumab and anastrozole.
E. Chemotherapy, radiotherapy, trastuzumab and tamoxifen.

2. A 55-year-old woman had breast cancer surgery followed by radiotherapy and tamoxifen five years ago. She presents with abdominal pain and nausea and investigations confirm liver and lung metastases. Her bilirubin is normal, but transaminases are approximately twice the upper limit of normal. Which one of the following would be the most appropriate course of action?

A. Anthracycline-based chemotherapy (the gold standard) as soon as possible as she has visceral disease and disease will progress quickly if not treated.
B. An aromatase inhibitor (e.g. letrozole) as she previously had tamoxifen and it is important to maintain quality of life in the palliative setting.
C. Further information is needed before recommending treatment.
D. Referral to palliative medicine as she is developing liver failure and so is very unlikely to respond to treatment.
E. She needs a bone scan before starting treatment as she may also have bone metastases and would, therefore, benefit from bisphosphonates.

3. A 40-year-old patient completed adjuvant breast cancer treatment two years ago. She had surgery, followed by anthracycline-based chemotherapy, trastuzumab and endocrine therapy but not radiotherapy. Which one of the following is the most likely genetic profile of her original cancer?

A. Luminal A.
B. Luminal B.
C. Her2-like.
D. Basal-like.
E. Normal-like.

4. A 45-year-old woman has recently completed breast cancer treatment. She is concerned about the possible increased risk to her children (daughters, aged 23 and 20, and son, aged 18) of developing cancer. Her aunt had breast cancer aged 50. Her brother died two years ago aged 65 from lung cancer and her father died in his 70s from prostate cancer. Her mother died when the patient was a child of 'blocked intestines'. Which one of the following is the most appropriate course of action?

A. Her daughters have a significantly increased risk of breast cancer and need to be referred to a breast cancer family history clinic for investigation. There is no increased risk to her son.
B. Her daughters and son have a significantly increased risk of breast cancer and need to be referred to a breast cancer family history clinic for investigation.
C. Her children may be at increased risk of cancer and should be referred to a specialist genetic screening unit.
D. Although her aunt had breast cancer, her brother and father had cancers not associated with breast cancer and so there is no increased risk with only one other family member, who is not a first-degree relative, affected.
E. A wider family history should be taken and, if there is one other family member with breast cancer, her daughters should be referred to the breast screening unit for earlier mammograms.

5. A 55-year-old woman presents with dyspnoea. She was treated for breast cancer three years ago with conservation surgery, chemotherapy, radiotherapy to the breast and supraclavicular fossa, trastuzumab and she has been on anastrozole as endocrine therapy since completing chemotherapy. She is a smoker. Which one of the following is most likely, given her breast cancer treatment?

A. The patient may have developed cardiac failure following chemotherapy.
B. The patient may have developed cardiac failure following trastuzumab.
C. The patient may have developed lung metastases.
D. The patient may have developed a pulmonary embolism secondary to endocrine therapy.
E. The patient may have developed pulmonary fibrosis secondary to radiotherapy.

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EDUCATION