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ABC of Breast Diseases

Fourth Edition

EDITED BY

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The incidence of breast cancer continues to increase year on year but thankfully the number of women who die from breast cancer continues to fall. Arguments surround how much of this reduction is due to earlier detection and how much is due to better treatments, but the falling death rate suggests that the vast amounts of money that has been invested in breast cancer is paying dividends. All this investment in research and clinical trials has resulted in an explosion of literature and keeping up to date with the latest advances in the treatment of benign and malignant breast conditions has never been more difficult. The aim of the fourth edition of the *ABC of Breast Diseases* has been to combine this new knowledge together with what we already knew in a concise, short, evidence based well illustrated book. Despite being compact, it is nonetheless comprehensive and I have tried to include everything even a breast disease specialist might want to know. My aim was also to make it of practical use to doctors in primary care, so the text covers guidelines for referral and management of common benign conditions which are much more frequently seen in general practice than is breast cancer. The numerous pictures make it equivalent in scope to many atlases of breast disease. If you see something related to the breast that you do not recognise the chances are there is a picture of it in the ABC. There have been many changes since the last edition. New chapters by new authors have been added on the epidemiology of breast cancer, genetics, prevention, management of high risk women and psychological aspects of breast disease. The chapter on systemic therapy of early breast cancer has also been completely rewritten and all other chapters have been revised extensively. New authors have been added to some of these chapters and many new illustrations, tables and graphs have been included.

I write or edit many textbooks on breast disease but the one I use most frequently in my daily clinical practice is the ABC. I use it as an aide memoire and to find it useful in discussions with patients, students and staff in breast clinics. I hope others in primary care and in all branches of hospital practice find this new edition of value and even more informative than the third edition.

Thanks to all who have made the book possible. The authors as always have done all that was asked of them. Monica McGill helped interpret my edits, coordinate the many images, and made sure the book arrived at the publishers in a timely and orderly manner. Keerthana Panneer, typesetter and Sally Osborne, copy editor at Wiley-Blackwell converted the authors’ words, my scribbles and the many pictures and tables into the book that you now read. Books take an enormous amount of time and I acknowledge the support my wife Pam and my sons Oliver and Jonathan for their patience while I wrote and edited at home. Most of the clinical photographs are from patients in Edinburgh and I want to personally thank all the women and a few men who agreed to be photographed and signed the medical photography forms to allow me to use their photographs in this book. My patients are my inspiration and the main reason I do what I do. They understand that in the field of breast diseases there is much we do not know. They are also aware however that there is much we do know and they want their doctors to deliver optimal management and treatments that are effective and evidenced based. That brings me full circle and explains why an updated version of the ABC outlining the current optimal approach to the management of patients with benign and malignant breast conditions is needed.

Mike Dixon
Edinburgh
CHAPTER 1

Symptoms, Assessment and Guidelines for Referral

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OVERVIEW

- Breast conditions account for approximately 25% of all surgical referrals
- Guidelines for referral exist to ensure that patients with breast cancer do not suffer delays in referral
- Cancer can present as localised nodularity, particularly in young women
- All discrete masses and the majority of localised asymmetric nodularities require triple assessment
- Delay in diagnosis of breast cancer is the single largest cause for medicolegal complaints

One woman in four is referred to a breast clinic at some time in her life. A breast lump, which may be painful, and breast pain constitute over 80% of the breast problems referred to hospital and breast problems constitute up to a quarter of all female surgical referrals (Table 1.1).

When a patient presents with a breast problem the question for the general practitioner is: ‘Is there a chance that cancer is present and, if not, can I manage these symptoms myself?’ (Figure 1.1; Tables 1.2 and 1.3).

For patients presenting with a breast lump, the general practitioner should determine whether the lump is discrete or there is nodularity, as well as whether any nodularity is asymmetrical or is part of generalised nodularity (Figure 1.2). A discrete lump stands out from the adjoining breast tissue, has definable borders and is measurable. Localised nodularity is more ill-defined, is often bilateral and tends to fluctuate with the menstrual cycle. About 10% of all breast cancers present as asymmetrical nodularity rather than a discrete mass. When the patient is sure that there is a localised lump or lumpiness, a single normal clinical examination by a general practitioner is not enough to exclude underlying disease (Tables 1.2 and 1.3). Reassessment after menstruation or hospital referral is indicated in such women.

Assessment of symptoms

Patient’s history

Details of risk factors, including family history and current medication, should be obtained and recorded. Knowing the duration of a symptom can be helpful, as cancers usually grow slowly but cysts may appear overnight.

Inspection should take place in a good light with the patient’s arms by her side, above her head, then pressing on her hips
Table 1.2 Conditions that require hospital referral.

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
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<tbody>
<tr>
<td>Lump</td>
</tr>
<tr>
<td>• Any new discrete lump</td>
</tr>
<tr>
<td>• New lump in pre-existing nodularity</td>
</tr>
<tr>
<td>• Asymmetrical nodularity in a woman over the age of 35</td>
</tr>
<tr>
<td>• Asymmetric nodularity in a younger woman that persists at review after menstruation</td>
</tr>
<tr>
<td>• Abscess or breast inflammation that does not settle rapidly after one course of antibiotics</td>
</tr>
<tr>
<td>• Palpable axillary mass including an enlarged axillary lymph node</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>• if associated with a lump</td>
</tr>
<tr>
<td>• Intractable pain that interferes with a patient’s lifestyle or sleep and that has failed to respond to reassurance, simple measures such as wearing a well-supporting bra or anti-inflammatory drugs</td>
</tr>
<tr>
<td>• Unilateral persistent pain in postmenopausal women that is in the breast rather than in the chest wall (see Chapter 3)</td>
</tr>
<tr>
<td>Nipple discharge</td>
</tr>
<tr>
<td>• All women aged &gt;50</td>
</tr>
<tr>
<td>• Women aged ≤50 with either</td>
</tr>
<tr>
<td>- bloodstained discharge</td>
</tr>
<tr>
<td>- spontaneous single duct discharge</td>
</tr>
<tr>
<td>- bilateral discharge sufficient to stain clothes</td>
</tr>
<tr>
<td>Nipple retraction or distortion</td>
</tr>
<tr>
<td>Nipple eczema</td>
</tr>
<tr>
<td>Change in skin contour</td>
</tr>
</tbody>
</table>

Family history
Request for assessment of a woman with a strong family history of breast cancer should be to a family cancer genetics clinic.

Table 1.3 Patients who can be managed, at least initially, by their GP.

- Women with bilateral tender, nodular breasts provided that they have no localised abnormality on examination
- Young women (≤35 years) with asymmetrical localised nodularity, these women require assessment after their next menstrual cycle, and if nodularity persists hospital referral is then indicated
- Women with minor and moderate degrees of breast pain who do not have a discrete palpable lesion
- Women aged <50 who have nipple discharge that is small in amount and is from more than one duct and is intermittent (occurs less than twice per week) and is not bloodstained. These patients should be reviewed in 2–3 weeks and if symptom persists hospital referral is indicated

(Figure 1.3). Skin dimpling or a change in contour is present in up to a quarter of symptomatic patients with breast cancer (Figure 1.4). Although usually associated with an underlying malignancy, skin dimpling can follow surgery or trauma, and can be associated with benign conditions or occur as part of breast involution (Figures 1.5–1.7).

Breast palpation
Breast palpation is performed with the patient lying flat with her arms above her head (Figure 1.8), and all the breast tissue is examined using the most sensitive part of the hand, the fingertips. It is important for the woman to have her hands under her head to spread the breast out over the chest wall, because it reduces the depth of breast tissue between your hands.

![Management of patient presenting in primary care with a breast lump or localised lumpy area or nodularity](image-url)
and the chest wall and makes abnormal areas much easier to detect and define. If an abnormality is identified, it should then be assessed for contour and texture. The presence of deep fixation is checked by tensing the pectoralis major, which is accomplished by asking the patient to press her hands on her hips. All palpable lesions should be measured with calipers. A clear
diagram of any breast abnormalities, including dimensions and the exact position, should be recorded in the medical notes.

Patients with breast pain should also be examined, the underlying chest wall being palpated for areas of tenderness while the woman lies on each side (see Chapter 3). Much so-called breast pain in fact emanates from the underlying chest wall.

**Assessment of axillary nodes**

Once both breasts have been palpated, the nodal areas in the axillary and supraclavicular regions are checked (Figure 1.9). Clinical assessment of axillary nodes can be inaccurate: palpable nodes can be identified in up to 30% of patients with no clinically significant breast or other disease, and up to a third of patients with breast cancer who have clinically normal axillary nodes have axillary nodal metastases.

**Mammography**

Mammography requires compression of the breast between two plates and is uncomfortable. Two views – oblique and cranio-caudal – are usually obtained. With modern equipment a dose of less than 1.5 mGy is standard. Mammography allows detection of mass lesions (Figure 1.10), areas of parenchymal distortion and microcalcifications. Breasts are relatively radiodense, so in younger women aged under 35 mammography is of more limited value and should not be performed unless on clinical examination, cytology or core biopsy there is a suspicion that the patient has a cancer (Figure 1.10). Digital mammography, which is now being used in most units, has a greater sensitivity for cancer detection in young women than standard film mammography. All patients with breast cancer, regardless of age, should have mammography before surgery to help with assessment of the extent of disease.

**Ultrasonography**

In ultrasonography high-frequency sound waves are beamed through the breast and reflections are detected and turned into images. Cysts show up as transparent objects; other benign lesions tend to have well-demarcated edges (Figure 1.11(a)), whereas cancers usually have indistinct outlines (Figure 1.11(b)). Blood flow to lesions can be imaged with colour flow Doppler ultrasound. Malignant lesions tend to have a greater blood flow than benign lesions, but the sensitivity and specificity of colour Doppler are insufficient to differentiate benign from malignant lesions.
Symptoms, Assessment and Guidelines for Referral

Figure 1.11 (a) Ultrasound showing a solid irregular mass lesion characteristic of a cancer. (b) Ultrasound of a fibroadenoma.

accurately. All patients with a diagnosis of breast cancer should have both a whole breast and an axillary ultrasound. If other evidence of disease is identified or abnormal nodes are seen, they should be biopsied under ultrasound guidance. Ultrasound contrast agents are available and continue to be investigated, but they are of no proven value in the routine assessment of breast masses or axillary nodes.

**Magnetic resonance imaging (MRI)**

Magnetic resonance imaging is an accurate way of imaging the breast (Figure 1.12). It has a high sensitivity for breast cancer and may be valuable in demonstrating the extent of both invasive and non-invasive disease. The problem with MRI is a relatively low specificity and a positive predictive value of only two-thirds. It appears to be particularly valuable in assessing the extent of invasive lobular cancers, which are sometimes not well seen on mammography and ultrasound. It is also of value in assessing early response to neoadjuvant therapy in women with established breast cancer. MRI is useful in the treated, conserved breast to determine whether a mammographic lesion at the site of previous surgery is due to scar or recurrence. It has been shown to be a valuable screening tool for high-risk women between the ages of 35 and 50. MRI is the optimum method for imaging breast implants.

**Fine needle aspiration cytology (FNAC)**

FNAC is no longer commonly used to assess breast masses, but is valuable in assessing enlarged axillary or supraclavicular nodes visualised on ultrasound. Needle aspiration can differentiate between solid and cystic lesions. Aspiration of solid lesions requires skill to obtain enough cells for cytological analysis, as well as to interpret the smears. Image guidance increases accuracy, particularly in small lesions. A 21- or 23-gauge needle attached to a syringe is introduced into the lesion and suction is applied by withdrawing the plunger; multiple passes are made through the lesion. The plunger is then released and the material is spread onto microscope slides. These are then either air dried or sprayed with a fixative, depending on the cytologist’s preference, and are stained (Figure 1.13). In some units a report is available within 30 minutes. The disadvantage of FNA in the breast is that it cannot differentiate invasive from in situ cancer.

**Touch prep cytology of core biopsy samples and sentinel lymph nodes** is possible and allows immediate reporting. If the biopsy sample contains a significant amount of tumour this technique is very accurate. Sensitivity of touch prep cytology of lymph nodes approaches 90%, which is better than the sensitivity of frozen section.

**Core biopsy**

Local anaesthetic containing adrenaline solution is infiltrated into the overlying skin and breast tissue surrounding the area to be
biopsied. After a minimum of 7–8 minutes, through a single small skin incision, multiple cores of tissue are removed from the clinical mass or the area of mammographic or ultrasound abnormality by means of a cutting needle technique (Figure 1.14). A 14-gauge needle combined with a mechanical gun produces satisfactory samples and allows the procedure to be performed single-handed. Unless the lesion is large, core biopsy should be performed with image guidance. For calcification at least three cores need to contain the target calcification or five calcifications need to be visible in the cores to ensure adequate sampling. For mass lesions the number of cores required is less clear, but with adequate local anaesthesia the procedure is painless, so multiple cores (three or more) are recommended to ensure adequate sampling of all parts of the lesion.

**Large-bore vacuum-assisted biopsy**

Performed under local anaesthesia, an 11- or 8-gauge needle attached to a vacuum device provides much larger specimens than a standard 14-gauge core biopsy. Such a device is particularly useful in areas of microcalcification because more tissue is obtained and there is a greater likelihood of the lesion being sampled adequately. These large-bore needles can be used to remove benign lesions such as fibroadenomas and small papillomas completely.

Vacuum assisted core biopsy devices are now available that allow 11- or 8-gauge cores of tissue to be obtained, enabling more extensive sampling without the need to withdraw the needle from the breast. They are more accurate than 14-gauge core biopsy in sampling microcalcifications.

**Open biopsy (Table 1.4)**

Open biopsy is rarely required to establish a histopathological diagnosis except in the screening setting. All women undergoing open biopsy should have been assessed by imaging and at least one attempt at core biopsy. Women who are told that core biopsy has shown their lesion to be benign do not often request excision. Breast biopsy is not without morbidity. A fifth of patients develop either a further lump under the scar or pain specifically related to the biopsy site over the ensuing decade.

**Frozen section**

Frozen section should no longer be used to diagnose breast cancer. The only exception would be its use in a patient with a cytological

---

**Table 1.4** Indications for excision of a breast lesion.

- Diagnosis of malignancy on cytology not confirmed by subsequent core biopsy when a mastectomy or axillary clearance is planned
- Certain benign lesions, e.g. benign phyllodes tumours
- Diagnosis of atypical hyperplasia on core biopsy
- Radial scar: diagnosed by imaging and core biopsy
- Indeterminate papillary lesion on core biopsy
- Suspicion of malignancy on one or more investigations with indeterminate or inadequate core biopsy, usually in patients with screen-detected microcalcification
- Large lesions such as large or giant fibroadenomas
- Request by patient for excision
and imaging diagnosis of breast cancer when core biopsy has failed to establish cancer and a one-stage surgical procedure is planned. Before proceeding to definitive surgery the patient should have been told that her lesion is considered to be malignant and have been appropriately counselled, and should have had time to consider treatment options.

The use of frozen section has been reported in the assessment of excision margins after a wide local excision to ensure the complete excision and assessment of axillary lymph nodes, particularly sentinel nodes, during an operation to identify patients who are node positive who can proceed to axillary dissection (Figure 1.15). In both assessing excision margins and axillary nodes reported sensitivity varies between 66% and 90%. Use of immunohistochemistry and multiple frozen sections improves the sensitivity of axillary node assessment, but considerably increases costs and the length of time required to obtain a definitive result. Imprint cytology of sentinel nodes has a higher sensitivity and seems a better alternative to frozen section. Imprint cytology of surgical margins is an alternative to frozen section if intraoperative assessment is considered necessary.

The routine use of frozen section to diagnose breast cancer is not acceptable.

### Accuracy of investigations

False positive results occur with all diagnostic techniques (Table 1.5). It is not acceptable to plan treatment solely on the basis of malignant cytology, even if supported by a diagnosis of malignancy on clinical examination and imaging. Cytology has a false positive rate of 0.2–0.5%; the lesions most likely to be misinterpreted are fibroadenomas, papillary lesions and areas of breast that have been irradiated. For this reason a histological diagnosis is necessary to proceed with mastectomy. Cytology also has a false negative rate of 4–5%. Core biopsy has the advantage of providing a histological diagnosis and can differentiate between invasive and in situ carcinoma. Errors with core biopsy occur mainly because of geographical misses and inadequate sampling. Image guidance, taking images to show that the needle has sampled the lesion and taking multiple cores are recommended to maximise sensitivity.

The sensitivity of clinical examination and mammography varies with age; only two-thirds of cancers in women aged 50 are deemed to be highly suspicious or definitely malignant on clinical examination or mammography (Figure 1.16). Breast cancer in women aged under 40 is a particular problem, as it often presents with asymmetric nodularity rather than a discrete lump. General practitioners need to be aware of this.

### Triple assessment

This is the combination of clinical examination, imaging (mammography with or without ultrasonography for women aged ≥35 and ultrasonography alone for women aged <35) and core biopsy, fine needle aspiration cytology or both (Table 1.6; Figure 1.17). Each component of the assessment is graded and for clinical examination (E), mammography (R) and ultrasound (U) the system used is 1: normal; 2: benign; 3: probably benign; 4: probably malignant; and 5: malignant. Cytology has a slightly different annotation as C1 is acellular not normal. Core biopsy likewise considers B1 as normal and therefore maybe unrepresentative if there is considered to be

### Table 1.5  Symptoms, assessment, and guidelines for referral.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity for cancers</th>
<th>Specificity for benign disease</th>
<th>PPV for cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination</td>
<td>86%</td>
<td>90%</td>
<td>95%</td>
</tr>
<tr>
<td>Mammography</td>
<td>86%</td>
<td>90%</td>
<td>95%</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>90%</td>
<td>92%</td>
<td>95%</td>
</tr>
<tr>
<td>MRI</td>
<td>98%</td>
<td>75%</td>
<td>66%</td>
</tr>
<tr>
<td>Fine needle aspiration cytology</td>
<td>95%</td>
<td>95%</td>
<td>99.8%</td>
</tr>
<tr>
<td>Core biopsy</td>
<td>98%</td>
<td>95%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*% of invasive cancers detected by test as malignant or probably malignant (that is, complete sensitivity).

†% of benign disease detected by test as benign.

‡% of lesions diagnosed as malignant that are cancers (that is, absolute PPV – positive predictive value).

§Sensitivity if core biopsy is image guided.
Table 1.6 Advantages and disadvantages of techniques for assessment of breast masses.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical exam.</td>
<td>Easy to perform</td>
<td>Low sensitivity in women ≤50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Operator dependent*</td>
</tr>
<tr>
<td>Mammography</td>
<td>Useful for screening women aged ≥50</td>
<td>Requires dedicated equipment and experienced personnel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low sensitivity in women ≥50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unpleasant (causes discomfort or actual pain)</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Same sensitivity in all ages</td>
<td>Operator dependent*</td>
</tr>
<tr>
<td></td>
<td>Useful in assessing impalpable lesions and the axilla</td>
<td>Slightly more sensitive than mammography; not useful for screening</td>
</tr>
<tr>
<td></td>
<td>Painless</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Useful to target core biopsy or FNA</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>High sensitivity in all ages</td>
<td>Costly and time consuming</td>
</tr>
<tr>
<td></td>
<td>Better at assessing size of cancer than other imaging techniques**</td>
<td>Low specificity and low positive predictive value</td>
</tr>
<tr>
<td>Core biopsy</td>
<td>Easy to perform</td>
<td>Operator dependent</td>
</tr>
<tr>
<td></td>
<td>Less painful than FNA</td>
<td>Cannot easily be reported immediately</td>
</tr>
<tr>
<td></td>
<td>Provides a definitive histological diagnosis</td>
<td>Uncomfortable but less painful than FNA</td>
</tr>
<tr>
<td></td>
<td>Almost zero false-positive rate</td>
<td>Bruising and swelling</td>
</tr>
<tr>
<td>Fine needle aspiration cytology</td>
<td>Cheap</td>
<td>Operator dependent</td>
</tr>
<tr>
<td></td>
<td>High sensitivity</td>
<td>Needs experienced cytopathologist</td>
</tr>
<tr>
<td></td>
<td>Provides differential diagnosis in most instances</td>
<td>Painful</td>
</tr>
<tr>
<td></td>
<td>Low incidence of false positives</td>
<td>Cannot differentiate invasive from in situ cancer</td>
</tr>
<tr>
<td></td>
<td>Can be reported immediately</td>
<td>Some false positives</td>
</tr>
</tbody>
</table>

*Sensitivity varies in relation to expertise of individual.

**MRI did not appear to be valuable in increasing the rate of complete excision of patients undergoing breast-conserving surgery in a randomised study, but it correlated better with the pathology size than either mammography or ultrasound.

*a definite lesion, B2 as benign, B3 as atypical, B4 as suspicious indeterminate, B5a as in situ carcinoma and B5b as invasive cancer.

Delay in diagnosis

Delay in diagnosis of breast cancer is a common reason for patients taking legal action against medical practitioners. Currently between 1.5% and 4% of patients with breast cancer experience a diagnostic delay of eight weeks or longer. Diagnostic delay is a particular problem in younger women, because cancers in such women often manifest as localised nodularity rather than a discrete lump. For this reason all women who have discrete lumps or localised areas of asymmetric nodularity should have full assessment by experienced clinicians. The doctor who orders the investigations...
should check and sign all results of these investigations, which should then be filed in the patient’s notes. Details of any clinical findings from clinic visits must be recorded legibly and include a diagram marking all areas of abnormality as well as a doctor’s signature.

**One-stop clinics**

In a patient with a discrete breast mass or a localised area of nodularity, some treatment centres offer immediate reporting of imaging and cytology from a fine needle aspirate or touch preparation from a core biopsy sample. Although one-stop clinics with cytology have potential advantages, with modern imaging few lesions are truly indeterminate. With the increasing use of core biopsy and the limited numbers of experienced cytologists, few one-stop clinics remain.

**Investigation of breast symptoms**

**Breast mass and localised nodularity**

All patients should have a clinical and imaging assessment with biopsy of any indeterminate or discrete lesion. It is not necessary to excise all solid breast masses, and a selective policy is recommended on the basis of the results of triple assessment. Core biopsy, preferably image-guided, has replaced cytology and is the diagnostic investigation of choice to achieve a definitive histological diagnosis in a solid lesion.

**Nipple discharge**

Treatment depends on whether the discharge is spontaneous and whether it is from one or several ducts (Figure 1.18). Single-duct discharge should be checked for the presence of haemoglobin. Only moderate or large amounts of blood are significant. About 5–10% of patients with bloodstained discharge will be found to have an underlying malignancy. Most bloodstained discharges are due to papillomas or other benign conditions. All patients with spontaneous discharge should have a clinical examination. All patients aged 35 or over with spontaneous discharge and younger patients with bloodstained or haemoserous discharge should have mammography. Ductography and ductoscopy can localise lesions and may have a role in young women to direct and limit any excision in an effort to maintain the ability to breastfeed. Physiological nipple discharge is common and is not usually spontaneous: two-thirds of premenopausal women can be made to produce nipple secretion by cleansing the nipple and applying suction (Figure 1.19). This physiological discharge varies in colour from white to yellow to green to blue-black.

<table>
<thead>
<tr>
<th>Surgery is indicated in cases of spontaneous discharge from a single duct that is confirmed on clinical examination and has one of the following characteristics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Is bloodstained or contains moderate or large amounts of blood on testing.</td>
</tr>
<tr>
<td>• Is persistent (occurs on at least two occasions per week).</td>
</tr>
<tr>
<td>• Is a new development in a woman older than 50 years of age but is not thick or cheesy.</td>
</tr>
</tbody>
</table>

Discharge from multiple ducts requires surgery only when it causes distressing symptoms such as persistent staining of clothes.

---

**Figure 1.18 Investigation of nipple discharge.**

*Some surgeons prefer total duct excision in women aged >45 to reduce incidence of discharge from other ducts.†If lesion on mammogram is incidental and unlikely to be related to nipple discharge, combine with investigation of single- or multiple-duct discharge as appropriate.
Figure 1.19 (a) Multiple physiological discharge. Note the range of colours characteristic of physiological discharge. (b) Physiological multiple duct colou red. Note the colours are lighter than those in Figure 1.19a; there is a whole range of colours from white to yellow to green to blue black.

**Galactorrhoea**

Galactorrhoea is copious bilateral milky discharge not associated with pregnancy or breastfeeding (Figure 1.20). Prolactin levels are usually but not always raised. A careful drug history should be taken, as various drugs, particularly psychotropic agents, can cause hyperprolactinaemia. In the absence of relevant drugs, a search for a pituitary tumour should be instituted in a patient with a raised prolactin greater than 1000 IU/l.

**Nipple retraction**

Slit-like retraction of the nipple is characteristic of benign disease (Figure 1.21), whereas nipple inversion, when the whole nipple is pulled in, occurs in association with both breast cancer and inflammatory breast conditions. For patients with congenital nipple retraction and acquired nipple retraction, which is unsightly and does not respond to conservative measures such as suction devices or nipple shields, surgery including duct division or excision can be successful at everting the nipple. Women need to be informed that duct excision can result in loss of ability to breastfeed and loss or reduction of nipple sensation or sometimes nipple hypersensitivity.

**Breast pain**

Breast pain should be assessed by means of a careful history and clinical examination. Mammography or ultrasonography, or both, is indicated in patients with unilateral persistent mastalgia or a localised area of painful nodularity. The management of breast pain is covered in Chapter 3.
Further reading


CHAPTER 2
Congenital Problems and Aberrations
of Normal Development and Involution

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OVERVIEW
• Congenital anomalies of the breast are not uncommon but can cause considerable anxiety. Treatment improves patients’ lives immeasurably
• Most benign abnormalities occur against the background of breast development, reproduction and involution
• Increasing numbers of men are attending breast clinics with breast enlargement
• Most conditions that affect the breast are benign and there are a huge range of these conditions
• Atypical hyperplasia is the only benign condition associated with a significantly increased risk of breast cancer

Congenital abnormalities
Extra nipples and breasts
Between 1% and 5% of men and women have supernumerary or accessory nipples or, less commonly, supernumerary or accessory breasts. These usually develop along the milk line: the most common site for accessory nipples is just below the normal breast (Figures 2.1–2.3), and the most common site for accessory breast tissue is the lower axilla (Figure 2.4). Accessory breasts below the umbilicus are extremely rare. Extra breasts or nipples only require treatment if they are unsightly. They are subject to the same diseases as normal breasts and nipples.

Absence or hypoplasia of the breast
One breast can be absent or hypoplastic (Figure 2.5), usually in association with defects in one or both pectoral muscles. Some degree of breast asymmetry is usual, and the left breast is more commonly larger than the right. True breast asymmetry can be treated by augmentation of the smaller breast, or both breasts, reduction or elevation of the larger breast, or a combination of procedures. Hypoplastic breasts are often tubular in morphology, so reshaping of the breast and division of any constricting bands together with the use of tissue expanders to reshape the breast prior to implant insertion is often required.

Tubular breasts
This is a congenital anomaly of the breast that manifests itself at puberty. The breast has a narrow base and resembles an hourglass (Figure 2.6). Surgical correction involves making incisions into the base of the breast to allow the constricted base to unfold.
This is combined either with tissue expansion followed by implant insertion or use of an implant alone (Figure 2.6(b))). The condition can be unilateral or bilateral.

Chest wall abnormalities
About 90% of patients with true unilateral absence of a breast (Figure 2.7) have either absence or hypoplasia of the pectoral muscles (Figure 2.8). In contrast, 90% of patients with pectoral muscle defects have normal breasts. Some patients have abnormalities of the pectoral muscles and absence or hypoplasia of the breast associated with a characteristic deformity of the upper limb. This cluster
of anomalies is called Poland’s syndrome and is more common in men than in women (Figure 2.9). Abnormalities of the chest wall, such as pectus excavatum, and deformities of the thoracic spine, such as scoliosis, can also result in normal symmetrical breasts seeming asymmetrical.

**Breast development and involution**

The breast is identical in boys and girls until puberty. Growth begins at about the age of 10 and may initially be asymmetrical: a unilateral...
breast lump in a 9–10-year-old girl is invariably a developing breast, and biopsy specimens should not be taken from girls of this age as this can damage the breast bud. The functional unit of the breast is the terminal duct lobular unit or lobule (Figures 2.10 and 2.11), which drains via a branching duct system to the nipple. The duct system does not run in a truly radial manner and the breast is not separated into easily defined segments. The lobules and ducts – the glandular tissue – are supported by fibrous tissue – the stroma. Most benign breast conditions and almost all breast cancers arise within the terminal duct lobular unit.

After the breast has developed, it undergoes regular changes related to the menstrual cycle. Pregnancy results in a doubling of the breast weight at term and the breast involutes after pregnancy. In nulliparous women breast involution begins at some time after the age of 30. During involution the breast stroma is replaced by fat so that the breast becomes less radiodense, softer and ptotic (droopy). Changes in the glandular tissue include the development of areas of fibrosis, the formation of small cysts (microcysts) and an increase in the number of glandular elements (adenosis). The life cycle of the breast consists of three main periods: development (and early reproductive life), mature reproductive life and involution. Most benign breast conditions occur during one specific period and

| Table 2.1 Aberrations of normal breast development and involution. |
|---------------|----------------|---------------|
| Age (years) | Normal process | Aberration |
| <25 | Breast development: | Juvenile hypertrophy |
| | Stromal | Fibroadenoma |
| 25–40 | Cyclic activity | Cyclic mastalgia; cyclical nodularity (diffuse or local) |
| 35–55 | Involution: | Macrocyts |
| | Lobular | Sclerosing lesions |
| | Stromal | Ductal | Ductal ectasia |

are so common that they are best considered as aberrations rather than disease (Table 2.1).

**Aberrations of breast development**

**Juvenile or virginal hypertrophy**

Prepubertal breast enlargement is common and requires investigation only if it is associated with other signs of sexual maturation. Uncontrolled overgrowth of breast tissue can occur in adolescent girls whose breasts develop normally during puberty but then continue to grow, often quite rapidly. No endocrine abnormality can be detected in these girls.

Patients present with social embarrassment, pain, discomfort and inability to perform regular daily tasks (Figure 2.12). Reduction

![Shoulder indentation resulting from bra strap in juvenile hypertrophy.](image)

Figure 2.12 Shoulder indentation resulting from bra strap in juvenile hypertrophy.
mammoplasty considerably improves their quality of life and should be more widely available (Figure 2.13).

Fibroadenoma
Although formerly classified as benign neoplasms, fibroadenomas are best considered as aberrations of normal development: they develop from a whole lobule and not from a single cell. They are common and are under the same hormonal control as the rest of the breast tissue. Fibroadenomas account for about 13% of all palpable symptomatic breast masses, but in women aged 20 they account for almost 60% of such masses (Figure 2.14; Table 2.2). There are three separate types of fibroadenoma: common fibroadenoma, giant fibroadenoma and juvenile fibroadenoma. There is no universally accepted definition of what constitutes a giant fibroadenoma, but most experts consider that it should measure over 5 cm in diameter. Juvenile fibroadenomas occur in adolescent girls and sometimes undergo rapid growth, but are managed in the same way as the common fibroadenoma (Figure 2.15).

Fibroadenomas have characteristic mammographic features in older patients if they calcify. A few patients have multiple fibroadenomas. Over a two-year period less than one tenth of common fibroadenomas increase in size, about one third get smaller or completely disappear and the remainder stay the same size. Fibroadenomas usually increase in size during pregnancy, sometimes dramatically. The appearance on ultrasonography also changes with spaces filled with fluid (milk); this should not be confused with the spaces seen sometimes in phyllodes tumours.

Phyllodes tumours are distinct pathological entities (Figure 2.16). They are usually larger than fibroadenomas, occur in an older age group, have malignant potential and cannot always be differentiated clinically from fibroadenomas. Phyllodes tumours focally may have an infiltrative margin, particularly in more aggressive forms, and range from benign (70%) to borderline (25%) to malignant (5%) (Figure 2.17). About 10% of benign phyllodes tumours recur after excision.

### Management of discrete mobile masses in young women

A diagnosis based on imaging alone is acceptable providing that the patient is young (<21) and the lesion is small (<3 cm). Otherwise a histological diagnosis should be established by core biopsy. In patients with multiple fibroadenomas, two or more lesions should be sampled and the rest should be imaged and monitored.

Fibroadenomas over 4 cm require full assessment by core biopsy. Multiple passes are required to ensure that the lesion is not a phyllodes tumour. Cytology alone is not recommended in these larger lesions, as it is not possible on cytology to distinguish with confidence fibroadenomas from phyllodes tumours. These larger lesions are usually excised because they are unsightly, but they can be observed providing that multiple core biopsies taken from different parts of the lesion show a simple fibroadenoma and imaging is benign. Large juvenile fibroadenomas can be excised through inframammary or circumareolar incisions, which give good cosmetic results (Figure 2.15). Common fibroadenomas diagnosed by core biopsy require excision only if this is requested by the patient. A cosmetic approach via an inframammary or circumareolar incision is recommended if they are to be excised. Removal of small fibroadenomas is possible using vacuum-assisted larger core biopsy devices, such as the 8-gauge mammotome.
Aberrations in the early reproductive period: Pain and nodularity

Cyclical pain and nodularity are so common that they can be regarded as physiological and not pathological. Severe or prolonged pain is regarded as an aberration (Chapter 3). Focal breast nodularity is the most common cause of a breast lump and is seen in women of all ages. The preferred pathological term for these areas is benign breast change, and terms such as fibroadenosis, fibrocystic disease and mastitis should no longer be used by clinicians or pathologists.

Aberrations of involution: Palpable breast cysts

About 7% of women in Western countries present at some time in their life with a palpable breast cyst (Figure 2.18). Palpable cysts constitute 15% of all discrete breast masses (Figure 2.19). Cysts are distended and involuted lobules and are most common in perimenopausal women. Most present as a smooth discrete breast lump that can be painful and is sometimes visible.

Cysts have characteristic halos on mammography and are readily diagnosed by ultrasonography. Imaging should be performed prior to needle aspiration. Only symptomatic or indeterminate cystic lesions should be aspirated or biopsied and providing that the fluid is not bloodstained it should not be sent for cytology. After aspiration the breast should be re-examined to check that the palpable mass has disappeared. About 1–3% of patients presenting with cysts have carcinomas, most of these are not associated with the cyst but are incidental findings on ultrasonography or mammography.

Patients with cysts have a slightly increased risk of developing breast cancer (twice to three times), but the magnitude of this risk is not clinically significant.
Sclerosing lesions

Aberrations of stromal involution include the development of localised areas of excessive fibrosis or sclerosis. Pathologically, these lesions can be separated into two groups: sclerosing adenosis and radial scars/complex sclerosing lesions (Figure 2.20).

These lesions are clinically important because of the diagnostic problems they cause during breast screening. Excision biopsy is often required to make a definitive diagnosis. Radial scars/complex sclerosing lesions are associated with malignancy – usually DCIS or low grade invasive cancers in about 10% of cases.

Duct ectasia

The major subareolar ducts dilate and shorten during involution and, by the age of 70, 40% of women have substantial duct dilatation or duct ectasia. Some women with excessive dilatation and shortening present with nipple discharge (Figure 2.21), nipple retraction or a palpable mass that may be hard or doughy. The discharge is usually cheesy and the nipple retraction is classically symmetrical and slit-like (Figure 2.22(a)) in contrast to whole nipple inversion and distortion with cancer (Figure 2.22(b)). Surgery is...
indicated only if the discharge is troublesome or the patient wants the nipple to be everted. Duct ectasia should not be confused with periductal mastitis, which is the condition underlying recurrent central breast infection.

**Benign disease in men: Gynaecomastia**

Gynaecomastia (the growth of breast tissue in males to any extent in all ages) is entirely benign and usually reversible. It is commonly seen during puberty (Figure 2.23) and old age (Figure 2.24). It occurs in 30–60% of boys aged 10–16 years and usually requires no treatment, as 80% of cases resolve spontaneously within two years. Embarrassment or persistent enlargement is an indication for surgical referral.

Senescent gynaecomastia commonly affects men aged between 50 and 80, and in most it does not seem to be associated with any significant endocrine abnormality. There are a variety of specific causes and a careful history and examination will often reveal the cause in a particular case (Table 2.3). A history of recent progressive breast enlargement without pain or tenderness and without an easily identifiable cause is an indication for blood, hormone and biochemical measurement. Mammography and ultrasound can differentiate between breast enlargement due to fat or gynaecomastia and are valuable if malignancy is suspected. Core biopsy should be performed if there is clinical or imaging suspicion of breast cancer.

In drug-related gynaecomastia withdrawal of the drug or change to an alternative treatment should be considered. Gynaecomastia is seen in body builders who take anabolic steroids; some have learnt that by taking tamoxifen they can combat this. Both tamoxifen and

**Table 2.3** Causes of gynaecomastia

<table>
<thead>
<tr>
<th>Cause</th>
<th>%</th>
<th>Cause</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puberty</td>
<td>25</td>
<td>Testicular tumours</td>
<td>3</td>
</tr>
<tr>
<td>Idiopathic (senescent)</td>
<td>25</td>
<td>Secondary hypogonadism</td>
<td>2</td>
</tr>
<tr>
<td>Drugs (including cimetidine, digoxin, spironolactone, androgens or anti-oestrogens)</td>
<td>10–20</td>
<td>Hyperthyroidism</td>
<td>1.5</td>
</tr>
<tr>
<td>Cirrhosis or malnutrition</td>
<td>8</td>
<td>Renal disease</td>
<td>1</td>
</tr>
<tr>
<td>Primary hypogonadism</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Danazol improve symptoms in patients with gynaecomastia, but recurrence after stopping drugs can be a problem. Tamoxifen at a dose of 10 mg is effective and produces fewer side effects than 20 mg of tamoxifen or danazol, so it is the drug of first choice. Surgery for gynaecomastia is not easy, should follow recognised protocols and should be performed by experienced breast or plastic surgeons.

**Benign neoplasms and proliferations: Epithelial hyperplasia**

Epithelial hyperplasia is an increase in the number of cells lining the terminal duct lobular unit. This was previously called epitheliosis or papillomatosis, but these terms are now obsolete. The degree of hyperplasia can be graded as mild, moderate or florid (severe).

If the hyperplastic cells also show cellular atypia, the condition is called atypical hyperplasia (Figure 2.25). The absolute risk of breast cancer in a woman with atypical hyperplasia who does not have a first-degree relative with breast cancer is 8% at 10 years; for a woman with a first-degree relative with breast cancer, the risk is 20–25% at 15 years.

Atypical hyperplasia is the only benign breast condition associated with a significantly increased risk of subsequent breast cancer.

**Duct papillomas**

These can be single or multiple. They are common and should be considered as aberrations rather than true benign neoplasms, as they show minimal malignant potential. The most common symptom is nipple discharge, which is often bloodstained (Figure 2.26). Papillomas are common abnormalities detected through breast screening. The problem is that core biopsy cannot always differentiate reliably between benign papillomas from papillary carcinomas. Following a diagnosis of a papillary lesion, excision is indicated unless there is obvious sclerosis indicating that the lesion is inactive and benign (Figure 2.27). Smaller papillomas can be excised by a suction large-volume core device, such as a mammatome.

Figure 2.25 (a) Atypical ductal hyperplasia – low power. (b) Atypical ductal hyperplasia – high power.

Figure 2.26 Bloodstained nipple discharge due to a duct papilloma.

Figure 2.27 Histology of a duct papilloma that measures 5 mm.
Lipomas
These soft, lobulated radiolucent lesions are common in the breast. Interest in these lesions lies in their confusion with pseudolipoma, a soft mass that can be felt around a breast cancer and that is caused by indrawing of the surrounding fat by a spiculated carcinoma. Ultrasound is helpful in establishing whether a lesion is a lipoma.

Nipple conditions
Nipple adenoma
This is an ulcerating lesion on the nipple that presents as a lump in the nipple or as nipple discharge (Figures 2.28 and 2.29). Treatment is wide excision. It is usually possible to save the nipple. Recurrence can occur if the lesion is not excised completely.

Jogger’s nipple
This results from recurrent trauma during regular exercise and is prevented by the application of Vaseline prior to exercise. It can be very sore, but resolves spontaneously.

Haematomas
These most commonly follow trauma such as a road traffic incident, but can occur after core biopsy, final needle aspiration or open biopsy. In extremely unusual circumstances a breast carcinoma may present with a spontaneous haematoma. Breast haematoma can also occur spontaneously in patients on anticoagulant therapy.

Fat necrosis
Fat necrosis of the breast is common. It is often called ‘traumatic fat necrosis’, although a history of trauma is present in only about
ABC of Breast Diseases

Figure 2.30 Seatbelt trauma leading to combination of early haematoma and fat necrosis.

Figure 2.31 Fat necrosis of the breast after trauma caused by seatbelt.

40% of patients. It is most dramatic after road traffic incidents as a result of seatbelt trauma to the breast (Figures 2.30 and 2.31).

Mondor’s disease

Thrombosis of superficial veins in the skin of the breast is known as Mondor’s disease (Figure 2.32). The thoracoepigastric vein is the most common site, but other unnamed veins can be affected. Most often seen after surgery or trauma, it can occur spontaneously, particularly in patients with an underlying clotting abnormality such as factor V Leiden. It is usually painful and tender to touch. No specific treatment is required, but it can take some time to resolve completely.

Hamartomas

Also known as fibroadenolipomas, hamartomas are common and consist of fibroglandular tissue admixed with fat surrounded by a capsule (Figure 2.27). They present clinically as a discrete breast mass and are often misinterpreted clinically as fibroadenomas. The surrounding halo of connective tissue differentiates these lesions on imaging from fibroadenomas. When biopsying a lesion likely to be a hamartoma, it is important to alert the pathologist otherwise the report may be B1 (normal) rather than B2 (benign) and the pathologist may not appreciate the findings as being consistent with a discrete lesion (Figure 2.33).

Figure 2.32 (a) Mondor’s disease of the right breast. Note the linear indentation in the breast at the site of the thrombosed vessel. (b) Mondor’s disease occurring after breast surgery.

Figure 2.33 Histology of a hamartoma with mixtures of tissue including smooth muscle.
Congenital Problems and Aberrations of Normal Development and Involution

Blocked Montgomery's tubercles
Montgomery’s tubercles are blind-ending ducts in the areola. Secretions from the lining cells may become inspissated and present as a periareolar lump that can be locally excised if troublesome (Figure 2.34). They can become infected.

Para areola cysts
These cysts are rare and occur in pubertal and postpubertal teenagers (11–16 years), presenting as discrete superficial cystic masses at the areola margin; occasionally they become infected. They can be interpreted as solid on ultrasonography because of numerous internal echoes. Diagnosis and treatment can be by aspiration, although if they cause no symptoms and ultrasonography shows a cystic lesion, no intervention is required as they disappear with time.

Morphea
This is a localised scleroderma of the breast and results in a thickened white distorted area of skin (Figure 2.35). When severe it can result in distortion of the breast contour. It is seen most frequently in women who have had radiotherapy after breast-conserving surgery for breast cancer. Treatment is symptomatic and local chemotherapeutic creams can be effective in resolution and in reducing the local pain that can be caused by such lesions.

Arteritis and aneurysm
Patients with generalised vascular disease can develop localised vasculitis involving vessels in the breast to produce a localised mass. Aneurysmal dilatation of arteries in the breast has been described and presents clinically as a discrete mass with an audible bruit on auscultation.

Sarcoidosis
Patients with sarcoidosis can present with single or multiple masses within the breast (Figure 2.36). A breast mass can occur either as the first presentation or in a patient with sarcoidosis elsewhere. Diagnosis is confirmed by core biopsy or excision.

Keloids of the Breast Skin
These can be seen on the breast and treated with steroids or liquid nitrogen (Figure 2.37).

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Figure 2.34 (a) Blocked Montgomery’s tubercle. (b) Histology of blocked Montgomery’s tubercle.

Figure 2.35 (a) Morphea affecting the skin of the breast. (b) Morphea following wide excision of the nipple-areolar complex and postoperative radiotherapy for invasive breast cancer.
Figure 2.36 Sarcoidosis of the breast.

Wegener’s Granulomatosis

Systemic conditions such as Wegener’s can produce changes in the breast skin (Figure 2.38).

Further reading


Mastalgia is pain in the breast. Up to 70% of women will experience this at some time during their life. The pain women describe as breast pain can arise either in the breast tissue itself or it can be referred pain, which is felt in the breast. The nerve supply to the breast is from the anterolateral and anteromedial branches of the intercostal nerves from T3 to T5 and irritation of these nerves anywhere along their course can lead to pain that is felt in the breast or nipple. A branch of T4 penetrates the deep surface of the breast and runs up to the nipple. Irritation of this nerve can result in the shooting pain up to the nipple that many women describe. Pain can also be referred from the breast or chest wall through the intercostobrachial nerve to the inner aspect of the arm.

Breast pain is a rare symptom of breast cancer. In a 10-year survey in Edinburgh of 8504 patients presenting with breast pain as their major symptom, 220 (2.7%) were subsequently diagnosed with breast cancer. During this period 4740 patients had breast cancer, which means that 4.6% of women with breast cancer had pain as an important presenting symptom.

It is important to differentiate between pain referred to the breast from the chest wall and true breast pain, because management of these two conditions is different. It is less important to differentiate cyclical mastalgia – pain that occurs only in the premenstrual part of the menstrual cycle – from non-cyclical mastalgia, as management of these conditions is similar. Pain may last throughout the cycle or bear no relation to the menstrual cycle.

Table 3.1 Classification of non-cyclical mastalgia.

<table>
<thead>
<tr>
<th>Chest wall causes</th>
<th>Non-breast causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Such as tenderness of costochondral junctions (Tietze’s syndrome)</td>
<td>Congenital and thoracic spondylitis</td>
</tr>
<tr>
<td>Lung disease</td>
<td>Gall stones</td>
</tr>
<tr>
<td>True breast pain</td>
<td>Exogenous oestrogens, such as hormone replacement therapy</td>
</tr>
<tr>
<td>Trigger spots in breast</td>
<td>Thoracic outlet syndrome</td>
</tr>
</tbody>
</table>

Primary care studies indicate that the most common type of mastalgia is pain referred from the chest wall. In breast clinics chest wall pain is now also more common than true breast pain. Clinical examination reveals that even in women with a classic history of cyclical breast pain, the chest wall is most often the site of origin of the pain (Table 3.1).

**Chest wall pain**

Features suggesting that breast pain is referred rather than originating in the breast include pain that
- is unilateral, and brought on by activity;
- is very lateral or medial in the breast; and
- can be reproduced by pressure on a specific area of the chest wall.

Women who are postmenopausal and not taking hormonal supplements or who are known to have spondylitis or osteoarthritis are much more likely to have musculoskeletal pain rather than true breast pain.

Careful clinical examination is essential to help determine the site of origin of the pain (Table 3.2; Figures 3.1–3.3). Any patient complaining of breast pain should have a complete breast examination including palpation with the woman lying on each side, allowing the breast to fall away from the chest wall, and palpation...
Figure 3.1 How to examine for lateral chest wall tenderness. The patient is rolled on her side with the breast falling away from the site of the pain laterally. The underlying chest wall is then palpated to identify any area of localised tenderness.

Figure 3.2 How to examine for medial chest wall tenderness over the costochondral junctions. The patient is rolled on her side with the breast falling away from the site of the pain medially. The underlying chest wall is then palpated to identify any area of localised tenderness.

Figure 3.3 How to examine for chest wall tenderness under the lower part of the breast. The breast is lifted upwards by one hand while the other hand pressing gently on the underlying chest wall to identify any area of localised tenderness.

of the underlying muscles and ribs. The patient should be asked to indicate whether there is any localised tenderness on palpation of the chest wall and whether any discomfort evident during examination is similar to the pain they normally experience. If the patient has pain in the lower part of the breast the underlying chest wall is examined by lifting the breast with one hand while palpating the underlying chest wall with the other hand. Allowing the woman herself to confirm that the site of maximal tenderness is in the underlying chest wall rather than the breast is an effective method of reassuring patients of the site of the pain.

Treatment of chest wall pain
The mainstay of treating chest wall pain is reassurance that there is no serious underlying cause for the pain. In women with troublesome pain, providing that there are no contraindications, non-steroidal anti-inflammatory drugs (NSAIDs) are usually effective. Although there is no evidence to suggest that topical NSAIDs have any benefit over oral preparations, there is some evidence that topical agents cause fewer gastrointestinal problems. Women often report a recent increase in activities, such as gardening, decorating, lifting or increased visits to the gym, after which they become aware of pain. Lifestyle is important in relation to breast pain. It is more common in women who spend many hours sitting at a desk in front of a computer. Identifying any underlying behaviour and modifying lifestyle accordingly form the cornerstone of treatment.

If the pain is very localised to one specific spot, then infiltrating the affected chest wall with prednisolone 40 mg in depot form combined with long-acting local anaesthetic can produce long-lasting pain relief (Table 3.3). If the correct area has been targeted, the pain should disappear quickly. About half of women with a localised tender spot get enduring benefit from a single injection. Repeating the injection after 4–6 weeks increases both the number of women getting benefit and provides long-lasting pain control for two-thirds of women with very localised troublesome pain that ‘interferes’ with regular daily activities.

Table 3.3 Outcome of women with chest wall pain treated by local infiltration of bupivacaine (Marcain) plus depot steroid (injected group) or observation alone (comparative group).

<table>
<thead>
<tr>
<th>outcome</th>
<th>injected group</th>
<th>comparative group</th>
</tr>
</thead>
<tbody>
<tr>
<td>no of women</td>
<td>104</td>
<td>34</td>
</tr>
<tr>
<td>no who attended follow-up</td>
<td>100</td>
<td>29</td>
</tr>
<tr>
<td>no (%) with complete resolution of pain</td>
<td>61 (61)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>no (%) with partial resolution of pain</td>
<td>22 (22)</td>
<td>8 (22.5)</td>
</tr>
<tr>
<td>no (%) with successful outcome</td>
<td>83 (83)</td>
<td>13 (44.4)</td>
</tr>
</tbody>
</table>

* Differences significant at p < 0.0001.
Chronic pain following breast surgery

Similar symptoms of chest wall pain are commonly reported after breast surgery, affecting up to 50% of women in some surveys. It is important to rule out underlying causes such as local recurrence or a prior underlying cause of chronic pain. Typically the introduction of gabapentin, pregabalin or amitryptiline is recommended in all forms of neuropathic pain such as scar pain or intercostobrachial neuralgia. The authors have used external neuromodulation for postoperative neuropathic pain with promising results. External neuromodulation consists of the application of electrical current through an external probe over the painful area, trigger zone or affected nerve. The pain reduction can be immediate and quality of life can be dramatically improved following regular applications. Further studies are required to establish the role of this treatment in chronic breast pain.

True mastalgia

Pain arising in the breast tissue itself is often associated with cyclical swelling and nodularity (Figure 3.4). Hormonal changes are thought to be responsible for these changes in the breast, as they are most commonly seen in the week before menstruation and are relieved by its onset. In addition, the pain can be brought on by hormonal manipulation such as oestrogen containing hormone replacement therapy. It is much less of a problem in women taking tibolone. There are several theories regarding the pathophysiology of mastalgia.

Too much oestrogen

Measurements of serum oestrogen concentrations have not shown any differences between women with pain and normal controls.

Not enough progesterone

A single study has shown reduced serum progesterone concentration in the luteal phase in women with mastalgia when compared with controls.

Too much prolactin

Measuring prolactin is complicated because of diurnal variation in hormone levels. Measurement of 24-hour serum prolactin profiles and of tissue concentrations of prolactin in breast biopsy samples taken either during the day or the night have not shown any differences between women with and without mastalgia. The prolactin response after stimulation has been studied, and women with mastalgia produced more prolactin for longer, suggesting that there may be a problem in the prolactin pathway at the level of the hypothalamus.

Increased receptor sensitivity in breast tissue/abnormal fatty acids

Women with mastalgia may have different fatty acid profiles to women without pain, in that they have an increased ratio of saturated fatty acids to essential fatty acids. Cell membranes that have a high proportion of saturated fats become rigid and membrane receptors are easier for ligands to bind to. If cell membranes are composed of unsaturated fats, they are more fluid and receptors can be enveloped in folds of the membrane, making it harder for ligands to access and stimulate the receptor. Because women with mastalgia have more saturated fatty acids, the theory is that oestrogen receptor is more available, making the cells in the breast more sensitive to the effects of oestrogen.

In reality there is no unifying hypothesis that explains why women get cyclical mastalgia.

Treatments for true mastalgia (Figure 3.5)

Reassurance

Breast pain often causes women to seek medical attention because they are afraid that it signifies serious pathology in the breast. Non-randomised studies have shown that reassurance is effective management in 70% of women (Figure 3.6).

Non-specific measures

Pain in bed at night is a problem for many women with both chest wall pain and true mastalgia. Wearing a soft, supportive bra at night stops the breast pulling down on the chest wall, supports tender breast tissue and helps many women to sleep. For chest wall pain, gentle exercise and stretching of the muscles, such as provided by swimming, seem sensible and are often advised, but this has not been studied. Lifestyle changes such as limiting the length of time spent sitting at a computer by taking regular breaks would also be sensible.

Researchers have suggested that some women get breast pain because of overstimulation of breast cells by methylxanthines as
Is the patient >40 years old?

- No
  - Is there clinical evidence of musculoskeletal origin for pain?
    - No
      - Is pain part of generalised premenstrual syndrome?
        - No
          - Pain relieved at 3 months?
            - No
              - Refer to breast clinic
            - Yes
              - Discharge
        - Yes
          - Consider treatment with non-steroidal anti-inflammatory drugs or local anaesthetic + Depot steroid
          - Consider selective serotonin reuptake inhibitors
          - Discuss endocrine treatments including side effects
    - Yes
      - Discharge
  - Yes
    - Mammography
    - Appropriate action

Is there a lump?

- No
  - Reassure patient and give advice*
  - Yes
    - Refer to breast clinic for triple assessment

Has pain resolved at 3 months?

- No
  - Try daily tamoxifen 20 mg or danazol 200 mg daily either in luteal phase or continuous
- Yes
  - Stop treatment

Is there a lump?

- No
  - Refer to breast clinic
- Yes
  - Refer to breast clinic for triple assessment

Wishes treatment

- Yes
  - Stop treatment
- No
  - Tamoxifen 10 mg daily in luteal phase (days 15 to 25 of menstrual cycle)

Pain relieved at 3 months?

- No
  - Discharge
- Yes
  - Stop treatment

Danazol

One double-blind randomised controlled trial of danazol 200 mg/day compared with placebo showed a significant improvement in breast pain. A second, larger double-blind randomised controlled trial compared danazol 200 mg/day with tamoxifen 10 mg/day or placebo. Both danazol and tamoxifen were effective in treating breast pain compared with placebo, but women taking tamoxifen reported fewer side effects. Restricting the use of danazol to the luteal phase of the menstrual cycle reduces side effects. In a double-blind randomised controlled trial of danazol taken only during the luteal phase compared with placebo, mastalgia was improved by danazol without an excess of adverse events compared with the placebo.

Tamoxifen

Tamoxifen 20 mg/day has been shown to be superior to placebo in one double-blind randomised controlled trial, and pain relief was maintained in 72% one year after use. When tamoxifen 10 mg/day was compared with danazol 200 mg/day, tamoxifen was superior to danazol. Women reported fewer adverse events with tamoxifen and more tamoxifen patients (33%) were pain free at one year than in the danazol group (39%). Giving tamoxifen only in the luteal phase of the menstrual cycle abolished pain in 85% of women in one study, regardless of whether they took 10 mg/day or 20 mg/day. A quarter of the women in the 10 mg group had pain at one year compared with 30% in the 20 mg group; adverse events were reported in 21% and 35% respectively, and included hot flushes and vaginal discharge. A meta-analysis of treatments for mastalgia restricted to tamoxifen, bromocriptine, danazol, evening primrose oil and placebo showed that tamoxifen was the most effective treatment with the least side effects.

Studies with tamoxifen gel applied to the breast indicate that this is an effective treatment, but it is not in common use and not widely available.

Low-fat diet

Two randomised controlled studies have shown that a low-fat diet is effective in improving cyclical mastalgia. Both studies limited the dietary fat intake to less than 15% of calories, and patients who responded showed changes in their serum lipid profiles. These studies were not blinded, so a placebo effect cannot be excluded. Such low-fat diets are difficult to maintain for longer than a few weeks.

Evening primrose oil (EPO), gamma-linoleic acid (GLA) and efamast

Preparations containing GLA were used in the treatment of mastalgia until October 2002, when they were withdrawn from prescription by the UK Medicines Control Agency, as it considered that there was no good evidence to support their use. Two double-blind randomised controlled trials of EPO compared with placebo have been conducted and published. Neither study showed any difference in outcome between treatment and control groups. There was a reported improvement in symptoms during the first three months of treatment with a worsening of symptoms after crossover, regardless of whether patients received treatment or placebo first. A further study showed improvement in pain scores in the treated group for both cyclical and non-cyclical pain, but this study did not report results after crossover and there was a high drop-out rate in the placebo arm. While other studies have been published, these were not randomised or blinded.

Figure 3.5 Management of breast pain in breast clinic.

Figure 3.6 Patient presents to GP with breast pain (wear supportive, well-fitting bra, take simple analgesics for pain, regular gentle exercise).
Other hormone-based treatments

Progestogens and progesterone have been used orally, topically (applied to the skin of the breast) and vaginally. Compared with placebo, oral medroxyprogesterone acetate did not produce any benefit in a dose of 20 mg/day given during the luteal phase. Topical progesterone produced no benefit in two randomised controlled trials, but in a double-blind randomised controlled trial of microionised progesterone administered in the luteal phase, 65% of treated women and 22% of patients receiving placebo had a 50% reduction in pain. Gestrinone, a synthetic steroid similar to danazol, has the advantage that the woman does not require additional contraception. Compared with placebo, gestrinone 2.5 mg twice a week produced a greater reduction in pain, but 41% of the women complained of adverse events. Dopamine agonists, such as bromocriptine and lisuride maleate, which inhibit prolactin release, seem effective in reducing breast pain. Although bromocriptine is effective at relieving pain compared with placebo, it is less effective than danazol and up to 80% of women develop side effects including headaches and dizziness. It is thus no longer used to treat breast pain. A placebo controlled trial has shown that lisuride is effective in reducing breast pain.

Non-hormonal treatments

Individual phyto-oestrogens, such as genistein and isoflavins, and soya milk, which is rich in genistein, have been investigated as treatments for breast pain. Only soya milk has been subjected to a double-blind randomised controlled study, with cows’ milk being used as a control. An improvement in symptoms was noted in 56% of test patients and 10% of controls, but the authors reported that non-compliance was a problem. Serum levels of phyto-oestrogens were not raised in some patients who reported a response to treatment, suggesting that they were not actually taking the soya. The major reason for non-compliance was that the soya drink was considered unpalatable.

Agnus castus, a fruit extract, has been subjected to a double-blind randomised controlled trial for the treatment of both premenstrual syndrome and mastalgia. Treatment with agnus castus showed a significant improvement in visual analogue pain scores and treatment was well tolerated. A double-blind randomised controlled trials of selective serotonin reuptake inhibitors (SSRIs) used in women with premenstrual symptoms, including four studies that specifically included physical symptoms, showed SSRIs to be more effective than placebo at relieving breast pain. Interestingly, SSRIs did have an effect on fatty acid profiles.

Conclusion

Several treatments are available to treat true mastalgia. There is no single ideal therapy. Reassurance is the mainstay of treatment and is effective. Tamoxifen 10 mg limited to the luteal phase of the menstrual cycle produces the highest rates of pain control with few short-term adverse events and the lowest recurrence rates of pain at one year, but it is not licensed for the treatment of mastalgia. Danazol given in the luteal phase is also effective and causes fewer adverse events compared to continuous treatment. For women who have mastalgia as part of premenstrual syndrome, agnus castus and an SSRI are options. Further studies of more tolerable dietary manipulations are needed. Research evaluating more palatable soya supplements may be worthwhile: EFO has not been shown to be an effective agent. It is important to remember that the majority of sufferers have chest wall pain and these agents offer little if any benefit for such pain.

Acknowledgement

The authors acknowledge the assistance of Patricia de la Torre in writing the section on external neuromodulation.

Further reading


Breast infection is now much less common than it used to be. It is seen occasionally in neonates, but it most commonly affects women aged between 18 and 50; in this age group it can be divided into lactational and non-lactational infection. Infection can affect the skin overlying the breast, when it can be a primary event, or it may develop secondary either to a lesion in the skin, such as a sebaceous cyst, or to an underlying skin condition, such as hidradenitis suppurativa.

**Treatment**

There are four guiding principles in treating breast infection:

- Appropriate antibiotics should be given early to reduce the likelihood of abscess development (Tables 4.1 and 4.2).
- Hospital referral is indicated if the infection does not settle rapidly following one course of antibiotic treatment.
- If an abscess is suspected it should be confirmed by ultrasonography, aspiration or both before surgical drainage is considered.
- Breast cancer should be excluded in patients with an inflammatory lesion that is solid on ultrasonography or on aspiration that does not settle despite apparently adequate antibiotic treatment.

All abscesses in the breast can be managed by repeated aspiration or incision and drainage (Figure 4.1).

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**Table 4.1** Organisms responsible for breast infection.

<table>
<thead>
<tr>
<th>Type of breast infection</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal, lactating and skin associated</td>
<td>Staphylococcus aureus (rarely E. coli)</td>
</tr>
<tr>
<td>Lactating and hidradenitis suppurativa</td>
<td>S. aureus (rarely S. epidermidis and streptococci)</td>
</tr>
<tr>
<td>Non-lactating</td>
<td>S. aureus, enterococci, anaerobic (streptococci, Bacteroides spp)</td>
</tr>
<tr>
<td>Skin associated</td>
<td>S. aureus</td>
</tr>
</tbody>
</table>

**Table 4.2** Antibiotics most appropriate for treating breast infections.

<table>
<thead>
<tr>
<th>Type of breast infection</th>
<th>No allergy to penicillin</th>
<th>Allergy to penicillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal, lactating and skin associated</td>
<td>Flucloxacillin (500 mg four times daily)</td>
<td>Erythromycin (500 mg twice daily)</td>
</tr>
<tr>
<td>Non-lactating</td>
<td>Co-amoxiclav (375 mg three times daily)</td>
<td>Combination of erythromycin (500 mg twice daily) with metronidazole (200 mg three times daily)</td>
</tr>
</tbody>
</table>

*Adult doses.
**Beware of MRSA in lactating infection. Follow advice of local microbiologist for appropriate antibiotic therapy.

**Figure 4.1** Breast abscess protocol.
Aspiration is best performed with ultrasound guidance (Figure 4.2), with the abscess cavity being lavaged with local anaesthetic to dilute out and to help aspirate pus and reduce pain. Repeated aspiration every 2–3 days is required to achieve resolution of larger breast abscesses. For the largest abscesses aspiration may need to be repeated five or more times.

Incision and drainage, if indicated, can almost always be performed under local anaesthesia except in children; placement of a drain or packing the abscess cavity after incision and drainage is unnecessary. Prior to incision and drainage, 1% lignocaine containing 1 in 200 000 adrenaline is injected into the skin overlying the abscess. Only a small incision is required to drain a breast abscess adequately. After incision the abscess is irrigated with the same local anaesthetic solution to wash out residual pus and to limit the pain of the procedure.

Neonatal infection

Neonatal breast infection is not common, but can occur in the first few weeks of life when the breast bud is enlarged (Figure 4.3). Although *Staphylococcus aureus* is the usual organism, occasionally infection is due to *Escherichia coli*. If an abscess develops, a small incision placed as peripherally as possible to avoid damaging the breast bud leads to rapid resolution.

**Lactating infection**

Better maternal and infant hygiene and early treatment with antibiotics have considerably reduced the incidence of abscess formation during lactation. Infection is more frequent following a first child and most commonly seen within the first six weeks of breastfeeding, although some women develop it during weaning. Lactating infection presents with pain, swelling and tenderness. There is usually a history of a cracked nipple or skin abrasion, but this is not the site of entry of organisms. *S. aureus* is the most common organism responsible, but *S. epidermidis* and *streptococci* are occasionally isolated. Drainage of milk from the affected area is reduced. Promotion of milk drainage and early antibiotic therapy are the cornerstones of treatment. Tetracycline, ciprofloxacin and chloramphenicol should not be used to treat lactating breast infection as they may enter breast milk and can harm the baby. The pain of lactation mastitis is helped by the application of gel packs or cold cabbage leaves to the breast; both are equally efficacious. In one very small randomised study, although more women preferred cabbage leaves, gel packs produced somewhat greater pain relief.

If infection does not settle after one course of antibiotics, no pus is detected on ultrasoundography, and if clinical and imaging assessments indicate that the lesion is infective or inflammatory, the antibiotic should be changed to cover other possible pathogens, including MRSA. If inflammation or an associated mass lesion persists, further investigation is required to exclude an underlying inflammatory carcinoma (Figure 4.4).

The management of breast abscesses (Figure 4.1) includes an initial ultrasound to determine whether an abscess with visible pus is present (Figure 4.2). An established abscess should be treated by either repeated aspiration – every 2–3 days until no more pus...
Breast infection is aspirated (Figure 4.5) – or incision and drainage (Figures 4.6 and 4.7). Women who want to continue breastfeeding should be encouraged to do so. Breastfeeding is often less painful than using a breast pump and is more effective at encouraging milk flow. There are some women who present with multiple areas of breast infection who are exhausted by breastfeeding (Figure 4.8) in whom consideration should be given to stopping breastfeeding and halting milk flow. Stopping milk production is achieved by prescribing cabergoline 2.5 mcg given twice a day for two days.

Figure 4.4 Inflammatory cancer.

Figure 4.5 (a) Lactating abscess, skin red but normal at presentation. (b) Lactating abscess following aspiration.

Figure 4.6 A breast abscess that developed during breastfeeding. Before treatment (a) and after min-incision and drainage (b).

Figure 4.7 Abscess being drained under local anaesthetic – only a small skin incision is needed.

Figure 4.8 Women are exhausted by breastfeeding.
Delay in hospital referral of breast feeding infection continues to be an issue (Figure 4.9).

Controversy surrounds the role of fungi and the value of fluconazole in breast pain and infection associated with breastfeeding. The evidence that fungi are important is largely anecdotal. There are no data from properly controlled clinical studies showing the value of fluconazole. Fluconazole should not be prescribed until further clinical trial evidence shows it to be beneficial. Some women do get Reynaud’s of the nipple during breastfeeding, which can cause considerable pain. This may respond to nifedipine.

**Non-lactating infection**

Non-lactating infections can be separated into those that occur centrally in the periareolar region and those that affect the peripheral breast tissue (Figure 4.10).

**Periareolar infection**

Periareolar infection is most commonly seen in young women (mean age 32). Histologically, there is active inflammation around non-dilated subareolar breast ducts – a condition that is called periductal mastitis. This condition has been confused with and called duct ectasia, but duct ectasia is a separate condition affecting older women and is characterised by subareolar duct dilatation and less pronounced and less active periductal inflammation. Current evidence suggests that smoking is the most important factor in the aetiology of periductal mastitis but not in duct ectasia: about 90% of women who get periductal mastitis or its complications smoke cigarettes, compared with 38% of the same age group in the general population. Substances in cigarette smoke may either directly or indirectly damage the wall of the subareolar breast ducts. Aerobic or anaerobic organisms then infect the damaged tissues. In North America, a widely held view is that periductal mastitis is due to duct obstruction by the squamous metaplasia seen commonly in this condition. All non-lactating women’s ducts are plugged with keratin, so duct obstruction cannot be important and squamous metaplasia is likely to be a consequence of infection, not the cause of it. Initial presentation of periductal mastitis may be with periareolar inflammation (Figure 4.11) (with or without an associated mass) or with an established abscess. Associated features include central breast pain, nipple retraction at the site of the diseased duct and nipple discharge.
Breast Infection

Figure 4.11 Periareolar inflammation due to periductal mastitis. Minor degree of nipple retraction is present at the site of the affected duct.

Treatment

A periareolar inflammatory mass should be treated with a course of appropriate antibiotics that includes anaerobic cover and be investigated by ultrasonography; any abscess should be managed by aspiration or incision and drainage (Figure 4.12). If the skin overlying the abscess is necrotic then the dead skin should be excised (Figure 4.10). If the mass is solid on ultrasonography or inflammation does not resolve after appropriate treatment, care should be taken to exclude an underlying neoplasm (Figure 4.4). Abscesses associated with periductal mastitis recur commonly because treatment by aspiration or incision does not remove the underlying diseased duct and most patients continue to smoke. Up to a third of patients develop a mammary duct fistula after drainage of a non-lactating periareolar abscess. Recurrent episodes of periareolar sepsis should be treated by excision of diseased ducts under antibiotic cover by an experienced breast surgeon.

Figure 4.13 Mammary duct fistula with arrow showing path of fistula probe. Dots around duct on left represent periductal mastitis, a precursor of a fistula.

Mammary duct fistula

A mammary duct fistula is a communication between the skin, usually in the periareolar region, and a major subareolar breast duct (Figure 4.13). A fistula can develop after incision and drainage of a non-lactating abscess, it can follow spontaneous discharge of a periareolar inflammatory mass, or it can result from biopsy of a periductal inflammatory mass.

Treatment

Treatment is by opening the fistula (fistulotomy) (Figure 4.14) or excising of the fistula (fistulectomy) and diseased duct or ducts under antibiotic cover. The best results are from fistula excision rather than fistulotomy (Figure 4.15). Recurrence is common after surgery. The lowest rates of recurrence and best cosmetic results are achieved by specialist breast surgeons.

Peripheral non-lactating breast abscesses

These are less common than periareolar abscesses and can be associated with an underlying condition such as diabetes, rheumatoid arthritis, steroid treatment, granulomatous lobular mastitis and trauma, although the majority have no obvious underlying cause (Figure 4.16). They should be treated with aspiration or incision and drainage and usually resolve rapidly, unless there is an underlying condition, and do not recur. Infection associated with granulomatous lobular mastitis can be a particular problem (Figure 4.17). This condition is described as affecting young parous women, but it is seen in nulliparous women as well. Clinically granulomatous lobular mastitis can present as a mass mimicking breast cancer with breast distortion, sometimes with skin ulceration, or it may present as large areas of infection with multiple simultaneous peripheral abscesses (Figure 4.17). The granulomas are centred around breast lobules (Figure 4.18). One study isolated corynebacteria from such lesions, but as antibiotics effective against these organisms do not lead to rapid resolution of disease, corynebacteria are very unlikely to be aetiological in this condition. There is a strong tendency for

Figure 4.12 (a) Non-lactating periareolar breast abscess secondary to periductal mastitis. (b) During incision and drainage. (c) Immediately following incision and drainage.
this condition to persist and for wounds to discharge and fail to heal after surgery.

Large incisions and extensive surgery should therefore be avoided. Steroids have been tried but with limited success, and reports of some improvement during therapy followed by relapse when steroids are reduced or stopped, and are not recommended. Peripheral breast abscesses should be treated by recurrent aspiration or incision and drainage. Otherwise management is conservative. Granulomatous lobular mastitis does resolve without specific treatment, but often takes many months and even years to do so.

Rarely subareolar or peripheral non-lactating infection can occur as a consequence of infection of an area of comedo necrosis associated with ductal carcinoma in situ. After antibiotic treatment or aspiration of pus, these areas can resolve completely and leave no residual mass. For this reason, all patients aged 35 should have a mammogram after resolution of an episode of breast infection for which there is no obvious cause.

**Skin-associated infection**

Primary infection of the skin of the breast, which can present as cellulitis or an abscess, most commonly affects the skin of the lower half of the breast (Figure 4.19). These infections are often recurrent in women who are overweight, have large breasts or have poor personal hygiene. Cellulitis is more common after surgery or radiotherapy (Figures 4.20 and 4.21) and in people with skin conditions such as eczema. *S. aureus* is the usual causative organism. Fungi such as *candida albicans* are not important organisms, despite antifungal creams being commonly used in these conditions. Cellulitis in the male breast is uncommon, but is seen in the neonatal and pubertal periods (Figure 4.22). Treatment of acute bacterial infection is with antibiotics and drainage or aspiration of abscesses. Women with recurrent infections and areas of intertrigo should be advised about weight.

Figure 4.14 (a) Mammary duct fistula. (b) Fistulotomy. (c) Cosmetic outcome that follows fistulotomy.

Figure 4.15 Mammary duct fistula. Left: external opening at areola margin, entire nipple is inverted. Middle: probe passed through opening of fistula and emerging from affected duct. Right: after excision of fistula and affected duct and primary closure under antibiotic cover. Operation performed through a circumareolar incision, which gives excellent cosmetic results.

Figure 4.16 Large peripheral abscess.
Breast Infection

Figure 4.17 (a) Granulomatous lobular mastitis in its various presentations with skin changes, a mass and multiple abscesses. (b) Patient in Figure 4.16 (top left) after resolution with conservative management only.

Figure 4.18 Pathology of granulomatous lobular mastitis with granulomas and giant cells.

Figure 4.19 Cellulitis of breast.

Figure 4.20 Cellulitis of left breast that occurred 18 months after left wide local excision and radiotherapy.

Figure 4.21 Cellulitis of right breast 10 years after mastectomy, insertion of prosthesis and mastectomy (left). Areas of ulceration are due to erosion of prosthesis through the skin (rarely seen with current radiotherapy techniques). Same patient (right) after wound settled and healed with treatment with co-amoxiclav.

reduction and keeping the area as clean and dry as possible (this includes careful washing of the area up to twice a day, using a hair dryer to dry the skin, avoiding skin creams and talcum powder, and wearing either a cotton bra or a cotton T shirt or vest worn inside the bra) (Figure 4.23). Antifungal agents should not be prescribed, as there is no evidence that they are effective or that fungi play an important role in this condition.

Sebaceous cysts are common in the skin of the breast and may become infected (Figures 4.24 and 4.25). Some recurrent infections in the inframammary fold are due to hidradenitis suppurativa.
Other infections and inflammatory conditions

Tuberculosis of the breast is now rare (Figure 4.27). It can be primary or, more commonly, secondary. Clues to its diagnosis include the presence of a breast or axillary sinus in up to half of patients. The commonest presentation of tuberculosis nowadays is with an abscess resulting from infection of a tuberculous cavity by an acute pyogenic organism such as *Staphylococcus aureus*. An open biopsy is often required to establish the diagnosis. Treatment is by a combination of surgery and antituberculous chemotherapy.

Syphilis, actinomycosis and mycotic, helminthic and viral infections occasionally affect the breast but are rare. Infection with
Breast Infection

Candida albicans has been implicated in causing deep breast pain after breastfeeding. The evidence for this association is extremely weak and does not justify the use of fluconazole in these women.

Nipple rings can cause problems with recurrent infection, particularly in smokers (Figure 4.28). Rarely, excision of the nipple areolar complex is required to control ongoing infection. Pilonidal abscesses affecting the nipple have been reported in hairdressers and sheep shearers. Also rarely, spontaneous infarction, also known as primary gangrene of the breast, occurs (Figure 4.29). This is most commonly seen in diabetics and patients with multiple other medical problems, such as renal failure. Treatment is excision of dead and infected tissue. Although it has been traditional to leave these wounds open, if wide excision of dead tissue is performed back to bleeding healthy breast, then primary wound closure is possible in some individuals.

Lymphocytic lobulitis

Also known as sclerosing lymphocytic lobulitis, lymphocytic lobulitis is associated with autoimmune disorders. A similar condition occurs in people with diabetes and is known as diabetic mastopathy or lymphocytic mastitis. These conditions present as a mass that can resemble malignancy. They are characterised histologically by intense fibrosis associated with lymphocytic infiltration around lobules and epithelioid fibroblasts in the stroma. No specific treatment is required once a specific histological diagnosis is established. Diagnosis is usually possible on core biopsy.

Factitial disease

Artefactual or factitial diseases are created by the patient, often through complicated or repetitive actions (Figure 4.30). Such patients may undergo many investigations and operations before the nature of the disease is recognised. The diagnosis is difficult to establish, but should be considered when the clinical situation does not conform to common appearances or pathological processes. There is often a history of multiple visits to both general practitioner and hospital with various symptoms. Psychiatric referral may help in establishing the diagnosis, but there is no recognised effective therapy.
Figure 4.30  Factitial disease is caused by repetitive trauma. When covered with an occlusive dressing the wounds in both patients healed. The patient on the top right had a history of seeking frequent medical attention.

Further reading


With over 1.4 million new cases in the world each year, breast cancer is the commonest malignancy in women and comprises 23% of all female cancers. In the United Kingdom, where the age-standardised incidence and mortality are among the highest in the world (Figure 5.1), the annual incidence among women aged 50 and over is almost 3 per 1000, rising to over 4 per 1000 at age 65–69. The disease is the commonest cause of death among women aged 40–50, accounting for about a fifth of all deaths in this age group. The introduction of the national screening programme in Britain in the late 1980s led to an increase in incidence as a pool of undiagnosed cancers was detected. Screening is offered every three years from age 50–70 and currently 8.1 per 1000 women screened are found to have cancer (including DCIS, ductal carcinoma in situ). Over the last 30 years the annual number of new cases of breast cancer in women has almost doubled. There are more than 12 000 deaths each year. Overall, in the last 10 years death rates from breast cancer have fallen by almost a fifth. Breast cancer survival rates vary by age at diagnosis (Figure 5.2), with those diagnosed in their 50s and 60s having higher survival rates than either younger or older patients.

Risk factors for breast cancer

Age
The incidence of breast cancer increases with age (Figure 5.3), doubling about every 10 years until the menopause, when the rate of increase slows dramatically. Compared with lung cancer, the incidence of breast cancer is higher at younger ages. In some countries there is a flattening of the age–incidence curve after the menopause (Figure 5.4).
Geographical variation/race
Breast cancer rates are similar around the world in premenopausal women, but there are striking differences after the age of 50 where the incidences in the Caucasian population in North America, Western Europe and Australia are higher than for most other regions (Figure 5.1). Age-adjusted incidence and mortality for breast cancer vary by up to a factor of five between countries. The difference between Far Eastern and Western countries is diminishing, but is still about threefold to fourfold. Studies of migrants from Japan to Hawaii show that the rates of breast cancer in migrants assume the rate in the host country within one or two generations, indicating that environmental factors are of greater importance than genetic factors (Figure 5.5).

Overall, breast cancer rates are lower in the Asian and African population after the age of 50, but similar prior to age 50 when compared to Caucasian women. In the United States, non-Hispanic whites have the highest incidence of breast cancer, whereas Asian Americans have the lowest rate. Among those aged 40–50, African American women have a higher incidence compared with non-Hispanic white women. African American and Hispanic women have also the highest death rate from breast cancer. This is at least partly due to a younger age at onset, where prognosis is generally poorer, but other factors may contribute to these variations, such as lifestyle differences, access to primary care and socioeconomic factors.

Breast density
Breast density constitutes the single largest population-attributable risk among known risk factors for breast cancer. Density of the breast decreases with age, but the increased risk in women with the most dense breasts is apparent for both pre- and postmenopausal women. Breast density is reduced in tamoxifen users, is increased with hormone replacement therapy use and is higher in nulliparous women and those with atypical hyperplasia. A meta-analysis of over 14 000 cases of breast cancer and 226 000 non-cases from 42 studies showed that the increase in relative risk of breast cancer was fourfold to fivefold comparing women with high-density versus low-density breasts.

Age at menarche and menopause
Women who start menstruating early in life or who have a late menopause have an increased risk of developing breast cancer. Women who have a natural menopause after the age of 55 are twice as likely to develop breast cancer as women who experience the menopause before the age of 45. At the other extreme, women who undergo bilateral oophorectomy before the age of 35 have only 40% of the risk of breast cancer of women who have a natural menopause.

Age at first pregnancy
Nulliparity and late age at first childbirth both increase lifetime incidence of breast cancer. The risk of breast cancer in a woman
who has had her first child after the age of 30 is about twice that of a woman who has had her first child before the age of 20. The highest-risk groups are those who have a first child after the age of 35; these women appear to be at even higher risk than nulliparous women. An early age at birth of a second child further reduces the risk of breast cancer.

Family history
Approximately 5% of breast cancer in Western countries is due to a strong genetic predisposition. Breast cancer susceptibility is generally inherited as an autosomal dominant with limited penetrance. This means that it can be transmitted through either sex and that some family members may transmit the abnormal gene without developing cancer themselves.

The last 20 years have seen first the development and second an expansion of genetic risk assessment and ‘family history’ clinics to deal with the ever-increasing demand for management of women at increased risk of breast cancer due to their family history. These clinics were originally centralised in a few major units, but the demand is such that management of moderate-risk women needs to be carried out in local units. A system of triage has developed, with ‘average-risk’ women being reassured in primary care, moderate-risk women receiving assessment in local units and high-risk women being referred to regional genetics centres. While mammography and MRI screening continue to be evaluated in the moderate- and high-risk categories, genetic testing for BRCA1 and BRCA2 is now routine in high-risk women and surgical risk-reduction options have gained validity. Much research is still necessary to improve risk prediction and early detection and to develop non-surgical means of prevention.

Although 5% of breast cancer is thought to be due to inheritance of a high-risk dominant cancer-predisposing gene, hereditary factors may play a part in a proportion of the remaining 95%+ of breast cancers (estimated as being important in up to 27% of breast cancers from twin studies); these have been hard to delineate (Table 5.1). Lower-risk genes have been identified from association studies. There are no external markers of risk (no phenotype) to help identify those who may carry a faulty gene, except in very rare cases such as Cowden’s disease where there are skin lesions and skull abnormalities. To determine the likelihood of there being a predisposing gene in a family, it is necessary to assess the family pedigree.

Inheritance of a predisposing gene results in breast cancer development at a young age and often involving both breasts. Certain gene mutations give rise to susceptibility to other cancers, such as ovarian cancer (BRCA1/2) or sarcomas and brain cancer (TP53).

Multiple primary cancers in one individual or related early-onset cancers in a pedigree are suggestive that a predisposing gene may be responsible. The risk of developing breast cancer almost doubles if a first-degree relative (mother, sister or daughter) has had breast cancer and triples if two relatives have (Table 5.2). The risk is higher when the relative’s cancer occurred at a young age and when the woman herself is young. For example, a woman whose sister developed breast cancer aged 30–39 has a cumulative risk of 10% of developing the disease herself by age 65, but that risk is only 5% (close to the population risk) if the sister was aged above 50 at diagnosis. The risk increases by between four and six times if two first-degree relatives develop the disease. For example, a woman with a two affected relatives, one who was aged under 50 at diagnosis, has a 25% chance of developing breast cancer by the age of 65.

The important features in a family history are the following:

1. Age at onset of breast cancer in affected relatives
2. Presence of bilateral breast cancer in affected relatives
3. Multiple cases of breast cancer in the family (particularly on one side)
4. Other related early-onset tumours such as sarcoma, glioma or childhood adrenal cancer.
5. Number of unaffected individuals (large families are more informative).

There are very few families where it is possible to be certain of the dominant inheritance of a cancer-predisposing gene. Where four first-degree relatives have early-onset or bilateral breast cancer, the risk of a sister or daughter having inherited a predisposing gene is close to 50%. Criteria for identifying women at substantial and very high risk are listed in Table 5.3. Approximately 80% of mutation carriers develop breast cancer at some point in their lifetime. Unless

---

Table 5.1 Gene evidence for differential treatment effect

<table>
<thead>
<tr>
<th>Gene</th>
<th>Allele</th>
<th>Frequency [%]</th>
<th>OR per allele</th>
<th>Evidence for differential treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>0.1</td>
<td>10</td>
<td>often triple (mega dose) should be NEGATIVE</td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>0.3</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHEK2</td>
<td>0.7</td>
<td>234</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATM</td>
<td>0.4</td>
<td>237</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGFR2</td>
<td>0.3</td>
<td>1.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDOC</td>
<td>0.46</td>
<td>1.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td>0.25</td>
<td>1.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G111</td>
<td>0.30</td>
<td>1.07</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.2 Established risk factors for breast cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative risk</th>
<th>High risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥50 years</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Age at menopause ≥54 years</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Age at first full pregnancy ≥30 years</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Body mass index &gt;30 in postmenopausal women</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption ≥10 Aged 55+</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives ≥10 Aged 55+</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Weight ≥10 Body mass index &gt;30 in postmenopausal women</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Combined hormone replacement therapy 2.5</td>
<td>Current use</td>
<td></td>
</tr>
<tr>
<td>Family history ≥2 patients</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Family history ≥3 patients</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Family history ≥4 patients</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Family history ≥5 patients</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Family history ≥6 patients</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Family history ≥7 patients</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Family history ≥8 patients</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Family history ≥9 patients</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Family history ≥10 patients</td>
<td>1.3</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.3 Genes predisposing to breast cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Allele</th>
<th>Frequency [%]</th>
<th>OR per allele</th>
<th>Evidence for differential treatment effect</th>
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<td>G111</td>
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<td>1.07</td>
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<td></td>
</tr>
</tbody>
</table>
Table 5.3  Criteria for identifying women at increased risk of breast cancer

- One first-degree relative (mother, sister or daughter) with bilateral breast cancer or breast cancer and ovarian cancer
- One first-degree relative with breast cancer diagnosed under the age of 40
- Two first- or second-degree relatives (grandmother, granddaughter, aunt or niece) with breast cancer diagnosed under the age of 60 or ovarian cancer at any age on the same side of the family
- Three first- or second-degree relatives with breast and ovarian cancer on the same side of the family. If no first-degree relatives then the second-degree relatives have to be on the paternal side

Risk estimation

Where there is no dominant family history, risk estimation is based on large epidemiological studies, which report a risk 1.5–3 times higher with family history of a single affected relative. Clinicians must be careful to differentiate between lifetime and age-specific risks. Some studies quote a ninefold or greater risk associated with bilateral breast cancer in a mother or with confirmed proliferative breast disease. The best way to assess risk is to take the strongest risk factor, which is nearly always family history. Risk is then assessed on this alone, minor adjustments can be made for other factors. Although studies do point to a greater risk if a family history is associated with other factors, a combination of risk factors may manifest through earlier expression of the gene, with breast cancer developing at a younger age. Risks between 40% and 8–10% are common, although lower risks are occasionally given. Higher risks are only applicable when a woman is shown to have a germline mutation and to have inherited a high-risk allele or to have proven proliferative breast disease together with a gene mutation. Several methods based on known risk factors have been devised to predict risk of breast cancer. Some depend on family history alone (e.g. the Claus and Ford models). Others depend on hormonal and reproductive factors in addition to family history (e.g. the Gail and Tyrer-Cuzick models). Outside clinics for high-risk areas where most women have a high risk of harbouring mutations in BRCA1, BRCA2 and TP53 genes, models that combine as many risk factors as possible are preferable. Only 10% of breast cancer occurs in individuals with a first-degree family history of breast cancer. The Gail model predicted accurately the number of cancers that developed in the Nurses Health Study, but the Tyrer-Cuzick model, which depends on extent of family history and endocrine factors, proved better than models using fewer risk factors in the Manchester family history clinic. A clinical manual assessment was as good as Tyrer-Cuzick and significantly better than other computer-based models. Models have reasonably good predictive power when estimating the number of cancer cases likely to be seen in a population, but are less accurate in their ability to identify which particular woman will develop breast cancer. At present, risk factors not related to family history, such as mammographic density, are not included in risk models. Further studies are in progress to determine whether inclusion of factors such as mammographic density, weight gain and serum steroid hormone measurements will improve prediction. Although breast density is an independent risk factor for BRCA1 and BRCA2 cancer risk, breast density may be heritable and may not increase risk in all women.

The breast cancer genes

High-risk genes

Numerous genes predispose to breast cancer. Not all of these have been identified. Two high-risk predisposing genes, BRCA1 and BRCA2, are thought to account for over 80% of highly penetrant inherited breast cancer (population frequency of approximately 0.2%; Table 5.2). The vast majority of families with breast and ovarian cancer are linked to BRCA1 or BRCA2. Population studies show risks as low as 40%, but more recent large-scale studies indicate higher levels of risk for both genes. The overall cumulative lifetime risk of developing breast cancer is believed to be in the range of 60–85% for breast cancer and 40–60% for ovarian cancer in BRCA1, and 50–85% and 10–30% respectively for BRCA2. Controversy still exists over the true lifetime risk associated with mutations in BRCA1/2.

The TP53 gene on chromosome 17p also predisposes to early breast cancer. Germine mutations account for over 70% of cases of the Li Fraumeni syndrome. In this syndrome soft tissue/osteosarcoma is seen in families with early onset breast cancer, glioma, childhood adrenal cancer and other early onset malignancies. The risk of breast cancer <30 years is higher than for BRCA1 and mutation carriers have a very substantially increased risk of sarcomas, brain malignancy and other tumours. The overall impact of Li Fraumeni syndrome on the overall breast cancer incidence is quite small.

Cowden’s disease caused by PTEN (phosphatase and tensin homolog) mutations is a high-risk inherited genetic mutation, but does not account for many familial breast cancers. Cowden’s disease can be recognised by extreme macrocephaly and scrotal tongue together with skin lesions such as trichilemmomas and pigmentation of the penis in males.

Moderate-risk genes

Carriers of mutations in ataxia telangiectasia (ATM), BRIP, PALB2 genes and the CHEK2 1100delC mutation are now thought to have a two-fold increased risk of breast cancer. Moderate risk genes are relatively rare (population frequency 0.1–2%).

Low-risk common alleles

Common single nucleotide polymorphisms (SNPs) have now been identified by genome-wide association studies. Around 20 validated SNPs with population frequencies of >5% are associated with increases in the relative risk of breast cancer varying from 1.05 to 1.24.
shown to have clinical utility.

Moderately increased risk

higher risk of breast cancer than exposure at an older age. Studies of survivors of atomic bomb explosions and other population studies indicate that exposure in the teens and early 20s carries a much greater risk than exposure at an older age.

Hodgkin's lymphoma who were treated with radiotherapy in their early 20s. These women are at greatly increased risk of developing breast cancer. This is a small effect in the developed world, but can be substantial in the developing world where women have four or more children and breastfeeding is continued for up to two years for each child.

Genetic testing

Currently genetic testing is largely concentrated on BRCA1/2. Gene testing is limited to women deemed to be at 10–20% lifetime risk as estimated by a scoring system. Testing for BRCA1/2 takes typically around 8 weeks to complete, but some laboratories have a short waiting list. Comprehensive testing for breast cancer involves 60–100 genetic loci. Private companies are already marketing testing of SNPs. These results have to be treated with caution and need to be interpreted alongside other risk factors, including family history. At present the 28 genetic loci associated with risk only account for about 38% of the inherited component of breast cancer. Testing of genes other than BRCA1/2 and, rarely, TP53 has not yet been shown to have clinical utility.

Table 5.4  Relative risk of invasive breast cancer associated with benign breast disease.

<table>
<thead>
<tr>
<th>No increased risk</th>
<th>Slightly increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mild hyperplasia</td>
<td>• Palpable cysts (cystic disease)</td>
</tr>
<tr>
<td>• Duct ectasia</td>
<td>• Moderate and florid hyperplasia</td>
</tr>
<tr>
<td>• Apocrine metaplasia</td>
<td>• Papilloma</td>
</tr>
<tr>
<td>• Simple fibroadenoma</td>
<td>• Complex fibroadenomas</td>
</tr>
<tr>
<td>• Mastitis</td>
<td>• Sclerosing adenosis</td>
</tr>
<tr>
<td>• Periioductal mastitis</td>
<td></td>
</tr>
<tr>
<td>• Adenosis</td>
<td></td>
</tr>
</tbody>
</table>

Moderately increased risk (4–5 times)

• Atypical hyperplasia

Previous benign breast disease

Benign breast disease in the absence of proliferation does not carry any increased risk, whereas simple hyperplasia roughly doubles the risk and atypical hyperplasia increases the risk of developing breast cancer about fourfold (Table 5.4). Women with atypical hyperplasia and a family history of breast cancer (first-degree relative) have a very high risk. Women with these lesions who develop cancer typically have their cancers distant from the site of the benign lesion. This is in contrast to ductal carcinoma in situ (DCIS), where the cancer develops directly or in close proximity to the lesion. Women with palpable cysts, complex fibroadenomas, duct papillomas, sclerosis adenosis and moderate or florid epithelial hyperplasia have a slightly higher risk of breast cancer (1.5–3 times) than the general population.

Radiation

Exposure to radiation is known to increase many types of cancer, but most of this research has been in people who have been exposed to a high level of radiation. A particular concern is for women with Hodgkin’s lymphoma who were treated with radiotherapy in their early 20s. These women are at greatly increased risk of developing breast cancer and the risk for them is probably about the same as for women with a strong family history of breast cancer. Studies of survivors of atomic bomb explosions and other population studies indicate that exposure in the teens and early 20s carries a much higher risk of breast cancer than exposure at an older age.

Lifestyle

Diet and alcohol

Although there is a correlation between the incidence of breast cancer and dietary fat intake at the population level, studies at an individual level have not found a relation between fat intake and breast cancer. Several studies have reported a consistent but small positive relationship with alcohol intake. The risk increases by about 7% for one drink per day (10g) and it appears that this is unrelated to the type of alcohol (beer, wine or spirits).

Weight and height

Obesity is associated with a twofold increase in the risk of breast cancer in premenopausal women, whereas among premenopausal women it is associated with a slightly reduced incidence. Furthermore, studies have shown that the risk is higher if the extra fat is around the waist. Overall, the relative risk increases by 1% for every kilogram of weight increase. Studies suggest that significant weight gain between the ages of 20 and 40 leads to an increase in breast cancer risk.

A woman’s height has been associated with an increased breast cancer risk in many studies (relative risk increases by 1% for every 1 cm in height). Taller women have a small increased risk of developing both premenopausal and postmenopausal breast cancer compared to shorter women. It is not clear how height affects breast cancer risk, but it is believed that interactions of genetics, nutrition and hormonal levels play an important role. One possible explanation suggests that the hormones that affect a woman’s height may also cause an increase in the amount of glandular tissue in the breast. Most breast cancers arise from this tissue and more breast parenchymal tissue could lead to increased susceptibility to breast cancer.

Breastfeeding

An overview of epidemiological studies found that the relative risk of breast cancer decreased by 4.3% for every 12 months of breastfeeding. The conclusion from this large meta-analysis was that the longer women breastfeed, the more they are protected from developing breast cancer. This is a small effect in the developed world, but can be substantial in the developing world where women have four or more children and breastfeeding is continued for up to two years for each child.

Smoking

The majority of studies have not found a relationship between smoking and breast cancer. It is unlikely that smoking plays a significant aetiological role in breast cancer.

Physical activity

Numerous studies have shown that moderate physical activity is associated with a reduced risk of developing breast cancer of about 30%. The European Prospective Investigation into Cancer and Nutrition investigated in over 210 000 pre- and postmenopausal women the role of different types of physical activities and found that household activity especially was associated with a significantly reduced risk of breast cancer.
Oral contraceptive (OC)

While women are taking oral contraceptives and for up to 10 years after stopping these agents, there is a small increase in the relative risk of developing breast cancer. There is no increase in risk of having breast cancer diagnosed 10 or more years following cessation of the oral contraceptive agent. Cancers diagnosed in women taking the oral contraceptive seem less likely to be advanced clinically, with those diagnosed in women who have never used these agents relative risk 0.88 (0.81–0.95). The higher relative risk applies at an age when the incidence of breast cancer is low, so the overall effect is minimal.

Hormone replacement therapy (HRT)

The first reports of an increased risk of breast cancer with HRT were published in the mid-1970s. Initial reports found an increased risk for both oestrogen-only and oestrogen–progestogen combined therapy. In 1996, the Collaborative Group on Hormonal Factors in Breast Cancer published a comprehensive analysis of case-control and cohort data from 51 studies. The main findings of this study were that risk was confined to current users of HRT and that risk increases with the duration of HRT use, leading to an excess relative risk of 2.3% per year of HRT use. Risk appears to revert to normal levels almost immediately after stopping. Similar results were published in the United States. Similar trends have been seen in other countries.

Tibolone is almost as effective as combined HRT in relieving menopausal symptoms. The MWS found a significant 45% increased risk of breast cancer in tibolone users. A similar 40% increase in recurrence risk was found with the LIBERATE trial when compared with those on oestradiol-only preparations (Figure 5.6). Indeed, the WHI study reported that those on oestrogen-only preparations had a non-significantly reduced risk of developing breast cancer. Data from the WHI study showed that the breast cancers diagnosed in women on HRT were larger and more likely to be node positive, possibly because HRT makes them hard to visualise on mammograms. Following the report of the WHI study, a steep decrease in HRT use and in breast cancer risk was seen. Data from the WHI study reported that breast cancer risk was larger for current users of combined HRT preparations than for those on oestrogen-only preparations (Figure 5.6). Indeed, the WHI study reported that breast cancer risk was larger for current users of combined HRT preparations than for those on oestrogen-only preparations (Figure 5.6).

Further reading

OVERVIEW

• Improvements in our understanding of the aetiology of breast cancer have helped to identify preventive interventions for high-risk women.

• A variety of drugs that interfere in the interaction between oestrogen and the oestrogen receptor (selective oestrogen receptor modulators) can reduce breast cancer development when given to high-risk women.

• Other drugs, including bisphosphonates, statins, metformin and aspirin, continue to be investigated as preventive agents.

• Prophylactic bilateral mastectomy reduces the risk of breast cancer in BRCA mutation carriers by over 90%.

• Prophylactic oophorectomy in BRCA mutation carriers reduces the risk of breast cancer by approximately 50%.

Screening as currently practised can reduce mortality but not the incidence of breast cancer, and is cost effective only among women for whom breast cancer is common (2–3/1000 per year). Advances in hormonal and cytotoxic treatment and better delivery of care have produced significant survival benefits. A greater appreciation of factors important in the aetiology of breast cancer is to find a preventive intervention for high-risk women. Strategies for breast cancer prevention encompass lifestyle changes as well as surgical and medical therapeutic interventions.

Management options

The options for a woman at significantly increased risk of breast cancer are limited (Table 6.1). While there is limited evidence that screening such young women is effective in reducing mortality, screening is currently offered to high-risk young women. Many women wish to explore other options to reduce their risk.

Selective estrogen receptor modulators (SERMs)

Four large trials with tamoxifen in high-risk women without breast cancer have been undertaken, and long-term follow-up information is now available. An overview of these trials has shown a 43% reduction in ER-positive invasive cancer, but no impact on ER-negative disease. Importantly, a reduced incidence has been seen in the period after active treatment was completed, with an additional 38% reduction in years 6–10. As side effects were minimal in the post-treatment period, the risk–benefit ratio has improved with longer follow-up, and an unanswered question is whether there is additional benefit after 10 years of follow-up. The effectiveness and side-effect profile of tamoxifen are now very well understood (Figure 6.1) and it is currently considered the agent of choice for preventive therapy, especially in premenopausal high-risk women or those with atypical hyperplasia (Figure 6.2) or lobular carcinoma in situ (LCIS) (Figure 6.3). See chapter 16.

Another SERM, raloxifene, has been evaluated in three randomised trials. In two of these trials breast cancer was not the...
Figure 6.2. Risk of subsequent development of invasive carcinoma in patients with no epithelial proliferation, proliferative disease without atypia (moderate or florid hyperplasia), atypical hyperplasia or atypical hyperplasia and a family history of cancer.

Figure 6.3. Reduction in invasive breast cancer observed in the National Surgical Adjuvant Breast and Bowel Project tamoxifen breast cancer prevention trial for women with a prior diagnosis of lobular carcinoma in situ (LCIS) and atypical hyperplasia. Diagnosis was based entirely on patient history. Neither the histology report nor the previous histology slides were reviewed.

Figure 6.4. Incidence of ER-positive invasive breast cancer in the prevention trials with tamoxifen or raloxifene.

primary endpoint, but nevertheless the results showed a marked decrease in breast cancer incidence with raloxifene. Early reports suggested a greater benefit than tamoxifen (Figure 6.4). The most recent direct comparison with tamoxifen in the STAR trial at 81 months indicated that the risk ratio of raloxifene: tamoxifen was 1.24 for invasive cancer and 1.22 for non-invasive disease. Adverse events were less common with raloxifene: RR 0.55 for endometrial cancer; RR 0.19 for endometrial hyperplasia; and RR 0.75 for thromboembolic events. Raloxifene for postmenopausal women thus appears to have advantages compared with tamoxifen (Figure 6.5).

More recently, lasofoxifene and arzoxifene have been investigated in randomised trials where the primary focus was on fracture prevention in osteoporotic women. Both trials have shown a significant decrease in ER-positive breast cancers with these agents.

None of the SERMs has demonstrated any impact on oestrogen receptor-negative tumours, so that other approaches are needed for this type of breast cancer.

An alternative strategy, particularly in BRCA1/2 carriers, is to opt for early risk-reducing salpingo-oophorectomy at about 40 years of age. This can reduce subsequent breast cancer risk by approximately 50% (Table 6.2). This can be seen for the risk of breast cancer in unaffected women and in the contralateral breast for those with breast cancer. The effects of an early menopause and doubts over long-term HRT use have to be considered if the primary purpose is breast cancer prevention.

Aromatase inhibitors (AI)

A reduction in contralateral breast cancer has been seen in all adjuvant trials comparing an aromatase inhibitor with tamoxifen.
Prevention of Breast Cancer

or placebo, with an overall reduction of 30% compared to tamoxifen suggesting a potential 75% reduction overall. The use of aromatase inhibitors in the preventive setting is being tested in two randomised clinical trials in high-risk women without breast cancer.

Other agents

In addition to antihormonal drugs, other agents have emerged that were initially developed for other diseases that may be useful for the prevention of breast cancer. Bisphosphonates were originally developed to inhibit the activity of osteoclasts and have been effective in the breast cancer setting in controlling bone loss induced by aromatase inhibitors and chemotherapy. Two cohort studies in women with osteoporosis have reported a 30% lower breast cancer incidence in users versus non-users. Furthermore, these results suggested that bisphosphonates may have a greater effect in ER-negative breast cancer. Overall, these agents are well tolerated and primary prevention trials are needed to investigate fully the risk–benefit ratio of these agents for breast cancer prevention.

Metformin is widely used in patients with type 2 diabetes and works by targeting the enzyme AMP-activated protein kinase (AMPK), which induces muscles to take up glucose from the blood. Cohort studies in women with type 2 diabetes have shown a reduced risk of breast cancer in those taking metformin. Small biomarker studies in women with breast cancer in a placebo-controlled setting are ongoing and these results may lead to larger chemoprevention trials with metformin.

In epidemiological and interventional studies, a chemopreventive effect of aspirin has consistently been shown for a number of cancers. Evidence from case-control and cohort studies indicates a reduction in breast cancer risk by about 10% for aspirin and a possibly a little more for ibuprofen. For colorectal cancers, it has been shown that the use of aspirin needs to be continued for at least 10 years to have any beneficial effect. Given the long-term effect of aspirin on cancer risk, further insight is best derived from a longer follow-up of current trials. Similar results have been found with other NSAIDs and COX-2 inhibitors. Evidence for other agents, such as statins, is inconsistent.

Regular screening

Annual mammographic breast screening will identify over 60% of cancers in young women, but interval cancers do occur. The young breast is denser and more difficult to interpret. Although the first evidence of a significant survival advantage has emerged for general population screening under 50 years, the frequency of disease in this young age group is probably too low to justify screening on economic grounds. BRCA1 carriers appear to have a worse prognosis, so the value of screening in terms of mortality benefit in gene carriers is unclear. Mammography may eventually be replaced by more sensitive techniques such as MRI. The costs and scarcity (Table 6.3) of scanners may mean that MRI is limited to very high-risk women. Currently MRI screening is recommended in the UK for BRCA1/2 and TP53 mutation carriers aged 30–49 as well as for very high-risk individuals without mutations (www.nice.org.uk).

Table 6.3  MRI scanning for women at high risk.

<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>MARIBS study group (2005).</td>
<td>77% detected by MRI, 94% detected by either MRI or mammography, mammography was more specific (93%) than MRI (81%).</td>
</tr>
</tbody>
</table>

Prophylactic surgery

One risk-reduction option is prophylactic bilateral mastectomy, which reduces the risk of breast cancer in unaffected BRCA mutation carriers by 90% (Figure 6.6). This option remains controversial, as there are still to date no data to support a reduction in mortality. Moreover, with the psychosocial and emotional issues that come with prophylactic mastectomy, the emotional needs of these women need to be addressed. Nipple-sparing mastectomy with...
reconstruction can be offered to most women and results in better cosmetic and psychological outcomes for suitable individuals. The most acceptable prophylactic operation to women is a skin- and nipple-areola sparing mastectomy and areola sparing mastectomy, but this may leave a small amount of breast tissue. Increasingly the nipple is being spared because it is clear that this can be done without compromising breast tissue excision and significantly increasing subsequent breast cancer risk.

Ovarian cancer

Intensive cancer screening

There is currently no evidence that an annual pelvic examination, transvaginal ultrasound and/or serum CA125 is effective in early diagnosis. Studies examining the sensitivity of such surveillance in detecting early cancer have mixed results and in general the sensitivity is only found to be 60% with no reduction in mortality. Women who carry a BRCA1/2 mutation should be advised to undertake bilateral salpingo-oophorectomy once their family is complete.

Men with BRCA1 and BRCA2 mutations

Males who are BRCA2 mutation carriers have a lifetime risk of breast cancer estimated to be approximately 6–8% compared with 0.1% for men who are not carriers. The lifetime risk of prostate cancer is increased to 4.7 times higher than non-carriers. Men who carry a BRCA2 mutation should be considered for breast screening.

Further reading


OVERVIEW

- Screening for breast cancer reduces mortality but does not reduce incidence.
- Screening of women (over the age of 50) has been shown to reduce morbidity and mortality from breast cancer.
- Currently mammographic screening is the only method of screening that has been shown to be effective on a population basis.
- MRI screening in younger women (<50 years of age) who are gene carriers has been shown in randomised studies to be effective in identifying cancers at an early stage.
- Screening is not without morbidity and efforts are continuing to reduce recall rates, false positive rates etc.

Lack of knowledge of the pathogenesis of breast cancer means that primary prevention is currently a distant prospect for most women. Early detection represents an alternative approach for reducing mortality from this disease.

Screening can be targeted at populations at risk (for example women aged ≥50) and high-risk groups (for example younger women with a significant genetic risk; see Chapter 5). There is no evidence that either clinical examination or teaching self-examination of the breast is an effective tool for early detection. The former has been the subject of clinical trials.

The aim of screening is to reduce morbidity and mortality from breast cancer by detecting it early and treating it when it is small and before it has had the chance to spread.

Screening tests should be simple to apply, cheap, easy to perform, straightforward and unambiguous to interpret, and identify those with disease and exclude those without. Mammography requires high-technology equipment, highly trained staff to perform the examinations and highly trained readers to interpret the images (Figure 7.1 and Table 7.1). Mammography is at present the best screening tool available for population screening and was the first screening method for any malignancy that has been shown to be of value in randomised trials. Digital mammography is now replacing conventional film/screen mammography as it offers significant logistic advantages and better screening performance, particularly in younger women and those with dense breasts. There is some evidence that ultrasonography of the mammographic dense breast can improve sensitivity. Magnetic resonance imaging seems to be valuable in screening younger high-risk groups. Digital mammography tomosynthesis (DBT) is currently being evaluated as a screening technique. Dedicated breast computed tomography (CT) is currently being developed as a potential technique to image the breast.

Population screening

Effect on mortality

Randomised controlled trials have shown that screening by mammography can significantly reduce absolute mortality from breast cancer.
cancer by up to 40% in those who attend (Figure 7.2). The benefit is greatest in women aged 50–70. Published data from the combined Swedish trials show an overall significant reduction in mortality from breast cancer of 21% during 15 years of follow-up in women aged 40–74, with the most benefit seen in women aged 55–69 (30%).

Acceptance, quality assurance and monitoring

Over 70% of the target population must participate if screening is to reduce mortality significantly, and the cost per life year saved rises if fewer participate. To achieve optimal participation, accurate lists of names, ages and current addresses are required (Table 7.2). Factors affecting attendance for screening include the level of encouragement by general practitioners, knowledge about the disease and the screening programme, and the views and experiences of family and friends. Screening programmes must include both the initial screening process and the assessment of abnormalities detected by screening and have clearly defined treatment pathways when these are necessary.

Standards must be set to ensure that targets for mortality reduction are likely to be achieved and that there is quality assurance at each stage of the screening process (Table 7.1). Multidisciplinary teams experienced in the management of breast disease should carry out screening and assessment.

Specific training and regular education programmes related to screening should be mandatory for all professionals involved, and regular audit and review of individual and programme results and performance are necessary.

Age range

Current data indicate that absolute reduction in mortality is greatest in women aged 55–69 (30%). A smaller reduction in mortality of 20% could be achieved in younger women (40–54), but screening is less cost effective because of the lower incidence of breast cancer in these women and the high proportion of false-positive screening results. In Europe the consensus view is that mammographic screening of younger women on a population basis cannot be justified. In the United Kingdom screening is by invitation from age 50–70 inclusive. The age range is being extended in England to 47–73 as a randomised study to assess the mortality benefit of starting screening from the age of 47 and continuing up to the age of 73.

Frequency of screening

In the United Kingdom the interval between mammographic screens was selected from evidence from the Swedish two counties study and is every three years. A UKCCCR trial comparing annual with standard triennial mammographic screens has shown a small but insignificant advantage for annual screening of women. Screening needs to be shorter than the mean sojourn time for age. For women over 60 an interval of three years seems to be effective. For women aged 50–60, the ideal screening interval is probably between two and three years. If screening is offered to women aged <50, it should be annual.

Screening method

There is clear evidence that two mammographic views of each breast (mediolateral oblique and craniocaudal) significantly improve both sensitivity, particularly for small breast cancers, and specificity.

Table 7.2 Requirements for organising population screening.

<table>
<thead>
<tr>
<th>Requirement</th>
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<tbody>
<tr>
<td>• Accurate population lists</td>
</tr>
<tr>
<td>• Well-trained multidisciplinary assessment team</td>
</tr>
<tr>
<td>• Encouragement by general practitioners to attend</td>
</tr>
<tr>
<td>• Built-in quality assurance</td>
</tr>
<tr>
<td>• Clear screening protocols</td>
</tr>
<tr>
<td>• Continual audit and education</td>
</tr>
<tr>
<td>• Agreed patterns of referral</td>
</tr>
</tbody>
</table>

Figure 7.2 Summary of 7–12-year mortality data from randomised and case-control (*) studies of breast cancer screening. Points and lines represent absolute change in mortality and confidence interval.

Figure 7.3 Screening mammogram (left) showing a small cluster of suspicious microcalcifications; (left middle) core biopsy specimen radiograph showing satisfactory sampling; (right middle) histology showing comedo DCIS; and (right) the excised specimen radiograph showing complete excision of this small focus of DCIS.
Small invasive cancers found (Invasive cancers found 27–36
Recall for assessment 700–100
Women screened 10,000
Table 7.4
the NHSBSP is 1.0 and the expected standard is 1.4, 40% higher
of 25% in the population. The minimum standard for SDR in
Sweden, an SDR of 1.0 is predicted to provide a mortality reduction
detection ratio (SDR). Using data from the two counties study in
of individual screening units is measured using the standardised
15 mm in diameter (measured pathologically). The effectiveness
More than 55% of all invasive cancers detected should be less than
invasive cancers and 5–10 DCIS per 10,000 are expected (Table 7.4).
At subsequent screens (at ages 53–70) at least 30 screen-detected
for every 10,000 women who attend an initial (prevalent) screen.
need to attain and maintain appropriate levels of sensitivity and
specificity. Among women aged 50–52, a minimum of 27 invasive
cancers and 4–9 ductal in situ cancers (DCIS) should be detected
for every 10,000 women who attend an initial (prevalent) screen.
At subsequent screens (at ages 53–70) at least 30 screen-detected
invasive cancers and 5–10 DCIS per 10,000 are expected (Table 7.4).
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detection ratio (SDR). Using data from the two counties study in
Sweden, an SDR of 1.0 is predicted to provide a mortality reduction of
25% in the population. The minimum standard for SDR in the
NHSBSP is 1.0 and the expected standard is 1.4, 40% higher
cancer detection than originally achieved, reflecting the increase in
underlying breast cancer incidence over the past 20 years. Recall
rates for assessment should be less than 7% among prevalent attendees and less than 5% at subsequent screens. Women with a ‘normal’ screening outcome should be informed of their result by letter within two weeks. Patients judged to have an important abnormality require further assessment. The positive predictive value of recall plotted against the recall rates is used as a comparative measure of screening and assessment quality (Figure 7.4).

There are only two possible endpoints to assessment: no relevant abnormality or a diagnosis of breast cancer. Assessment should be by the triple approach, combining further imaging (mammography and ultrasonography) with clinical examination and proceding to needle biopsy where indicated (Figures 7.5 and 7.6). A dedicated team should carry out assessments. The team should include radiologists, surgeons and pathologists and be supported by specialist imaging and breast care nursing.

About 80% of screen-detected abnormalities prove to be unimportant on further mammography or ultrasonography. When an important abnormality is thought to be present, diagnosis by needle biopsy should be attempted after clinical assessment. In the United Kingdom up to 85% of important abnormalities detected by screening are impalpable, and image-guided biopsy is necessary. Automated wide-bore (14-gauge) needle core biopsy is the preferred method as it provides a histological diagnosis, which has the advantage of differentiating invasive from in situ disease and can provide an indication of grade (Figure 7.7). Where immediate reporting is required fine needle aspiration may be preferred, but this method generally has lower sensitivity than core techniques.

Vacuum-assisted mammotomy (VAM) is being used increasingly to sample suspicious microcalcifications and other abnormalities where there is likely to be diagnostic uncertainty. VAM will under-stage DCIS and invasive disease in about 10% of cases, compared with 20% for core biopsy. VAM can also be used to excise papillary and mucocrcl-like lesions and avoid the need for surgical excision.

Core of microcalcifications (Figure 7.6) should be x-rayed to ensure that enough representative material has been sampled where small areas of calcification are biopsied a tissue marker should be placed (Figure 7.8). Image-guided biopsy of impalpable lesion using ultrasonography (Figures 7.9 and 7.10), or x-ray stereotaxis, for abnormalities not visible on ultrasonography is highly accurate. Impalpable lesions may be localised by ultrasonography if visible on this modality or by mammography. Ultrasound-guided biopsy is the method of choice as it is more accurate, quicker, easier to perform, cheaper and associated with less discomfort for the patient than x-ray-guided techniques. Ultrasonography is also an accurate means of performing needle biopsy of palpable abnormalities. Most benign lesions can be diagnosed with these needle techniques, and open surgery to establish a diagnosis should be avoided. For malignant lesions definitive preoperative diagnosis can be achieved in over 98% of invasive cancers. The minimum standard for preoperative diagnosis of cancers in the NHSBSP is 90%.

Needle sampling can be carried out freehand, but image guidance is more accurate and is recommended (Figure 7.11). Diagnostic open surgical biopsy is indicated when two separate attempts at needle sampling of suspicious lesions fail to provide a definitive diagnosis.

A comparison of performance in UK screening units showed a 42% increase in the detection of carcinomas measuring 15 mm in units that use two views (Table 7.3). There is also emerging evidence that digital breast tomosynthesis increases the specificity of screening mammography. Trials are ongoing to assess the sensitivity effect of this technique. Double reading of films improves sensitivity by 5–12%. Single reading with computer-aided detection (CAD) has been shown to provide near equivalent sensitivity to double reading.

The screening process
The first part of screening is the basic screen. All screening units need to attain and maintain appropriate levels of sensitivity and specificity. Among women aged 50–52, a minimum of 27 invasive cancers and 4–9 ductal in situ cancers (DCIS) should be detected for every 10,000 women who attend an initial (prevalent) screen. At subsequent screens (at ages 53–70) at least 30 screen-detected invasive cancers and 5–10 DCIS per 10,000 are expected (Table 7.4). More than 55% of all invasive cancers detected should be less than 15 mm in diameter (measured pathologically). The effectiveness of individual screening units is measured using the standardised detection ratio (SDR). Using data from the two counties study in Sweden, an SDR of 1.0 is predicted to provide a mortality reduction of 25% in the population. The minimum standard for SDR in the NHSBSP is 1.0 and the expected standard is 1.4, 40% higher cancer detection than originally achieved, reflecting the increase in underlying breast cancer incidence over the past 20 years. Recall rates for assessment should be less than 7% among prevalent attendees and less than 5% at subsequent screens. Women with a ‘normal’ screening outcome should be informed of their result by letter within two weeks. Patients judged to have an important abnormality require further assessment. The positive predictive value of recall plotted against the recall rates is used as a comparative measure of screening and assessment quality (Figure 7.4).

Table 7.3 Results from the NHSBSP 2007–08 in women aged >50.

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of women invited</td>
<td>2,578,136</td>
</tr>
<tr>
<td>Acceptance rate (50–70 years)</td>
<td>73.40%</td>
</tr>
<tr>
<td>Number of women screened (invitation)</td>
<td>1,889,470</td>
</tr>
<tr>
<td>Number of women screened (self-referral)</td>
<td>105,181</td>
</tr>
<tr>
<td>Total number of women screened</td>
<td>1,994,651</td>
</tr>
<tr>
<td>Number of women recalled for assessment</td>
<td>83,222</td>
</tr>
<tr>
<td>% women recalled for assessment</td>
<td>4.2%</td>
</tr>
<tr>
<td>Number of benign biopsies</td>
<td>1,716</td>
</tr>
<tr>
<td>Number of cancers detected</td>
<td>16,449</td>
</tr>
<tr>
<td>Number of in situ cancers detected</td>
<td>3,257</td>
</tr>
<tr>
<td>Number of invasive cancers &lt;15 mm</td>
<td>6,878</td>
</tr>
<tr>
<td>Standardised detection ratio (invited women 50–70 years only)</td>
<td>1.45</td>
</tr>
</tbody>
</table>

Table 7.4 Expected results from screening 10,000 women.

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of women</th>
</tr>
</thead>
<tbody>
<tr>
<td>First prevalent screening: women aged 50–52</td>
<td></td>
</tr>
<tr>
<td>Women screened</td>
<td>10,000</td>
</tr>
<tr>
<td>Recall for assessment</td>
<td>700–100</td>
</tr>
<tr>
<td>Invasive cancers found</td>
<td>27–36</td>
</tr>
<tr>
<td>Small invasive cancers found (&lt;15mm)</td>
<td>15–20</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>4</td>
</tr>
<tr>
<td>Benign surgical biopsies</td>
<td>18–36</td>
</tr>
<tr>
<td>Repeat (incident) screen: women aged 53–70</td>
<td></td>
</tr>
<tr>
<td>Women screened</td>
<td>10,000</td>
</tr>
<tr>
<td>Recall for assessment</td>
<td>500–700</td>
</tr>
<tr>
<td>Invasive cancers found</td>
<td>31–42</td>
</tr>
<tr>
<td>Small invasive cancers found (&lt;15mm)</td>
<td>17–23</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>5</td>
</tr>
<tr>
<td>Benign surgical biopsies</td>
<td>10–20</td>
</tr>
</tbody>
</table>
Multidisciplinary assessment

When the results of all diagnostic procedures are available, the multidisciplinary team should discuss these together and decide on appropriate management. Preoperative diagnosis of cancer facilitates informed patient counselling and choice of treatments.

Localisation biopsy and excision

Impalpable lesions need to be localised for surgery. This can be achieved by using image guidance to place a hooked wire in the tissues adjacent to the lesion. The surgeon can then identify the site of the abnormality and excise it. Accurate placement of the

Figure 7.4 PPV diagrams. (a) Prevalent screen showing more variable performance and (b) incident screens showing everyone performing well above the minimum standards.

Source: NHS Breast Screening Programme.

Figure 7.5 Microcalcifications representing screen-detected high-grade ductal carcinoma in situ.

Figure 7.6 Comparative sizes of 18-, 14- and 11-gauge core specimens, yielding on average 17, 100 and 300 mg of tissue per core respectively.
localising wire is essential (Figure 7.7). Various systems are available. Radiolabelled occult lesion localisation (ROLL) and intraoperative ultrasound are alternative methods to wire marking and may be associated with less discomfort (Figure 7.12). Superficial lesions can also be effectively localised by skin marking.

If the procedure is being performed to establish a diagnosis, a representative portion of the lesion is excised through a small incision, so leaving a satisfactory cosmetic result if the lesion proves to be benign (the European surgical quality assurance guidelines require such diagnostic surgical excision specimens to weigh <30 g) (Figures 7.13 and 7.14). In therapeutic excisions the lesion should be excised with a 10 mm macroscopic margin of normal tissue (Figure 7.15). Intraoperative specimen radiography is essential, to check that the lesion has been removed and, if cancer has been diagnosed, to ensure an adequate wide local excision with radiological clear margins (Figure 7.16).

Figure 7.7 Cancer left breast in patient with a breast implant with marker clip in situ.

Figure 7.8 Discrete lesion identified on screening: Ultrasound examination of the lesion showed it to be benign.

Figure 7.9 Core biopsy showing that lesion above was a fibroadenoma.

Figure 7.10 Ultrasound guided biopsy of an impalpable lump in the upper right breast (left) and scan showing needle in lesion (right).

Figure 7.11 Mammogram showing (left) iodinated contrast marking the site of injections for ROLL using high molecular weight colloid and (right) subsequent radiograph of specimen confirming satisfactory surgical excision.
Figure 7.12 Impalpable stellate lesion detected by screening. Lesion is either a radial scar or an invasive carcinoma and so biopsy is required.

Figure 7.13 Histology of the lesion showed a radial scar (low-power view).

Figure 7.14 Cosmetic result of recent diagnostic excision biopsy showing small scar and no visible loss of tissue.

Figure 7.15 Oriented specimen radiograph of therapeutic excision showing adequate excision at all lateral margins (S = superior, M = medial, L = lateral).

Screening high-risk groups

Women who are at high risk of developing breast cancer due to family history, previous radiotherapy (for example mantle radiotherapy for Hodgkin’s lymphoma) or benign lesions (atypical hyperplasia) may be selected for screening at a young age. No screening test has yet been shown to reduce mortality in such women, although a single-arm study of annual mammography in over 6000 women who have at least moderate-risk family history predicted a 30% relative reduction in mortality compared to non-screened women. Screening should not be offered to those at minimal increased risk (less than three times the relative risk by age 50).

Methods of screening young women at high risk

Mammography has a greater positive predictive value in young women at high risk compared with age-matched controls, but it lacks sensitivity. This may be a particular problem in women with BRCA1 mutations. Ultrasound screening significantly improves sensitivity when there is a dense mammographic background pattern, but has a lower positive predictive value. While magnetic resonance imaging (MRI) seems to be the most sensitive method of imaging young women, it is expensive. It can detect cancers that are missed by mammography and has a role in screening young women carrying a BRCA1 or BRCA2 mutation (Figure 7.16). Whichever imaging method is selected the process should be repeated annually. Even in the high-risk setting, mammography should not be used routinely for screening women under the age of 40.
Age to start screening in young women at risk
The age for starting screening should be based on risk rather than the age of affected relatives. For women at high risk (more than eight times the relative risk by age 50) screening can be started at age 30–35 with MRI. For those at moderate risk (more than four times the risk by age 50) screening should start at age 40, usually with mammography alone. In each case screening should be annual and women must be advised about the limitations and risks of screening at a young age.

Benefits and potential drawbacks of screening
Characteristics of screen-detected cancers
Compared with symptomatic cancers, those detected by screening are smaller and are more likely to be non-invasive (in situ), while any invasive cancers detected are more likely to be better differentiated, of special type (Figure 7.17 and Table 7.5) and node negative (Figure 7.18). The ability of screening to affect mortality from breast cancer indicates that early diagnosis identifies breast cancers at an earlier stage in their evolution when the chance of metastatic disease being present is smaller (Table 7.6). Inevitably, mammographic screening will result in overdiagnosis of cancers that may never have developed to a life-threatening stage, such as low-grade ductal carcinoma in situ. Current evaluation, however, suggests that such overdiagnosis occurs in only a small proportion of cases and that the overall benefits exceed the potential harm. Women should, however, be fully informed of both the potential benefits and harms associated with mammographic screening.

Table 7.5  Histological types of screen detected and symptomatic breast cancers.

<table>
<thead>
<tr>
<th>Type</th>
<th>Screen-detected carcinoma</th>
</tr>
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<tbody>
<tr>
<td>Non-invasive</td>
<td>21%</td>
</tr>
<tr>
<td>Invasive</td>
<td></td>
</tr>
<tr>
<td>Special type*</td>
<td>27%</td>
</tr>
<tr>
<td>No special type</td>
<td>52%</td>
</tr>
</tbody>
</table>

Note: * These have a better prognosis than cancers of no special type and include invasive tubular, cribriform, medullary, mucoid, papillary and micromassive cancers.

Table 7.6  Percentage of invasive cancers.

<table>
<thead>
<tr>
<th></th>
<th>Screen detected (n = 150)</th>
<th>Symptomatic presentation (n = 306)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>II</td>
<td>38</td>
<td>35</td>
</tr>
<tr>
<td>III</td>
<td>36</td>
<td>54</td>
</tr>
<tr>
<td>Lymph node:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>80</td>
<td>58</td>
</tr>
<tr>
<td>Positive</td>
<td>20</td>
<td>41</td>
</tr>
<tr>
<td>Median size (mm)</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Nottingham Prognostic Index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>Moderate</td>
<td>48</td>
<td>53</td>
</tr>
<tr>
<td>Poor</td>
<td>5</td>
<td>22</td>
</tr>
</tbody>
</table>
The effectiveness of mammographic screening is influenced by several factors. A dense background pattern on mammography significantly reduces the sensitivity of screening. The sensitivity of mammography for malignancy is as high as 98% where the background pattern is fatty, but this falls to less than 50% in the dense breast. Younger age and use of hormone replacement therapy are independently associated with increased mammographic density and hence reduced sensitivity of mammographic screening.

Breast cancer in a woman with the BRCA1 susceptibility gene is more likely to be occult on mammography, as it tends to be high grade and to grow rapidly, typically producing little desmoplastic reaction in the surrounding breast and often not associated with microcalcification. Recent evidence suggests that mammography may not be suitable for screening women with the BRCA1 gene and that magnetic resonance imaging is preferable.

Psychological morbidity induced by screening

Invitation to breast screening can increase anxiety. There does seem to be a short-term increase in anxiety associated with recall for assessment, but three months later, women who are shown to have no important abnormality (false positives) are no more anxious than control women. The excess years as a breast cancer patient caused by a cancer being diagnosed earlier might diminish a patient’s quality of life, but the psychological morbidity in women with breast cancer detected by screening has been reported to be similar to or less than that in age-matched controls.

Risks of mammography

It has been calculated that for every two million women aged 50 who have been screened by means of a single mammogram, one extra cancer a year after 10 years may be caused by the radiation delivered to the breast. Compared with an incidence of breast cancer that approaches 2000 in every million women aged 60, this risk is very small. Regular mammography should be avoided in women under the age of 40.

Unnecessary biopsies

Some women who undergo biopsy will be found not to have cancer, but in Britain the number of women undergoing a biopsy for benign disease is monitored and is falling over time. The proportion of such biopsies performed in a screening programme should be monitored and compared with that in an unscreened group of women of the same age. Women who require biopsy are likely to be extremely anxious, but there is no evidence that this anxiety is sustained if the results are benign.

Further reading


Breast cancers are derived from epithelial cells that are found in the terminal duct lobular unit. Cancer cells that remain within the basement membrane of the elements of the terminal duct lobular unit and the draining duct are classified as in situ or non-invasive. An invasive breast cancer is one in which there is dissemination of cancer cells outside the basement membrane of the ducts and lobules into the surrounding adjacent normal tissue. Both in situ and invasive cancers have characteristic patterns by which they can be classified.

**Classification: Invasive breast cancer**

The most commonly used classification of invasive breast cancers divides them into ductal and lobular types. This was based on the belief that ductal carcinomas arise from ducts and lobular carcinomas from lobules. As all invasive ductal and lobular breast cancers arise from the terminal duct lobular unit, this terminology is confusing, although it is still used. Some tumours show distinct patterns of growth and cellular morphology, and so certain types of breast cancer can be identified (Figure 8.1). Those with specific features are called invasive carcinomas of special type, the others are considered to be of no special type (Table 8.1). This classification has clinical relevance in that certain special-type tumours have a better prognosis or different clinical characteristics and clinical behaviour compared with tumours of no special type.

**Tumour differentiation**

Among the cancers of no special type, grading the degree of differentiation of the tumour can yield prognostic information (Figure 8.2). Degrees of glandular formation, nuclear pleomorphism and frequency of mitoses are scored from 1 to 3. These values are combined and converted into three groups: grade I (score 3–5), grade II (scores 6 and 7) and grade III (scores 8 and 9).

Tumour grade is an important predictor of both disease-free and overall survival. The introduction of molecular diagnostics has heralded a change in the way breast cancers are now reported.
Markers such as hormone receptors and the growth factor receptor HER2 ne are reported routinely.

**Oestrogen receptor**

Approximately three-quarters of breast cancers express significant amounts of oestrogen receptor (ER). This can be assessed immuno-histochemically and scored using an Allred score that ranges from 0–8 (there is no 1), a histoscore that multiplies the percentage of cells staining positively by the intensity of the stain (1 weak, 2 moderate, 3 strong) to produce a score of 0–300 or can just be reported as the percentage of positively staining cells in the range of 0–100. An estimate of the RNA messenger for ER is included as one component of the recurrence score (Chapter 14). Cancers that express ER tend to be ER rich and most ER-positive cancers have an Allred score of 7 or 8, with few scores falling between 2 and 6.

**Progesterone receptor**

The majority of ER-positive cancers express progesterone receptors (PgR). Cancers which are both ER- and PR-positive have the greatest probability of responding to hormone therapy. There are very few PgR-positive ER-negative cancers. Scoring for PgR is as for ER.

**Human epidermal growth factor receptors**

There are four human epidermal growth factor receptors (HER). These are HER1, also known as epidermal growth factor receptor (EGFR); HER2, also known as cerb2 (it is called this because it causes erythromblastosis in chickens); and the other two, which are lesser known, HER3 and HER4. Currently HER2 is the only epidermal growth factor receptor assessed routinely. Initial screening is usually with an antibody with staining being classified as 0, + (both are considered HER negative), ++ (considered equivocal) and +++ (considered positive). All +++ cases are assessed by fluorescence in situ hybridisation (FISH) and the ratio of copies of HER2 to copies of the chromosome 17 (the chromosome where HER2 is situated on the long arm). A score of ≥2.0 is considered positive. Methods that use other markers other than fluorescence are also available and are used in some laboratories as their only test.

Approximately 15–20% of all cancers are HER2 positive. Most ER-positive cancers (90% +) are HER2 negative. Cancers that are ER negative, PgR negative and HER2 negative are called triple-negative cancers. These are more common in BRCA1 carriers. Approximately half of triple-negative cancers respond well to chemotherapy, but some triple-negative cancers are chemotherapy resistant. Originally HER2-positive and triple-negative cancers had a poorer outlook than HER2-negative ER-positive cancers. With the advent of specific anti-HER2 therapies the survival of HER2 positive cancers patients has increased dramatically over recent years.

**Other features**

Several other histological features in the primary tumour are valuable in predicting local recurrence and prognosis.

**Lymphatic or vascular invasion (LVI)**

The presence of cancer cells in blood or lymphatic vessels (Figure 8.3) is a marker of more aggressive disease, and patients with this feature are at increased risk of both local and systemic recurrence.

**Extensive in situ component**

Patients with 25% of the main tumour mass consisting of non-invasive disease with in situ cancer in the surrounding breast tissue
have been classified as having an extensive in situ component (EIC) and were formerly considered to be at increased risk of local recurrence after breast-conserving treatment. It is now appreciated that if an invasive cancer with EIC is excised to clear margins then the risk of recurrence is not greater than for cancers without EIC.

**Investigation**

All patients with invasive breast cancers should have 2-view mammography with or without magnification mammography and whole breast ultrasound. Any evidence of multifocality or multicentricity or of suspected extensive in situ disease that might influence surgical treatment should be confirmed by image-guided core biopsy. Patients with invasive cancer should also have axillary ultrasound with FNA or core biopsy of any suspicious axillary nodes. Ultrasound with subsequent FNA or core can detect up to 60% of patients with involved axillary nodes.

MRI may be valuable in selected patients, but has not been shown to be of value when performed routinely in women who are suitable for breast-conserving surgery. The COMICE randomised trial of MRI in patients suitable for breast-conserving surgery showed that MRI did not increase the rate of complete excision or in the short term reduce the number of local recurrences after breast-conserving therapy.

**Staging of invasive breast cancers**

The extent of invasive disease should be assessed and the tumour staged. The current staging classifications are not well suited to breast cancer: the tumour node metastases (TNM) system (Table 8.2) depends on clinical measurements and clinical assessment of lymph node status, both of which are inaccurate, and the International Union Against Cancer (UICC) system (Table 8.3) incorporates the TNM classification (Figures 8.2 and 8.3). To improve the TNM system, a separate pathological classification has been added to include tumour size and node status, as assessed by a pathologist. Prognosis in breast cancer relates to the stage of the disease at presentation.

**Table 8.2** TNM classification of breast tumours.

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T ≤ 2 cm (T &lt; 0.5 cm), N = 0, M = 0</td>
</tr>
<tr>
<td>II</td>
<td>T &gt; 2 cm, N = 0, M = 0</td>
</tr>
<tr>
<td>III</td>
<td>Any T, N = 1–3, M = 0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T, any N, M = 1</td>
</tr>
</tbody>
</table>

**Table 8.3** Correlation of UICC (1987) and TNM classification of tumours.

<table>
<thead>
<tr>
<th>UICC stage</th>
<th>TNM classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T ≤ 2 cm, N = 0, M = 0</td>
</tr>
<tr>
<td>II</td>
<td>T &gt; 2 cm, N = 0, M = 0</td>
</tr>
<tr>
<td>III</td>
<td>T &gt; 2 cm, N = 1–3, M = 0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T, any N, M = 1</td>
</tr>
</tbody>
</table>

**Figure 8.4** Survival associated with invasive breast cancer according to stage of disease. Adapted from West Midlands Cancer Registry.

Patients with stage I and stage II disease have a low incidence of detectable spread, and in the absence of specific signs or symptoms they should not undergo further investigations to identify metastatic disease (Figure 8.4). Patients with larger or more advanced tumours should be considered for CT or CTPET scans (Figure 8.5).

**Surgical treatment of localised breast cancer**

Most patients will have a combination of local treatments to control local disease and systemic treatment to combat any micrometastatic disease. Local treatments consist of surgery and radiotherapy. Surgery can be excision of the tumour with surrounding normal breast tissue (breast-conservation surgery) or mastectomy.
At least 12 randomised clinical trials have compared mastectomy and breast-conservation treatment and shown a non-significant 2% (SD 7%) relative reduction in death in favour of breast-conserving therapy. Local recurrence rates were similar, with a non-significant 4% (SD 8%) relative reduction in favour of mastectomy (Figure 8.6). Two large randomised trials comparing mastectomy and breast-conserving therapy have shown no significant differences in survival after 20 years of follow-up.

Selection for breast-conserving surgery or mastectomy

Clinical and pathological factors may influence selection for breast conservation or mastectomy because of their impact on local recurrence after breast-conserving therapy (Table 8.4). Complete excision of all invasive and in situ disease is essential (Figure 8.7). Local recurrence is 3.4 (95% confidence interval 2.6

Table 8.4: Indications and contraindications for breast-conserving surgery.

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1, T2 (&lt;4 cm), N0, N1, M0</td>
<td>Patients who prefer mastectomy</td>
</tr>
<tr>
<td>T2 &gt;4 cm in large breasts</td>
<td>Relative contraindications</td>
</tr>
<tr>
<td>Single clinical and mammographic lesion</td>
<td>Collagen vascular disease</td>
</tr>
<tr>
<td>Clinically evidence multifocal/multicentric disease</td>
<td>Large or central tumours in small breasts</td>
</tr>
<tr>
<td>Women with a strong family history of breast cancer including BRCA1 or BRCA2 mutation carriers</td>
<td></td>
</tr>
</tbody>
</table>

Figure 8.5: PET scan, cancer in left breast with axillary nodes.

Figure 8.6: Patient who was treated with breast conservation and developed a new primary cancer in the lower part of the treated breast. The metal clips mark the site of the original cancer. Up to half of so-called recurrences after breast conservation are second primary cancers.

Figure 8.7: (a) Wide local excision showing invasive and in situ cancer that has been completely excised. As the lesion was close to the skin, overlying skin has been removed. (b) Wide local excision specimen showing a positive margin affected by cancer.
to 4.6) times more likely if margins are involved. Wider margins (beyond 1 mm) do not reduce local recurrence further, but do adversely affect cosmetic outcomes (Figure 8.8). Neither atypical ductal hyperplasia nor lobular carcinoma at the margins increases local recurrence and re-excision based on their presence at a resection margin is not necessary. The risk of local recurrence falls with increasing age; young patients (<35) are two to three times more likely to develop local recurrence than older patients (Table 8.5). Cancers with evidence of lymphatic or vascular invasion (LVI) (Figure 8.3) have about twice the risk of local recurrence of tumours without LVI. Histological grade I cancers have a 1.5 times lower rate of local recurrence than grade II or III cancers (Figure 8.5).

There is no consensus on the use of prophylactic antibiotics to reduce rates of wound infection after surgery for breast cancer. One meta-analysis did show a significant reduction in infection rate after a single preoperative dose of antibiotic.

<table>
<thead>
<tr>
<th>Table 8.6</th>
<th>Relation between age and local recurrence of cancer after breast conservation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Recurrence after 5 years</td>
</tr>
<tr>
<td>&lt;35</td>
<td>17%</td>
</tr>
<tr>
<td>35–50</td>
<td>12%</td>
</tr>
<tr>
<td>&gt;50</td>
<td>6%</td>
</tr>
</tbody>
</table>

**Breast-conservation surgery**

Breast-conservation surgery for invasive cancer consists of excision of the tumour with a 1 cm macroscopic margin of normal tissue (wide local excision) combined with removal of the sentinel or all the axillary nodes. There are lower levels of psychological morbidity following breast conservation compared with mastectomy; it also improves body image, freedom of dress, sexuality and self-esteem. More extensive excisions of a whole quadrant of the breast (quadrantectomy) have worse cosmetic outcomes and do not significantly lower local recurrence rates compared with wide excisions. Patients who get a good or excellent cosmetic outcome achieve the greater psychological benefits from breast-conserving surgery (Figure 8.9(a)).

There is no size limit for breast-conservation surgery, but adequate excision of lesions over 4 cm often produces a poor cosmetic result (Figure 8.10(a)). In most breast units conservation surgery tends to be limited to lesions of ≤4 cm. About 10% of the breast volume can be removed without serious cosmetic deficit (Figure 8.8(a)). Where larger volumes need to be excised to get clear margins, consideration should be given to using neoadjuvant therapy or an oncoplastic procedure and reducing the size of both breasts by performing a therapeutic mammoplasty on one side and a contralateral breast reduction simultaneously (Figure 8.11). Bilateral therapeutic mammoplasty has the advantage of reducing breast volume, which helps in reducing dose inhomogeneity, a particular problem when delivering radiotherapy to larger breasts. Another option is using a local flap such as a latissimus dorsi miniflap.

There is no age limit for breast conservation. Failure to offer appropriate patients a choice of breast-conservation surgery may represent a failure of care. Breast-conserving surgery can be performed safely for most central cancers if they are small (Figure 8.12). Saving the breast is possible even in multifocal or multicentric cancers as long as all disease is excised and the final cosmetic result is satisfactory.
Incomplete excision at breast-conserving surgery is seen in 20–25% of patients (Figure 8.7). Patients should be warned of this. The majority of patients are suitable for re-excision. If multiple margins are positive, the chances of excising all disease by breast-conserving surgery is small, so such patients are usually recommended to have mastectomy. Multiple re-excisions can be performed providing that the final cosmetic outcome is acceptable.

Patients who carry BRCA1 and BRCA2 mutations have a high incidence of new ipsilateral (Figure 8.6) and contralateral breast cancers after breast-conserving surgery. For this reason bilateral mastectomy with or without reconstruction should be discussed with such patients.

**Breast-conserving surgery after neoadjuvant therapy**

Large breast cancers can be made suitable for breast-conserving surgery by shrinking the cancer with neoadjuvant chemotherapy or neoadjuvant endocrine therapy. Rates of complete excision are less after neoadjuvant chemotherapy than after neoadjuvant endocrine therapy, because the pattern of response is more often a diffuse reduction in cellularity rather than a reduction in tumour volume with chemotherapy.

**Factors affecting cosmetic outcome**

Around 17% (95% confidence interval 13–23%) of women have a poor cosmetic result after wide excision and radiotherapy (Figure 8.10). Patients with a good cosmetic outcome suffer significantly less anxiety and depression and also have a better body image, sexuality and self-esteem than women with poor cosmetic results. The single most important factor affecting cosmetic outcome is the volume of tissue excised. Large-volume excisions (>10% of the breast volume) are associated with a significantly worse cosmetic outcome than smaller volume (<10%) excisions. Removal of skin moves the nipple position and adversely influences cosmetic results, so only dimpled or retracted skin overlying a localised breast cancer should be excised. For patients who get a poor cosmetic result after breast conservation, options include replacing the tissue lost with fat (lipfilling), using a myocutaneous or a local flap or performing reduction surgery to the opposite breast (Figure 8.10).

**Mastectomy**

About one third of symptomatic localised breast cancers are unsuitable for treatment by breast conservation but can be treated
Table 8.7 Patients who are best treated by mastectomy.

- Those who prefer treatment by mastectomy
- Those for whom breast-conservation treatment would produce an unacceptable cosmetic result (includes some but not the majority of central lesions and most carcinomas >4 cm in diameter, although breast-conserving surgery is now possible if these lesions are treated by primary systemic therapy, if the breast is reconstructed with a latissimus dorsi mini-flap or the patient has larger breasts suitable for therapeutic mammoplasty)
- Patients unsuitable for radiotherapy

by mastectomy (Table 8.7). A few patients who are suitable for breast-conservation surgery opt for mastectomy. Mastectomy removes breast tissue with some overlying skin, usually including the nipple. Increasingly nipple-sparing mastectomy is being performed. The breast is removed from the chest wall muscles (pectoralis major, rectus abdominus and serratus anterior), which are left intact. Mastectomy should be combined with some form of axillary surgery. The pectoral fascia does not require to be removed unless involved.

Mastectomy should be performed through a cosmetically acceptable incision. Transverse scars frequently leave ‘dog ears’, which are ugly and avoidable (Figure 8.9(b) and (c)).

Complications

Complications after breast-conserving surgery include failure to excise all the disease, bleeding, infection and seroma.

The accumulation of fluid under mastectomy flaps after suction drains have been removed (seroma) occurs in a third to a half of all patients. It is more common after a mastectomy and axillary node clearance than after mastectomy and sentinel node biopsy. Securing the mastectomy flaps to the chest wall with rows of absorbable sutures seems to reduce the rate of seroma formation. Seromas can be aspirated if they are troublesome. Seroma fluid is inflammatory in nature. Recurrent seromas thus respond well to triamcinolone (10–40 mg) injected into the cavity. Infection is uncommon, and when it occurs it is usually secondary to flap necrosis or infection entering through the drain site or as a consequence of seroma aspiration. Treatment is with antibiotics and aspiration and irrigation of the infected cavity with local anaesthetic, as for breast abscesses. Opening up the mastectomy wound and packing the cavity is rarely required and leaves an ugly contracted scar. Most patients treated by mastectomy are suitable for some form of breast reconstruction, which may be performed at the same time as the initial mastectomy (see Chapter 17).

Follow-up of patients after surgery

The time course of recurrences vary in ER positive and ER negative breast cancers (Figure 8.13). Local recurrences continue at a steady rate over a 20 year period after breast conserving surgery. Local recurrence after mastectomy is most common in the first two years and decreases with time. By contrast, local recurrence after breast conservation occurs at a fixed rate for up to 20 years. Follow-up schedules should take this into account. The aim of follow-up is to detect local recurrence or a new cancer in the treated breast or contralateral disease as early as possible. This reduces the extent of any further treatment, potentially improving long-term disease control and survival. Patients with carcinoma of one breast have a higher risk of developing cancer in the other breast, the rate being about 0.6% a year. All patients after breast cancer should therefore undergo mammography annually. Scarring from surgery can result in the formation of a stellate opacity and localised distortion on mammography, which may be difficult to differentiate from cancer recurrence. Magnetic resonance imaging is useful in this situation (Figure 8.14).

Radiotherapy

All patients should receive radiotherapy to the breast after breast-conserving surgery (Figures 8.15 and 8.16). Radiotherapy reduces significantly the number of local recurrences and also improves overall survival (Table 8.8; Figure 8.17). Doses range from 37 Gy in 13 fractions over three weeks or 50 Gy in 25 fractions over five weeks. Recent data shows that shorter durations are as effective as longer courses with no more local morbidity. A top-up or boost of 10–20 Gy can be given to the tumour bed, usually with electrons. Boost reduces local recurrence in all age groups, but the absolute benefit in women aged >60 is small.
of breast diseases.

Figure 8.15 Effect of radiotherapy on local recurrence after wide local excision. Fisher and Redmond (1992).

Figure 8.16 Effect of radiotherapy on local recurrence after quadrantectomy. Veronesi et al. (1993).

Table 8.8 Effect of radiotherapy after breast-conserving surgery at 10 years.

<table>
<thead>
<tr>
<th></th>
<th>No radiotherapy</th>
<th>Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence rate</td>
<td>31.9%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Mortality</td>
<td>24.7%</td>
<td>20.9%</td>
</tr>
</tbody>
</table>

Of 7311 women included in the analysis, 6097 were node negative and 1214 were node positive. There was a 3.8% survival benefit (SE 1.1%) in node-positive women and a 2.1% survival benefit (SE 1.1%) at 10 years in node-negative women.

and so can be omitted in patients aged >60 with clear margins. Partial-breast radiotherapy, either by external beam radiotherapy or intraoperative radiotherapy, is still under investigation. To date results look promising, but most studies have enrolled low-risk patients, some of whom have a low recurrence rate even without radiotherapy. More follow-up and larger numbers are required before it can be considered equivalent in efficacy to whole-breast radiotherapy. There are various options for partial-breast radiotherapy, including the use of both external beam and a postoperative catheter placed either at the time of surgery or percutaneously, allowing delivery of radiotherapy with an after-loading system.

After mastectomy, radiotherapy should be considered for patients at high risk of local recurrence (Table 8.9), which includes those with involvement of pectoralis major or with known risk factors associated with a significant increased risk of recurrence. Three recent studies have shown that a combination of radiotherapy and systemic therapy in both premenopausal and postmenopausal high-risk women improves survival for patients who received chest wall radiotherapy. There was a 30.6% reported local recurrence rate after breast surgery without radiotherapy at 15 years, compared with a 10.3% rate with radiotherapy. The biggest difference was in the first five years. Breast cancer mortality was also reduced from 48.1% to 44.0% at 15 years. Although the risk factors for local...
recurrence after mastectomy are well known, there is no consensus on how to combine risk factors and decide which lower-risk patients might benefit from radiotherapy. The selection of which patients receive radiotherapy varies widely from centre to centre. The ongoing SUPREMO trial is addressing this. Radiotherapy has a significant impact on the cosmetic outcome of breast-reconstructive surgery and for this reason should not be administered unless the radiation significantly improves the absolute risk of local recurrence.

Complications

With modern machinery the incidence of immediate skin reactions and subsequent skin telangiectasia is small. With tangential fields, only a part of the left anterior descending artery and a small fraction of lung tissue are now included routinely within radiotherapy fields. Reports of increased cardiac deaths many years after radiotherapy for left-sided breast cancer relate to old radiotherapy techniques that delivered higher doses of radiotherapy to a much greater proportion of the heart.

Radiation pneumonitis, which is usually transient, affects less than 2% of patients treated with tangential fields. Rib doses are also smaller, so rib damage is now much less common. Pain in the treated area is rarely mentioned in reviews, but is a problem for a significant number of patients and may be due to the vasculitis caused by radiotherapy. Cutaneous radio necrosis and osteoradionecrosis are still seen in patients treated many years ago (Figure 8.19).

Further reading


Management of Regional Nodes in Breast Cancer

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OVERVIEW
- The single most important factor predicting patients’ prognosis is the presence or absence of cancer in the regional nodes
- All patients with invasive cancer should have their regional node status assessed by node biopsy
- An effective method of assessing lymph node status in patients with clinically and imaging node-negative nodes is to perform a sentinel lymph node biopsy
- It has been standard care until recently to treat all patients with histologically proven involved axillary nodes by axillary node clearance or axillary radiotherapy
- New data suggest that selected patients with limited node positivity on sentinel lymph node biopsy who have whole-breast radiotherapy and adequate systemic therapy may be spared further treatment of the axilla

Lymph drainage of breast

Lymph drainage from the breast is via the axillary and internal mammary nodes (Figure 9.1). To a lesser extent, lymph also drains by intercostal routes to nodes adjacent to the vertebrae. The axillary nodes receive about 95% of the total lymph drainage, and this is reflected in the greater frequency of tumour metastases to these nodes.

The axillary nodes, which lie below the axillary vein, can be divided into three groups in relation to the pectoralis minor muscle: level I nodes lie lateral to the muscle; level II (central) nodes lie behind the muscle; and level III (apical) nodes lie between the muscle’s medial border, the first rib, and the axillary vein (Figures 9.2 and 9.3). There are on average 20 nodes in the axilla, with about 13 nodes at level I, 5 at level II and 2 at level III. The drainage from level I nodes passes into level II nodes and on into the apical nodes. An alternative route, by which lymph can reach level III nodes without passing through nodes at level I, is through lymph nodes on the undersurface of the pectoralis major muscle, the interpectoral nodes. The orderly drainage of lymph explains why few patients with cancer have affected lymph nodes at levels II or III without involvement at level I. These so-called skip metastases are seen in less than 5% of patients with affected axillary nodes. The first node (or nodes) that received lymph drainage in the axilla or internal mammary region is known as the sentinel node or nodes. The majority of sentinel nodes are in the axilla at level I. The average number of sentinel nodes in most recent studies is between 2 and 3.

Preoperative clinical or radiological assessment of lymph node involvement is not completely accurate, with only 70% of involved nodes being clinically detectable. Only histopathological assessment of nodes visualised on ultrasonography, or excised at surgery, provides accurate prognostic information. Cytology of enlarged axillary nodes visualised on ultrasound can also detect axillary node metastasis (Figure 9.3). Micrometastatic disease detected only by immunohistochemistry does not have the same implications for prognosis and management. Lymph nodes are ineffective barriers to the spread of cancer, and metastasis indicates biologically aggressive disease that requires systemic adjuvant treatment. Involvement of axillary nodes occurs in up to 40% of symptomatic breast cancers and in 20–25% of those detected by screening.

The factors that correlate with lymph node involvement in breast cancer are outlined in Table 9.1.
Management of Regional Nodes in Breast Cancer

Identifying patients with involved nodes before surgery

Enlarged axillary nodes can be visualised with ultrasonography (Figure 9.3). Features that indicate the node is potentially involved include thickened cortex (normal is \( \leq 2 \) mm, \( 2-4 \) mm is indeterminate, \( >4 \) mm suspicious of malignancy) and distortion of architecture or increase in size. Ultrasound-guided fine needle aspiration cytology (FNAC) or core biopsy of visibly abnormal or enlarged nodes can identify more than half of patients with involved nodes before surgery. This can allow definitive axillary therapeutic surgery to be undertaken in patients with cytological or histological evidence of axillary lymph node involvement. Utilisation of axillary ultrasound or FNAC or core should result in less than 15% of women with sentinel lymph nodes being positive at surgery.

Role of axillary surgery in patients with operable breast cancer

Axillary surgery can be used to stage the axilla or to treat axillary disease, or both (Tables 9.2 and 9.3).

Table 9.1 Factors associated with lymph node involvement.

- Large tumour
- Poorly differentiated tumour (grade III)
- Symptomatic (compared with screen-detected) tumour
- Presence of lymphatic or vascular invasion in and around tumour
- HER2-positive breast cancer
- ER-negative tumour

Table 9.2 Options for axillary surgery procedures to stage but not treat the axilla in patients with invasive breast cancer.

- Sentinel node biopsy using blue dye and radioactive isotope colloid
- Sentinel node biopsy with blue dye and radioactive isotope combined with sampling removing blue and hot nodes and any palpable suspicious-feeling lymph nodes
- Axillary node sampling (removal of at least four lymph nodes with the help of blue dye alone)

*Not recommended given evidence of the value of the combined blue dye/radioisotope technique (Figure 9.4).

Table 9.3 Procedures to treat the axilla in patients with involved axillary lymph node involvement.

- Level I and II dissection
- Level I, II, and III dissection
- Axillary radiotherapy

Figure 9.2 (a) Levels of axillary nodes. (b) Anatomy of the axilla split into zones A, B, C and D. Sentinel nodes are never found in zone D, but the main nodes in the axilla that drain the arm are always in zone D.

Figure 9.3 Ultrasound pictures of involved axillary nodes. All patients with invasive breast cancer should have axillary ultrasound with fine needle aspiration cytology or core biopsy to assess whether any enlarged or abnormal node is involved. Up to half of patients with involved nodes can be detected using ultrasound-guided biopsy.
Staging the axilla

The presence or absence of involved axillary lymph nodes is the single best predictor of surviving breast cancer, and important treatment decisions are based on it (Figures 9.5 and 9.6). Both the number of involved nodes and the level of nodal involvement predict survival (Figure 9.7). Only involvement on routine histopathological examination has been shown consistently to be of prognostic importance.

The significance of micrometastatic disease detected only by examining multiple sections of lymph nodes by immunohistochemistry is much less clear. A single non-targeted node biopsy does not adequately stage the axilla. In patients with a clinically and ultrasound-negative axilla the optimal procedure is a sentinel lymph node biopsy. Identification of the sentinel node by peritumoural, intradermal or subareolar injection of both blue dye (isosulfan blue or patent blue V) and radioisotope colloid followed by histological assessment of blue (Figures 9.4 and 9.8) and/or radioactive nodes assesses axillary node involvement with a sensitivity of at least 91% (95% CI 74–96%) and a false-negative rate of 4–10% (Figure 9.9). Subareolar injection seems to have the highest rate of sentinel node detection. In most patients there is more than one sentinel node and about 25% of all nodal metastases are not in the bluest or hottest sentinel node. The more sentinel nodes removed, the lower the false-negative rate. The average number of sentinel nodes in more recent studies is between 2 and 3, but it is important that the
surgeon does not remove large numbers of sentinel nodes as this increases morbidity without affecting diagnostic utility.

Although some centres have found that sampling (surgically dissecting out four separate palpable nodes combined with blue dye alone) provides reliable information on whether axillary nodes are involved, others have found it difficult to identify and dissect out four separate axillary nodes, even with blue dye guidance. The probability of a false-negative result on sentinel node biopsy or axillary sampling decreases as the number of nodes sampled increases. Level II or III dissections (removing all nodes at levels I and II or I, II and III) provide more accurate assessments of the number and level of node involvement, but are only justified in patients with cytological or histological evidence of axillary lymph node involvement.

Some surgeons combine sentinel node biopsy with axillary lymph node sampling, removing any palpable suspicious non-sentinel nodes in an attempt to decrease the false-negative rate. The extra value of removing these extra nodes is not clear.

In some patients (range from 2–30%) injected with radioisotope colloid, scintigraphy will visualise a sentinel node in the internal mammary chain (Figure 9.9). Drainage either to more than one axillary node or to a combination of axillary and internal mammary nodes is often seen on scintigraphy. The rate of detection of isolated internal mammary sentinel node metastases is less than 1% and is seen with both medial and laterally situated cancers. Debate continues on the value of removing internal mammary nodes identified on preoperative scintigraphy. Removing internal mammary nodes is not without morbidity, as an extra incision is necessary in some patients and there is a small risk of pleural damage.

Treating affected internal mammary nodes is also a problem, as these nodes are difficult to target with radiotherapy. Randomised trials of surgical excision and radiotherapy targeted at internal mammary node recurrences have not as yet shown that they improve survival and isolated mammary node recurrences are rare (Table 9.4).

### Table 9.4 Current consensus on sentinel node biopsy.

- Subareolar injection gives the highest rate of sentinel node detection
- Scintiscans are probably unnecessary
- No proven value in removing internal mammary nodes
- Need to use both radioisotope and blue dye

### Assessment of sentinel nodes

Immediate assessment of frozen sections of sentinel nodes has a false-negative rate of up to 20%. Intraoperative touch-prep cytology misses fewer metastases and has a sensitivity of over 90%; it is also quicker than frozen section. The importance of micrometastases in a sentinel node identified by serial sectioning and immunohistochemistry is not clear. Haematoxylin and eosin (H&E) detected micrometastases ≤2 mm in sentinel nodes are unlikely to be associated with spread to adjacent non-sentinel lymph nodes (Figures 9.8 and 9.10). Techniques during operation that assess whether sentinel nodes are involved using molecular techniques are available. Their utility and cost effectiveness continue to be evaluated. Although such an assessment can be carried out successfully, there are at least 9% of patients who have false-positive results, leading to unnecessary axillary node clearance, and there are no studies showing that the technique is cost effective. Results take a minimum of 20 minutes for one sentinel node and 40 minutes for two or more nodes and this can make planning of operation lists problematic. The equipment is only available in a few centres. Sentinel node biopsy is now routine for clinically and radiologically N1 tumours, particularly in patients with small tumours (≤2 cm), where the likelihood of axillary lymph involvement is low and routine axillary dissection can no longer be justified.

Sentinel node biopsy in clinically N0 patients using a combined technique of radioisotope and blue dye is the current standard of care.

### Comparison of sentinel node biopsy and routine axillary dissection

Randomised controlled trials comparing sentinel node biopsy and axillary dissection have shown that sentinel node biopsy produces less morbidity (decreased sensory loss, decreased arm swelling) than a full axillary dissection. Hospital stay is shorter in women undergoing sentinel node biopsy compared with axillary dissection. Sentinel node biopsy can be performed as an outpatient procedure.

Patients with involved nodes have traditionally been treated by subsequent complete axillary dissection or axillary radiotherapy. A number of algorithms have been used to help identify patients whose risk of having residual lymph node metastases is so small that they can be spared axillary clearance or completion axillary lymph node dissection. The fact that there are so many algorithms indicates that none of these is very accurate. The need for axillary dissection

**Figure 9.8** Scintiscan showing drainage of technetium 99m human albumin colloid to show both multiple sentinel and internal mammary nodes.

**Figure 9.10** (a) Lymph node with isolated tumour cells – H&E and immunohistochemistry by cytokeratin.
in patients with one or two positive sentinel lymph nodes has been challenged by the Z11 study. This study randomised patients who had breast-conserving surgery and sentinel node biopsy had one or two positive nodes to axillary dissection or no subsequent axillary surgery. All patients had whole-breast radiotherapy and 58% in both arms had adjuvant chemotherapy. 47% in both arms had hormonal adjuvant therapy. Thus 96% and 97% of the axillary dissection group and 97% of the sentinel lymph node only group had adjuvant systemic therapy. Local recurrence and overall survival at a median of 6.3 years were not significantly different (Figure 9.11).

Combined with the B04 study in mastectomy patients, which showed no benefit in overall survival for patients having axillary radiotherapy or axillary dissection compared with no axillary surgery, this questions whether all patients with involved nodes who have adjuvant systemic therapy require either a completion dissection of the remaining nodes or axillary radiotherapy. Certainly for patients with a single positive sentinel node who have whole-breast radiotherapy after breast-conserving surgery and appropriate systemic therapy, the available evidence suggests that further axillary treatment may be unnecessary. Given this lack of benefit of axillary clearance in such patients, there needs to be a rethink of the role of ultrasound assessment of single abnormal nodes with minor degrees of abnormality and also a questioning of the routine use of intraoperative node assessment. After Z11 new algorithms need to be developed to ensure that there is consistency of axillary node management between units in patients with disease that would have made them eligible for entry into Z11. Routine axillary dissection for all patients with positive axillary nodes cannot be supported by the available evidence.

### Management of the axilla in patients treated with neoadjuvant chemotherapy

Axillary node disease can be cleared in approximately one third of all patients by neoadjuvant chemotherapy. This figure is approximately 50% in triple-negative breast cancers and over 50% in HER2-positive cancers treated by neoadjuvant trastuzumab and chemotherapy, but less than 10% in ER-positive cancer. There is a move to use sentinel node biopsy after chemotherapy in patients who at N1 at diagnosis and in proven N1 patients with triple-negative and HER2-positive cancers who have an excellent in-breast tumour and nodal response. There appears to be no merit in performing sentinel lymph node biopsy prior to chemotherapy.

### Treatment of axillary disease

In patients who have large suspicious axillary lymph nodes (Figure 9.12) seen on ultrasound and confirmed by FNAC or core biopsy, axillary node clearance remains standard treatment. Level 1 and level 2 clearance leaves behind potentially involved nodes. Up to 25% of level 3 nodes are involved if level 1 nodes are involved. Patients with negative nodes after either an adequate sentinel node biopsy or axillary sampling procedure require no further treatment, but a sentinel node biopsy or axillary sampling procedure cannot be considered therapeutic. In patients with only one abnormal node on ultrasound assessment, consideration now should be given to either axillary clearance or sentinel node biopsy.

Randomised studies comparing four-node sampling with a level III axillary dissection in patients with involved nodes have reported a significantly higher rate of axillary relapse with sampling followed by axillary radiotherapy, but axillary recurrence after sampling was salvageable by subsequent axillary dissection and overall survival did not differ between the two groups. Axillary radiotherapy continues to be an option to treat the involved axillae following sentinel lymph node biopsy. An ongoing European study is comparing the outcomes in a randomised study of axillary dissection or axillary radiotherapy in women who have a positive sentinel lymph node biopsy.

### Morbidity of axillary surgery

Arm swelling and lymphoedema (Figures 9.13 and 9.14) are the major morbidity after axillary clearance, whereas reduction in shoulder mobility is seen after axillary radiotherapy (Figure 9.15). In the ALMANAC trial, 28% of women developed lymphoedema.
after axillary sampling alone and almost 40% after an axillary clearance (Figure 9.16). The rate of lymphoedema is lowest with sentinel node biopsy, but even following SNB lymphoedema is reported in 4% of patients. The morbidity of level II and III dissections is similar and the rates of local recurrence after removing nodes at levels I, II and III are exceedingly low. Although axillary radiotherapy given after a level II dissection will control metastases at level III, this combination of procedures is associated with high rates of lymphoedema.

Recurrence in the axilla (Figures 9.17 and 9.18) produces the most extreme lymphoedema (Figure 9.19). UK guidelines now advise preoperative baseline measurements of the arms with either perometer scanning to measure arm volume or multifrequency bioimpedance. Early arm swelling within the first six months in excess of 5% is associated with a high rate of lymphoedema at 18 months. Early detection of this arm swelling could potentially allow intervention with a compression sleeve. A small, non-randomised American study suggests that such intervention may prevent progression to more severe lymphoedema. Radiotherapy should not be given after a level III axillary dissection. There is no satisfactory treatment for lymphoedema, but symptoms can be improved and, in some patients, the lymphoedema controlled.
Symptomatic pneumonitis occurs rarely after radiotherapy to the axilla but is more likely when treatment is combined with breast or chest wall irradiation. The risk should be less than 3% with modern radiotherapy technology.

**Morbidity of axillary treatments**

Damage to nerves in the axilla occurs commonly during axillary dissection, but less so with sampling and sentinel node biopsy. The most common nerve damaged is the sensory intercostobrachial nerve; preservation of this nerve during axillary node surgery reduces the number of patients who develop numbness and paraesthesia down the upper aspect of the arm (Figure 9.20).

Radiotherapy may rarely result in brachial plexopathy. This complication appears in part to overlap of fields, which can result in high doses of radiation being delivered to the brachial plexus. With modern planning techniques, treatment schedules and newer equipment this complication is rare. Brachial plexopathy can also be due to apical axillary recurrence; this complication is much less common if initial treatment of axillary disease has been optimal.

Wound infection complicates about 5% of axillary surgical procedures and is more common after axillary clearance than sampling or sentinel node biopsy: about one half of patients develop seromas after a level III axillary clearance compared with less than 5% of patients who undergo sentinel node biopsy or four-node sampling. Closing the axillary space by tacking the skin to the chest wall has been reported to reduce the rate of seroma formation. Both surgery and radiotherapy are associated with a reduction in the range of movement of the shoulder in some patients, and about 5% develop a frozen shoulder. This can be minimised with regular exercise programmes developed and supervised by physiotherapists. Patients with a frozen shoulder require a prolonged course of intensive physiotherapy.

**Treatment of internal mammary and supraclavicular nodes**

The value of prophylactic irradiation of the internal mammary and supraclavicular nodal areas is unproved. For anatomical and geometrical reasons the supraclavicular nodes can readily be included when axillary radiotherapy is given and, providing there is no overlap of fields, adds little in the way of morbidity. Such treatment reduces the rate of supraclavicular recurrence but has no impact on survival. Over 90% of women with metastases to the nodes...
internal mammary nodes have axillary node involvement. Of the 1% or less who have internal mammary node involvement in isolation, although most will have tumours involving the medial half of the breast, a significant number have lateral tumours. Patients whose tumours drain to the internal mammary nodes can be identified with radioisotope injection and preoperative scintigraphy. There is less drainage to internal mammary nodes with subareolar injection compared with an injection around the tumour. Internal mammary node biopsy does identify a small number of patients with isolated internal mammary node metastases, but the value of identifying patients with isolated internal mammary node metastasis is not proven and most surgeons do not biopsy these nodes.

Physical management of lymphoedema

Lymphoedema is defined as arm swelling greater than 10% increase in volume from baseline or a 200 ml or greater increase in arm volume as measured by perometry or water displacement. It is a chronic swelling that is essentially incurable, although the physical symptoms can be controlled with treatment. There are four cornerstones of treatment:

- **Skin care** is required to maintain good skin condition and reduce the risk of infection.
- **Exercise** promotes lymph flow and maintains good limb function.
- **Manual lymphatic drainage** is a gentle skin massage that encourages lymph flow and is carried out by a trained therapist.
- **Support/compression** with multilayer lymphoedema bandaging is applied to reduce the size and improve the condition of the limb to allow fitting of elastic compression garments, which when fitted correctly control swelling and encourage lymph flow. Compression garments should be worn while the patient is exercising to reduce lymphatic filtration. Maintaining an adequate weight helps to prevent lymphoedema development, so dietary advice is important in all patients, but particularly those who are overweight.

Presentation of breast cancer with enlarged axillary nodes (Figure 9.21)

Fewer than 1 in 300 patients with breast cancers present with nodal metastases and an occult primary cancer. Up to 70% of women shown histologically to have metastatic adenocarcinoma in the axillary nodes will have an occult breast cancer, most of which will be visible on mammography. In patients with no mammographic lesion, MRI will identify occult breast cancer in 70% of patients (Figure 9.22). Treatment of these women is as for breast cancer with palpable nodal metastases. In the remaining 30%, axillary node clearance (level I, II and III dissection) should be performed and the breast kept under regular observation or irradiated. Both groups of patients should receive appropriate adjuvant systemic treatment.

Treatment of axillary recurrence

Treatment of axillary recurrence depends on whether it occurs in isolation or in association with other sites of recurrence.
not previously given) or systemic treatment or both; these are sometimes effective at palliation but rarely produce long-lasting control of disease. Radiotherapy given for recurrent disease should be in a higher dose than is required in the adjuvant setting, which increases acute skin toxicity and the possibility of late side effects such as lymphoedema. When axillary disease occurs in association with metastases at other sites, systemic treatment is indicated. The most effective strategy is to try to prevent recurrence by ensuring adequate initial treatment.

Acknowledgements

The picture of axillary recurrence causing lymphoedema has been reproduced from N.J. Bundred and R.E. Mansel (eds) (1994) Wolfe Coloured Atlas of Breast Disease (Wolfe Medical Publications, London), with permission of the publishers. The management of lymphoedema was written by Miss Barbara Lyle, senior physiotherapist and lymphoedema specialist, Edinburgh Breast Unit, Western General Hospital, Edinburgh. The bar chart on p. 70 is adapted from data collected by the ALMANAC group, and the two graphs using data from the Edinburgh axillary surgery trials are adapted from J.M. Dixon (unpublished data) presented at meetings.

Further reading


CHAPTER 10
Breast Cancer: Treatment of Elderly Patients and Uncommon Conditions

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²Princess Anne Hospital, Southampton, UK

Table 10.1 Management of elderly patients with breast cancer.

<table>
<thead>
<tr>
<th>Tumour stage and size</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1, or T2 ≤ 4 cm, N0, M0</td>
<td>Wide local excision, axillary surgery and radiotherapy or mastectomy, if contraindications to breast conservation or patient choice</td>
</tr>
<tr>
<td>T2 &gt;4 cm or T3, N0, M0</td>
<td>Mastectomy, or neoadjuvant letrozole and then if tumour regresses wide local excision, axillary surgery and radiotherapy</td>
</tr>
<tr>
<td>Oestrogen receptor positive or no response to letrozole T1 or N0, M0</td>
<td>Letrozole*</td>
</tr>
<tr>
<td>Oestrogen receptor positive or no response to letrozole</td>
<td>Radical radiotherapy or in selected patients and in those responding to letrozole, mastectomy and radiotherapy, neoadjuvant chemotherapy also an option</td>
</tr>
<tr>
<td>Oestrogen receptor negative</td>
<td>Neoadjuvant chemotherapy; neoadjuvant letrozole, mastectomy and adjuvant tamoxifen</td>
</tr>
<tr>
<td>Any T, any N, M1</td>
<td>Palliation if oestrogen receptor positive</td>
</tr>
</tbody>
</table>

*Anastrazole and exemestane are alternatives to letrozole and should be followed by surgery and/or radiotherapy depending on response.

OVERVIEW
- Approximately 40% of all breast cancers occur in women over the age of 70 years.
- Older patients should be treated to the same standard as younger patients.
- As most elderly patients’ cancers are oestrogen receptor positive, endocrine therapy can be used either to shrink the cancer prior to surgery or as adjuvant therapy after surgery.
- Paget’s disease of the nipple is uncommon, but is often diagnosed late and needs to be considered in patients with nipple ulceration.
- There is no evidence that pregnancy after treatment for breast cancer has an influence on patient survival.
- Male breast cancer is rare and is not treated significantly different to female breast cancer.

Approximately 40% of all breast cancers occur in women aged over 70 (Figure 10.1); this percentage will increase over the next decade. Overall, breast cancers that develop in older women are biologically less aggressive compared with those seen in younger patients, although survival rates for older women have been poorer in this age group, mainly because of undertreatment. The average life expectancy of a 70-year-old woman is in excess of 15 years and is over 9 years for a woman aged 80. Elderly women with breast cancer should be treated in a similar way to younger patients. Few patients are truly unfit for surgery because wide local excision or even mastectomy can, if necessary, be performed under local anaesthesia with sedation, although with modern anaesthetic techniques this is not required very often. There is no evidence to suggest that elderly patients tolerate radiotherapy less well than younger patients and when radiotherapy is given it should be in a radical dose.

Operable tumours suitable for breast conservation

Options for small operable breast cancers ≤ 4 cm are breast-conservation surgery (wide local excision and radiotherapy).

Operable tumours suitable for mastectomy

For larger tumours that are operable, options include mastectomy combined with sentinel node biopsy or axillary node clearance.

Randomised studies have demonstrated that aromatase inhibitors are superior to tamoxifen in this setting (Figure 10.4). There are data using letrozole, anastrozole and exemestane. The data are most impressive for letrozole. This is the only aromatase inhibitor that has a product licence for use in the neoadjuvant setting. During treatment the tumour should be monitored clinically and by imaging (Figure 10.5): two-thirds of appropriately selected women will get a significant response to an aromatase inhibitor and over half of patients with ER-rich cancers become eligible for breast-conserving treatment within three months. Response is higher in patients with higher ER levels. Prolongation of therapy improves response rates and the optimal duration is probably between 9 and 10 months. Studies show that local control rates in patients converted to breast-conserving surgery are low providing that radiotherapy is given in a standard dose (Figure 10.6).

**Locally advanced breast cancer**

Patients with ER-positive disease should be considered for neoadjuvant treatment with an aromatase inhibitor. More than half of patients with ER-positive tumours treated by letrozole will have regression of disease to an extent that some form of local surgery is appropriate (Figure 10.7); response rates are highest in ER-rich tumours (Figures 10.3 and 10.8). ER-rich inflammatory cancers also respond to these agents. Patients with ER-positive tumours that show no response by three months should receive adequate locoregional treatment. Fit elderly patients with locally advanced

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**Figure 10.1** Breast cancer in elderly woman.

**Figure 10.2** Breast cancer stained for oestrogen receptor: nuclei that stain brown indicate cells are receptor positive.

**Figure 10.3** Response in the Q24 randomised trial of letrozole vs tamoxifen related degree of expression of oestrogen receptor as assessed by Allred score. Adapted from Ellis et al. (2001).

**Figure 10.4** Breast-conserving surgery rates: Summary and meta-analysis of randomised trials comparing tamoxifen with the aromatase inhibitors letrozole, anastrozole and exemestane.

**Figure 10.5** Serial ultrasound scans of breast tumour (a) before and (b) after 3 months treatment with letrozole 2.5mg: tumour significantly reduced in volume.

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q24</td>
<td>Letrozole</td>
<td>1.29 (1.09, 1.50)</td>
</tr>
<tr>
<td>IMPACT</td>
<td>Anastrozole</td>
<td>1.45 (1.02, 2.06)</td>
</tr>
<tr>
<td>PROACT</td>
<td>Anastrozole</td>
<td>1.27 (0.98, 1.65)</td>
</tr>
<tr>
<td>Exemestane</td>
<td>1.84 (1.07, 3.16)</td>
<td>8.62</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.627)</td>
<td>1.36 (1.16, 1.59)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Treatment of Elderly Patients and Uncommon Conditions

ER-negative tumours can be treated by neoadjuvant chemotherapy or with radiotherapy with or without surgery. Regimens more suitable for use in an older population, such as weekly paclitaxel, are tailored to the patient’s general fitness. Patients who respond to primary chemotherapy may subsequently become suitable for surgical treatment and even breast-conserving surgery.

**Radiotherapy**

Radiotherapy is delivered in a radical dose to the breast, chest wall and axillary nodes with full dose to skin. Selected patients with

**Adjuvant systemic therapy**

All patients with tumours expressing any ER should be given adjuvant hormone therapy with or without chemotherapy. For patients with higher-risk ER-negative disease, adjuvant systemic chemotherapy is tailored to the patient’s fitness and risk of recurrence. Trastuzumab is licensed for use only with chemotherapy, but can be delivered safely to older patients with standard or modified chemotherapy regimens.

**Metastatic disease**

Patients with ER-positive tumours should be treated with an aromatase inhibitor unless they have already received this as part of their adjuvant therapy. All three aromatase inhibitors have been shown to be more effective than tamoxifen in this group of patients, but the data are most impressive for letrozole. Bisphosphonates should be considered in patients with bony disease, to reduce fracture and improve pain. Patients with ER-negative tumours should be treated symptomatically. Palliative chemotherapy may provide a worthwhile response without appreciable toxicity in suitable patients. Palliative radiotherapy to local disease or painful bony metastases should be considered in symptomatic patients.

**Very elderly or infirm patients**

An extremely small group of very elderly or infirm patients are unfit for treatments other than hormonal agents such as an aromatase

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*Figure 10.6* Local recurrence in patients after neoadjuvant endocrine therapy and breast conservation surgery with or without radiotherapy. Adapted from Dixon JM et al. Neoadjuvant treatment. In: Aromatase Inhibitors for the treatment of breast cancer. Ellis LJ, ed. CMP United Business Media, 2005; 70.

*Figure 10.7* Locally advanced breast cancer – 2 examples of before and after letrozole with re-epithelialisation of ulcerated cancer (previous 9.4 (i) and 9.4 (ii)).

ER-negative tumours can be treated by neoadjuvant chemotherapy or with radiotherapy with or without surgery. Regimens more suitable for use in an older population, such as weekly paclitaxel, are tailored to the patient’s general fitness. Patients who respond to primary chemotherapy may subsequently become suitable for surgical treatment and even breast-conserving surgery.

*Figure 10.8* Mammogram of an inflammatory cancer before (a) and after (b) treatment with letrozole.

Locally advanced breast cancer due to a direct skin involvement are suitable for an initial mastectomy or wide local excision with radiotherapy. Adjuvant systemic therapy after surgery should be based on the patient’s general condition, her wishes, oestrogen receptor status, the risk of recurrence and the absolute benefit for the individual accruing from treatment (Figure 10.6).
inhibitor. It is only in those infirm patients with ER-positive breast cancer that hormonal agents should be considered as a sole treatment. Even in these patients, if aromatase agents do not establish disease control, limited surgery under local anaesthesia is possible and can improve any local symptoms.

**Paget’s disease of the nipple**

Paget’s disease is an eczematoid change of the nipple associated with an underlying malignancy and is present in 1–2% of patients with breast cancer (Figure 10.9 and Table 10.2). In half of these patients there is an underlying mass lesion and 90% of such patients have an invasive carcinoma. In those without a mass lesion, 30% have an invasive carcinoma and the remainder have in situ disease alone.

Paget’s disease may be localised or occupy a large area; the lesion should be differentiated from eczema of the nipple/areola area (Figure 10.10) and from direct infiltration into the nipple by an underlying cancer (Figure 10.11). Clinically, Paget’s disease always affects the nipple from the start, whereas eczema affects the areolar region initially and only rarely involves nipple skin (Figures 10.9, 10.12 and 10.13). If Paget’s disease is suspected on clinical examination, mammography should be performed to determine whether there is an underlying lesion. Then a punch biopsy removing a portion of abnormal skin under local anaesthesia should be performed to obtain tissue for pathological examination.

**Table 10.2 Paget’s disease of the nipple.**

- Associated with 1–2% of all breast cancers
- Occurs in similar age range as other breast cancers
- Often associated with delay in diagnosis
- Diagnosis established by core or wedge biopsy of nipple

**Treatment**

- Mass lesion – mastectomy, axillary node surgery* and radiotherapy or wide local excision, axillary node surgery* and radiotherapy
- No mass lesion – wide local excision, axillary node surgery* and radiotherapy or mastectomy and axillary node surgery*

*Sentinel node biopsy or axillary clearance as appropriate.

**Management**

If a mass lesion is present and is remote from the nipple, the treatment has traditionally been mastectomy and sentinel node biopsy or axillary node clearance as appropriate (60% of patients with a mass lesion have involved axillary nodes). Wide excision of the mass combined with a separate wide excision of the nipple/areolar complex and whole-breast radiotherapy can be successful in selected patients without any evidence of intervening disease. When Paget’s disease is associated with an underlying central mass lesion, wide excision of the nipple, areola and underlying mass followed by radiotherapy can give a satisfactory cosmetic result and satisfactory control of local disease (Figure 10.14). Rotating a local skin...
Treatment of Elderly Patients and Uncommon Conditions

Figure 10.12 Histology of Paget’s disease of the nipple. Clear Paget’s cells can be seen within the epidermis.

Figure 10.13 Eczema of the nipple (left) and histology of nipple crusting of the epidermis associated with a chronic dermatitis reaction (right).

and breast tissue flap maintains the breast contour and improves cosmetic outcome.

For patients without a mass lesion, wide local excision of the nipple and underlying ducts followed by postoperative radiotherapy appears to produce satisfactory local control rates. Mastectomy with or without sentinel node biopsy (less than 10% of patients without a clinical mass have nodal metastases) is an alternative treatment and provides long-term disease control in over 95% of patients.

Breast cancer and pregnancy

About 1–2% of all breast cancers occur during pregnancy (Figure 10.15) or during lactation and a quarter of women who develop breast cancer under the age of 35 do so either during or within one year of pregnancy (Table 10.3). There is no evidence that breast cancer occurring during pregnancy is more aggressive than other breast cancers, but diagnosis is often delayed because of the difficulty of identifying a discrete mass in an enlarging breast. This means that women tend to present with cancers at a later stage, with approximately 65% having involved axillary nodes.

Management

Treatment during the first two trimesters is a modified radical mastectomy. Radiotherapy should not be delivered during pregnancy. Chemotherapy can be given, but it is associated with a small risk of foetal damage, particularly in the early stage of pregnancy. Breast
Sentinel node biopsy or axillary clearance as appropriate. Sentinel node biopsy can be performed safely in pregnancy.

Treatment
- First and second trimester — mastectomy and axillary node surgery
- Third trimester — ideally delay treatment and deliver baby at 30–32 weeks; consider primary systemic treatment if tumour large or locally advanced, consider mastectomy and axillary node surgery and radiotherapy if tumour growing rapidly.

Pregnancy after treatment of breast cancer
There is only limited information on the effect of pregnancy on the outcome of a patient with breast cancer, but what data are available show no detrimental effect on pregnancy or survival. It is generally recommended that there should be a delay of two to three years between treatment for breast cancer and pregnancy, because there is a peak of relapses in high-risk patients in the first two years. Women having breast-conserving treatment including radiotherapy can sometimes breastfeed from the treated breast with no deleterious effects to mother or baby.

Male breast cancer
Less than 0.5% of all breast cancers occur in men (Figure 10.16), and breast cancer comprises 0.7% of all male cancers (Table 10.4).

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**Table 10.3** Breast cancer and pregnancy.
- Affects 1–3 of every 10 000 pregnancies
- 25% of all breast cancers in women aged <35 associated with pregnancy
- 15% of all breast cancers in women aged >40 associated with pregnancy
- 65% of pregnant women with breast cancer have involved axillary nodes

**Table 10.4** Male breast cancer.
- 0.7% of all male cancers
- 0.5% of all breast cancers
- Peak incidence 5–10 years later than in women
- Klinefelter’s syndrome increases risk
- Diagnosis by mammography and fine needle aspiration cytology

**Treatment**
- Mastectomy, axillary node clearance and radiotherapy
- Adjuvant endocrine therapy (usually tamoxifen)
- Consider adjuvant chemotherapy in fit patients if tumour oestrogen receptor negative and axillary nodes involved

The prevalence of BRCA2 mutations in male breast cancer patients has been reported as between 4% and 40% depending on the population studied, with a mean age at diagnosis of about 60 years. The peak incidence is 5–10 years later than it is in women. Carriage of a BRCA2 mutation and Klinefelter’s syndrome are the only known risk factors for male breast cancer.

Presentation is usually with a lump or with skin dimpling, ulceration or retraction of the nipple. Some men present with a palpable axillary node as their first symptom. Male breast cancers are usually eccentric masses, whereas gynaecomastia is almost always central. Infiltration of the skin or nipple occurs much earlier in male breast cancer because of the smaller breast volume, and compared with female breast cancer the disease is more likely to be advanced at diagnosis. Mammography is valuable in determining whether breast enlargement is due to gynaecomastia or breast cancer. When there is concern that the lesion may be malignant, a core biopsy should be performed to establish a definitive diagnosis. The histology and prognosis for each tumour stage are similar to those for female breast cancer.

**Management**
Treatment of localised breast cancer is usually by mastectomy and sentinel lymph node biopsy or axillary clearance as appropriate and radiotherapy to the chest wall. Radiotherapy is usually given because it is more difficult to get wide excision margins and the disease is often locally advanced. Small breast cancers can be treated by wide local excision with sentinel lymph node biopsy or clearance of axillary nodes as appropriate and postoperative radiotherapy. Adjuvant tamoxifen is effective at reducing recurrence in oestrogen receptor-positive breast cancers (more than 80% of male breast cancer is oestrogen receptor positive). There are few data with aromatase inhibitors, but they have been used in patients where tamoxifen is contraindicated. Testosterone levels should be monitored and an LHRH analogue combined with an aromatase inhibitor if testosterone levels increase. Adjuvant chemotherapy should be considered for fit patients with tumours that have nodal involvement and that are oestrogen receptor negative. Systemic chemotherapy should be considered for fit patients with life-threatening disease or for patients with symptomatic, recurrent or metastatic disease that does not respond to hormone therapies. The regimens are identical to those used in female breast cancer.

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Figure 10.16 Breast cancer of the left breast is an elderly man. The black mark in the axilla marks the site of the palpable lymph node.
Other rare neoplasms

Lymphomas rarely occur in the breast. Staging investigations are necessary for patients with lymphoma because there is usually disease outside the breast and regional nodes. Localised lymphoma should be treated by excision, radiotherapy and chemotherapy. The extent of the excision depends on the size of the lesion. Small lesions can be excised completely, but large lesions are best treated by a combination of chemotherapy and radiotherapy. More generalised lymphoma requires systemic chemotherapy.

Proliferative fibroblastic lesions characterised by spindle cells range from benign areas of fibrosis to malignant sarcomas. Lesions in the middle of this range include fibromatosi (Figures 10.18 and 10.19) and nodular fasciitis, which masquerade clinically and mammographically as breast cancers. They are rare but can recur locally after excision. They should be treated by adequate wide local excision and careful surveillance. These lesions have been reported to be oestrogen receptor positive and tamoxifen has been used in patients with recurrence, but in practice most are ER negative. While there are few reports of the use of radiotherapy, where there is local recurrence that is inoperable it may delay further recurrence.

Sarcomas can develop in breast tissue or may affect overlying skin (Figure 10.20). Rarely, angiosarcomas follow radiotherapy to the chest wall (Figure 10.21). Diagnosis is established by core biopsy. Sarcomas are best treated by as wide an excision as possible. As many of these tumours are large at diagnosis, mastectomy is generally necessary (Figure 10.22). Sentinel node biopsy is advised rather
than axillary clearance because axillary nodes are rarely involved. Radiotherapy should be given to the chest wall after excisional surgery if not previously used, but there is little evidence that adjuvant chemotherapy is of benefit, although it continues to be used in larger lesions. Survival seems to be related to the size and grade of the sarcoma.

Some breast cancers have areas of ‘sarcomatous differentiation’ and are classified as metaplastic cancers. Even in the areas with spindle cell morphology, immunohistochemistry for epithelial cell markers is positive. Treatment is as for other breast cancers, although they are more likely to be grade III, be triple negative and disseminate through the bloodstream and commonly to metastasise to the lung.

Phyllodes tumours are rare fibroepithelial neoplasms that range from benign to malignant in their behaviour (Figures 10.23–10.25). The current classification recognises benign, borderline and malignant lesions, with two-thirds being benign. In malignant lesions it is the sarcomatous element that recurs (Figure 10.26), and almost a quarter of those lesions classified as malignant metastasise. Initial treatment is by wide excision and mastectomy is often required. The role and efficacy of radiotherapy and chemotherapy in treating these lesions are unclear.

Figure 10.21 (a) Subtle angiosarcoma of breast. (b) More extensive angiosarcoma of breast.

Figure 10.22 (a) Patient with sarcoma with direct involvement of the overlying skin. (b) Mammogram of osteosarcoma of breast. Dense bone formation can be seen within the circumscribed lesion.

Figure 10.23 Recurrent malignant phyllodes tumour in left breast of 19-year-old woman. Her initial excision had been two months before.

Figure 10.24 An ulcerated large borderline malignant phyllodes tumour before (left) and after (right) excision and reconstruction.

Figure 10.25 Mammogram showing circumscribed phyllodes tumour.
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Figure 10.26 Histology of breast with recurrence of previously excised borderline phyllodes tumour: note cellular pleomorphic spindle cell lesion with frequent mitoses in the recurrence (a) low (b) high power.

Further reading


CHAPTER 11
Role of Systemic Treatment of Primary Operable Breast Cancer

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2Breast Unit, Royal Marsden Hospital and Institute of Cancer Research, UK

OVERVIEW
• Approximately half of women with operable breast cancer who do not receive any systemic therapy will die from metastatic disease
• Randomised trials have shown that giving patients adjuvant hormone therapy, chemotherapy or specific immunotherapy significantly improves survival
• In patients whose cancers overexpress HER2, trastuzumab has been shown to improve overall survival
• Patients with large tumours (Figure 11.1) can be treated initially with chemotherapy, with or without trastuzumab if HER2 positive or hormonal therapy, to make the cancer smaller and permit breast-conserving surgery
• Evidence demonstrates that adjuvant therapies such as chemotherapy and hormonal agents should be delivered to the majority of patients with breast cancer

Mortality from breast cancer in the United Kingdom fell by over 15% in the first decade of the twenty-first century and continues to do so despite a rising incidence. This fall coincides with the widespread uptake of adjuvant systemic therapy and evidence of its survival benefit. The basis for this treatment is that more than half the women with operable breast cancer who receive local regional treatment alone die from metastatic disease, indicating the presence of micrometastases at initial clinical presentation. The major risk factors for the development of metastatic disease are axillary node involvement, a poor histological grade, large tumour size and histological evidence of lymphovascular invasion in and around the tumour site. The absence of oestrogen and/or progesterone receptors (ER/PgR) also carries an adverse prognosis at least for the first few years after diagnosis; the same used to be the case for the overexpression of the HER2 growth factor receptor, but prognosis in this subset has improved significantly with trastuzumab and chemotherapy. Systemic medical treatments, including endocrine therapy, chemotherapy or targeted therapy with trastuzumab, are therefore crucial, along with surgery and radiotherapy to improve survival. Systemic treatment may be given after (adjuvant) or before (neoadjuvant, primary or preoperative) locoregional treatment.

The effectiveness of adjuvant and to a lesser extent neoadjuvant treatment has been shown in randomised clinical trials.

The key potential benefits of the neoadjuvant approach include:
• Downstaging a large primary, allowing conservative surgery rather than mastectomy in some patients (Figure 11.1).
• Using the tumour as an in vivo measure of responsiveness to treatment (although clinical benefit based on this approach remains to be demonstrated).
• Using short-term outcome measures in relatively small neoadjuvant trials to predict for long-term outcome in the adjuvant setting.

A central current issue in adjuvant medical therapies is how best to use molecular tumour markers including ER, PgR and HER2 to select the most appropriate treatment option for individual patients, and in particular to determine which patients do not benefit from chemotherapy, with all its inherent toxicities.

Endocrine therapies
These include those described in the following sections.

Tamoxifen
• Is a partial oestrogen agonist (has antagonistic actions in breast cancers, but has agonist actions on endometrium, lipids and bone).
• Is effective at 20 mg/day with no gain from higher doses.
• Is effective in all age groups, including both premenopausal and postmenopausal women with ER-positive but not ER-negative cancers (Figure 11.2; Table 11.1).
• Is more effective when given for five years rather than two. Current evidence suggests there may be little additional benefit if taken for more than five years (Figure 11.3).
• Reduces risk of contralateral breast cancer by 40–50%.
• Is currently considered more effective when given after chemotherapy (when this is also indicated) rather than concurrently.

Aromatase inhibitors (AIs)
• In contrast to tamoxifen, these act by inhibiting oestrogen synthesis.
Role of Systemic Treatment of Primary Operable Breast Cancer

Figure 11.1 Outline of options for systemic treatment of large, operable breast cancer.

Figure 11.2 About five years of tamoxifen versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of breast cancer mortality. Adapted from Early Breast Cancer Trialists’ Collaborative Group (2005).

- Include the non-steroidal agents anastrozole and letrozole and the steroidal agent exemestane.
- Are effective only in postmenopausal women with ER-positive breast cancer.
- Have been shown to improve disease-free survival and metastatic-free survival with five years’ treatment compared with tamoxifen.
- Have been shown in one trial to improve survival very marginally compared with tamoxifen.

Table 11.1 About five years of tamoxifen versus not in ER-positive (or ER-unknown) disease by age: Event rate ratios.

<table>
<thead>
<tr>
<th>Age</th>
<th>Deaths/women</th>
<th>Allocated tamoxifen</th>
<th>Adjusted control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2p</td>
<td>Entry age</td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>74/417</td>
<td>(17.7%)</td>
<td>(29.9%)</td>
</tr>
<tr>
<td>40–49</td>
<td>173/1119</td>
<td>(15.3%)</td>
<td>(19.2%)</td>
</tr>
<tr>
<td>50–59</td>
<td>330/1591</td>
<td>(20.7%)</td>
<td>(25.7%)</td>
</tr>
<tr>
<td>60–69</td>
<td>379/1822</td>
<td>(20.8%)</td>
<td>(29.5%)</td>
</tr>
<tr>
<td>≥70</td>
<td>62/266</td>
<td>(23.3%)</td>
<td>(31.1%)</td>
</tr>
</tbody>
</table>

Data from Early Breast Cancer Trialists’ Collaborative Group (2005).

- Improve disease-free survival if patients are switched after two or three years of tamoxifen to an AI rather than continuing on tamoxifen.
- Reduce the risk of recurrence when given for three to five years as extended adjuvant therapy in women still in remission after five years of tamoxifen and improve survival in node-positive patients (Figure 11.4).
- Reduce the risk of contralateral breast cancer by a further 40–50% when given instead of, or after, tamoxifen (i.e. predicted total risk reduction around 75%).

Oophorectomy or ovarian suppression with gonadotrophin-releasing hormone (LHRH) analogues

- Is of benefit only in premenopausal women with ER-positive cancer.
• May provide benefit in addition to chemotherapy in premenopausal women who continue to menstruate after chemotherapy (but confirmatory trials still underway). Whether they have benefit in addition to tamoxifen is uncertain.

Chemotherapy
Clinical trials have shown the following:
• The benefits of chemotherapy (Figure 11.5) depend on the biological subtype and benefits are greatest in women with ER-negative and/or HER2-positive cancers.
• The absolute benefit relates to absolute risk and therefore increases with increasing adverse risk factors such as axillary node involvement, increasing tumour size and grade 3 histology.
• Chemotherapy is not of benefit for many postmenopausal women with ER-positive, HER2-negative breast cancers (the commonest subtype) and in particular for most of those with grade I or II, oestrogen-receptor-rich breast cancers, which are best treated with appropriate endocrine treatment, even when some axillary nodes are involved.
• A key challenge is to identify women with ER-positive HER2-negative breast cancers who receive hormone therapy who do not get a benefit from addition of chemotherapy. These include women with grade 3 tumours. Gene-expression assays may have an important role here.
• Anthracycline-containing combinations with doxorubicin or epirubicin are more effective than traditional CMF chemotherapy combinations.

• Taxanes (paclitaxel and docetaxel) in addition to anthracyclines are of further benefit for women with ER-negative and/or HER2-positive cancers where absolute 10-year survival gains of more than 30% can be achieved in women at highest risk. Their additional value in ER-positive HER2-negative cancers (the major subgroup) is less certain.

Side effects: Endocrine therapy (Table 11.2)

Tamoxifen may cause vaginal dryness or discharge, loss of libido and hot flushes, and these may have considerable impact on quality of life (so a significant percentage of patients stop treatment because of side effects). In postmenopausal women prolonged use of tamoxifen is associated with a three to four times increased incidence of endometrial cancer and a small increased risk of venous thromboembolism (similar to that associated with the contraceptive pill or hormone replacement therapy). Oophorectomy or LHRH analogues often cause severe menopausal symptoms and carry a markedly increased risk of bone loss, which can lead to osteoporosis.

Management of side effects

All premenopausal women on tamoxifen or ovarian suppression and all postmenopausal women on AIs should have regular monitoring of bone mineral density and be advised to take regular moderate weight-bearing exercise. Those with mild/moderate osteopenia should also be recommended to take calcium/vitamin D supplements and those with significant bone loss or frank osteoporosis should also be started on a bisphosphonate. Trial data have shown that bone loss can be reduced markedly or prevented by prophylactic intravenous zoledronic acid given once every six months, but this has not yet become the standard of care.

First-line treatment for vaginal dryness with tamoxifen or ovarian suppression is with locally applied lubricants. Oestrogen creams and pessaries should be used with caution with AIs, since the small systemic oestrogenic spillover effect may potentially negate their efficacy. Therefore with AIs a non-oestrogenic cream such as Replens is another option, or treatment can be changed to tamoxifen.

Hot flushes are hard to treat. Neither clonidine nor evening primrose oil has been shown to be clinically effective in randomised
trials. Megestrol acetate in a dose of 20 mg once or twice a day significantly improves flushing in 80% of patients; hot flashes often increase immediately after starting treatment and patients should be informed that treatment for two to four weeks is required to reduce the frequency of hot flashes. Selective serotonin reuptake inhibitors (SSRIs) are partially effective for hot flashes. Some SSRIs reduce the metabolism of tamoxifen to its most active metabolite, endoxifen, by inhibition of the cytochrome P450 enzyme, CYP2D6. When co-prescription of tamoxifen with an antidepressant is necessary, it has been recommended that preference should be given to antidepressants that show little or no inhibition of CYP2D6 such as venlafaxine or citalopram. However, the importance of CYP2D6 is not at all clear, with recent large studies casting doubt on its relevance in relation to tamoxifen effectiveness, so switching antidepressants may not be of any clinical value. Trials have shown that oestrogen replacement and tibolone therapy increase the risk of recurrence and so are not recommended.

**Side effects: Chemotherapy (Table 11.2)**

Although hair loss is the most common concern of patients before starting chemotherapy, 80% report fatigue and lethargy as the most troublesome side effects. Alopecia caused by some chemotherapy regimens may be reduced by scalp cooling. Nausea and vomiting are unpleasant side effects, but can be controlled in most patients by appropriate antiemetic drugs, including the serotonin-3 antagonists granisetron and ondansetron (Table 11.3). These should be used as first-line treatment, even for moderately emetogenic chemotherapy. The introduction of the NK1 receptor antagonist aprepitant as second-line treatment has further improved the ability to prevent both acute and delayed emesis in patients receiving highly and moderately emetogenic chemotherapy.

Haematological toxicity (particularly neutropenia) is a common side effect of most chemotherapy regimens, and neutropenic infection occurs in about 10% of patients, depending on the regimen. This requires urgent treatment with appropriate intravenous antibiotics and fluids. Trials have shown that dose reductions or delays in treatment may compromise efficacy, and for this reason haematopoietic support with GCSF should be used in patients in whom neutropenia would otherwise compromise treatment. Chemotherapy-induced ovarian suppression with loss of fertility is an important problem for younger women; the risk of this increases rapidly at age >35. Gonadotrophin-releasing hormone agonists are being investigated as ovarian protection against infertility.

Other side effects include oral mucositis, chemical conjunctivitis and diarrhoea. Some drugs have specific problems (for example fluid retention with docetaxel and neuropathy with either paclitaxel or docetaxel) and all chemotherapy requires specialist supervision.

### Selection of adjuvant treatment (Table 11.4)

Choice of treatment depends on risk of relapse, potential benefits of different treatments, oestrogen-, progesterone- and HER2 receptor status, age, menopausal status and acceptability of treatment to the patient.

**Endocrine therapy**

Until recently, tamoxifen was the most commonly used hormonal agent in the adjuvant setting in both premenopausal and postmenopausal women. A major development in postmenopausal women has been the emergence of the so-called third-generation AIs (anastrozole, letrozole and exemestane), which all have a small but statistically significant efficacy benefit over tamoxifen. The AIs act by blocking the synthesis of oestrogen, which is mediated through the aromatase enzyme, in contrast to tamoxifen, which is an oestrogen receptor antagonist. The efficacy of AIs has been established only in postmenopausal women.

### Results from trials

In the ATAC (arimidex, tamoxifen, alone or in combination) trial involving around 9000 women, anastrozole achieved a small but significant disease-free survival (DFS) improvement at eight years with a hazard ratio (HR) of 0.87 (95% CI 0.78–0.97) in the hormone receptor-positive group compared with tamoxifen.

### Table 11.4 Indications for treatment modalities.

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine therapy</td>
<td>Any ER staining</td>
</tr>
<tr>
<td>Anti-HER2 therapy</td>
<td>ASCC/CAP HER2 positive/HER2 3+ &gt;30% intense and complete staining ICH or FISH &gt;2.2+</td>
</tr>
<tr>
<td>In HER2-positive disease</td>
<td>Trial evidence for trastuzumab is limited to use with or following chemotherapy</td>
</tr>
<tr>
<td>In triple-negative disease</td>
<td>Most patients</td>
</tr>
<tr>
<td>In ER-positive, HER2-negative disease* (with endocrine therapy)</td>
<td>Lower ER and/or PgR level</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td></td>
<td>High-proliferation rate</td>
</tr>
<tr>
<td></td>
<td>Node positive (≥4 involved nodes)</td>
</tr>
<tr>
<td></td>
<td>Extensive lymphocascular invasion</td>
</tr>
<tr>
<td></td>
<td>Size &gt;5 cm</td>
</tr>
</tbody>
</table>

*Currently there is considerable uncertainty on relative risk factors for chemotherapy benefit in this large subgroup. Modified from St Gallen (2009).
A series of trials have shown that a switch to anastrozole, letrozole or exemestane after two to three years of tamoxifen improves outcome compared with continuing tamoxifen to five years, and since the gain was sometimes greater than that seen with AIs given up front in the ATAC and BIG 1–98 trials, the hypothesis was made that sequential tamoxifen followed by an AI might be overall more effective than starting with an AI. However, two randomised trials addressing this question, BIG 1–98 and TEAM (Tamoxifen, Exemestane, Adjuvant, Multicenter), have both shown no advantage in the sequential approach (Figures 11.8 and 11.9). As shown in Figure 11.8, the risk of recurrence of breast cancer from the BIG 1–98 trial, did not differ either overall (Figure 11.8, panels A and B) or according to nodal status (Figure 11.8, panels C and D) among women in each of the two sequential-regimen groups as compared with the letrozole-monotherapy group. Current standard of care for postmenopausal women considered appropriate for an aromatase inhibitor as initial therapy is to start with an AI and continue this for five years rather than use a sequential approach with tamoxifen first.

**Extended adjuvant endocrine therapy**

Current data have shown little or no advantage for continuing tamoxifen for longer than five years, although two large trials addressing this question are still running. A disadvantage of this approach is that the risk of endometrial cancer increases with the duration of tamoxifen. In contrast, the Canadian-led MA17 trial has shown that letrozole given after five years of tamoxifen decreases the risk of recurrence compared with placebo, with a predicted absolute gain of 6% four years after randomisation (Figure 11.4). Benefit was seen in women with both node-positive and node-negative tumours. In the final updated analysis, the HRs for DFS (distant disease-free survival) and OS in node-negative patients are 0.45 (0.27–0.75), 0.63 (0.31–1.27) and 1.52 (0.76–3.06) respectively, and in node-positive patients the HRs are 0.61 (0.45–0.84), 0.53 (0.36–0.78) and 0.65 (0.38–0.98) respectively. Two other similarly designed trials (NSABP B-33 and ABCSG-6a) have shown similar benefits with exemestane and anastrozole respectively. Follow-up data from the MA17 trial suggest that the proportional benefit increased the longer letrozole was continued, at least up to four years.

Over 1500 women who had been randomised after tamoxifen to placebo rather than letrozole chose to start letrozole after the trial was unblinded. These women also experienced an improvement in DFS (HR 0.57; 95% CI 0.37–0.86; P < .0001) and distant metastases and fewer contralateral breast cancers. However, there was still no significant difference in overall survival (HR 0.95; 95% CI 0.84–1.06).

**Updated analysis of the ATAC trial, at a 100-month median follow-up:** Kaplan-Meier prevalence curves for disease-free survival (DFS) in hormone receptor-positive patients. (Forbes et al., 2008.)

![Figure 11.7](image-url)
Figure 11.8 Cumulative incidence of relapse in the intention to treat analysis in the TEAM study. Adapted from van de Velde et al. (2011).

Figure 11.9 Cumulative incidence of recurrence of breast cancer from the BIG I-98 trial, among women in each of the two sequential-regimen groups as compared with the letrozole-monotherapy group. Overall results (panels A and B) and according to nodal status (panels C and D). Adapted from BIG 1–98 Collaborative Group (2009).

DFS (HR 0.39; 95% CI 0.20–0.74; \( P = .004 \)), despite a substantial lapse in time between therapies of up to five years from the discontinuation of adjuvant tamoxifen (median 2.8 years). Furthermore, recently reported data on a subset analysis of women in the MA17 trial who were premenopausal at initial diagnosis but became postmenopausal during adjuvant tamoxifen suggest that those women also benefit from switching to letrozole after around five years. Women diagnosed with premenopausal breast cancer had significantly greater benefit (HR 0.25; 95% CI 0.12–0.51) from letrozole treatment in terms of DFS compared with those who were postmenopausal at initial diagnosis (HR 0.69; 95% CI 0.52–0.91).
The MA17 trial has reminded doctors of the long natural history of ER-positive breast cancer. More recurrences develop 5–15 years after diagnosis in these women than are seen in the first five years (Figure 11.10). Letrozole after five years of tamoxifen in estrogen receptor-positive postmenopausal patients has become the standard of care for all but low-risk women. A further randomisation in this trial is investigating whether letrozole for up to ten years after tamoxifen completion is of continuing benefit.

### Ongoing trials

The optimal duration of treatment with an AI is unknown and several trials are addressing this issue. For some women indefinite treatment may be required for optimal protection, given the very long natural history of the disease. All of the trials of adjuvant AI have shown a reduction in the rate of contralateral breast cancers and a reduction in new breast cancers in the treated but conserved breast. These observations have led to studies of the use of AIs in preventing breast cancer in high-risk postmenopausal women.

### Premenopausal hormone therapy

In premenopausal women, options include tamoxifen alone or tamoxifen combined with ovarian suppression/ablation (OS/OA), most commonly using an LHRH analogue such as goserelin. The addition of tamoxifen to goserelin in younger premenopausal women may improve survival in younger women with estrogen receptor-positive disease. There may, however, be little overall benefit from adding goserelin to tamoxifen. Comparing goserelin and tamoxifen with goserelin and anastrozole data so far indicates an improved DFS for tamoxifen and goserelin. This is somewhat surprising and needs confirmation in other studies.

### Chemotherapy

The benefits of chemotherapy are greater in younger compared with older women (Table 11.5). It used to be thought that in some way this was simply age related. It is now clear that biological factors strongly influence benefit and that chemotherapy is most effective against estrogen receptor-negative and/or HER2-positive tumours. These subtypes are commoner in younger women, but when they occur in older women who are otherwise fit, chemotherapy is still likely to be of benefit. In contrast, there is increasing evidence that chemotherapy is of little additional benefit over endocrine therapy alone for many women with estrogen receptor-positive, HER2-negative tumours, particularly grade I or II tumours. The greatest current challenge in planning adjuvant chemotherapy is identifying which women in this large subset benefit from additional chemotherapy. Risk–benefit considerations are important because of toxicity, and individual patient choice following informed discussion is an important factor.

#### Which chemotherapy regimen?

There is currently no one gold standard chemotherapy regimen in early-stage breast cancer.

Convincing evidence shows that anthracycline regimens with doxorubicin or epirubicin achieve a significant further survival improvement (around 4–5%) over CMF. In the United Kingdom, a sequential combination of anthracyclines followed by CMF is still sometimes used after it was found to be superior to CMF alone in the UK NEAT (National Epirubicin Adjuvant Trial), but this regimen uses eight courses of treatment over seven months. Shorter-duration anthracycline regimens of around six courses over four months (e.g. 5FU, epirubicin and cyclophosphamide) appear to provide similar benefit to eight cycles of sequential anthracycline and CMF. There remain some concerns regarding anthracycline-associated cardiotoxicity and the drugs’ leukemogenic potential.

The taxanes (paclitaxel or docetaxel) are now also widely used, either sequentially after anthracyclines or in combination, based...
on positive data from a series of trials and two meta-analyses (Figures 11.11 and 11.12).

A large UK trial involving over 4000 patients, TACT (Taxotere as adjuvant chemotherapy trial), failed to show any additional benefit for the addition of docetaxel. However, this trial and others have suggested that the gain with taxanes may be greatest in tumours that are ER negative and/or HER2 positive. A frequently used regimen in the United Kingdom for high-risk patients, including those with axillary node involvement, is so-called FEC-T (three cycles of FEC were followed by three cycles of docetaxel), based on positive results from a French trial (PACS-01) that demonstrated a 27% reduction in the relative risk of death for the FEC-T regimen (HR 0.73; 95% CI

Figure 11.11 Meta-analysis of DFS for trials of taxane-based versus anthracycline-based adjuvant chemotherapy. Adapted from Ellis et al. (2009).

Figure 11.12 Kaplan-Meier estimates of overall survival for patients randomised on PACS-01 on either FEC or FEC-T. Adapted from Chiang et al. (2006). 24(36), 5664–5671.
Role of Systemic Treatment of Primary Operable Breast Cancer

Figure 11.13 Outcome related to Ki67 in ER positive cancers and their response related to the use of taxane.

Curiously, current NICE guidelines state that paclitaxel should not be used in the United Kingdom as adjuvant treatment. These guidelines ignore level 1 randomised data showing similar efficacy between weekly paclitaxel and three-weekly docetaxel, and they deny UK women access to a drug that is both less toxic and less expensive than docetaxel.

**Dose density**

Dose-dense therapy intensifies the chemotherapy dose by shortening the inter-treatment interval. The use of recombinant hematopoietic growth factors allows the same chemotherapy doses to be safely administered every 14 rather than every 21 days.

The Cancer and Leukemia Group B 9741 (CALGB 9741) trial of accelerated chemotherapy showed that a combination of Adriamycin and cyclophosphamide for four courses followed by paclitaxel for four courses could be given safely at two-weekly rather than three-weekly intervals, supported by GCSF with marginally greater efficacy and with a shortened total treatment duration, which is attractive to patients (Figure 11.14).

**Combinations of chemotherapy and hormonal therapy**

Some data suggest that when chemotherapy and tamoxifen are both indicated for adjuvant treatment, then the efficacy is greater when tamoxifen is given after chemotherapy rather than concurrently, although the issue remains uncertain. No data exist on whether the same is true for AIs. Current practice tends to favour the sequential approach, based on extrapolation from the tamoxifen data, but trials are needed in this area, since there may be a disadvantage in delaying hormonal treatment for the four to six months required to complete chemotherapy.

Retrospective data suggest that premenopausal women who undergo chemotherapy-induced amenorrhoea have a better outlook than those who continue to menstruate. This raises the possibility that ovarian suppression may be beneficial after chemotherapy. If menes persist an LHRH analogue can be given, but this must be balanced against the side effects of the menopause. The Premenopausal

**High-dose chemotherapy with haemopoietic stem cell rescue**

Randomised trials and meta-analyses show high morbidity and no significant benefit from this approach. This is in contrast to major progress with clinical developments in targeted therapies, including trastuzumab.

**Trastuzumab**

Around 20% of breast cancers overexpress the transmembrane growth factor receptor HER2, and this is associated with an adverse prognosis. Trastuzumab is a humanised monoclonal antibody directed against the external domain of the receptor, with clinical activity initially shown as a single agent and more strikingly in combination with chemotherapy in patients with metastatic disease whose cancers overexpress HER2.
Four large randomised trials (HERA, NSABP B-31, N9831, BCIRG006) involving approximately 11 500 women with early-stage HER2-positive breast cancer have shown that the addition of trastuzumab to chemotherapy further improves DFS by around 40–50% and OS by around 33% (Figure 11.15). Most patients were treated with anthracycline chemotherapy, often but not always with sequential taxane. The only significant clinical problem with trastuzumab is a risk of cardiac dysfunction in a small minority of patients. Usually this is subclinical, with impaired left ventricular ejection fraction, and only very rarely is clinical cardiac failure induced. This is usually reversible and is very largely associated with prior or concurrent anthracycline treatment. Trastuzumab is usually not given concurrently with anthracyclines, therefore, and left ventricular ejection fraction is monitored before and at approximately four-month intervals during its administration. Because of this risk, one trial also stops phosphorylation and thus activation of HER2. Its role in early breast cancer instead of, or in combination with, trastuzumab is currently being investigated in the international ALTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) trial. The major clinical toxicity is diarrhoea.

Duration of trastuzumab

On an empirical basis, and to some extent by analogy with endocrine therapy, the major trials all used trastuzumab for one year. One trial, HERA (Herceptin Adjuvant), evaluated trastuzumab for one or two years versus observation, but no data are so far available for the two-year arm. In contrast, a small Finnish trial (FinHer) randomised HER2-positive patients to only nine weeks of trastuzumab or not concurrently with either vinorelbine or docetaxel, and then followed by anthracyclines. At a median follow-up of three years, patients who received trastuzumab achieved a significant benefit of similar magnitude to the large one-year duration trials but this difference has reduced in magnitude with longer follow up. Ongoing prospective randomised trials comparing shorter regimens of nine weeks or six months with the conventional one-year schedule.

Sequential or concurrent treatment

In the HERA trial trastuzumab was given sequentially after chemotherapy, whereas in the other trials it was given concurrently with a taxane. Although direct comparisons cannot be made with other trials, there is the suggestion that the benefit may be numerically less with the sequential HERA approach. The only negative trastuzumab trial so far, the French trial (PACS-04), failed to show any benefit with trastuzumab given after chemotherapy. Only one US trial has directly compared sequential with concurrent trastuzumab in a third arm, and a recent analysis has shown a strong trend in favour of trastuzumab given concurrently rather than sequentially, with a 25% further improvement in DFS (Figure 11.16).

Other anti-HER2 therapies: Lapatinib

Lapatinib is an oral anti-HER2 drug that is sometimes active in patients with metastatic HER2-positive breast cancer who have relapsed after trastuzumab. It is a tyrosine kinase inhibitor and stops phosphorylation and thus activation of HER2. Its role in early breast cancer instead of, or in combination with, trastuzumab in early-stage disease is currently being investigated in the international ALTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) trial. The major clinical toxicity is diarrhoea.

Bisphosphonates

Bisphosphonates prevent treatment-related bone loss associated with oestrogen suppression in early breast cancer. This has been demonstrated for zoledronate 4 mg by IV infusion once every six months, both for postmenopausal patients on an AI (Z-FAST and Zo-FAST) and for premenopausal patients either on tamoxifen or anastrazole and an LHRH analogue (ABC3G–12). Both these trials also suggested that the risk of breast cancer recurrence may also
be reduced with this treatment. However, results from the recently presented AZURE (Adjuvant Zoledronic acid redUce Recurrence) trial showed no effect on breast cancer recurrence or overall survival from the addition of zoledronic acid to standard adjuvant adjuvant therapy for women with stage II or III breast cancer. A preplanned subset analysis demonstrated a significant effect on both recurrence and survival for women who had been menopausal for at least five years, but routine use of zoledronic acid to prevent breast cancer recurrence is not indicated at present. Results from further bisphosphonate trials are awaited, including NSABP B-34 (oral clodronate given daily) and SWOG-S0307 (Zoledronic Acid, Clodronate or Bisdronate in adjuvant therapy of breast cancer), before these observations can be confirmed.

Patients with early breast cancer who are at risk of treatment-related oestrogen suppression (the majority) should have a baseline dual-energy X-ray absorptiometry (DEXA) scan to assess bone-mineral density at the start of endocrine therapy and around every two years during treatment (see Reid et al. (2008) in Further Reading).

Neoadjuvant chemotherapy and endocrine therapy

The main clinical aim of neoadjuvant treatment before surgery for operable breast cancers is to downstage large cancers to reduce the need for mastectomy or to make locally advanced breast cancers operable (Chapter 12).

An important research aim of neoadjuvant therapy is to find short-term surrogate markers (clinical, pathological or biological) in small trials that can predict long-term outcome in the adjuvant setting accurately, and also to identify the optimal medical treatment for individual patients. In the immediate preoperative aromide compared with tamoxifen (IMPACT) trial, biological changes in tumour proliferation as measured by the Ki67 levels after two weeks of treatment were shown to predict correctly the superiority of anastrozole over both tamoxifen and the combination of these two agents in the adjuvant ATAC trial. This approach is now being investigated more widely.

### Neoadjuvant endocrine treatment

A randomised trial in postmenopausal women with large oestrogen receptor-positive cancers that would otherwise require mastectomy showed that letrozole for four months is superior to tamoxifen in terms of clinical response (55% v. 36%) (Figure 11.17) and breast-conserving surgery (45% v. 35%). In contrast, the IMPACT trial, which compared neoadjuvant anastrozole versus tamoxifen versus the combination (neoadjuvant ATAC), showed no significant difference in response rate (37% v. 36% v. 39%). A second study that compared three months of preoperative anastrozole or tamoxifen (PROACT) has again shown similar response rates with the two drugs, but a higher rate of breast-conserving surgery with anastrozole. Aromatase inhibitors are now preferred, given their superior efficacy in the neoadjuvant setting (Figure 11.18). When the results of PROACT and IMPACT were combined, a significantly greater response rate was seen in tumours that were locally advanced or required a mastectomy at presentation. The standard treatment duration of neoadjuvant endocrine therapy used to be three to four months, based largely on experience with neoadjuvant chemotherapy. More recent studies suggest that prolonging

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**Table 11.18** Meta-analysis of preoperative aromatase inhibitor versus tamoxifen in postmenopausal women with hormone receptor-positive breast cancer. Adapted from Seo, Kim and Kim (2009). Response rate of 1 equals equivalence.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
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<tbody>
<tr>
<td>PO24</td>
<td>1.29 (0.99, 1.68)</td>
<td>33.47</td>
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<tr>
<td>IMPACT</td>
<td>1.45 (1.02, 2.06)</td>
<td>19.26</td>
</tr>
<tr>
<td>PROACT</td>
<td>1.27 (0.88, 1.85)</td>
<td>38.66</td>
</tr>
<tr>
<td>Exemestane</td>
<td>1.84 (1.07, 3.16)</td>
<td>8.62</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.627)</td>
<td>1.36 (1.16, 1.59)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Figure 11.17** Carcinoma of left breast before (left) and after (right) four months of neoadjuvant letrozole.

**Figure 11.18** Meta-analysis of preoperative aromatase inhibitor versus tamoxifen in postmenopausal woman with hormone receptor-positive breast cancer. Adapted from Seo, Kim and Kim (2009). Response rate of 1 equals equivalence.
treatment duration to eight to nine months increases the overall response rate and may be a more effective strategy for invasive lobular cancers, which due to their biological profile seem to be more responsive to hormonal therapy and less to chemotherapy. The American College of Surgeons has compared all three aromatase drugs in the neoadjuvant setting. The numbers in the study were insufficient to distinguish small differences in efficacy. There was no significant difference in response rate, although letrozole and anastrozole were the two agents selected for further study. Letrozole is most used in clinical practice, as it is the only drug in the United Kingdom that has a product licence for this indication.

**Neoadjuvant chemotherapy**

Neoadjuvant chemotherapy achieves clinical regression of tumours in around 70–80% of patients (Figures 11.19 and 11.20), with around 10–20% of them achieving a complete pathological response (pCR) of their tumour (disappearance of the tumour from breast and axillary nodes). This is much more common in oestrogen receptor-negative than oestrogen receptor-positive tumours, and complete pathological response has been shown to be a powerful predictor for good long-term outcome in ER-negative but not ER-positive cancers. Randomised trials have shown that survival is similar whether chemotherapy is given before or after surgery, although there may be an improvement in longer-term outcome with the neoadjuvant approach (Figure 11.21). Neoadjuvant chemotherapy reduces the need for mastectomy and provides potentially valuable data on clinical and biological responsiveness to treatment. It is worth mentioning, however, that the NSABP (National Surgical Adjuvant Breast and Bowel project) trial B-18 of preoperative versus postoperative chemotherapy demonstrated a trend in favour of preoperative chemotherapy for DFS and OS in women less than 50 years old (HR 0.85, \( p = .09 \) for DFS, HR 0.81, \( p = .06 \) for OS) and a significant interaction of age in relation to survival, \( p = .01 \) (Figure 11.21b).

The regimens used for neoadjuvant chemotherapy are generally the same as those used for adjuvant treatment. Despite these encouraging results, the problem with the use of pCR as a short-term surrogate predictor for long-term outcome is that the pCR rate following chemotherapy is relatively low, missing many patients who also have a good prognosis despite not achieving pCR.

Neoadjuvant chemotherapy clears axillary nodal disease in approximately 35% of patients. Patients with triple-negative cancer will have their nodes cleared in approximately 50% of cases and patients with ER-positive disease in less than 10%. With a combination of chemotherapy and trastuzumab, nodes are converted from involved to clear in up to 70% of patients. Therefore, the use of short-duration (two to three weeks) pre-operative therapy can provide useful information on biological parameters that may predict long-term outcome irrespective of pCR and tumour size (neoadjuvant trials usually relate to larger tumours of 3 cm or more).

**Neoadjuvant trastuzumab**

The value of adding trastuzumab to chemotherapy in the adjuvant trials led to its incorporation into neoadjuvant therapies. Several trials have now shown a major increase in pCR rates of around 40–50%. A combination of chemotherapy with trastuzumab should now therefore be considered standard treatment when neoadjuvant treatment is given to patients with HER2-positive breast cancer.

**Neoadjuvant lapatinib and pertuzumab**

According to recent results from the NeoALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) study, the addition of combined trastuzumab and lapatinib to neoadjuvant chemotherapy improved pCR rates to 51%, versus only 29% with the addition of trastuzumab alone and 24% with the addition of lapatinib alone (\( p = \leq 0.0001 \) (Table 11.6). Similar results were reported with the dual anti-HER2 combination of trastuzumab and the novel agent pertuzumab, a monoclonal antibody designed to prevent heterodimerisation of HER2 with other HER receptors, including in particular HER3. The addition of pertuzumab to trastuzumab with neoadjuvant chemotherapy increased the pCR rates to 46% compared with 29% with the
Figure 11.21 Updated disease free survival in NSABP B18 which compared neoadjuvant AC vs adjuvant AC. (a) disease free survival from year 1–5 then replotted to analyze events from 5–15 years (b) overall survival subdivided by age <50, ≥50 years.

Table 11.6 NeoALLTO primary endpoint: Pathologic complete response.

<table>
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<tr>
<th>Parameter</th>
<th>Lapatinib</th>
<th>Trastuzumab</th>
<th>P Value</th>
<th>Lapatinib vs Trastuzumab</th>
<th>Lapatibnib + Trastuzumab</th>
<th>P Value</th>
<th>Trastuzumab vs Lapatinib + Trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR overall</td>
<td>24.7 (n = 154)</td>
<td>29.5 (n = 149)</td>
<td>.34</td>
<td>51.3</td>
<td>.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PCR*</td>
<td>20.0 (n = 150)</td>
<td>27.7 (n = 145)</td>
<td>.13</td>
<td>46.9</td>
<td>.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR by hormone receptor status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Positive</td>
<td>16.2 (n = 86)</td>
<td>22.7 (n = 75)</td>
<td>.24</td>
<td>41.6</td>
<td>.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>33.8 (n = 74)</td>
<td>36.5 (n = 74)</td>
<td>.75</td>
<td>61.3</td>
<td>.005</td>
<td></td>
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</tbody>
</table>

*Excludes 15 patients with non-evaluable nodal status. Adapted from Baselga et al. (2010).
addition of trastuzumab alone and 24% with pertuzumab alone. Furthermore, the combination of trastuzumab and pertuzumab without chemotherapy achieved a pCR rate of 17% with minimal toxicity, raising the possibility that some patients might be cured with targeted therapy alone, without all the toxicity associated with chemotherapy (Figure 11.22).

The potential long-term benefits of these dual-targeted therapies await the results of adjuvant trials.

Pathology of response to neoadjuvant therapy

The main feature seen in response to letrozole is the formation of a central scar (Figure 11.23a), which explains how cancers reduce in volume by central implosion. This feature is rarely seen after chemotherapy. Scattered and diffuse cellular patterns are seen much more commonly with chemotherapy than endocrine therapy. There are also more pathological complete responses with chemotherapy (Figure 11.23b). The pathology changes explain the higher rate of incomplete excision after neoadjuvant chemotherapy compared with neoadjuvant endocrine treatment.

Multidisciplinary teams

The roles of adjuvant and neoadjuvant medical treatments in improving survival in early breast cancer emphasise the importance of patients being assessed and managed by multidisciplinary teams.

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OVERVIEW

- Locally advanced breast cancer has a much poorer outlook than operable breast cancer.
- Specific types of breast cancer such as inflammatory breast cancer have a particularly poor outlook.
- The cornerstone of treatment of locally advanced breast cancer is initial systemic therapy, trying to make the cancer operable followed by local surgery and/or radiotherapy.
- Maintaining local control of breast cancer is an important goal in the treatment of locally advanced breast cancer.
- Local recurrence after surgery in locally advanced breast cancers continues to be a problem.

Locally advanced disease of the breast is characterised clinically by features suggesting infiltration of the skin or chest wall by tumour or matted involved axillary nodes. Large operable breast cancers and tumours fixed to muscle should not be considered as locally advanced.

Locally advanced breast cancer may arise because of:

- The position in the breast (for example peripheral or superficial).
- As a consequence of neglect (some patients do not present to hospital for months or years after they notice a mass). There is undoubtedly a major contribution from neglect, as many cases arise in elderly patients in whom the cancers behave in a rather indolent manner and are often well controlled by endocrine therapy alone if surgery is not feasible due to general frailty.
- Biological aggressiveness (this includes all inflammatory cancers and most with peau d’orange). Inflammatory carcinomas are uncommon and are characterised by brawny, oedematous, indurated and erythematous skin changes and have the worst prognosis of all locally advanced breast cancers (Figures 12.1 and 12.2).

Classification

Tumours involving chest wall muscles including not only the pectoralis major but underlying intercostal muscle and ribs are classified as T4 (Table 12.1). Cancers involving skin ulceration or with satellite nodules and peau d’orange are T4b. Tumours with both chest wall and skin involvement are T4c (Figures 12.3). Inflammatory breast cancers are classified as T4d.

Prognosis of locally advanced breast cancer

Recent data suggest that 5–10% of breast cancers present as locally advanced disease (Figure 12.4). Overall five-year survival is about 50%, but the prognosis relates to the biology of the underlying...
Locally Advanced Breast Cancer

Figure 12.3 (a) Locally advanced and ulcerated cancer right breast. (b) Ulcerated cancer with skin nodules.

Table 12.1 Clinical features of locally advanced breast cancer.

<table>
<thead>
<tr>
<th>Skin</th>
<th>Chest wall</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ulceration</td>
<td>• Nodules</td>
</tr>
<tr>
<td>• Dermal infiltration</td>
<td>• Nodules</td>
</tr>
<tr>
<td>• Erythema over tumour</td>
<td>• Nodules</td>
</tr>
<tr>
<td>• Satellite nodules</td>
<td>• Nodules</td>
</tr>
<tr>
<td>• Peau d’orange</td>
<td>• Interstitial muscle</td>
</tr>
</tbody>
</table>

Axillary nodes
• Nodes fixed to one another or to other structures

Figure 12.4 Mammogram of locally advanced breast tumour (left). Mammogram of the same breast (right) after hormone therapy showing substantial reduction in tumour volume (tumour was operable after treatment).

Figure 12.5 Invasive lobular cancer before and after neoadjuvant letrozole.

disease; indolent hormone-sensitive disease does much better than hormone-insensitive inflammatory breast cancer. Prognostic factors in locally advanced disease are similar to those in operable breast cancer: node status, tumour size, tumour biology including grade and proliferation rate, and response to treatment. A cancer that is locally advanced is much more likely than a cancer of the same size to have metastasised. For this reason patients with locally advanced breast cancer should have adequate staging investigations following diagnosis of invasive cancer.

Treatment
Current treatments have increased the local control of disease and have reduced the rate of metastatic progression. Despite changes in treatment, local and regional relapse remains a major problem and affects up to half of patients.

Role of systemic and local treatment
The mainstay of local treatment has been radiotherapy. This is because surgery, generally mastectomy, results in high rates of local recurrence. By contrast, though radiotherapy alone can produce high rates of local remission in both the breast and axilla, only 30% of patients remain free of locoregional disease at death. A sequence of appropriate systemic treatment and radiotherapy can increase the initial rate of local response to over 80% and has now superseded the use of radiotherapy alone.

The aim of systemic treatment in locally advanced breast cancer is to shrink the cancer and make it operable, thus improving local control and at the same time prolonging survival. Most randomised controlled trials in true locally advanced disease have been of exceedingly poor quality.

If patients are fit, systemic therapy is administered before local therapy with a view to reducing the extent of disease in the breast or axilla, or both (Figure 12.5). If the response is sufficient, surgery, mastectomy or breast-conserving surgery combined with axillary surgery should be performed. This should be followed by postmastectomy radiotherapy.
Choice of systemic treatment

Systemic treatment should be administered as part of a planned programme of combined systemic and local treatment (Tables 12.2 and 12.3). For frail patients treatment may initially be by endocrine therapy, with radiotherapy held in reserve for relapse.

Chemotherapy

Standard chemotherapy regimens have increased the initial rates of control. Studies of intensifying drug doses given in a fixed period either by giving smaller doses more frequently or by combining higher doses with factors to encourage regeneration of bone marrow does not produce survival benefits. Taxanes are being used increasingly in locally advanced breast cancer.

Results have shown significantly higher rates of clinical response and pathological complete remission with the addition of docetaxel to Adriamycin and cyclophosphamide (Figures 12.6–12.8). Two studies have shown that patients responding to four courses of

Table 12.2 Factors affecting choice of systemic treatment for locally advanced breast cancer.

<table>
<thead>
<tr>
<th>Hormonal treatment</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow-growing or indolent disease</td>
<td>Inflammatory cancer</td>
</tr>
<tr>
<td>Oestrogen receptor-positive cancer</td>
<td>Oestrogen receptor-negative cancer</td>
</tr>
<tr>
<td>Elderly or unfit patients</td>
<td>Rapidly progressive cancer</td>
</tr>
</tbody>
</table>

Table 12.3 Choice of systemic treatment for locally advanced breast cancer.

<table>
<thead>
<tr>
<th>Hormonal treatment</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal woman – ovarian ablation (surgery, radiation or gonadotrophin-releasing hormone agents) plus tamoxifen*</td>
<td>Intravenous anthracycline/taxane regimen**</td>
</tr>
<tr>
<td>Postmenopausal women – letrozole*</td>
<td>Trastuzumab in HER2 overexpression (3+ or 2+ and fluorescent in situ hybridisation positive)</td>
</tr>
</tbody>
</table>

*Anastrazole and exemestane are other options.
**For example, doxorubicin and cyclophosphamide or epirubicin and cyclophosphamide and paclitaxel or docetaxel.

Figure 12.6 Locally advanced breast cancer (left) with complete clinical response after chemotherapy (right).

Figure 12.7 Inflammatory cancer of the breast (left) before and (right) after chemotherapy showing an excellent response.

Figure 12.8 (a) Inflammatory cancer T4d right breast with erythema and peau d’orange. (b) Same patient after chemotherapy which produced no change in oedema, so patient received radiotherapy and then underwent mastectomy and LD flap.
anthracycline-based chemotherapy and subsequently randomised to four further courses of doxorubicin had a higher overall rate of response and pathological remission than those receiving four further cycles of the same chemotherapy.

Updated NSABP results have shown a reduction in local recurrence with the addition of docetaxel, but no improvement in survival. All the trials included patients with large operable breast cancer, and some included patients with locally advanced breast cancer. However, not all trials have shown a benefit from adding taxanes; a UK study that included patients with large operable and locally advanced breast cancer found that the response rate to the combination of Adriamycin and doxorubicin was identical to that obtained with Adriamycin and cyclophosphamide.

Reports of trials investigating the role of trastuzumab in patients whose tumours express the erbB2 or HER2 oncogene product have been impressive, with higher response rates for patients treated with neoadjuvant chemotherapy and trastuzumab together than for patients treated with neoadjuvant chemotherapy alone (Figure 12.9). The addition of pertuzumab to neoadjuvant chemotherapy and trastuzumab appears to increase response rates significantly in HER2 positive cancers (see Chapter 11).

As data from trials mature, it may be possible to obtain better initial clinical and radiological responses, enabling more patients to become suitable for surgery and radiotherapy. Increasing response rates and improving the quality of the responses should improve long-term local control and may also delay metastatic relapse and improve survival.

**Hormonal therapy**

An EORTC study has shown that hormonal therapy plays an important part in reducing the risk of locoregional failure, distant

<table>
<thead>
<tr>
<th>Operable breast cancer, HER2 positive (IHC 3+ or FISH+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomisation</td>
</tr>
<tr>
<td>Paclitaxel x 4</td>
</tr>
<tr>
<td>FEC x 4 + trastuzumab x 12 weeks</td>
</tr>
<tr>
<td>Local therapy</td>
</tr>
</tbody>
</table>

**Pathologic complete response rates for neoadjuvant therapy**

<table>
<thead>
<tr>
<th>Trastuzumab</th>
<th>P = FEC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=2319)</td>
<td>65.2%</td>
<td>26.3%</td>
</tr>
<tr>
<td>Hormone receptor-positive (n=1811)</td>
<td>61.6%</td>
<td>27.2%</td>
</tr>
<tr>
<td>Hormone receptor-negative (n=508)</td>
<td>70.0%</td>
<td>25.0%</td>
</tr>
</tbody>
</table>

Figure 12.9 MD Anderson randomised trial of neoadjuvant trastuzumab and chemotherapy (FEC = fluorouracil, epirubicin and cyclophosphamide. FISH = Fluorescent in situ hybridisation, IHC = immunohistochemistry, P = paclitaxel). Adapted from Buzdar, A.U. et al (2004) presentation at ASCO 2004.

Figure 12.10 Locally advanced breast cancer before and after three months of anastrozole. This patient was treated by breast-conserving surgery and radiotherapy and the postoperative result is shown on the right. She remains well with no recurrence five years later.

Figure 12.11 (a) Cancer at presentation. (b) After nine months of letrozole. (c) After breast-conserving surgery and radiotherapy.
metastases and mortality in patients with hormone receptor-positive disease. Substantial reductions in tumour volume with endocrine therapy alone can be achieved in patients with tumours with high levels of oestrogen receptor. The newer aromatase inhibitors are superior to tamoxifen in postmenopausal women (Figures 12.10–12.12). Drugs such as letrozole can also be effective, even in inflammatory cancers, providing that the tumour is oestrogen receptor rich.

Radiotherapy

Radiotherapy is generally well tolerated, even by elderly and frail patients. It can be given concurrently with systemic hormonal treatment or after a course of primary chemotherapy. The breast skin requires a full dose, and this will result in temporary erythema and probable moist desquamation (Table 12.4). If possible, palpable tumour masses should receive treatment boosts with either electrons or interstitial brachytherapy. Such boosts should be considered for palpable disease in the breast or axilla, or both. For particularly refractory tumours, radiotherapy is sometimes given concurrently with radiosensitising chemotherapy agents such as 5 fluorouracil.

Surgery

Mastectomy is generally not possible in the presence of features of locally advanced disease, but the role of surgery is changing. Treatment with a combination of cytotoxic drugs or initial hormonal treatment often causes the primary tumour to regress to a lower stage (with the disappearance of peau d’orange and erythema and a reduction in tumour volume), making surgery feasible some weeks or months after the start of systemic treatment. In such cases surgery may be a wide excision and sentinel node biopsy (Figure 10) or clearance of axillary nodes, but is more usually a total mastectomy and node clearance, both being followed by radiotherapy to the remaining breast or the chest wall.

Breast conservation is possible in patients whose tumours have reduced in size with systemic therapy. Wide excision after hormone therapy is usually successful, with clear margins being obtained; in contrast, after neoadjuvant chemotherapy in some patients multiple residual islands of tumour are sometimes seen, requiring re-excision or mastectomy to ensure complete excision of all remaining disease. In approximately 35% of patients chemotherapy can convert patients with positive to negative nodes and visible scarring is evident (Figure 12.13)

Management of residual disease

In some patients residual disease remains in the breast following a combination of systemic treatment and then radiotherapy. The disease can be excised by a salvage mastectomy, ideally followed by coverage with a myocutaneous flap (latissimus dorsi or transverse rectus abdominus) (Figures 12.8 and 12.14). 'Toilet' surgery, used in an effort to control fungating cancers or the recurrence and

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**Table 12.4** Radiotherapy for locally advanced breast cancer.

<table>
<thead>
<tr>
<th>Treatment areas</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast</strong></td>
<td><strong>Axilla and supraclavicular fossa (the axilla should be omitted if the patient has had a complete axillary dissection)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td><strong>Megavoltage X-rays</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Technique for enhancing skin dose</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>40–50Gy in 15–25 fractions over three to five weeks</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Boost to tumour mass if possible by external beam or radioactive implant of 10–20Gy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td><strong>Lethargy</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Skin erythema and areas of moist desquamation</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Temporary mild dysphagia</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Less than 1% risk of pneumonia</strong></td>
<td></td>
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</tbody>
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Figure 12.12 Locally advanced breast cancer before and after three months of letrozole. This patient was treated by breast-conserving surgery and radiotherapy.

Figure 12.13 (a) Central scarring seen following neoadjuvant letrozole. (b) Picture of complete pathological response after neoadjuvant chemotherapy. (c) Scarring seen in an axillary node after response to neoadjuvant chemotherapy.
Locally advanced cancer left breast T4b with multiple skin nodules before (top) and after LD flap (below).

progression of disease, is often ineffective and should be performed only for breast cancers that are locally advanced, either because of their peripheral position in the breast or because of a delay in presentation. In this group surgery should be combined with radiotherapy and appropriate adjuvant systemic treatment.

Despite the best efforts with combined treatments, a proportion of patients who present with locally advanced disease develop uncontrolled disease of the chest wall. Although chemotherapy can relieve symptoms in up to half of these patients, the overall efficacy of systemic chemotherapy is poor.

Recently, other cytotoxic agents have been shown to have an effect in locally recurrent and locally advanced breast cancer. Thus, third and even fourth lines of chemotherapy, using, for example, the oral agent capecitabine or intravenous vinorelbine, are sometimes effective in patients with these intractable and unpleasant conditions.

Rarely, retreatment with radiotherapy is possible using brachytherapy with radioactive sources applied to the surface or superficial X-rays. An alternative may be local hyperthermia, which is available in a few centres.

Patients with hormone-sensitive disease may experience temporary responses from a change in hormone therapy using, in sequence, aromatase inhibitors, antiestrogens (tamoxifen or fulvestrant or both), progestogens and even oestrogens.

**Local recurrence after mastectomy**

This usually occurs in the skin flaps adjacent to the scar and is presumed to arise from viable cells shed during surgery. It can be diagnosed by core biopsy. Local disease can be isolated, but in up to half of patients it heralds systemic relapse. For this reason a search for distant metastases should be undertaken in all patients.

Local recurrence after mastectomy can be classified as single-spot relapse, multiple-spot relapse or field change (Figure 12.15). Treatment differs for these three categories, as does prognosis, with the worst survival in those with field change.

**Treatment**

If the recurrence is focal and occurs many years after the original surgery, excision alone can provide long-term control.

If the recurrence is focal but occurs within the first few years after mastectomy, then excision should be combined with radiotherapy if not previously given. If the recurrence is not single but still localised, then the options are radiotherapy or more radical excision followed by radiotherapy. A change in systemic therapy should also be considered for patients with localised or multiple-spot recurrence.

In more widespread recurrence, standard treatments are often disappointing. Radiotherapy giving a high skin dose should be
Figure 12.17 (a) Cancer and necrosis with added infection pre-maggots. (b) Cancer post-maggots. (c) Maggots in teabag.

Table 12.5 Treatment of local recurrence in chest wall.

<table>
<thead>
<tr>
<th>Recurrence Type</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single spot</td>
<td>- Excise and consider radiotherapy – consider hormonal treatment if tumour is oestrogen receptor positive</td>
</tr>
<tr>
<td>Multiple spot</td>
<td>- Radiotherapy, unless already given, or more radical excision (possible with coverage with myocutaneous flap), consider change in systemic treatment</td>
</tr>
<tr>
<td>Widespread</td>
<td>- Consider radiotherapy, unless already given or disease too widespread</td>
</tr>
<tr>
<td></td>
<td>- Give appropriate systemic therapy (hormonal or chemotherapy) depending on oestrogen receptor and disease behaviour</td>
</tr>
<tr>
<td></td>
<td>- Consider oral capecitabine</td>
</tr>
</tbody>
</table>

considered if it has not been given before. Failure to halt the progress of local disease can lead to cancer en cuirasse, in which the chest wall is encircled by tumour – an extremely unpleasant situation for the patient. Systemic therapies used for this are the same as for the management of residual disease.

Recurrence on the chest wall can sometimes be quite indolent and slowly growing, and can occur in the absence of metastases elsewhere. Multiple small-spot recurrences of less than 1 cm in the dermis may respond for several months to topical cytotoxic agents such as miltefosine. The control of ulceration and focal malodorous infected tissue is a considerable problem for carers, and patients with such disease have a miserable existence. Excision of dead tissue (Figure 12.16) and the use of topical and oral antibiotics with anti-anaerobic activity combined with charcoal dressings can help to control the odour (Figure 12.13). Maggots are another option (Figure 12.17). The best form of treatment is prevention by ensuring that initial local treatment is optimal. Major surgery is sometimes effective (Figure 12.18).

Further reading


OVERVIEW

• Approximately one third of all patients with operable breast cancer develop metastatic disease.
• Metastatic breast cancer has a hugely variable natural history.
• Therapy should be based on the most current information on disease extent, oestrogen receptor, progesterone receptor and HER2 receptor.
• Patients who become resistant to one drug can frequently respond to second- or third-line endocrine or chemotherapeutic agents.
• Supporting drugs that have direct effects on bones such as bisphosphonates or denosumab have an important role in disease that has metastasised to bone.
• Symptom control is important in the terminal phase of patients with breast cancer.

About one third of patients treated with curative intent will eventually develop secondary breast cancer with ultimately fatal results. A small but significant percentage of women who present with breast cancer have metastases at the time of their initial presentation. Thus at any given time there are in the United Kingdom around 100 000 women who have metastatic breast cancer, with 12 000 or so dying each year. Globally around 500 000 women die annually from breast cancer.

Few other cancers when they metastasise have such a variable natural course and effect on survival as breast cancer. Patients with hormone-sensitive cancers may live for many years without any intervention other than various sequential hormonal manipulations (Table 13.1). Also some with metastatic HER2-positive cancers who previously had a poor outlook can live many years on trastuzumab. In contrast, patients with disease that is not hormone or trastuzumab sensitive tend to have a much shorter interval free of disease and shorter survival, reflecting the more aggressive biology of most hormone-independent cancers.

Clinical patterns of relapse predict future behaviour. There is a peak of metastatic relapses that occur within the first two years after diagnosis and treatment of localised disease. Patients with a long interval without disease (more than two years) after primary diagnosis and favourable sites of recurrence (such as local lymph nodes and chest wall) survive longer than patients with either a short interval without disease or recurrence at other sites (Figure 13.1). Patients with visceral disease have the poorest outlook; these patients tend to have a short interval between diagnosis and development of metastatic disease and a short interval free of progressive disease between systemic therapies, as these cancers are biologically more aggressive. Quoting an overall median survival of three years for metastatic breast cancer thus has little meaning for an individual patient.

Table 13.1 Endocrine drugs for breast cancer.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-oestrogens</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
</tr>
<tr>
<td>Toremifene</td>
<td></td>
</tr>
<tr>
<td>Fulvestrant</td>
<td></td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td></td>
</tr>
<tr>
<td>Anastrozole</td>
<td></td>
</tr>
<tr>
<td>Letrozole</td>
<td></td>
</tr>
<tr>
<td>Exemestane</td>
<td></td>
</tr>
<tr>
<td>Progestins</td>
<td></td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td></td>
</tr>
<tr>
<td>Oestrogens</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td></td>
</tr>
<tr>
<td>Diethylstilbestrol</td>
<td></td>
</tr>
<tr>
<td>Androgens</td>
<td></td>
</tr>
<tr>
<td>Fluoxymestrone</td>
<td></td>
</tr>
<tr>
<td>Luteinising hormone-releasing hormone analogues</td>
<td></td>
</tr>
<tr>
<td>Goserelin</td>
<td></td>
</tr>
<tr>
<td>Leuprolide</td>
<td></td>
</tr>
<tr>
<td>Buserelin</td>
<td></td>
</tr>
</tbody>
</table>

Figure 13.1 Median time of survival associated with sites of metastatic in patients with breast cancer.
Treatment of metastatic disease

A patient may present with metastatic breast carcinoma or develop a systemic recurrence after treatment for an apparently localised breast cancer. The aim of treatment is to produce effective control of symptoms with minimal side effects and to improve survival if feasible.

Although endocrine therapy is the most widely used treatment, it is only useful in patients who have proven hormone-responsive disease or where there is clear presence of oestrogen and/or progesterone receptor in the tumour. Surrogates for hormone sensitivity may be useful, such as a long period from first diagnosis (more than two years is conventional) and non-visceral sites of involvement. However, we are now in an era when the overwhelming majority of patients should have already had immuno-histochemical profiling of the primary cancer. Biopsy of any metastatic lesion, provided that the risk of complications is small, is also valuable in planning therapy, because the hormone receptor status and even the HER2 status change in up to 30% of metastatic cancers.

Hormonal treatment

A variety of hormonal drugs is available for use in metastatic breast cancer. Objective responses to hormonal treatment are seen in 30% of all patients and in 50–60% of patients with oestrogen receptor-positive tumours (Figure 13.2(a)). Response rates of 25% are seen with second-line hormonal treatments, although less than 15% of patients who show no response to first-line hormonal treatment will respond to second-line treatment, and 10–15% respond to third-line treatment.

Premenopausal women

A combination of tamoxifen and goserelin is superior to either agent alone (Figure 13.3). Studies have compared this combination in the adjuvant setting. Combining goserelin and anastrozole, an aromatase inhibitor, showed no benefit compared with tamoxifen and goserelin in the adjuvant setting. There are no data on metastatic disease. Following progression on goserelin and tamoxifen switching to goserelin and an aromatase inhibitor such as letrozole is appropriate.

Postmenopausal women

Tamoxifen used to be the most commonly prescribed drug in patients who had not received this as adjuvant treatment, but the advent of potent third-generation aromatase inhibitors has changed this (Figure 13.2(b)). Results from large randomised trials comparing tamoxifen with anastrozole or letrozole have demonstrated that aromatase inhibitors are well tolerated and have superior efficacy to tamoxifen. A combined analysis of North American and European studies comparing anastrozole versus tamoxifen in the first-line metastatic setting demonstrated a superior time to progression in patients with ER-positive breast cancer for anastrozole (Figure 13.4). A large study comparing letrozole and tamoxifen
showed letrozole to be superior in all outcomes in all groups of patients (Figure 13.5), with a superior response rate of 31% versus 21%, longer time to progression and treatment failure, prolonged time to chemotherapy and a significantly better survival profile in the first two years. Data comparing exemestane and tamoxifen show superiority for exemestane in most outcomes, but no difference in survival (Figure 13.6). Letrozole or anastrozole is the agent of choice for patients with ER-positive breast cancer who have not received these agents in the adjuvant setting.

After failure of the non-steroidal aromatase inhibitors letrozole or anastrozole, the choice of agents includes tamoxifen, if not used previously, or exemestane, a steroidal aromatase inactivator (Table 13.2), and the anti-oestrogen fulvestrant. Having a novel mechanism of action, the anti-oestrogen fulvestrant downregulates ER expression. Given as an intramuscular injection at a dose of 250 mg once a month, fulvestrant was compared with anastrozole in the second-line setting and with tamoxifen as first line. Fulvestrant was as effective as anastrozole at this dose and was as effective as tamoxifen in patients with ER-positive cancer. Given in a dose of 500 mg, fulvestrant appears more effective than anastrozole.

Chemotherapy

With chemotherapy, a balance must be achieved between a high rate of response and limiting the side effects. In randomised trials more active regimens have been shown to improve survival. The best palliation is also usually obtained with regimens that produce the highest response rates. Overall rates of response to chemotherapy are about 40–60%, with a median time to relapse of six to ten months. Subsequent courses of chemotherapy have lower rates of response of less than 25% (Figure 13.7). The chemotherapy regimens used for metastatic breast cancer are similar to those used for adjuvant and primary systemic treatment. The main reason for considering agents such as epirubicin and mitoxantrone is a greater safety margin for the cardiotoxic effect that results from continued anthracycline exposure.

Which cytotoxics are effective?

A variety of agents are effective and active in the treatment of metastatic breast cancer (Table 13.4). Anthracyclines may be considered even after adjuvant therapy exposure if the
Toxicity is as follows: * = 30–50% response m++; + = 20–30% response m++; + = 10–20% response m++; = 5–10% response m++; n = no response. Neurotoxicity is usually more severe with weekly than with three-weekly paclitaxel, but side effects and morbidity are much greater with doxetaxel. Giving paclitaxel weekly increases its efficacy and at the same time reduces side effects.

The orally active fluoropyrimidine, capecitabine, mimics the pharmacology of continuously infused intravenous 5-fluorouracil in the management of metastatic disease. It is active with response rates of 30–40%, usually well tolerated, given by mouth twice daily. As a result of this and other studies, trastuzumab is now a standard of care. About 20% of breast cancers overexpress the oncoprotein HER2 (c-erbB2). The humanised murine antibody, trastuzumab, has antitumour activity against HER2 overexpressing cells. The results of large randomised trials have demonstrated that trastuzumab is effective as a single agent and that it acts synergistically with some chemotherapeutic agents. Patients with doxorubicin refractory breast cancer treated by trastuzumab and paclitaxel had almost a doubling of the response rate and improvements in both time to progression and survival when compared with paclitaxel alone (Figure 13.9; Table 13.5). As a result of this and other studies, trastuzumab is now a standard of care.

**Established and new targeted agents**

In recent years there has been a real ‘explosion’ of novel non-cytotoxic agents, which are being examined as drugs on their own, in combination with other targeted agents or with chemotherapy.

**Table 13.4: Common regimens for metastatic breast cancer.**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Efficacy</th>
<th>Toxicity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC/E/EC/FEC††</td>
<td>40–50% response m++; +++; n++;</td>
<td>Not useful if recent adjuvant anthracyclines</td>
<td></td>
</tr>
<tr>
<td>Docetaxel††</td>
<td>35–45% response m++; +++; n++;</td>
<td>Use if anthracycline in adjuvant regimen</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel†</td>
<td>25–35% response m++; +++; n++;</td>
<td>Use if anthracycline in adjuvant regimen</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel/gemcitabine†</td>
<td>40% response m++; +++; n++;</td>
<td>Alternative to paclitaxel alone</td>
<td></td>
</tr>
<tr>
<td>Docetaxel/capcitabine††</td>
<td>50–60% response m++; +++; n++;</td>
<td>Alternative to docetaxel alone</td>
<td></td>
</tr>
<tr>
<td>Taxane/trastuzumab†††</td>
<td>50–60% response m++; +++; n++;</td>
<td>HER2-positive only</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab††</td>
<td>20–30% response Cardiotoxicity, rarely allergic reaction</td>
<td>HER2-positive only</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>20–30% response m++; +++; n++;</td>
<td>HER2-positive only</td>
<td></td>
</tr>
<tr>
<td>Vinorelbine/trastuzumab†</td>
<td>30–50% response m++; +++; n++;</td>
<td>HER2-positive only</td>
<td></td>
</tr>
<tr>
<td>Capcitabine**</td>
<td>30% response m++; +++; n++;</td>
<td>Usually after docetaxel failure</td>
<td></td>
</tr>
</tbody>
</table>

†††Usually first relapse setting.

**Figure 13.8: Overall survival of patients with metastatic breast cancer randomised to receive taxotere alone or a combination of capcitabine and taxotere.**

and is not significantly myelotoxic. It also does not cause hair loss. Routinely, it is given at doses 20–30% below the labelled dose and this seems to allow prolonged, tolerable and effective treatment. The vinca alkaloid, vinorelbine, is well tolerated but has limited activity as a third-line therapy, either alone or in combination.

**Figure 13.7: Selection for treatment of metastatic or recurrent breast cancer.**

disease-free interval is 12 months or more. Taxanes are effective in anthracycline-resistant disease, with a response rate of between 30% and 40%, and are the most commonly used agents following relapse in women exposed to anthracyclines used either in metastatic disease or in the adjuvant setting. The activity of three-weekly doxetaxel is higher than that of three-weekly paclitaxel, but side effects and morbidity are much greater with doxetaxel. Giving paclitaxel weekly increases its efficacy and at the same time reduces side effects.

The orally active fluoropyrimidine, capecitabine, mimics the pharmacology of continuously infused intravenous 5-fluorouracil (Figure 13.8). Most oncologists now use capcitabine at some point in the management of metastatic disease. It is active with response rates of 30–40%, usually well tolerated, given by mouth twice daily.
Metastatic Breast Cancer

Trastuzumab has changed the natural history of HER2-positive disease. Patients with HER2-positive metastatic breast cancer (MBC) treated with trastuzumab now have much better outcomes than previously.

Table 13.5 Results from trials with trastuzumab in patients with metastatic breast cancer whose tumours overexpressed HER2 and who received first-line treatment with chemotherapy alone or chemotherapy with trastuzumab. Source: Adapted from Slamon et al. (2001).

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Objective response rate</th>
<th>Time to progression (months)</th>
<th>Overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy alone</td>
<td>35%</td>
<td>4.6</td>
<td>20.3</td>
</tr>
<tr>
<td>Chemotherapy and trastuzumab</td>
<td>50%</td>
<td>7.4</td>
<td>25.1</td>
</tr>
<tr>
<td>Paclitaxel alone</td>
<td>15%</td>
<td>3.0</td>
<td>18.4</td>
</tr>
<tr>
<td>Paclitaxel and trastuzumab</td>
<td>42%</td>
<td>6.9</td>
<td>22.1</td>
</tr>
</tbody>
</table>

P value of change from chemotherapy alone:
- Paclitaxel: <0.001
- Paclitaxel and trastuzumab: <0.001

Adding trastuzumab to endocrine therapy also improves the control of hormone-sensitive disease where HER2 overexpression is present (Figure 13.11).

In the last five years several new drugs targeting HER2 have been identified, resulting in trials at all stages of disease. Lapatinib is an oral agent that targets the intracellular pathways of HER2 and its related molecule HER1 (Figure 13.12). It adds benefit to palliative chemotherapy (capecitabine) and may improve the control of cerebral metastases. Pertuzumab also targets the HER2 receptor and inhibits the pairing of the HER2 protein with other members of the HER family. HER1, HER3, and HER4 (Figure 13.13). It seems to be of a similar efficacy to trastuzumab. Combining the two agents increases the antitumour effect safely, but at considerable extra cost. A study comparing the combinations of a taxane together with trastuzumab and the same two agents but with pertuzumab showed a highly significant benefit for the addition of pertuzumab — progression-free survival increasing from 12.4 months to 18.5 months (HR 0.62).
Another agent targeting HER2 is TDM1, which is a combination of a cytotoxic agent bound to trastuzumab (Figure 13.13, Table 13.6). It has shown efficacy in patients whose disease is resistant to trastuzumab and is being used in a range of trials in HER2-positive breast cancer.

Table 13.6 TDM: Objective response in heavily treated patients with metastatic breast cancer that is HER2 positive.

<table>
<thead>
<tr>
<th>Response</th>
<th>Relapsed Metastatic Disease (n = 48)</th>
<th>Untreated Metastatic Disease (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, % (95% CI)</td>
<td>34.8 (22.2–50.0)</td>
<td>57.1 (34.0–78.2)</td>
</tr>
<tr>
<td>CBR, % (95% CI)</td>
<td>45.7 (30.9–62.0)</td>
<td>61.9 (39.8–80.3)</td>
</tr>
<tr>
<td>Best response, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CR</td>
<td>2.2</td>
<td>0.5</td>
</tr>
<tr>
<td>• PR</td>
<td>32.6</td>
<td>47.6</td>
</tr>
<tr>
<td>• SD</td>
<td>47.8</td>
<td>33.8</td>
</tr>
<tr>
<td>• PD</td>
<td>15.2</td>
<td>19.0</td>
</tr>
<tr>
<td>• Missing</td>
<td>2.2</td>
<td>0</td>
</tr>
</tbody>
</table>

*Objective response of SD for ≥6 months from baseline; Other monoclonal antibodies

Both trastuzumab and pertuzumab are monoclonal antibodies against HER2. Bevacizumab is a monoclonal antibody raised against vascular endothelial growth factor. Continued debate surrounds the use of bevacizumab and it continues to be evaluated in clinical trials. There is some evidence that it improves time to progression with evidence in some trials for an early survival advantage, but this is not consistent. There is some suggestion of a benefit for bevacizumab in triple-negative metastatic breast cancer.

Another promising agent is the m-TOR (intracellular pathway) inhibitor, everolimus. Combined with endocrine agents such as tamoxifen or letrozole, it increases response rate. In one study everolimus increased the clinical benefit rate from 42.1% with tamoxifen alone to 61.3% with tamoxifen and everolimus combined. Recent studies have shown the addition of the drug everolimus in a dose of 15mg to exemestane increased progression free survival compared with exemestane alone from 3.2 months to 7.4 months with the combination (HR 0.4).

Finally, even ‘triple-negative’ breast cancers have come under focus for treatment in their own right. The majority of these cancers are of the basal cell type and share some characteristics with BRCA1 or BRCA2 cancers, in that the main cancer cell-repair mechanism is single-strand DNA repair. Some very striking clinical responses were reported initially with PARP (poly adenosine-disposhate-ribose polymerase) inhibitors, this being the critical enzyme in that repair process. More recent results with these agents have been less impressive.

Support drugs: Bone disease

Bisphosphonates are a established part of the routine treatment of widespread bony disease, having been shown in randomised trials to reduce both the need for radiotherapy and symptomatic complications of patients with metastatic bone disease. Cost is an issue in determining their roles in the management of symptomatic advanced bone disease (Table 13.7). They are given either as
Table 13.7  Scoring system for long-term bisphosphonate treatment for metastatic breast cancer – total score for a patient is calculated and aids selection of patients who should receive long-term bisphosphonate treatment.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiemetic</td>
<td>Haloperidol 1.5 mg nocte/bd</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Ondansetron</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Ondansetron</td>
</tr>
<tr>
<td>Raised intracranial pressure (cerebral metastases, brain stem or meningeval disease)</td>
<td>Cyclizine 50 mg tds or 150 mg/24 hr SC</td>
</tr>
<tr>
<td>Bowel obstruction (if surgery inappropriate)</td>
<td>Cyclizine 50 mg PO tds</td>
</tr>
<tr>
<td>Gastric stasis/outlet obstruction</td>
<td>Metoclopramide or domperidone 10–20 mg qds</td>
</tr>
<tr>
<td>Vestibular disease (base skull tumour)</td>
<td>Cyclizine 50 mg PO tds</td>
</tr>
</tbody>
</table>

monthly infusions or orally, although their relatively poor bioavailability reduces absorption. Zoledronate is the most widely used and is available for use intravenously as a 15-minute infusion. Ibandronate is a potent oral agent. Trials comparing it with zoledronate are underway. Guidelines on which patients benefit most from these agents have been produced.

The only serious concerns are the rare complications of some renal impairment and, exceptionally, some cases of osteonecrosis of the jaw after invasive dental procedures.

There is accumulating evidence that a monoclonal antibody (denosumab) that binds to a mediator of bone loss is effective and has efficacy similar to bisphosphonates. Denosumab is even more effective than bisphosphonates in the management of advanced breast cancer affecting the bones. Denosumab reduced pathological fractures from 28.1% with zoledronic acid to 23.5%. Radiofrequency of the jaw, although rare, has also been reported with this agent as with bisphosphonates.

Specific problems

The management of nausea/vomiting due to cancer and its treatment are outlined in Table 13.7.

Sites of relapse and their management:

Bone disease

The bony skeleton is a site of relapse in three-quarters of patients who develop secondary breast cancer (Figure 13.14). Widespread bone disease may be associated with indolent behaviour and often responds well to hormonal treatment, but in young patients cytotoxic agents may be required. Measuring the benefit of anticancer drug treatment in terms of objective regression of tumour may be difficult, as bone scans are unreliable indicators of response to treatment. For this reason, repeated MRI scans or measurement of tumour markers is often used to assess response in bony metastatic disease (Figure 13.15). Collagen markers NTX and CTX are being evaluated as a potential markers of bone activity and thus treatment efficacy.

Localised bone pain should be treated by radiotherapy (Table 13.8): a single dose is often all that is required. For patients with more widespread disease or recurrence in previously irradiated areas, alternative measures are required. Analgesic drugs are the mainstay of treatment, either as a prelude to effective anticancer treatment or as a long-term alternative or supplement.
Table 13.8 Treatment of bone metastases.

<table>
<thead>
<tr>
<th>Consider bisphosphonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localised bone pain</td>
</tr>
<tr>
<td>• External beam radiotherapy</td>
</tr>
<tr>
<td>• Analgesics including opiates</td>
</tr>
<tr>
<td>• Non-steroidal anti-inflammatory drugs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Widespread bone pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Radioactive strontium</td>
</tr>
<tr>
<td>• Sequential hemibody radiotherapy</td>
</tr>
<tr>
<td>• Analgesics including opiates</td>
</tr>
<tr>
<td>• Non-steroidal anti-inflammatory drugs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathological fractures*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Internal fixation and radiotherapy</td>
</tr>
</tbody>
</table>

*Also prophylactic treatment for patients at risk of fracture.

to this treatment. Non-steroidal anti-inflammatory drugs are surprisingly potent in dealing with bone pain, even compared with opiates. Combining the two classes of drugs increases efficacy while minimising side effects.

Widespread bone pain may also be treated by simple analgesia combined with radiotherapy and bisphosphonates.

Pathological fractures due to bone metastases should be avoided and can be predicted by a sharp increase in pain over a few days or weeks. When bone lysis threatens fracture, internal fixation followed by radiotherapy (low dose in a few fractions) will improve quality of life and mobility and can be associated with a reasonable survival rate. If a pathological fracture does occur, the same combination of internal fixation and radiotherapy is used, but the functional result is inferior to that of prophylactic treatment.

Marrow infiltration

Any of the peripheral blood elements may be reduced by marrow infiltration, but a leukoerythroblastic picture (immature cells in the peripheral blood) suggests extensive marrow infiltration. Chemotherapy is generally required and should be given initially in reduced doses, with careful monitoring and adequate supportive care. A weekly regimen of bolus epirubicin or doxorubicin (25–30 mg/m²) or weekly paclitaxel (80–90 mg/m²) is well tolerated and effective. In hormone receptor-positive disease, excellent and long-lived responses are seen with endocrine therapy, even with bone marrow infiltration.

Malignant pleural effusion

Up to half of patients with metastatic breast cancer will develop a malignant pleural effusion, but only some of these will require specific treatment. Cytological examination of effusion fluid is positive for malignant cells in around 85% of patients. Aspiration of fluid alone is ineffective in controlling malignant pleural effusions and 97–100% of patients re-accumulate fluid. By contrast, tube drainage alone is effective in controlling effusions in just over a third of patients. For most patients, however, installation of bleomycin, tetracycline, talc or inactivated Corynebacterium parvum is required to control recurrence. All are relatively safe, with the main problems being pain, which is usually transient, and pyrexia.

Malignant hypercalcaemia

This is a potentially fatal complication. The onset is often insidious and may present as a non-specific illness and general deterioration of health, leading to confusion, dehydration, renal failure and coma. The treatment of this complication has been transformed by the availability of bisphosphonates, and these are the agents of choice after hydration with saline (about 3 litres given over 24 hours) (Table 13.9). Hypercalcaemia is nearly always symptomatic if the blood calcium concentration is more than 3 mmol/l after effective hydration. Effective anticancer treatment reduces the risk of recurrence, but patients whose disease is refractory to this treatment and who exhibit continuing hypercalcaemia can be treated with intravenous bisphosphonates given every two to four weeks.

Neurological complications

Although non-metastatic syndromes of the central nervous system can occur with breast cancer, any focal neurological symptom must be investigated. Computed tomography or, better, magnetic resonance imaging can detect even small volumes of disease in the brain (Figure 13.16). Isotope brain scanning is unhelpful. Cord disease is best detected by magnetic resonance imaging. The initial treatment of brain metastases is to reduce oedema with high-dose corticosteroids (16 mg daily of dexamethasone), pending local treatment with fractionated radiotherapy. Radiotherapy produces most benefit in patients whose neurological symptoms improve after taking steroids. Radiotherapy may be given in 5–10 fractions. Long-term survival may occur in patients with a solitary brain
metastasis if there is no evidence of involvement of visceral sites and the disease is hormone responsive. Isolated disease at a favourable site in the brain is best treated by excision of the metastasis followed by postoperative radiotherapy, or by stereotactic radiosurgery and whole-brain radiotherapy and appropriate systemic treatment.

The long term results of treating disease of the central nervous system are disappointing, with most patients dying within three or four months.

Cord compression is not usually amenable to surgery and is seen most often in patients with thoracic spinal metastases. Treatment with steroids and fractionated radiotherapy (5–10 treatments) may produce dramatic responses, provided that treatment is started as soon as possible before neurological deficits (paraparesis and bladder and bowel dysfunction) are severe. Patients with isolated metastases causing cord compression who are fit can be treated by emergency laminectomy. Occasionally patients develop meningeal infiltration, which can result in cranial nerve damage. Treatment by drugs (intrathecal methotrexate) and/or radiotherapy is not very effective. Infiltration or compression of nerves (such as infiltration of the brachial plexus) by a tumour can produce pain, paraesthesia. Palliative radiotherapy helps, but analgesic treatment may be required.

Drugs, often in combination with agents such as carbamazepine, also have analgesic activity but can contribute significantly to pain control, provided that treatment is started as soon as possible before neurological deficits (paraparesis and bladder and bowel dysfunction) are severe. Patients with isolated metastases causing cord compression who are fit can be treated by emergency laminectomy. Occasionally patients develop meningeal infiltration, which can result in cranial nerve damage. Treatment by drugs (intrathecal methotrexate) and/or radiotherapy is not very effective. Infiltration or compression of nerves (such as infiltration of the brachial plexus) by a tumour can produce pain, paraesthesia. Palliative radiotherapy helps, but analgesic drugs, often in combination with agents such as carbamazepine, amitriptyline or mexiletine, may be required.

Control of pain

Most patients with metastatic breast cancer complain of pain at some stage of their illness. These patients rarely have one site of pain, and most have several pains that may have different causes. Each site of pain and the mechanism underlying the pain should be identified. Patients' emotional states (anger, despair, fear, anxiety or depression) may be important in relation to how they respond to their pain and these need to be assessed and treated as part of their pain.

Analgesia should be simple and flexible and appropriate for the severity of the pain (Table 13.10). If simple or weak opioid analgesics do not bring the pain under control quickly, treatment with strong opioid analgesics or adjuvant drugs should be started (Table 13.11). Laxatives should be given to patients treated with opiates to prevent constipation. Some drugs have no intrinsic analgesic activity but can contribute significantly to pain control when used in combination with analgesics. Anxiety, restlessness and insomnia may be treated with benzodiazepines. The place of antidepressants in the management of chronic pain is not clear, although some patients with advanced or terminal malignant disease do seem to respond to them.

Patients with breast cancer can also have other symptoms that require treatment, including anorexia, dysphagia, nausea and vomiting, respiratory symptoms, headache and malodorous chest wall ulceration. While it may not be possible to cure or prolong the lives of some patients with metastatic breast cancer, much can be done to improve their quality of life. Management of cancer patients with end-stage disease should be multidisciplinary and include palliative care physicians or those with an interest in treating pain (Table 13.12). Control of symptoms is only one aspect of palliative care, and the resources of a skilled multidisciplinary team are needed to ensure that the psychological and social problems of patients and their family are addressed appropriately.

### Table 13.10 Choice of analgesic for control of pain.

<table>
<thead>
<tr>
<th>Pain</th>
<th>Class of analgesic</th>
<th>Preferred drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Simple analgesic</td>
<td>Paracetamol (preferable to aspirin because of lack of gastrointestinal side effects)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Weak opioid analgesic (alone or in combination with simple analgesics)</td>
<td>Codeine with paracetamol</td>
</tr>
<tr>
<td>Severe</td>
<td>Strong opioid analgesic</td>
<td>Morphine</td>
</tr>
</tbody>
</table>

### Table 13.11 Adjunct drugs for control of pain.

<table>
<thead>
<tr>
<th>Cause of pain</th>
<th>Useful adjuvant drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue infiltration</td>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Bone pain</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>Hepatic enlargement</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>Raised intracranial pressure</td>
<td>Dexamethasone**</td>
</tr>
<tr>
<td>Compression or infiltration of nerves</td>
<td>Dexamethasone**</td>
</tr>
<tr>
<td>(Dysaesthetic pain)</td>
<td>Carbamazepine Mexatine</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>Diazepam Batifen</td>
</tr>
<tr>
<td>Fungating tumour</td>
<td>Antibiotics Systemic co-amoxiclav or metronidazole Topical metronidazole</td>
</tr>
</tbody>
</table>

### Table 13.12 Control of other symptoms with metastatic breast cancer.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>Prednisolone of progestogens</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Antifungal drugs if related to candidiasis External beam irradiation, surgical intubation or endoscopic laser treatment if mechanical evidence of obstruction Consider chemotherapy if dysphagia results from mediastinal node compression</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Treat underlying cause Antiemetics (such as metoclopramide or cyclizine) with or without prednisolone</td>
</tr>
<tr>
<td>Constipation</td>
<td>Laxative</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Morphine and benzodiazepines</td>
</tr>
<tr>
<td>Cough</td>
<td>Codeine or methadone intramus or morphine oral solution Neub rationalised local anaesthetics</td>
</tr>
</tbody>
</table>
Further reading


OVERVIEW

- Prognostic factors are useful in guiding therapeutic decisions.
- Axillary node metastasis, histological tumour grade and tumour size are the most powerful prognostic factors.
- Oestrogen receptor and HER2, while prognostic, also have value in selecting treatment as both are targets for therapy.
- Multiple molecular and biological markers have been identified, but few are, as yet, of clinical benefit.
- Microarray (RNA) based technologies are in clinical trials being compared against conventional clinical prognostic and predictive parameters.

Prognostic factors have been of value for three main reasons:

- To predict outcome for an individual patient.
- To allow comparisons of treatment between groups of patients at similar risk of recurrence and death.
- To improve our understanding of breast cancer and develop new therapeutic approaches.

Prognostic factors should:

- Have clear biological significance.
- Be applicable to clearly defined patient populations.
- Be based on robust, reproducible data.

Prognostic factors put individual patients in a low- or high-risk group that indicates a relative rather than an absolute prediction of the future behaviour of the disease. The patient profile cannot always predict prognosis precisely. The factors often interrelate with each other. Nonetheless, they are useful in guiding therapeutic decisions, and biological factors are becoming more helpful, especially in predicting a patient’s response to certain types of treatment.

Clinical factors

Tumour size

The size of a cancer, as measured by the pathologist on the fresh or fixed macroscopic specimen and confirmed or amended after histological examination, correlates with survival (Figure 14.1).

Patients with smaller cancers have a better survival than those with larger tumours.

Axillary status

Axillary nodal metastasis that has been proven by histology is the most powerful prognostic factor in breast cancer in the majority of studies. Survival is correlated directly with the number and level of axillary lymph nodes involved (Table 14.1; and see Chapter 9).

Recent interest has focused on the assessment of small deposits of tumour within axillary lymph nodes known as micrometastases. Different definitions for these micrometastases are used with different methods of identification, including step sectioning, immunohistochemistry and reverse transcription polymerase chain reaction. Their importance, however, is unclear. The new tumour node metastasis staging system uses a pragmatic definition of a...
Table 14.1  Survival of patients with breast cancer according to involvement of axillary lymph nodes.

<table>
<thead>
<tr>
<th>Lymph node involvement</th>
<th>Survival at 10 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>66</td>
</tr>
<tr>
<td>Negative axillary nodes</td>
<td>77</td>
</tr>
<tr>
<td>Positive axillary nodes</td>
<td>40</td>
</tr>
<tr>
<td>≥4 nodes</td>
<td>51</td>
</tr>
</tbody>
</table>

Survival without disease (%)

Local recurrence

- Age (years)
  - <35: 64%
  - ≥35: 40%

Distant disease

- Years after treatment
  - 0: 63%
  - 5: 72%
  - 10: 63%

Figure 14.2  Freedom from recurrence of cancer in patients in relation to age when breast cancer first diagnosed (proportional hazards model showed women <35 to have a relative risk of 1.6 for distant disease).

Metastatic disease

- Micrometastasis as measuring between 0.2 mm and 2 mm in size. Such metastatic foci are treated in a similar manner to negative nodes in terms of therapeutic decision making. Isolated tumour cells are classified as node negative.

Histological factors (Table 14.2)

<table>
<thead>
<tr>
<th>Histological markers of prognosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary metastasis</td>
</tr>
<tr>
<td>Histological grade</td>
</tr>
<tr>
<td>Tumour size</td>
</tr>
</tbody>
</table>

Histological grade

Histological grade is assessed on tubule formation, nuclear pleomorphism and mitotic frequency, and the assessment is done by a trained pathologist. Three histological grades (1, 2 and 3) correlate with survival (Figure 14.3; see Chapter 8). The quality of fixation (and hence preservation of cellular architecture) is critical in determining the tumour grade accurately.

Histological type

- Special types of invasive breast cancer, including tubular, mucinous and invasive cribriform cancer, are associated with a better prognosis than invasive carcinoma of ductal/no special type (see Chapter 8). In addition, histological type provides information about the biological behaviour of invasive breast carcinoma – for example, invasive lobular carcinomas probably be oestrogen receptor positive, lack p53 expression, have a low proliferation rate and metastasise in a different pattern of spread to invasive ductal cancers.

Lymphovascular invasion

- In the breast, it may not be possible to distinguish lymphatic channels from blood vessels on routine haematoxylin and eosin-stained sections, so the term lymphovascular invasion is used. Tumour cells in the lumen of lymphovascular channels are present in up to a quarter of patients with breast cancer (see Chapter 8).
- Lymphovascular invasion is associated with local disease recurrence and a high risk of short-term systemic relapse.

Figure 14.3  Overall survival by histological grade in 3718 primary operable invasive breast cancers. Adapted from Nottingham Tenovus Primary Breast Cancer Series.
Other histological markers

Peritumoral angiogenesis, and micrometastases within draining lymph nodes (whether detected by histology, immunohistochemistry or molecular-enrichment techniques such as the polymerase chain reaction) require more evidence to determine whether they have prognostic importance.

Prognostic indices

Many histological and biological factors that determine prognosis are interrelated. Some are difficult to determine, and many do not have confirmed independent prognostic value. The Nottingham Prognostic Index (NPI) (Box 14.1) incorporates invasive tumour size, lymph node status and histological grade.

Box 14.1 Nottingham Prognostic Index.

Nottingham Prognostic Index = 0.2 \times \text{invasive size in cm} + \text{lymph node stage (score 1 for no nodes, 2 for 1–3 nodes, 3 for \geq 4 nodes)} + \text{grade (score 1 for grade 1, 2 for grade 2, 3 for grade 3)}

Originally the NPI was used to divide women into good, intermediate or poor prognostic groups. Confirmatory studies have led to a refined NPI with six categories (Figure 14.4; Table 14.3).

Biological factors

A range of biological factors have been associated with prognosis in breast cancer, often in small, selected series and some without multivariate statistical analysis. Few have confirmed clinical use (Table 14.4). Oestrogen receptor protein is associated with a good prognosis in the first three years after diagnosis. In addition, oestrogen receptor status predicts response to hormone treatment.

Table 14.3 There has been a dramatic improvement in survival over the last decade. These data are from the Nottingham Tenovus Primary Breast Cancer Series of patients with primary operable breast cancer treated from 1990 to 1996.

<table>
<thead>
<tr>
<th>Group</th>
<th>Index value</th>
<th>Survival at 10 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent (EPG)</td>
<td>2.0–2.4</td>
<td>96</td>
</tr>
<tr>
<td>Good (GPG)</td>
<td>2.41–3.4</td>
<td>93</td>
</tr>
<tr>
<td>Moderate 1 (MPG 1)</td>
<td>3.41–4.4</td>
<td>92</td>
</tr>
<tr>
<td>Moderate 2 (MPG 2)</td>
<td>4.41–5.4</td>
<td>75</td>
</tr>
<tr>
<td>Poor (PPG)</td>
<td>5.41–6.4</td>
<td>53</td>
</tr>
<tr>
<td>Very poor (VPPG)</td>
<td>\geq 6.4</td>
<td>39</td>
</tr>
</tbody>
</table>

Table 14.4 Biological markers of prognosis.

<table>
<thead>
<tr>
<th>Clinically useful</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Oestrogen receptor</td>
<td>• DNA alterations</td>
</tr>
<tr>
<td>• HER2</td>
<td>• RNA expression</td>
</tr>
<tr>
<td>• HER3, HER4</td>
<td>• Intracellular proteins</td>
</tr>
<tr>
<td>• HER5</td>
<td>• Extracellular proteins</td>
</tr>
</tbody>
</table>

Table 14.5 Biological markers of uncertain clinical significance.

<table>
<thead>
<tr>
<th>Proliferation markers: Ki67, MIB1, thymidine labelling, %S phase, topoisomerase II alpha, mitotic activity index</th>
<th>DNA alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apoptosis-regulating genes: Bcl2, Bcl-xl, bak, survivin</td>
<td>RNA expression</td>
</tr>
<tr>
<td>Cell cycle-regulatory genes: cyclin A, B, D, E, E1, overexpression of p21, p27, p39</td>
<td></td>
</tr>
<tr>
<td>Cell adhesion molecules: E cadherin, integrins, fibronectin, MNF</td>
<td></td>
</tr>
<tr>
<td>Proteases: cathepsin D, matrix metalloproteinase, tissue inhibitor of matrix metalloproteinases</td>
<td></td>
</tr>
<tr>
<td>Oncogenes: HER3, HER4</td>
<td></td>
</tr>
<tr>
<td>Oestrogen receptor related: progesterone receptor, p53</td>
<td></td>
</tr>
<tr>
<td>Signal transduction pathways: extracellular signal regulated kinase 1/2, J N-terminal kinase and p38</td>
<td></td>
</tr>
<tr>
<td>Allelic imbalance – 1p, 9q, 11q, 12q, 14q, 15q, 16q, 17p, 17q</td>
<td></td>
</tr>
</tbody>
</table>

*Denotes biological markers for which a number of studies have shown an association with outcome.

Epidermal growth factor receptor (HER1) correlates inversely with oestrogen receptor and is associated with reduced survival. HER2 overexpression (formerly CerbB2/neu) is associated with poor prognosis (Table 14.4, Figure 14.5).

These three markers have different therapeutic approaches:

• Oestrogen receptor: tamoxifen, selective oestrogen receptor modulators, aromatase inhibitors and ovarian suppression.
• Epidermal growth factor receptor: lapatinib, pertuzumab and gefitinib.
• HER2: trastuzumab, lapatinib, pertuzumab, T-DM1.

Many other biological markers are of uncertain clinical significance (Table 14.5).

Future

Tissue microarrays, in which cores (often 0.6 mm) from multiple samples can be incorporated into a single paraffin block,
allow evaluation of a large number of cases on a single histological section. They have been used in the evaluation of marker expression by immunohistochemistry in breast cancer. In addition, RNA- and DNA-based microarray technology, which examines thousands of genes on a single slide, has been used to assess the relation between gene expression or DNA alterations and outcome in several series. A range of complex statistical techniques show that clusters of some 70 genes (including some of those mentioned above) have been associated with prognosis in breast cancer (Figure 14.6), and there has been confirmation of their clinical value (Figure 14.7). These methodologies are currently being prospectively tested in randomised controlled trials and also compared against immunohistochemical markers (oestrogen receptor, progesterone receptor, HER2 and Ki67) (Figures 14.5 and 14.8).

An alternative to the 70-gene analysis is the 21-gene recurrence score (Genomic Health). Performed on paraffin-embedded tissue, proliferation, oestrogen-related genes, HER2 genes and four others are assessed and a numerical score computed. The score then correlates with a likelihood of recurrence (Figures 14.9 and 14.10). Although developed on a node negative population it is also effective in node positive patients and may help in selecting patients for chemotherapy (Figure 14.11).

Studies of recurrence score versus outcome in clinical trials have shown that chemotherapy has maximum benefit in patients with high recurrence scores.

Ongoing studies are determining whether the 70-gene analysis (mammaprint) or the 21-gene recurrence score (oncotype DX) is
Prognostic Factors

Figure 14.10 Overall survival of patients divided by the Recurrence Score (Genomic Health) into the three risk groups (see Figure 14.9).

Figure 14.11 Breast Cancer Specific Survival of Node-Positive Patients by Treatment and Recurrence Score® (RS) Group in a randomised trial of tamoxifen alone or chemotherapy + tamoxifen (CAF-T).

Shared Decision Making
Name: _________________________________________ (Breast Cancer)
Age: 60     General Health: Good
Estrogen Receptor Status: Positive     Histologic Grade: 2
Tumor Size: 2.1 - 3.0 cm     Nodes Involved: 1 - 3
Chemotherapy Regimen: Second Generation Regimen
Decision: No Additional Therapy
38 out of 100 women are alive and without cancer in 10 years.
18 out of 100 women relapse
6 out of 100 women die of other causes.
Decision: Hormonal Therapy
25 out of 100 women are alive and without cancer because of therapy.
Decision: Chemotherapy
12 out of 100 women are alive and without cancer because of therapy.
Decision: Combined Therapy
32 out of 100 women are alive and without cancer because of therapy.

Data from www.adjuvantonline.com showing calculations for a 60 year old patient with an oestrogen receptor positive grade 2 cancer measuring 2.5 cm with 2 positive nodes for relapse (top panel) and mortality (bottom panel) and the benefits from the addition of endocrine therapy and a second generation chemotherapy regimen such as a combination of anthracycline and a taxane.
of value in being able to select patients who would benefit from chemotherapy.

Proteomic arrays to examine expression of known and novel proteins in tissues or serum from patients present alternative markers of response to therapy and may be related to prognosis. Certain internet sites provide useful information on individual patient prognosis and give an outline of likely benefits from different adjuvant therapies. For example, www.adjuvantonline.com is a continually updated site that provides information on the probability of relapse and survival using patient details including age, general health, oestrogen receptor status, tumour size, grade, node status and in the publicly available version will in future include HER2. It provides details of recurrence rates and survival with and without adjuvant therapy and the likely benefits in terms of reduction of recurrence and improvements in survival from different endocrine and chemotherapy adjuvant therapies (Figure 14.12).

Box 14.2 Prognostic guides for therapeutic decisions.

- Nottingham Prognostic Index
- Adjuvant Online
- RNA microarrays
- Protein immunohistochemistry expression panels

Acknowledgements

The sources of the data presented in the graphs are Nixon, A.J. et al. (1994) Relationship of patient age to pathologic features of the tumor and prognosis for patients with Stage I or II breast cancer. Journal of Clinical Oncology, 12, 888–894 for disease-free survival related to age, and the Nottingham Tenovus Primary Operable Breast Cancer Series for graphs comparing tumour size, histological grade and Nottingham Prognostic Index group to survival.

Further reading


CHAPTER 15
Psychological Impact of Breast Cancer
Belinda Hacking
Western General Hospital, Edinburgh, UK

OVERVIEW
- Breast cancer has a significant psychological impact
- All centres treating patients with breast cancer would benefit from access to applied psychologists and a well developed system of psychosocial support
- Breaking bad news requires experience and training
- Patients often need support in decision making
- A significant percentage of patients with breast cancer suffer from anxiety and depression. It is important to identify and treat these patients

Breaking bad news
Being given a diagnosis of breast cancer is a life-changing event. While many people’s first thoughts when being told that they have breast cancer relate to their mortality, they also have to face the challenge of treatment and the disequilibrium that this generates. All patients who are told that they have breast cancer will experience distress, although the extent of this varies. A proportion of patients will experience severe psychological problems that interfere with their quality of life and their capacity to function normally. The majority of patients will find ways to accommodate and adapt to the experience of breast cancer.

Adjustment to the diagnosis of breast cancer
Psychological adjustment is defined in the psychological literature as the ‘cognitive and behavioural responses the patient makes to the diagnosis of cancer’. This description is rather literal and lacks the existential and social components of psychological adjustment. Psychological adjustment to cancer involves accommodating the following:
- Searching for meaning
- Dealing with loss of control
- Managing uncertainty about the future
- Need for openness
- Need for emotional and medical support

Psychological adjustment is not an end point in itself, but is a dynamic and evolving process. When understanding the challenges inherent in adjustment, the task for many patients with breast cancer is not only to return to their premorbid functioning, but also to accommodate a fundamental shift in their worldview. One patient who had been treated for breast cancer commented:

Nothing will ever be the same. I do not think that that is all a bad thing, as it has made me rethink what is most important to me in my life. I know now that I used to spend most of my time doing things that I no longer think are valuable and important. It is as if everything has been put in stark relief and I know now what I think is important. What is hard is living with that feeling of vulnerability. Life feels more valuable than it has ever been, the support I have from friends and family has pulled me through, but I do not feel in control of my body anymore with the fear that the cancer could come back.

In adjusting to the experience of breast cancer, patients often describe feeling as if their body has ‘let them down’ and not knowing if they can ‘trust their bodies again’. The concept that they had of feeling inherently healthy is disrupted as they come to terms with the recognition that they have breast cancer. For some, the search for meaning can take the form of needing to understand why they have developed breast cancer and the possible contributing factors (Tables 15.1 and 15.2). The expected life trajectory for most people is significantly disturbed by a diagnosis of breast cancer, as they face the unexpected uncertainty of their future. Inherent in this process of adjustment is a sense of vulnerability; patients with breast cancer need support from both family and friends and medical and nursing teams to help them navigate their way through treatment.

For those men diagnosed with breast cancer, the process of adjustment can be particularly complex due to the stigma that they associate with their condition. Perhaps as a response to this, men with breast cancer do not tend to seek formal support services but rely instead on family and friends. The majority of men report that

Table 15.1 Reasons for non-disclosure of psychological morbidity.
- Problems are inevitable
- Problems cannot be alleviated
- To avoid being judged inadequate
- Relevant questions not asked by health professionals
- Guesstimated by distancing, such as ‘you are bound to be upset’
they would like more information about their condition that is specific to their circumstances, and that much of the information available is inappropriate as it relates to women’s experiences.

Life changes and coping strategies

The diagnosis of breast cancer and its aftermath undoubtedly lead to major life changes for most patients, but these changes are not always negative. In one study of 200 cancer survivors, 30% had changed their jobs and 23% had moved homes or changed their living arrangements in the two years after their cancer treatment. The way in which a person who has a diagnosis of breast cancer copes is likely to be consistent with their normal functioning style or personality traits. Coping skills that are characterised by an active and optimistic approach, such as a ‘fighting spirit’, tend to lead to better outcomes in psychological terms. This kind of active approach to managing the disease and treatment may involve becoming an ‘expert patient’ and adopting goals such as healthy eating in order to increase their sense of control over the disease and their future. Although there has been some reservation expressed about those women who appear to have an exaggerated belief that they can control their disease through alternative therapies, maintaining a positive attitude and healthy living, a recent study suggests that these approaches are adaptive and may help to reduce anxiety (Table 15.3).

Denial of the experience of cancer tends to lead to higher distress and maladaptive adjustment, although denial in a pure sense is an unusual response. More often, patients understand and acknowledge that they have cancer, but this reality is so painful that they prefer not to focus on it. This may be evident because the patient seems unconcerned or uninterested in the management of their cancer. Such approaches, often described as passive and avoidant coping reactions, are likely to lead to greater psychological distress in the long term, as patients do not accept and adjust to their condition and treatment, which is part of the work of psychological adjustment. Coping strategies described as helplessness/hopelessness, fatalism, denial/avoidance and anxious preoccupation have been consistently correlated with depression and poor psychological adjustment. Patients who are low in mood are also more likely to have higher fears of recurrence.

Psychological morbidity

The incidence of psychological morbidity following a diagnosis of breast cancer varies widely, although it is generally accepted that about 20% of patients will experience major clinical depression, anxiety or adjustment disorders. These women benefit from being referred to specialist clinical psychology or liaison psychiatry services. One observational cohort study of 202 women with early breast cancer found that three months after the diagnosis, the prevalence of depression or anxiety was 24%, which is twice that of the general female population. This fell to 15% for those patients in remission at one year. Risk factors for developing clinical depression or anxiety up to five years after diagnosis or recurrence were not related to the disease type or treatment, but to the woman’s personal circumstances. Those women who were younger and had previous psychological problems, outstanding non-cancer-related difficulties and little social support are more likely to develop significant psychological distress (Figure 15.1). This is consistent with

Table 15.2 Disclosure by patients.

<table>
<thead>
<tr>
<th>Inhibited by</th>
<th>Promoted by</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Closed questions</td>
<td>• Open directive questions</td>
</tr>
<tr>
<td>• Leading questions</td>
<td>• Questions with a psychological focus</td>
</tr>
<tr>
<td>• Multiple questions</td>
<td>• Clarification of psychological aspects</td>
</tr>
<tr>
<td>• Questions with a physical focus</td>
<td>• Summarising</td>
</tr>
<tr>
<td>• Offering advice or reassurance, especially if premature</td>
<td>• Screening questions</td>
</tr>
<tr>
<td></td>
<td>• Empathy</td>
</tr>
<tr>
<td></td>
<td>• Educated guesses</td>
</tr>
</tbody>
</table>

Table 15.3 Criteria for an anxiety state.

• Persistent anxiety, tension or inability to relax
• Present for more than half of the time for four weeks
• Cannot pull self out of it or be distracted by others
• Substantial departure from normal mood
• Insomnia
• Irritability
• Impaired concentration
• Intolerance of noise
• Panic attacks
• Somatic manifestations

Figure 15.1 ‘The Beautiful Greek’, Marie Pauline Bonaparte by Counis. Marie Pauline, Napoleon’s sister, died from breast cancer in 1824. She was 45. Reproduced by permission of the Bridgeman Art Library.
other studies that have described the predictive factors for women developing depression after breast cancer treatment as being under the age of 50 at diagnosis and having ongoing experience of pain and lower levels of support and self-esteem. These characteristics appear to be independent of severity of the disease and type of surgical treatment. If a woman is depressed at the time of the treatment planning, this is likely to be predictive of a poor psychological adjustment three years later. The experience of depression early in the treatment process leads to avoidant or passive coping skills, which result in poorer outcomes.

**Effects of treatment**

Studies have generally not found a significant difference in coping and adjustment between women who have had a mastectomy as opposed to those having a lumpectomy for treatment of their breast cancer. If a woman perceives herself to be less attractive and has an impaired body image following treatment for her breast cancer, this increases the long-term risk of developing psychological disorders (Figures 15.2 and 15.3). Treatments such as adjuvant chemotherapy may have a short-term negative impact on mood. Some patients drop out of treatment due to an intense emotional disturbance, which can be rated by some patients as being more overwhelming than the physical side effects, such as nausea and hair loss. In spite of the advantages of tamoxifen and aromatase inhibitor treatment for improving survival rates, non-adherence or stopping treatment early is a common problem, estimated to be up to half of women prescribed this over five years. Most women who stop their endocrine treatment do so within the first year. This decision is often associated with ambivalence about menopausal symptoms and taking ongoing medication that acts as a reminder of their experience of breast cancer, as well as a dislike of the side effects of the treatment. This demonstrates the complex way in which women perceive their experience of cancer and the burden of treatment. In order to improve patients’ treatment adherence and their longer-term management, health professionals need to engage with women to understand their perspective, preferences, difficulties and to gauge their support and information needs.

**Communication**

In spite of the increasing commitment to communication training, patients’ most common complaints about medical consultations relate to not understanding what the doctor has said, not being able to ask questions, not feeling supported to express their affective state and not having enough control. Although the majority of patients report being satisfied with the outcome of reconstructive surgery, a significant proportion who regret this decision expressed dissatisfaction with the information given about surgery. A recent study showed that oncologists regularly addressed the effects of treatment with patients, but they tended to emphasise the physical management issues. In fact, many patients are very concerned about the psychosocial impact of breast cancer, but these concerns are unlikely to be expressed unless the consultations are patient centred. If physicians are more at ease with discussing the biomedical and not the psychosocial implications of breast cancer, significant psychological distress is unlikely to be detected in outpatient clinic settings.

**Support in decision making**

Effective patient-centred care is strongly associated with improved psychological adjustment, treatment adherence and functional outcomes. A critical aspect of patient-centred care is supporting the patient in the decision-making process or shared decision making. Supporting patients to participate in decision making facilitates active coping, contributes to good psychological adjustment and leads to greater satisfaction with decision choices; the majority of patients want to be involved in decisions. Although many doctors consider that they engage in shared decision making, this is not necessarily reflected in patients’ experiences. Information needs to be tailored to each patient at a suitable pace in order to create an environment in which the patient is encouraged to ask questions.
Table 15.4  What is shared decision making?
Appropriate in any clinical situation when range of treatment options available. It involves:
• Recognising and clarifying the problem
• Identifying potential approaches
• Discussing options and uncertainties
• Providing information about benefits/harms/uncertainties
• Checking understanding and reactions
• Agreeing treatment approach
• Implementing chosen treatment
• Arranging a follow-up
• Evaluating outcome
Adapted from Coulter (2009).

Table 15.5  Preventing psychological morbidity.
• Elicit patient’s awareness of diagnosis
• If patient is unaware, ‘test water’ by using euphemisms and tailor statements according to patient’s responses
• If patient is aware, confirm diagnosis:
  ◦ Pause to let news sink in
  ◦ Acknowledge subsequent distress
  ◦ Establish contributive concerns
  ◦ Check patient’s needs for information
  ◦ Give information and advice
  ◦ When appropriate discuss treatment options and evaluate the responses given. Decision aids such as the use of audiotapes, question prompt sheets or personalised summaries of consultations have been demonstrated as being effective in enabling patients to engage in their consultations and to participate more in shared decision making (Table 15.4).

It is important that the systems of treatment for patients with breast cancer do not generate additional distress. Sensitive and patient-centred communication by surgeons has been shown to protect some women from psychological morbidity and to facilitate psychological adjustment. At present, significant psychological distress in women with breast cancer continues to be underdetected and therefore undertreated. Referral to specialist services should be considered for those patients who are recognised as experiencing adjustment disorders or depression (Tables 15.6 and 15.7); there is a substantial body of evidence that describes the effectiveness of cognitive behavioural treatments for cancer patients to improve mood, psychological adjustment and quality of life. There are a variety of websites (Tables 15.8) and self help groups, some of which are specifically for patients with breast cancer.

Names and addresses of self-help groups
Macmillan Cancer Support
89 Albert Embankment, London, SE1 7UQ
Freephone helpline: 0808 808 00 00. Lines open Monday – Friday, 9 a.m. – 8 p.m.
A free interpreting service is available for people whose first language is not English.
Website: www.macmillan.org.uk
Scotland office: Suite 2, 3rd Floor, Cranston House, 104–114 Argyle Street, Glasgow, G2 8BH
Office tel.: 0141 223 7676

Breakthrough Breast Cancer
Weston House, 246 High Holborn, London, WC1V 7EX.
Tel: 08080 100 200
Email: info@breakthrough.org.uk

Breast Cancer Care
5–13 Great Suffolk Street, London, SE1 0 NS
Main switchboard: 0845 092 0800
Helpline: 0808 800 6000
Email: emailsupport@breastcancercare.org.uk
Website: www.breastcancercare.org.uk

Breast Cancer Care Scotland:
4th Floor, 40 St Enoch Square, Glasgow, G1 4DH
Tel: 0845 077 1892
Email: sco@breastcancercare.org.uk

Table 15.6  Criteria for depressive illness.
- Persistent low mood
- Present for more than half of the time for four weeks
- Cannot be distracted out of it by self or others
- Qualitatively or quantitatively significantly different from normal mood
- Inability to enjoy oneself
- Plus at least four of the following:
  - Diurnal variation of mood
  - Repeated or early waking
  - Impaired concentration or indecisiveness
  - Feeling hopeless or suicidal
  - Feelings of guilt, self-blame, being a burden or worthlessness
  - Irritability and anger for no reason
  - Loss of interest
  - Relatiation or agitation

Table 15.7  Markers of risk for affective disorders.
- Past psychiatric illness
- Toxicity as a result of radiotherapy or chemotherapy
- Lymphoedema or pain
- Problems with body image
- No confiding tie
- Low self-esteem
- Unresolved concerns

Table 15.8  Useful websites.
http://cancerhelp.cancerresearchuk.org – Cancer Research UK
www.healthtalkonline.org – Healthtalkonline
www.maccancersupport.org.uk – Macmillan Cancer Voices
www.maggiescentres.org – Maggie’s Cancer Caring Centres
www.cancer.gov – National Cancer Institute at the National Institutes of Health, USA
www.optionsforbreastreconstruction.com – Options for Breast Reconstruction
www.macmillan.org.uk – Macmillan Cancer Support
www.breastcancercare.org.uk – Breast Cancer Care
www.breakthrough.org.uk – Breakthrough Breast Cancer
www.maggiescentres.org – Maggie’s Cancer Caring Centres
Psychological Impact of Breast Cancer


Carcinoma in situ

Nigel Bundred \(^1\) and J Michael Dixon \(^2\)

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\(^2\)Edinburgh Breast Unit, Western General Hospital, Edinburgh, UK

OVERVIEW

- The number of women with carcinoma in situ continues to increase and comprises approximately 25% of all 'malignancy' detected through screening.
- Localised DCIS can be treated by breast-conserving surgery with or without radiotherapy.
- The role of hormone therapy in preventing recurrence of DCIS after breast-conserving surgery continues to be investigated.
- For patients with larger areas of DCIS, mastectomy with or without breast reconstruction is effective.
- Factors that influence local recurrence in DCIS after breast-conserving surgery include completeness of excision, radiotherapy, patient age and histological grade.

Carcinoma in situ

Two main types of non-invasive (in situ) cancer can be recognised from the histological pattern of disease and cell type (Table 16.1). Ductal carcinoma in situ is the most common form of non-invasive carcinoma, making up 3–4% of symptomatic and 20–25% of screen-detected cancers. It has increased in frequency because of the widespread use of screening mammography (Figure 16.1). The increase is across all age groups, with a 12% annual increase in the 30–39-year age group and an 18.1% annual increase in women over the age of 50. Ductal carcinoma in situ is characterised by distortion, distention and complete involvement by a similar and neoplastic population of cells of adjacent ducts and lobular units (Figure 16.2). By contrast, lobular carcinoma in situ, now known as lobular intraepithelial neoplasia (LIN), which incorporates what was previously known as lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH), is rare (<1% of screen-detected cancers) and presents as relatively uniform expansion of the whole lobule by regular cells with regular, round or oval nuclei. While each involved lobular unit has a uniform cellular population, the pattern and even cytology often do vary between units, with some intervening ones being minimally involved or uninvolved. Despite the ease of separating these two processes most of the time, there are cases with combined features that should be regarded as having clinical features of both processes.

Previously there was agreement about the criteria distinguishing atypical hyperplasia (with specific histological criteria and validation of clinical implications with follow-up studies) from in situ carcinoma. The heterogeneity of some lesions has led pathologists to incorporate LCIS and ALH into LIN. Discussions about classification of so-called DCIS and atypical ductal hyperplasia (ADH) lesions into a single classification of DIN are ongoing. In general, lesions that involve only a few membrane-bound spaces and that measure less than 2–4 mm in their greatest diameter should be regarded as hyperplastic lesions (with or without atypia) and not in situ carcinoma. There is better agreement about larger lesions. Even if there are greatly enlarged lobular units with partial involvement by foci of ADH, this should not be regarded as DCIS for clinical purposes. They are usually in the 5–8-mm size range, and have not been proven to have the natural history of DCIS.

Ductal carcinoma in situ

Different classifications of ductal carcinoma in situ have been described, and these correlate to some degree with mammographic patterns of microcalcification.

Presentation

Patients with symptomatic ductal carcinoma in situ present with a breast mass, nipple discharge or Paget's disease. Screen-detected carcinoma is most commonly associated with microcalcifications.

| Table 16.1 Features of ductal and lobular carcinoma in situ. |
|-----------------------|-----------------------|-----------------------|
|                        | DCIS                  | LCIS                  |
| Average age            | Late 50s              | Late 40s              |
| Menopausal status      | 70% postmenopausal    | 70% premenopausal     |
| Clinical signs         | Breast mass, Paget's  | Disease, nipple       |
|                       | disease, nipple       | discharge             |
| Mammographic signs     | Microcalcifications   | None                  |
| Risk of subsequent     | 30–50% at 10–18 years | 25–30% at 15–20 years |
| carcinoma              | Same breast           | Same breast           |
| Site of subsequent     | 99%                   | 99%                   |
| invasive carcinoma     | Other breast          | 1%                    |
| Same breast            | 50–60%                | 40–50%                |
| Other breast           | 1%                    | 1%                    |
Carcinoma in situ

Figure 16.1 DCIS cases detected by breast screening up to 2008 in UK.

Figure 16.2 Ductal carcinoma in situ: cribiform DCIS (top left); calcification in an area of DCIS (top right); comedo DCIS (bottom left); micropapillary DCIS (bottom right).

Table 16.2 Classification of DCIS.

<table>
<thead>
<tr>
<th>Histology</th>
<th>Cytology</th>
<th>Necrosis</th>
<th>Calcification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comedo</td>
<td>High grade</td>
<td>Extensive</td>
<td>Branched</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Limited</td>
<td>Limited</td>
</tr>
<tr>
<td>Non-comedo*</td>
<td>Low grade</td>
<td>Absent</td>
<td>Microfoci inconsistent</td>
</tr>
</tbody>
</table>

*Cribriform, solid or micropapillary.

(Table 16.2; Figure 16.3), which may be localised or widespread and are characteristically branching within the involved duct system and of variable size and density.

Natural course

Several studies have assessed the risk of subsequent invasive carcinoma in patients in whom ductal carcinoma in situ was not diagnosed by the pathologist or the diagnosis was made but mastectomy was not performed. These studies relate to low-grade carcinoma in situ and show that approximately 40% will develop invasive cancer over a 30-year period, with the majority of these evolving within the first decade. Those who developed invasive cancer did so at the original biopsy site and were in the group where the biopsy was thought not to have removed all the DCIS. Information on the behaviour of inadequately excised intermediate and high-grade DCIS is derived from therapeutic trials documenting local recurrence of DCIS or the development of invasive cancer. This natural history of intermediate and high-grade DCIS is thus continued disease extension and evolution to invasion.

DCIS is a heterogeneous group of lesions, which differ in growth pattern and cytological features, and these different types have marked biological and behavioural differences. Up to 80% of high-grade DCIS overexpress the oncogene or HER2 or erbB2, whereas only 10% of low-grade DCIS express HER2. The presence of a significant amount of oestrogen receptor also differs between
histological grades, with 59% (range 16–57%) of high-grade DCIS being oestrogen receptor positive compared with 79% (range 70–91%) of low- and intermediate-grade DCIS (Figure 16.4). Pure cases of micropapillary DCIS, although rare, are often extensive within the breast and frequently involve more than a single quadrant.

Treatment
Symptomatic DCIS usually involves much larger areas of the breast than carcinoma in situ detected by screening and has traditionally been treated by mastectomy (Figure 16.5). Such treatment is associated with excellent long-term outcomes (99% survival at five years). With the advent of breast screening and the use of conservative surgery for invasive carcinoma, wide local excision has been increasingly used for localised carcinoma in situ (Table 16.3). The relative merits of wide excision and mastectomy should be discussed with each individual patient (Figure 16.6). There is an increasing trend to treat DCIS regardless of size and grade by breast-conserving surgery if feasible with or without postoperative radiotherapy.

Radiotherapy after breast-conserving surgery for DCIS
Four randomised trials involving almost 3000 women have shown an approximate 50% reduction in the rate of ipsilateral tumour
Carcinoma in situ

Table 16.3  Recommended treatment for ductal carcinoma in situ.*

<table>
<thead>
<tr>
<th>Localised carcinoma in situ (≤4 cm)†/‡/***</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Wide local excision (WLE)‡</td>
<td></td>
</tr>
<tr>
<td>• Ensure that mammographic lesion has been completely excised with clear histological margins (at least 1 mm)</td>
<td></td>
</tr>
<tr>
<td>• Re-excite if margins are involved</td>
<td></td>
</tr>
<tr>
<td>• Consider mastectomy if DCIS &gt;4 cm in size or if micropapillary</td>
<td></td>
</tr>
<tr>
<td>• Postoperative radiotherapy especially if ER/PR negative</td>
<td></td>
</tr>
<tr>
<td>• Consider tamoxifen, 20 mg a day if ER positive</td>
<td></td>
</tr>
</tbody>
</table>

| Widspread carcinoma in situ (>4 cm)†/‡/*** |
|------------------------------------------|--|
| • Mastectomy (with or without breast reconstruction) |
| • Tamoxifen not indicated after mastectomy |
| • Radiation not indicated after mastectomy |

*Outside trials of experimental treatments.
†Extent of carcinoma can be estimated in 80% of patients by measuring extent of malignant microcalcification on mammograms.
‡Size per se is not an indication for WLE or mastectomy, larger lesions can be treated by WLE in larger breasts.
§Complete excision to clear margins.

Figure 16.6  Mammogram of recurrent DCIS seen as microcalcification adjacent to the metal clip, in a patient treated by wide excision alone.

Factors predicting recurrence after wide local excision of ductal carcinoma in situ (Table 16.4)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Bad prognosis feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excision margins</td>
<td>Margins &lt;1 mm after breast-conserving surgery</td>
</tr>
<tr>
<td>Tumour grade</td>
<td>High grade (III)</td>
</tr>
<tr>
<td>Comedo necrosis</td>
<td>Present</td>
</tr>
<tr>
<td>Histological type</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>Patient age</td>
<td>Younger age at diagnosis &lt;40 years</td>
</tr>
<tr>
<td>Biological markers</td>
<td></td>
</tr>
<tr>
<td>Oestrogen receptor</td>
<td>HER2 (erb-B2)</td>
</tr>
<tr>
<td>Progesterone receptor</td>
<td></td>
</tr>
<tr>
<td>Bcl2</td>
<td></td>
</tr>
<tr>
<td>P53</td>
<td></td>
</tr>
<tr>
<td>Ki67</td>
<td></td>
</tr>
<tr>
<td>Patient presentation</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Tumour size</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

Factors predicting recurrence after wide local excision of ductal carcinoma in situ (Table 16.4)

Randomised trials have indicated that symptomatic high-grade lesions, comedo necrosis and incomplete excision of DCIS are associated with a higher rate of local recurrence. In addition, young age (less than 50 years) (Figure 16.9) at diagnosis is associated with an increased risk of local recurrence in several DCIS trials. Local recurrence is in the form of invasive cancer in up to 50% of cases, while the remainder are recurrent DCIS. The EORTC study indicated that invasive carcinoma developing after excision of high-grade DCIS is more likely to be node positive compared with lower or intermediate-grade invasive ‘recurrence’, regardless of whether radiotherapy is given (Figure 16.10). Size does not appear to be
Adjuvant endocrine therapy

Two studies have examined the benefit of tamoxifen in preventing local recurrence (Figure 16.12). In the American B24 trial (Table 16.5), the significant reduction in local recurrence from tamoxifen was due predominantly to a 40% reduction in women under 50 years of age; older women had a smaller (20%) non-significant reduction. The UK/ANZ trial found a 30% reduction in recurrent DCIS but not in invasive cancer development in tamoxifen-treated patients, but this study included few patients under 50 years of age. A pathological review of ER status in a subset of the American trial indicates that tamoxifen reduced the risk of recurrence in ER-positive DCIS by 60% (RR 0.41; 95% CI 0.26–0.65), but did not affect relapse rate in ER-negative DCIS. There is thus no indication for using tamoxifen in women with ER-negative DCIS or after mastectomy for DCIS.

Ongoing trials are examining the management of DCIS in specific subgroups (e.g. oestrogen receptor-positive DCIS, HER2-positive DCIS) to provide a basis for individualisation of treatment in this condition. One such trial is the International Breast Interventional Study II comparing anastrazole, an aromatase inhibitor, with tamoxifen in women with oestrogen receptor-positive DCIS.
Another is looking at the value of using trastuzumab concurrently with radiotherapy as a radiosensitizing agent.

**Lobular intraepithelial neoplasia (lobular carcinoma in situ/atypical lobular hyperplasia)**

Most studies that have reported on this range of lesions have noted that the lobular units involved lack the continuous involvement of adjacent lobular units and ducts that characterise DCIS. There is no proof that patients with larger lesions or those with more pleomorphic cytology have a higher risk of breast cancer development than women with more localised or less pleomorphic lobular carcinoma in situ (LCIS) lesions. Controversy does exist however as to whether the natural history of pleomorphic LIN is more similar to that of DCIS. More studies are needed.

Presentation is often an incidental finding during a breast biopsy and there are no characteristic clinical or mammographic...
features. It is the associated features of dense mammary tissue, enlarged lobular units and calcifications that are visible on mammograms and explain the increased incidence in the screening population.

Natural course
About 15–20% of women with a diagnosis of lobular intrapithelial neoplasia (LIN) will develop breast cancer in the same breast, and a further 10–15% will develop an invasive carcinoma in the contralateral breast.

Treatment
There are four possible approaches to LIN observation: with yearly bilateral mammography; treating the patient with a preventive agent; entering the patient into a trial of treatments to prevent breast cancer; or bilateral mastectomy. Bilateral mastectomy should be confined to women who experience severe anxiety that significantly reduces their quality of life. In the National Surgical Adjuvant Breast and Bowel Project tamoxifen breast cancer prevention trial, there was a 56% reduction in the risk of invasive cancer in patients diagnosed with LCIS who received tamoxifen. Ongoing trials are evaluating anastrozole in postmenopausal women with LIN.
Table 16.5 Recurrence rates for localised DCIS treated by wide local excision and radiotherapy in a randomised trial of tamoxifen (National Surgical Adjuvant Breast and Bowel Project B-24).

<table>
<thead>
<tr>
<th>Type of recurrence</th>
<th>Cumulative recurrence rate at five years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 902)</td>
</tr>
<tr>
<td>Ipsilateral non-invasive</td>
<td>5.1</td>
</tr>
<tr>
<td>Ipsilateral invasive</td>
<td>4.2</td>
</tr>
<tr>
<td>All breast cancer events</td>
<td>13.4</td>
</tr>
</tbody>
</table>

Further reading


Acknowledgement

CHAPTER 17

Breast Reconstruction

J Michael Dixon1, Cameron Raine2 and Eva M Weiler-Mithoff3

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2St John’s Hospital, Livingston, UK
3Canniesburn Hospital, Glasgow, UK

OVERVIEW

- Breast reconstruction should be offered to the majority of patients undergoing mastectomy
- There are a wide range of options for breast reconstruction, including using implants alone, myocutaneous flaps alone or the two together
- Surgeons performing breast reconstruction need specific training
- Patients who smoke or who have had radiotherapy are at high risk of complications from breast reconstruction
- Patients who have had breast-conserving surgery and have a poor cosmetic outcome can be offered partial breast reconstruction to improve results

The purpose of the operation is to reconstruct a breast mound that matches the opposite breast in size, shape, position and contour to produce breast symmetry (Figure 17.1). Demand for reconstructive surgery has increased consistently, and up to half of patients offered immediate breast reconstruction choose to have it. No evidence shows that immediate reconstruction increases the rate of local or systemic relapse or that it makes relapse more difficult to detect. Breast reconstruction reduces the psychological trauma experienced by patients after mastectomy. Breast reconstruction (particularly immediate reconstruction, which gives substantially better cosmetic and psychological outcomes) should therefore be widely available.

Treatment options (Table 17.1)

The choice of operation for an individual patient depends on several factors. Immediate breast reconstruction is less time consuming for the patient (although not for the surgeon), but care must be taken that the oncological operation is not compromised for a better cosmetic result. Reconstruction can be carried out by immediate placement of a prosthesis (implant), but this gave poor results in the majority prior to the introduction of dermal matrix. Other options include insertion of a tissue expander or insertion of a flap of skin and subcutaneous fat with or without muscle (myocutaneous or fasciocutaneous flap) with or without prosthesis.

Implants and expanders are usually inserted under the muscles of the chest wall (the pectoralis major and parts of the serratus anterior, rectus abdominis and external oblique); the expander is inflated over several months to stretch the skin and muscle and is eventually replaced with a definitive breast prosthesis. This technique involves no additional scars. The long-term results of implant-based breast reconstruction depend on the tolerance of skin and chest wall muscle and the need for adjuvant radiotherapy. Although at first glance this might seem a simple and quick operation, this type of reconstruction is associated with a high rate of reoperation over time and in the majority the need for symmetry surgery to the contralateral breast.

The two most common myocutaneous flaps used require movement of the latissimus dorsi muscle (with or without overlying
Breast Reconstruction

Latissimus dorsi flap

TRAM flap

Thoracodorsal vessels

Pectoralis major

Latissimus dorsi

Deep superior epigastric vessels

De-epithelialised flap buried for contour

Latissimus dorsi

Skin paddle

Area of skin undermining Rectus abdominis

Areas of dubious viability discarded

Rectus abdominis

Donor site closed as abdominoplasty and umbilicus resited

Prosthesis

Areas of skin (Figure 17.1) or the lower abdominal fat and skin based on the rectus abdominis muscle (transverse rectus abdominis myocutaneous (TRAM) flap) (Figures 17.2 and 17.3). They allow for simultaneous replacement of skin and soft tissue and allow for the creation of larger and more pendulous breasts. All flap reconstructions leave scars at the donor site on the back or the lower abdomen respectively. Latissimus dorsi flaps often require a breast implant to be placed between them and the chest wall to create a breast mound, although by extending the flap to include overlying fat it is often possible to get sufficient bulk to reconstruct the whole breast without using a prosthesis. Transverse rectus abdominis myocutaneous (TRAM) flaps can be performed as a pedicled flap based on the superior epigastric artery or as a free flap based on the inferior epigastric vessels (Figure 17.3) with a microvascular anastomosis. Muscle sparing perforator flaps such as the Deep Inferior Epigastric Perforator (DIEP) or the Superficial Inferior Epigastric (SIEA) flaps harvest the same amount of lower abdominal tissue but protect the rectus abdominis musculature and preserve abdominal wall function. These flaps are bulkier and do not usually need an implant to be inserted.

All of the above reconstructions can give pleasing results in correctly selected patients when performed by experienced surgeons. All forms of breast reconstruction are substantial surgical operations, and preoperative counselling is essential.

Tissue expansion and prostheses

Silicone implants are currently licensed in the United Kingdom and United States for breast reconstructions. The newer silicone implants are ‘solid’ gel implants and come in a variety of shapes and sizes; these are not liquid at body temperature, should have a longer lifespan and should leak less silicone than liquid silicone implants. Saline prostheses are also available, but they do not have the same doughy consistency of silicone gel and breast tissue. Prostheses can occasionally provide satisfactory results if inserted immediately at the time of operation or as a delayed procedure in patients with small breasts who have adequate skin flaps.

The use of tissue expanders and implants has increased since the availability of human and porcine acellular dermal matrices. These are decellularised human (Alloderm®) or porcine

---

**Figure 17.2** Breast reconstructions with myocutaneous flaps.

**Table 17.1** Options for breast reconstruction: Patient factors.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Immediate reconstruction</th>
<th>Delayed reconstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthesis</td>
<td>Small breasts</td>
<td>As for immediate reconstruction plus well healed scar plus no radiotherapy*†</td>
</tr>
<tr>
<td></td>
<td>Adequate skin flaps</td>
<td>As for immediate reconstruction plus well healed scar plus no radiotherapy*†</td>
</tr>
<tr>
<td>Tissue expansion and prosthesis</td>
<td>Adequate skin flaps</td>
<td>As for immediate reconstruction plus well healed scar plus no radiotherapy*†</td>
</tr>
<tr>
<td></td>
<td>Tension free skin closure</td>
<td>As for immediate reconstruction plus well healed scar plus no radiotherapy*†</td>
</tr>
<tr>
<td>Myocutaneous flaps</td>
<td>Large skin incision</td>
<td>As for immediate reconstruction</td>
</tr>
<tr>
<td></td>
<td>Doubtful skin closure</td>
<td>Can be used if previous radiotherapy</td>
</tr>
<tr>
<td></td>
<td>Large breasts</td>
<td></td>
</tr>
</tbody>
</table>

*Unless using acellular dermal matrix.
†Radiotherapy significantly increases complication rates.

**Figure 17.3** Anatomy of the deep inferior epigastric artery.
Figure 17.4 Patient who had a previous mastectomy on the right and subsequently had a left subcutaneous mastectomy and bilateral implant based breast reconstruction with Strattice®.

Figure 17.5 (a) Strattice being inserted (b) Lateral view of the subcutaneous mastectomy shown in Figure 17.4.

Figure 17.6 Patient who had immediate placement of bilateral breast tissue expanders.

Figure 17.7 Textured tissue expander used for breast reconstruction which has an integral filler port that is located by a magnet as shown.

(continued)

(continued)
Breast Reconstruction

Figure 17.8 Patient who had bilateral reconstruction with tissue expanders replaced by implants and subsequent nipple reconstructions and tattooing.

Figure 17.9 Patient who had a left mastectomy with removal of nipple, but areola was left intact and right prophylactic mastectomy was reconstructed with bilateral Becker expander/prosthesis. Injection ports can be seen in situ below and lateral to protheses.

Figure 17.10 Patient with left breast reconstruction by tissue expansion and prosthesis; she subsequently had her right breast reduced to achieve symmetry.

expander. Textured tissue expanders seem to produce less chest wall distortion and less discomfort. This technique is likely to give better symmetry in bilateral cases or in patients who desire a concomitant augmentation of the contralateral breast.

It is difficult to create large breast mounds by tissue expansion. If this technique is to be used in a patient with large or very pendulous breasts, the possibility of reducing the contralateral breast should be considered and discussed with the patient (Figure 17.10). Further surgery to the contralateral breast may be required in future because implant based reconstructions do not mature and droop like autologous breast reconstructions over time.

Complications with breast prostheses: Capsular contracture

The most common complication after the use of prostheses is the formation and subsequent contraction of fibrous capsules around implants. The use of textured prostheses has reduced the incidence of capsular contracture from 50% with smooth implants at one year to 10% at 10 years with textured implants. Capsular contracture results in hardening, distortion, an inferior cosmetic appearance of the reconstructed breast mound, and often discomfort and embarrassment. Postoperative radiotherapy substantially increases the rate of capsular contracture. Possible treatments include capsulotomy or capsulectomy, with change of prosthesis to a textured implant if a smooth implant was used. Recent evidence suggests that fat grafting or lipomodelling around the capsule of the implant may improve capsular contracture. Closed capsulotomy (forced manual rupture of the fibrous capsule) is not an appropriate treatment. Recurrent capsular contracture may eventually require removal or replacement of the implant with autologous tissue.

Infection occurs in less than 5% of patients and results in the prosthesis having to be removed (Figure 17.11). Most units use prophylactic antibiotics to limit the rate of infection. Low-grade infection can occasionally manifest as early capsular contracture or erosion of the prosthesis through the overlying skin (Figure 17.12).
Implant fatigue and rupture are a major concern among patients, as they lead to leakage of silicone gel (Figures 17.13 and 17.14). All implants will need replacement at some stage in the future. In most patients with ruptured implants, the leakage is intracapsular, whereby the silicone remains contained within the capsule of scar tissue around the implant with no leakage into the surrounding tissue or body. Extracapsular ruptures can occur, particularly if the breast sustains significant trauma such as in a road traffic accident and leakage of the silicone gel into the tissues can lead to silicone granulomas in the surrounding tissue. It is not uncommon for silicone implants to bleed a small amount of silicone gel, although this is much less with the newer generation of low-bleed implants. There is no convincing evidence to show that leaking silicone is carcinogenic or causes problems in other organs. In particular, women with implants do not seem to have a higher rate of connective tissue disorders (such as scleroderma, systemic lupus erythematosus or rheumatoid arthritis) than age-matched women without implants. The optimum method to image implants is MRI (Figure 17.15).

The lack of an association between silicone and connective tissue disorders is confirmed by the observation that other patients exposed to silicone (for example patients with silicone rubber joints, heart valves containing silicone or siliconised arteriovenous shunts) do not have an excess of these disorders. Saline-filled implants are available for breast reconstruction, but have a recognised risk of deflation and produce less satisfactory cosmetic results than silicone-filled implants. All implants containing alternative fillers such as soya bean oil or hydrogel are no longer available amid fears about the long-term safety of the filler materials.

**Myocutaneous flap reconstructions**

These have developed from the early ‘breast-sharing’ operations to the recent use of free tissue transfer with microvascular anastomoses. In immediate reconstructions with myocutaneous flaps and perforator based flap reconstructions, breast skin away from the carcinoma can be preserved (skin sparing), which substantially improves the final cosmetic outcome (Figure 17.16). Myocutaneous flaps are more time consuming and can be performed by...
one or two teams of surgeons. Although these are more extensive procedures, completely autologous techniques provide permanent results without the need for maintenance surgery in the future. The emergence of oncoplastic surgeons who perform the cancer operation and the reconstruction has increased the availability of reconstructive surgery.

**Latissimus dorsi flaps**

First described in 1896, this pedicled flap is a reliable and versatile method of breast reconstruction (Figure 17.17). Although traditionally used in combination with a variable-volume Becker expander/prosthesis or a fixed-volume prosthesis, extended flaps that harvest extra fat above and below the muscle allow purely autologous tissue reconstruction (Figures 17.16, 17.18–17.20). The volume of the flap can be doubled by the incorporation of six areas of additional fat harvest.

The thoracodorsal nerve is usually left intact, but it can be divided later if twitching is a problem. Harvest of the latissimus dorsi muscle does not generally lead to a significant interference with shoulder function for most activities of daily living. The deficits are significant in only a specific range of activities, such as rowing, cross-country skiing, mountain climbing, tennis and golf. Infection
Figure 17.21 Partial necrosis of upper part of latissimus dorsi myocutaneous flap.

Figure 17.22 Patient with superficial necrosis of back wound following an extended LD flap reconstruction.

Figure 17.23 Patient underwent delayed latissimus dorsi flap reconstruction. Because of the high mastectomy scar, the flap was inserted through a separate incision just above the inframammary fold.

Figure 17.24 (a), (b) & (c) Examples of free TRAM flap reconstruction.

can be a problem in latissimus flaps if an implant is inserted. Up to 50% of patients develop seromas at the donor site on the back, but the frequency can be reduced by suturing the skin flaps to the underlying muscle (quilting) or injection of triamcinolone.

Fat necrosis and skin loss is extremely rare after a latissimus dorsi myocutaneous flap, although minor degrees of necrosis can occur in up to 5% of patients (Figures 17.21 and 17.22). An LD flap can be
Breast Reconstruction

used for immediate (Figure 17.17) or delayed breast reconstruction (Figure 17.23).

**Transverse rectus abdominus myocutaneous flaps**

Pedicled transverse rectus abdominus myocutaneous (TRAM) flaps sacrifice one or both rectus muscles (Figure 17.25). Removal of the rectus abdominis can cause significant weakness of the abdominal wall. Abdominal hernias occur in up to 5% of patients, but they can be reduced by careful abdominal closure.

Free TRAM flaps include a smaller part of the rectus muscle, but require a microsurgical anastomosis to re-establish circulation to the reconstructed breast. Muscle and fascial harvest may be minimised by raising a perforator flap based on one or two myocutaneous perforators arising from the deep inferior epigastric vessels (DIEP flap) (Figure 17.26).

The more muscle is preserved the better the abdominal wall strength and function, but the more technically complex the procedure. Patients for TRAM or DIEP flaps should ideally be fit, healthy, non-smokers and well motivated. Although TRAM or DIEP flaps can be performed in smokers, the incidence of complications associated with smoking is higher. Patients who do smoke should cut down or stop smoking for as long as possible before surgery. While pedicled TRAM flaps rarely fail completely, the greatest problem with them is necrosis of skin and fat. Major necrosis occurs in up to 10% (some studies show partial flap necrosis of up to 40%) of patients who have pedicled TRAM flaps, but it affects fewer than 5% of patients with free TRAM flaps or DIEP flaps. Free tissue transfer, although routine in most plastic surgery units, carries a small risk of complete flap failure in the range of 2–5%.

All these procedures involve a lengthy anaesthetic and a prolonged recovery period of up to three months, which must be discussed fully with the patient. The recovery is shorter after a DIEP flap, because the rectus abdominus is left intact. The use of lower abdominal skin and fat in TRAM or DIEP flaps is often looked on by the patient as a bonus, because it gives a cosmetic improvement of the donor site in the form of an abdominoplasty or ‘tummy tuck’.

Alternative donor sites for free flap breast reconstruction include buttocks, thighs and flanks. These may be indicated if the abdomen is not available or does not have enough tissue, for example if the patient requires bilateral breast reconstruction.

**Choice of technique**

Selection of who is suitable for the different techniques is not always easy and is summarised in Table 17.2.

**Nipple reconstruction**

In general, it is best to wait at least six months after breast reconstruction before reconstructing the nipple complex to allow the breast time to settle. The nipple complex consists of the nipple and the areola, and each is reconstructed by different methods.

**Nipple**

Several techniques have been devised to make use of local tissue to produce nipple prominence (Figures 17.27 and 17.28). When the contralateral nipple is particularly prominent, ‘nipple sharing’ is a possibility.
## Options of breast reconstruction: patient factors.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Suitability</th>
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<tr>
<td>Skin-sparing mastectomy + Becker prosthesis/expander</td>
<td>Small to medium breast size, little or no ptosis unless contralateral mastopexy performed, non-smoker, no postoperative radiotherapy</td>
</tr>
<tr>
<td>LD flap + implant</td>
<td>Moderate/large breast size, non/light smoker, no postoperative radiotherapy</td>
</tr>
<tr>
<td>Extended LD flap</td>
<td>Small/medium/large breast size, non/light smoker, no postoperative radiotherapy</td>
</tr>
<tr>
<td>TRAM flap/DIEP flap</td>
<td>Any breast size, non/ex-smoker (&gt;6 months), no postoperative radiotherapy</td>
</tr>
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**Areola**

Dark skin for the new areola used to be obtained from the upper inner thigh, or sometimes part of the contralateral areola was used. Now tattooing is used to recreate the areola, but the colour intensity of the tattooed areola fades with time, so the procedure may have to be repeated (Figures 17.27 and 17.28).

**Use of prosthetic nipples (Figure 17.29)**

A false nipple can give a satisfactory shape and colour. An impression is made of the remaining nipple and a colour-matched silicone nipple is prepared by the lost wax technique. This can be prepared in a dental laboratory in two or three days. Patients apply the nipples with medical adhesive and wear them for a month at a time, thereafter peeling them off to wash the skin underneath.

**Radiotherapy**

Tissue expansion is difficult in patients who have had chest wall radiotherapy and it is generally not recommended in patients who are likely to require postoperative radiotherapy. Radiotherapy causes fibrosis in the chest wall muscles and in the overlying skin, which makes it difficult to obtain satisfactory expansion. Most patients who have already had postoperative radiotherapy are better reconstructed with a myocutaneous flap. In selected patients with sufficient skin, expanders or implants together with one of the tissue matrices can produce a pocket of reasonable volume.

Patients who undergo tissue expansion or women with a prosthesis in situ, however, can have postoperative chest wall radiotherapy if this is considered appropriate. This may be better delivered over a longer period (in a larger number of fractions) than standard schedules to reduce tissue reaction and fibrosis. However, capsular contracture and inferior cosmetic outcomes are common after irradiation of implants. One option for patients who are known to require chest wall radiotherapy is to place a temporary expander under the chest wall muscle to retain excess skin. The expander is deflated during radiotherapy and reinflated two weeks after completion of radiotherapy. After radiotherapy, the extra retained skin is used as part of a definitive reconstruction and the expander can be replaced with autologous tissue.

Chemotherapy can be given to patients with prostheses, tissue expanders or flaps as soon as the wound has healed (areas of skin-edge necrosis should preferably have re-epithelialised) and providing that there are no signs of underlying infection (Figure 17.11) and extrusion during chemotherapy. Radiotherapy increases the risk of fat necrosis in TRAM flaps, but not in extended latissimus dorsi flaps.
Reduction mammoplasty and mastopexy

It is not always possible to reconstruct a breast mound that matches the natural breast. Both size and shape can pose problems. Major problems with mainly implant-based breast reconstructions are that they can sit high and proud and often display little ptosis. If a good match of breast volume has been achieved, this lack of ptosis can be hidden by a suitable bra, thus achieving symmetry when the patient is fully clothed. Whereas some women are happy with this, others want to have the contralateral breast lifted surgically by mastopexy.

When there is a substantial difference in size, symmetry (even when clothed) can sometimes be achieved only by reduction of the natural breast (Figures 17.10 and 17.28). Some women who have chosen to wear an external prosthesis after a mastectomy and who have no interest in breast reconstruction may also seek reduction of their remaining breast to allow them to wear a smaller and lighter prosthesis.

Complications of Mastopexy and Reduction Mammoplasty

These operations can produce considerable permanent scarring, which can be of a variable quality but is usually covered by a bra. Delayed healing, skin and fat necrosis, change in or loss of nipple sensation, partial or total nipple loss and an inability to breastfeed as well as future size and shape changes of the native breast leading to recurrent asymmetry are specific problems related to reduction mammoplasty and mastopexy.

Other operations

Augmentation mammoplasty after contralateral breast reconstruction

Occasionally, in women with small breasts the reconstructed side may be larger and more projected than their natural breast. This can be corrected by augmenting the unoperated side with a prosthesis filled with silicone gel or saline (Figure 17.30). Some women take the opportunity of breast reconstruction to achieve larger breasts. Apart from the previously discussed potential complications of infection, capsular contracture and the need for replacement of breast implants can cause possible problems with mammographic surveillance of the contralateral breast.

Reconstruction after wide local excision

Tumour size is not a factor associated with local recurrence after breast conservation. The only reason large cancers are treated by mastectomy is that their removal causes a serious volume and cosmetic defect. Primary treatment options for these large cancers include neoadjuvant therapy to shrink the cancer prior to excision, oncoplastic surgery that combines wide excision of the cancer with immediate reconstruction of the breast mound, and simultaneous breast reduction of the contralateral breast or filling the volume defect by means of a local flap such as a latissimus dorsi myocutaneous flap (Figures 17.31 and 17.32).

This last operation is best performed in two stages. First the cancer is removed and then, once excision is complete, a second
operation is performed by an axillary incision to remove the axillary lymph nodes and to mobilise the latissimus dorsi muscle and overlying fat so that the breast defect is filled. Delayed reconstruction of a wide local excision defect is often required. More than 25% of patients who undergo breast-conservation therapy have moderate or poor cosmetic results. To obtain symmetry in these patients, the treated breast may be suitable for a variety of procedures ranging from simple scar revision to reshaping of the breast or volume augmentation by lipofilling, tissue transfer in form of local or regional flaps, fat transfer or in very selected cases even an implant. If the volume loss is large, transfer of skin and underlying fat or muscle is required, and reduction of the opposite breast may be needed for symmetry.

**Fat transfer**

Fat transfer or lipomodelling has become a very popular adjunctive technique to correct localised contour defects and volume discrepancies after implant-based or autologous breast reconstruction and for breast-conservation defects. Fat is harvested by gentle liposuction to preserve viability, refined by centrifugation and then regrafted as tiny parcels of viable fat cells into the recipient site. Large defects may require several treatments. This is technically a very successful technique and is currently used for numerous indications. Studies so far on oncological safety of fat transfer have not raised any concerns.

**Revision operations**

Patients should have their breast reconstruction performed by a surgeon trained in the whole range of techniques, who can select an appropriate technique of reconstruction for the individual patient. Reconstructive surgery is rarely a single operation, so patients should be warned that obtaining symmetry will require two or three operations (Figure 17.33). Results should be audited and shown to be of a similar standard to those published in the literature. Some patients require major revision of their reconstructions because they develop complications or have poor symmetry.

**Breast cancer after cosmetic breast augmentation (Figure 17.34)**

Patients who develop breast cancer after breast augmentation can be treated by breast-conserving treatment (wide local excision and breast radiotherapy) (Figure 17.35), if their lesion is appropriate for this approach, or by mastectomy. Radiotherapy given to an augmented breast may be better delivered over a longer period in an attempt to reduce tissue reaction and fibrosis around the prosthesis and optimise the final cosmetic result, but capsular contracture and implant extrusion can still occur. One option in such women is to replace the implant and perform a capsular excision approximately following completion of radiotherapy. For women who require a mastectomy, symmetry can be achieved by immediate breast reconstruction.

**Figure 17.33** Poor reconstruction result (left) and after revision and reduction (right).

**Figure 17.34** Magnetic resonance image of a patient who developed cancer of the breast with an implant in situ. The cancer is arrowed. The palpable lesion was marked by a gel-filled capsule on the skin, which is visible on the magnetic resonance image to confirm that the palpable mass and the cancer imaged by MRI are the same.

**Figure 17.35** Patient with a breast cancer in the upper outer quadrant of the right breast over a breast implant treated by wide excision and postoperative radiotherapy and subsequent change of implant.
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