1 Diagnosis and staging of breast cancer and multidisciplinary team working

Common symptoms and signs

Over 90% of breast cancers (BCs) are local or regional when first detected. At least 60% of patients present with a breast lump, which may or may not be painful, fixed or demarcated from the surrounding tissue.

BC may cause skin or nipple retraction, discharge from the nipple, and/or changes in breast size or shape. Skin rash, ulceration, erythema and eczema of the nipple–areola complex may also occur.

Change in the size and shape of the breast

Breast lump with skin ulceration

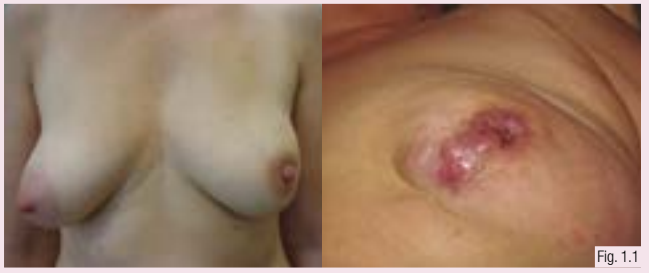


Fig. 1.1

A lump in the axilla or the supraclavicular fossa, skeletal or abdominal pain, cough, breathlessness or neurological signs or symptoms are suggestive of metastatic cancer.

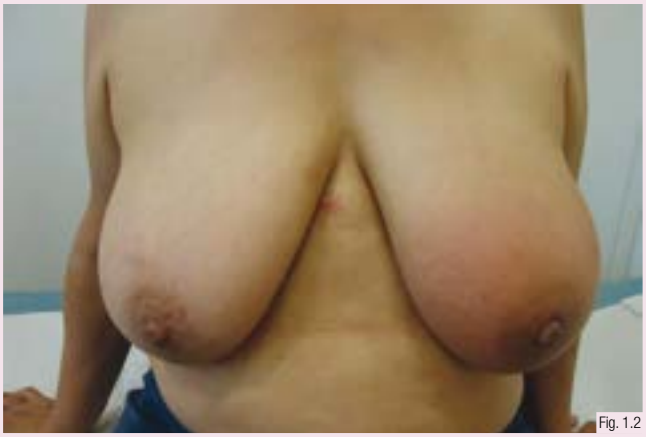


Fig. 1.2

Inflammatory carcinoma is characterised by erythema and oedema of the breast. It usually encompasses the entire breast or at least one third of the skin. The breast skin may resemble "orange peel". A large diffuse mass is often present in the breast.

It is usually caused by poorly differentiated ductal cancer. Cancer cells obstruct the dermal lymphatic vessels and cause the skin oedema. A skin biopsy can give the diagnosis, as tumour emboli are found in the dermal lymphatic vessels, but a negative skin biopsy does not exclude the diagnosis.

Breast infection-related skin redness and oedema is often associated with fever and tenderness, which is not typical of inflammatory BC. In addition, some large-breasted women have mild erythema of the lower part of the breast. This is of no concern and disappears when lying down.

Paget's disease is an eczema-like *in situ* cancer that involves the areola, the nipple or both.

Paget's disease is associated with invasive or *in situ* cancer in approximately 90% of affected individuals. On the other hand, fewer than 5% of BCs are associated with Paget's disease.

A skin biopsy and breast imaging (mammography and breast ultrasound examination) should always be performed when a patient has persistent eczema in the nipple or the areola.

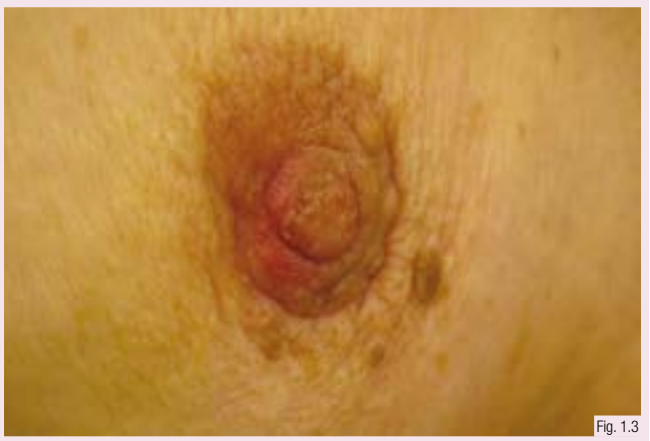


Fig. 1.3

REVISION QUESTIONS

1. How large a proportion of BCs are local or locoregional at the time of the diagnosis?
2. What are the typical signs and symptoms of BC?
3. What is the pathophysiology behind the typical symptoms and signs of inflammatory BC?

Clinical examination and imaging

Family history of BC, age at menarche, number of births and pregnancies, age at first birth, history of breast biopsies and breast operations, date of the last menstrual period, use of hormone replacement therapy and detection of breast tumour in mammography screening are the key events to note.

The breasts should be palpated when the patient is sitting or standing, the arms hanging freely as well as elevated (A, B). The examination is repeated when the patient is lying supine (C, D).

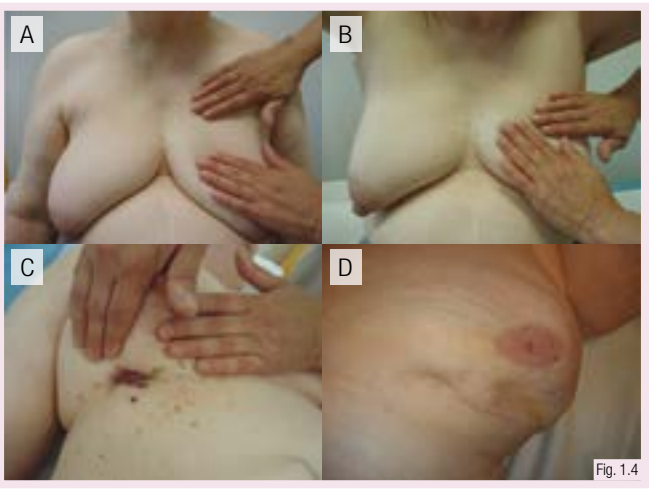


Fig. 1.4

Lesions located in the upper parts of the breast are best detected with the patient sitting or standing (A, B). Lesions in the lower parts of the breast may become obvious only when the patient is lying supine with the arms elevated (D).

The triple diagnosis

I Clinical examination
- history
- inspection and palpation

II Breast imaging
- mammography
- breast and axillary ultrasound
- breast magnetic resonance imaging

III A core biopsy from suspicious lesion

Fig. 1.5

The triple diagnostic approach consists of breast inspection and palpation, breast imaging usually with mammography and ultrasound, and a core needle biopsy (CNB) of the breast lesion.

When one of the components of the triple diagnostic approach is suspicious, a repeated core biopsy or surgical biopsy should follow, even when the other components do not suggest cancer.

Breast imaging should precede a biopsy, since a haematoma or other tissue alterations may interfere with image interpretation. Breast imaging usually consists of mammography and ultrasound examination of the breast and the axilla.

Typical findings suggestive of cancer in mammography include an irregular mass, star-like (stellate) or spicular lesions, microcalcifications and structural distortions. The sensitivity of mammography is lower in patients with dense breast tissue, typically associated with younger age.

BC usually causes an echo-poor irregular lesion in ultrasonography.

Benign and malignant lesions cannot always be reliably distinguished by breast imaging. Some BCs resemble a benign lesion, viewed as a regular and well-defined mass.

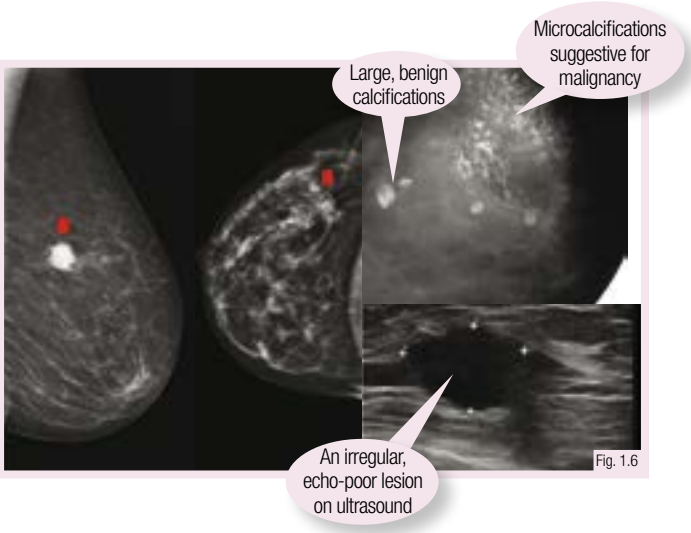


Fig. 1.6

REVISION QUESTIONS

1. What are the key events to note in the patient history?
2. What components are included in the triple diagnosis?
3. What are the findings typical of BC at mammography?

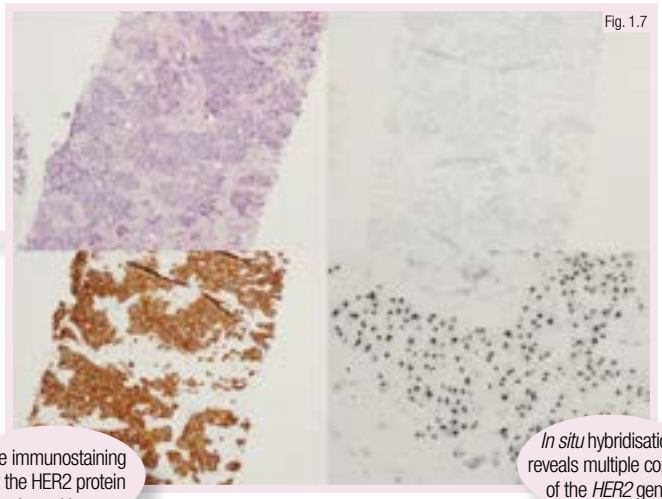
Percutaneous needle biopsy and axillary staging

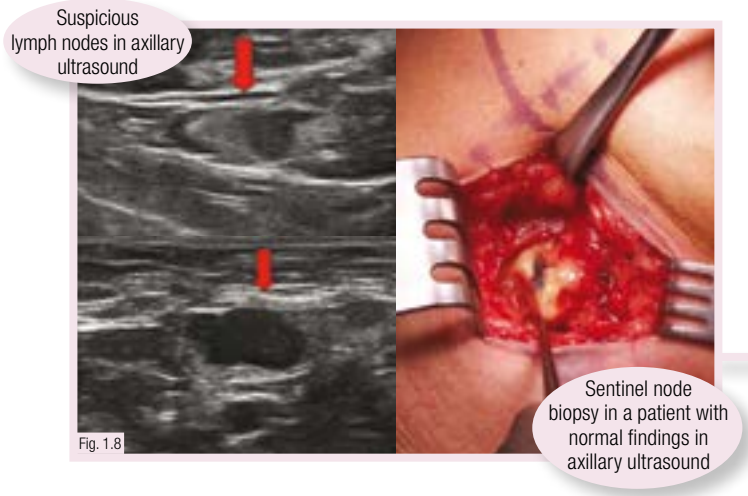
A CNB or a vacuum-assisted biopsy (VAB) is taken from the breast. The biopsy is frequently guided by ultrasonography, sometimes with mammography or magnetic resonance imaging (MRI). Sensitivity exceeds 98%. False-positive findings are rare.

The tissue material obtained with CNB and VAB usually allows detection of invasive tumour growth, histological typing of cancer and the carrying out of assays to determine tumour oestrogen receptor status, human epidermal growth factor receptor 2 (HER2) status and Ki-67 expression.

Fine needle aspiration cytology (FNAC) does not make a reliable distinction between invasive and *in situ* cancer. The specificity and sensitivity varies depending on the skill of the investigator. FNAC is useful in the diagnosis and treatment of breast cysts.

A core needle biopsy shows Grade 3 invasive ductal carcinoma with negative oestrogen receptor staining





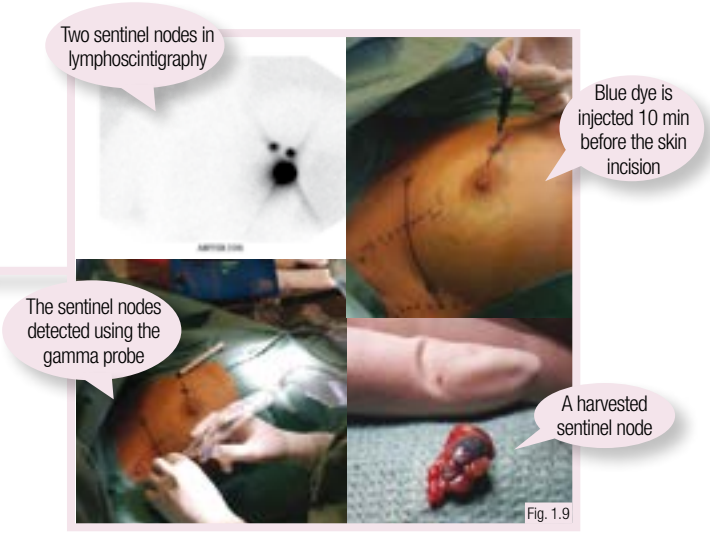
The axillary nodal status is considered the most important single prognostic factor, and may help in the selection of patients for adjuvant systemic treatments and radiation therapy.

Axillary ultrasonography is performed prior to starting cancer treatment. A needle biopsy is taken from the nodes suspicious of containing cancer at ultrasound.

A sentinel node biopsy is carried out when metastases are not detected at axillary ultrasound.

The sentinel node is the first node to receive lymph drainage from the tumour site in the breast. Sentinel node biopsy is currently the gold standard in nodal staging of patients without metastases at axillary ultrasound.

The sentinel nodes are usually detected following injection of a radioactive tracer and/or a blue dye at the tumour site in the breast.



Patients with axillary node metastases, detected before surgery, undergo axillary lymph node dissection (ALND). Until recently, ALND has also been the standard treatment for patients with sentinel node metastases. For this latter group, axillary radiotherapy or observation may also be an option, especially when adjuvant systemic therapy is offered.

REVISION QUESTIONS

1. What are the advantages of CNB when compared with FNAC?
2. What methods are used for axillary nodal staging?
3. What is the sentinel node?

Other staging examinations

MRI may identify BCs not detected by mammography or ultrasonography. MRI may be associated with reduced re-excision rates in patients with lobular BC, but at the expense of an increased mastectomy rate.

False-positive MRI findings occur in 10%–15% of patients. A biopsy should be considered when a lesion is visible only at MRI.

When assessing response to neoadjuvant chemotherapy, and screening women who are susceptible to BC, MRI is superior to other imaging methods, although ultrasound may be equally useful for response assessment. It is also useful in the detection of occult BC in a patient with overt axillary metastases from an unknown primary.

A 29-year-old woman with a small breast cancer on mammography and ultrasound, but cancer encompasses almost the entire breast on MRI

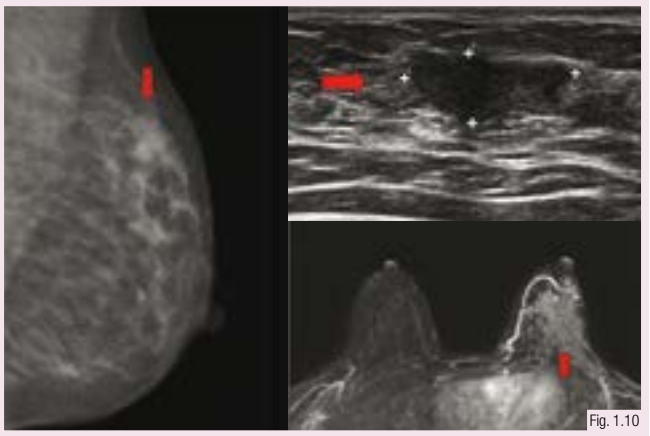


Fig. 1.10

A 61-year-old patient with multicentric invasive ductal breast cancer of the right breast and axillary metastases. A CT scan shows several small pulmonary metastases in both lungs

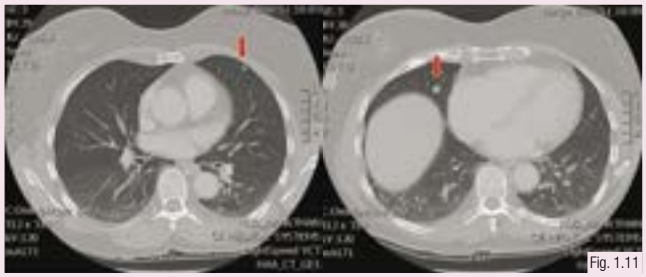


Fig. 1.11

For the assessment of general health status, full blood count, liver, renal and cardiac function tests, and alkaline phosphatase and calcium levels are recommended.

For patients at high and intermediate risk of distant relapses, before systemic treatments are administered, imaging of chest, abdomen and bone is recommended. This can be done through isotope bone scintigraphy, X-ray or computed tomography (CT) of the chest, or CT or ultrasound of the abdomen. If clinical signs or laboratory values suggest the presence of metastases, imaging exams are mandatory.

Positron emission tomography (PET), usually based on uptake of fluorine-18 labelled glucose (fluorodeoxyglucose, FDG) in tumour or PET combined with CT (PET-CT) are not indicated in the staging of most BCs (clinical Stage I, II or operable Stage IIIA).

The spatial resolution of PET (5–6 mm) does not allow detection of small lesions. PET-CT may show false-positive findings due to inflammation or other non-malignant conditions with increased glucose uptake.

PET may show response to systemic therapy earlier than CT or MRI. FDG-PET may identify regional or distant metastases undetected by other means, such as bone metastases undetected by CT, and may be helpful when the findings of standard imaging are unclear.

Breast cancer metastases in lumbar vertebrae III, IV and V and the sacrum in an FDG-PET scan. The metastases were not visible on CT

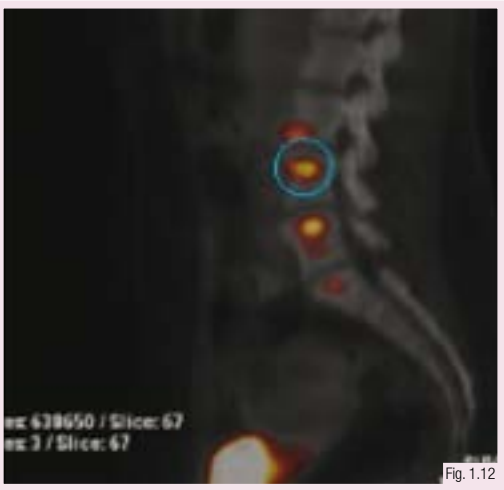


Fig. 1.12

CT, Computed tomography; FDG-PET, fluorodeoxyglucose-positron emission tomography.

REVISION QUESTIONS

1. What are the indications for breast MRI?
2. When is staging with imaging indicated to detect distant metastases?
3. Which imaging methods can be used for staging?

Multidisciplinary work

All BC patients should have their case discussed at a multidisciplinary team meeting, pre- and post-surgery. Metastatic BC should be discussed when a treatment decision is necessary.

The team should include a breast surgeon, a medical oncologist, a radiation oncologist, a radiologist and a pathologist. In addition, nurses with experience in BC patient care are essential team members.

Plastic surgeons, nuclear medicine specialists, geneticists, physiotherapists and social workers may also contribute substantially to treatment planning.

Fig. 1.13

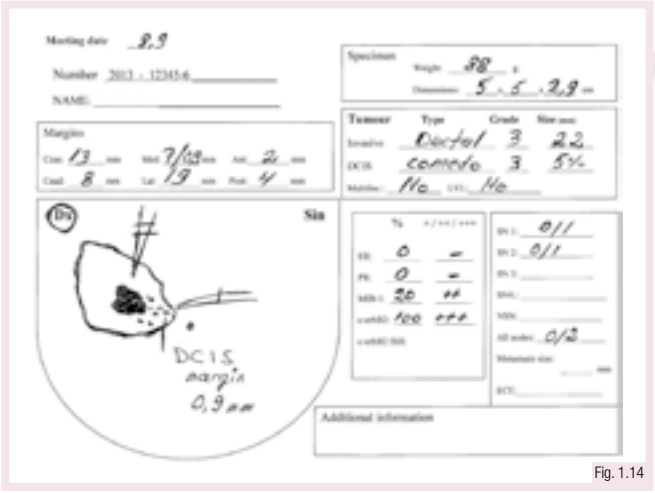


Fig. 1.14

The pathology report is a key document at the team meeting and should include the dimensions of the tumour(s) and the width of the surgical margins in millimetres, regardless of the type of breast surgery. Cancer histological type and grade and presence of lymphovascular invasion are also reported.

The number of examined regional lymph nodes, lymph nodes containing cancer, the size of the largest nodal metastatic deposit and any presence of cancer growth beyond the node capsule should be reported.

At the minimum, tumour biological profiling includes immunostaining for the oestrogen receptor, the progesterone receptor, HER2 and Ki-67 to estimate cell proliferation rate. An *in situ* hybridisation assay to demonstrate HER2 amplification complements immunostaining for HER2. Multiple gene expression arrays may provide further prognostic information.

The sequence and timing of staging examinations, neoadjuvant and adjuvant systemic therapies, selection of the type of surgery, breast reconstruction and radiation therapy are optimised at the team meeting.

The fluent flow to and the exact documentation of information from all parties are essential for successful multidisciplinary team work.

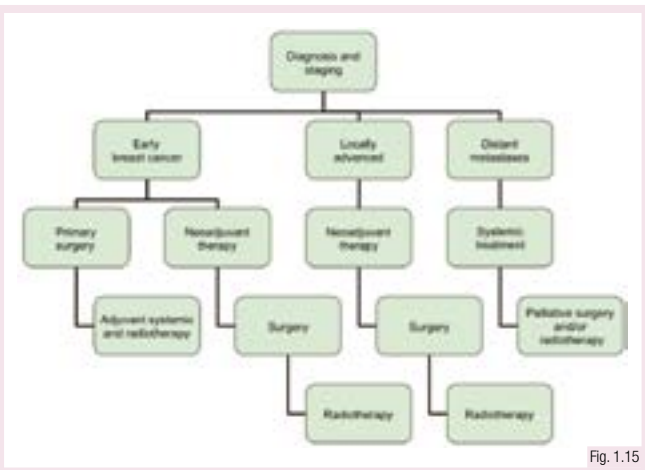


Fig. 1.15

REVISION QUESTIONS

1. What are the goals of a multidisciplinary team meeting?
2. Which health care professionals should be included in the core team?
3. What information should be available in the pathology laboratory report?

Summary: Diagnosis and staging of breast cancer and multidisciplinary team working

- Frequent BC symptoms and signs include a palpable breast lump, skin or nipple retraction, bloody discharge from the nipple, changes in breast size or shape, skin rash, ulceration, erythema and eczema of the nipple–areola complex
- The gold standard for diagnosis is the triple diagnostic approach consisting of clinical examination, breast imaging and needle biopsy of suspicious lesions
- The diagnostic accuracy of CNB is superior when compared with FNAC. Moreover, hormone receptor and HER2 status can be determined from CNB, especially relevant if neoadjuvant systemic treatment is considered
- Breast MRI is beneficial when planning breast conservation in patients with invasive lobular cancer, when assessing response to neoadjuvant treatment and in surveillance of high-risk women with genetic propensity for BC
- Axillary ultrasound and needle biopsy from suspicious nodes is an essential part of the diagnostic procedure
- Sentinel node biopsy is the gold standard in patients without evidence of axillary nodal metastases in the pre-treatment ultrasound examination of the axilla
- Staging by imaging to detect distant metastases is considered for high-risk patients
- PET-CT scan may detect distant metastases undetected by other imaging methods but should not be used routinely
- The pathologist's report should include all data needed for the planning of further locoregional and systemic adjuvant treatments. As a minimum: histological type and grade of invasive cancer, size, lymph nodes, lymphovascular invasion, oestrogen receptor, progesterone receptor, HER2 and cell proliferation
- The main goal of the multidisciplinary team meeting is to optimise the treatment for each patient. It is mandatory for all BC patients

Further Reading

Del Turco MR, Ponti A, Bick U, et al. Quality indicators in breast cancer care. Eur J Cancer 2010; 46:2344–2356.

Harris LN, Ismaila N, McShane LM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2016; 34:1134–1150.

Houssami N, Ciatto S, Turner RM, et al. Preoperative ultrasound-guided needle biopsy of axillary nodes in invasive breast cancer: meta-analysis of its accuracy and utility in staging the axilla. Ann Surg 2011; 254:243–251.

Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. Ann Surg 2013; 257:249–255.

Kesson EM, Allardice GM, George WD, et al. Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13 722 women. BMJ 2012; 344:e2718.

Krag D, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010; 11:927–933.

Lieske B, Ravichandran D, Wright D. Role of fine-needle aspiration cytology and core biopsy in the preoperative diagnosis of screen-detected breast carcinoma. Br J Cancer 2006; 95:62–66.

Perry N, Broeders M, de Wolf C, et al. European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis, fourth edition. European Commission, 2006, 2013.

Robertson F, Bondy M, Yang W, et al. Inflammatory breast cancer: the disease, the biology, the treatment. CA Cancer J Clin 2010; 60:351–375.

Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26(Suppl 5):v8–v30.

Wilson AR, Marotti L, Bianchi S, et al; EUSOMA (European Society of Breast Cancer Specialists). The requirements of a specialist Breast Centre. Eur J Cancer 2013; 49:3579–3587.