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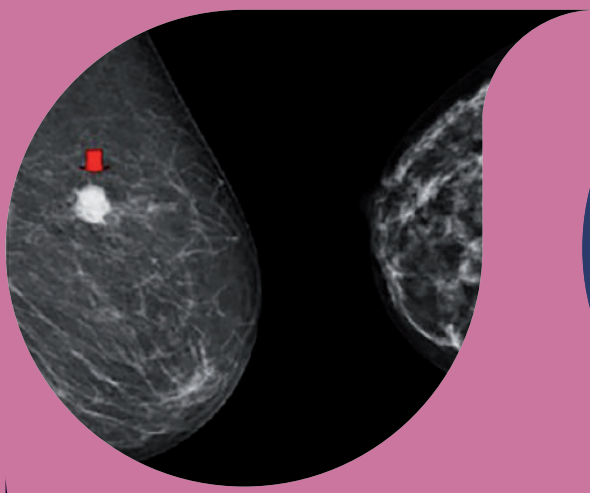
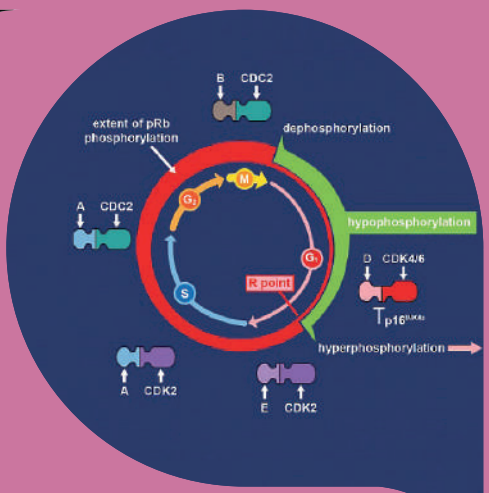
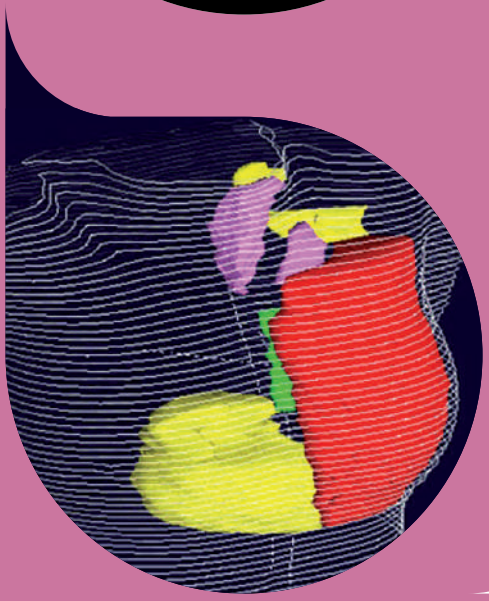
edited by
Fatima Cardoso
Vesa Kataja
Vivianne Tjan-Heijnen

BREAST CANCER

ESSENTIALS *for* CLINICIANS







ESMO Press

Breast Cancer
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Preface

The European Society for Medical Oncology (ESMO) has decided to publish a series of books, *Essentials for Clinicians*, dedicated to specific tumours or tumour groups. We present to you the first edition of the "Breast Cancer" book. We also invite all readers to comment on this work, contributing to the improvement of future editions.

The field of breast cancer has seen many changes in recent years, from biology to diagnosis and treatment. Having a book with a complete overview on current standards, supported by attractive images and other illustrations, may be especially helpful to young colleagues in obtaining a quick introduction to disease management. For experienced oncologists also, the book may be helpful to remedy gaps in knowledge and to implement new insights in daily practice. Our aim is, therefore, to provide a quick, but complete, overview on different clinical situations, always in line with the *ESMO Clinical Practice Guidelines* for patients with breast cancer.

One may wonder, why dedicate effort to write a book in this era of digital information? However, to be able to easily and critically absorb the wealth of online information, one needs to possess a backbone of knowledge. We hope that this book may provide this structured basic knowledge that will render the additional information, found online and presented at conferences, easier to interpret.

Some of the most prominent experts in the field of breast cancer, both clinicians and researchers, have contributed their expertise to the different chapters, covering broad areas such as surgery, radiotherapy and systemic therapy, but also specific challenging clinical situations such as the very young, the elderly and male breast cancer patients. We believe their work has resulted in a very attractive reader-friendly book. We hope that it will support clinicians in their daily practice, to offer the best possible management for breast cancer patients.

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Abbreviations

AC	Doxorubicin/cyclophosphamide
AD	Axillary dissection
ADCC	Antibody-dependent cellular cytotoxicity
ADH	Atypical duct hyperplasia
ADM	Acellular dermal matrix
AI	Aromatase inhibitor
ALND	Axillary lymph node dissection
AR	Androgen receptor
BC	Breast cancer
BCS	Breast-conserving surgery
BCT	Breast-conserving therapy
BLBC	Basal-like breast cancer
BM	Bone metastasis
BMA	Bone-modifying agent
BSE	Breast self-examination
CBE	Clinical breast examination
CDK	Cyclin-dependent kinase
ChT	Chemotherapy
CI	Confidence interval
CMF	Cyclophosphamide/methotrexate/fluorouracil
CNB	Core needle biopsy
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CWI	Chest wall irradiation
DBT	Digital breast tomosynthesis
DCIS	Ductal carcinoma *in situ*
DDFS	Distant disease-free survival
DFS	Disease-free survival
DIN	Ductal intraepithelial neoplasia
DMFI	Distant metastasis-free interval
DMFS	Distant metastasis-free survival
EBRT	External beam radiotherapy
EMA	European Medicines Agency
ER	Oestrogen receptor
ET	Endocrine therapy
FDA	Food & Drug Administration
FDG	Fluorodeoxyglucose
FFDM	Full field digital mammography
FNA	Fine needle aspiration
FNAC	Fine needle aspiration cytology
GnRH	Gonadotrophin-releasing hormone
GoR	Grade of recommendation
HER2	Human epidermal growth factor receptor 2
HT	Hormone therapy
IBC	Invasive breast cancer
IBE	Ipsilateral breast event
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IMRT	Intensity modulated radiotherapy
ISH	*In situ* hybridisation
ITC	Isolated tumour cells
LBD	Ligand binding domain
LCIS	Lobular carcinoma *in situ*
LHRH	Luteinising hormone-releasing hormone
LIN	Lobular intraepithelial neoplasia
LoE	Level of evidence
LRF	Locoregional failure
LRR	Locoregional recurrence
Lum	Luminal
LVEF	Left ventricular ejection fraction
MBC	Metastatic breast cancer
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
MRM	Modified radical mastectomy
mTOR	Mechanistic target of rapamycin
NACT	Neoadjuvant chemotherapy
NPI	Nottingham Prognostic Index
OFS	Ovarian function suppression
OS	Overall survival
PARP	Poly(ADP-ribose) polymerase
PBI	Partial breast irradiation
pCR	Pathological complete response
PD-1	Programmed death 1
PET	Positron emission tomography
PFS	Progression-free survival
PgR	Progesterone receptor
PI3K	Phosphatidylinositol 3-kinase
PMRT	Postmastectomy radiotherapy
pRb	Retinoblastoma protein
PS	Performance status
PTEN	Phosphatase and tensin homologue
QoL	Quality of life
RCB	Residual cancer burden
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Relapse-free survival
RNI	Regional nodal irradiation
RT	Radiotherapy
SBCS	Salvage breast-conserving surgery
SBR	Scarff-Bloom-Richardson
SBRT	Stereotactic body radiotherapy
SERD	Selective oestrogen receptor down-regulator
SERM	Selective oestrogen receptor modulator
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy
SNP	Single nucleotide polymorphism
SRE	Skeletal-related event
TDLU	Terminal duct lobular unit
TIL	Tumour-infiltrating lymphocyte
TNBC	Triple-negative breast cancer
TNM	Tumour node metastasis
Tras	Trastuzumab
TT	Targeted therapy
VAB	Vacuum-assisted biopsy
VATS	Video-assisted thoracoscopic surgery
WBRT	Whole brain radiotherapy
WHO	World Health Organization

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Fatima Cardoso, Vesa Kataja and Vivianne Tjan-Heijnen

A

What every oncologist should know

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

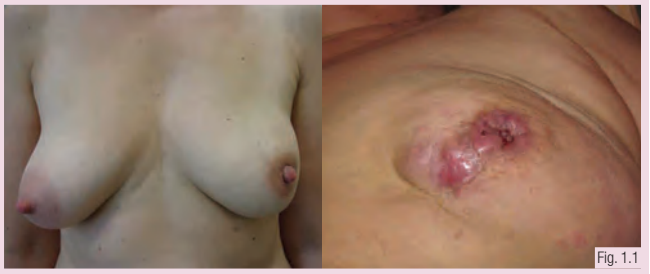

Fig. 1.1

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.

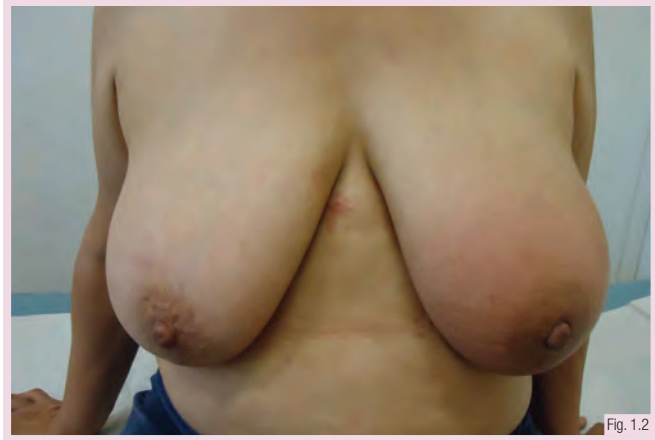

Fig. 1.2

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.

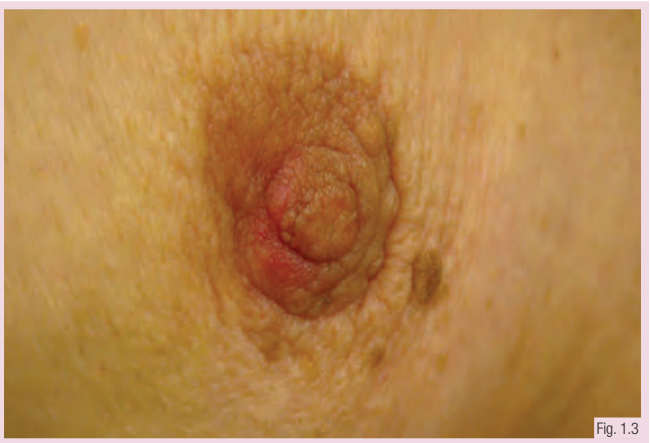

Fig. 1.3

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).

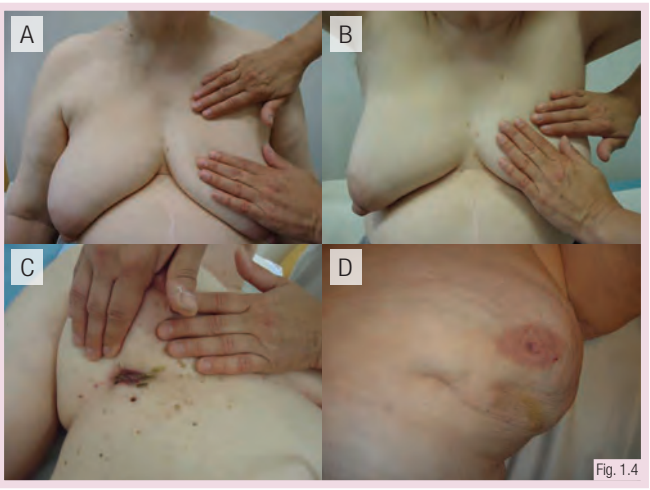

Fig. 1.4

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.

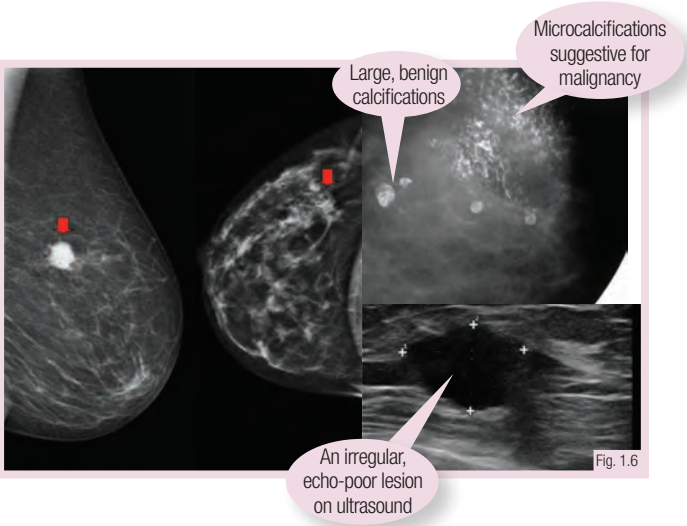

Fig. 1.6

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

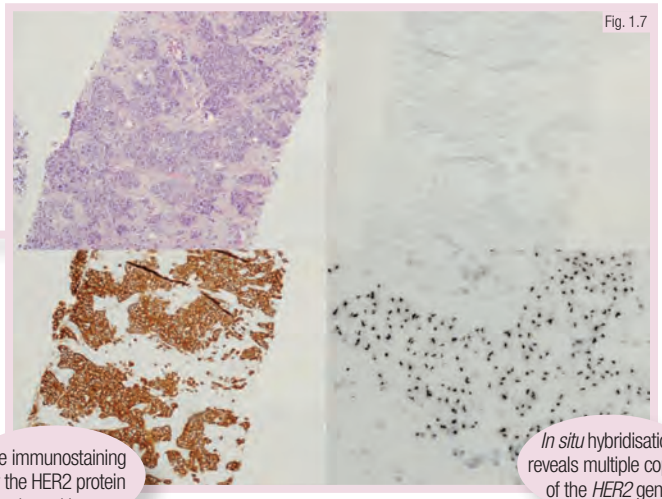

Fig. 1.7

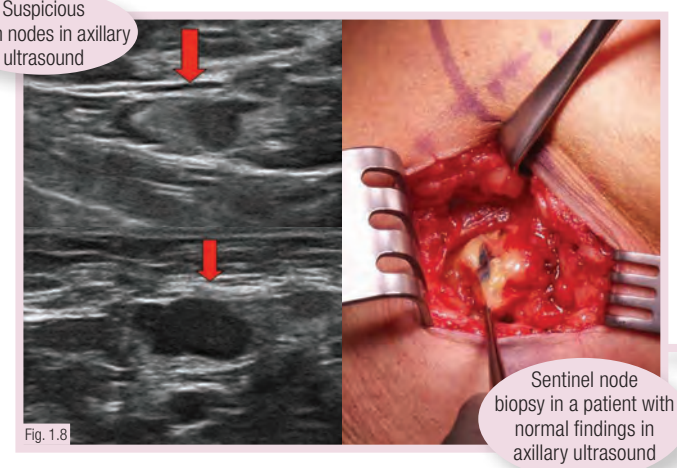

Fig. 1.8

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.

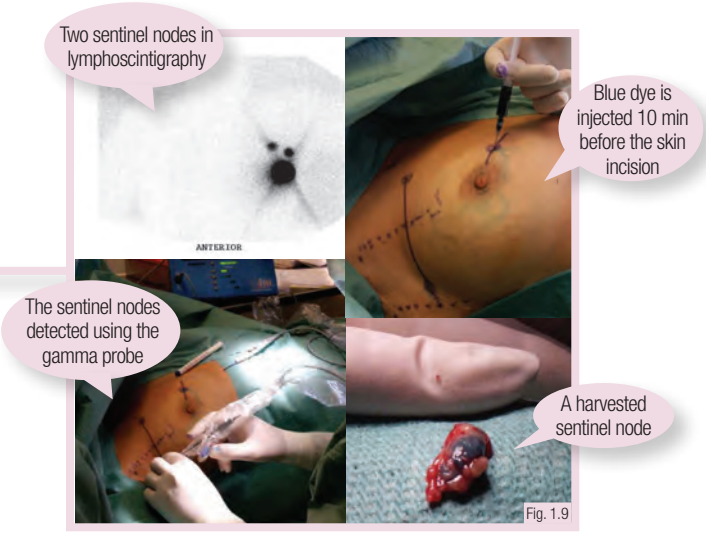

Fig. 1.9

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

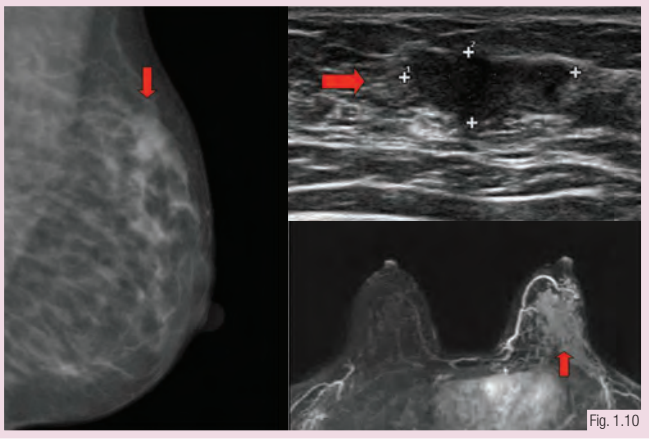

Fig. 1.10

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

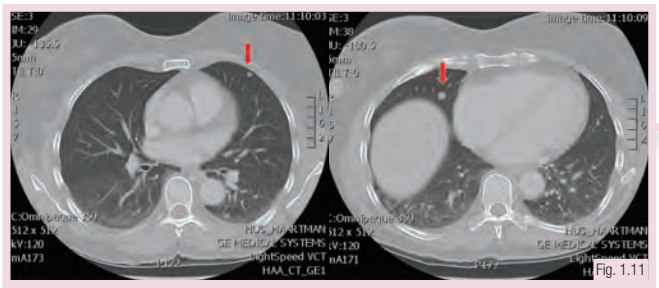

Fig. 1.11

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

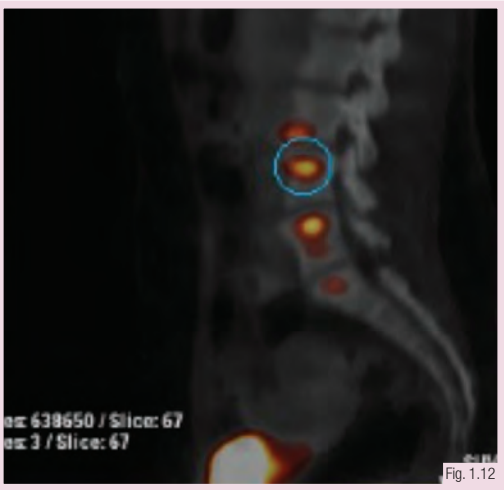

Fig. 1.12

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

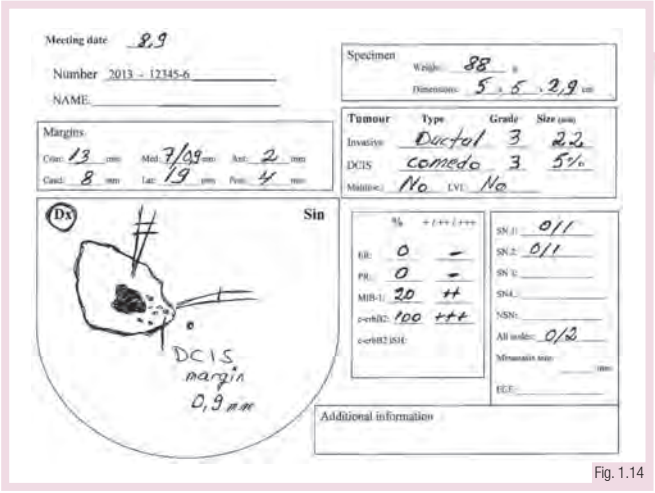

Fig. 1.14

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.

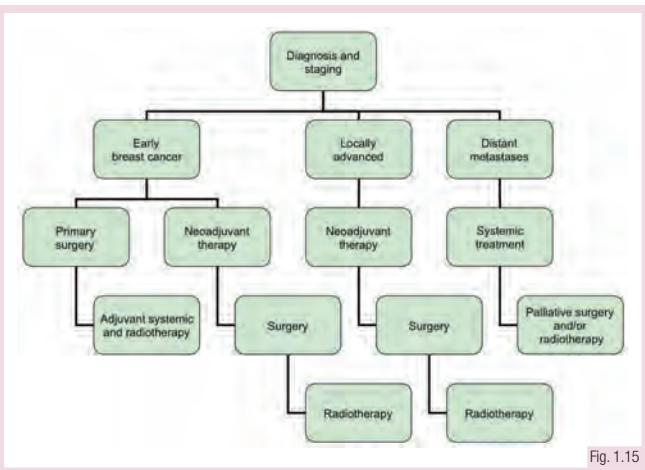

Fig. 1.15

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

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2 Pathology (including normal breast) and disease subtypes

Normal breast and diagnostic approach

Mammary glands are modified tubulo-alveolar sweat glands, with about 12 lobes, that are separated by fibrous tissue and surrounded by abundant fatty tissue.

Each lobe contains many ductulo-lobular units lined by a double layer of cells: the luminal is composed of epithelial cells, the peripheral of contractile myoepithelial cells.

Age, menopausal status, menstrual cycle or pregnancy and lactation change the morphological features of terminal units.

Low magnification showing normal breast histology (lobules and ducts)

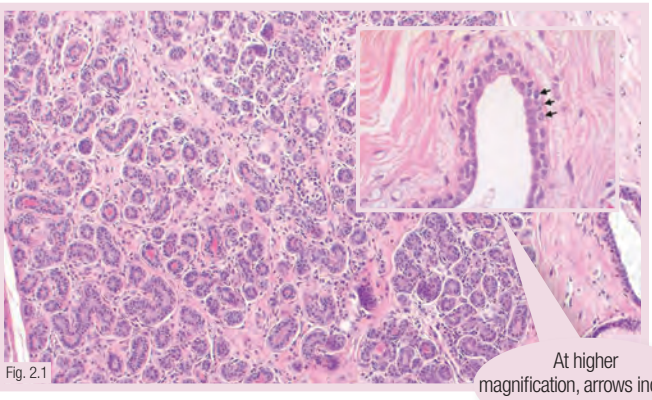


Fig. 2.1

If breast disease is suspected, it is mandatory to obtain a representative sample of the lesion, as this will determine the direction of subsequent procedures.

Fine needle aspiration cytology (FNAC) is a rapid, cheap, safe and easy technique for obtaining lesional cells to examine. The aspiration is performed with a fine needle, making *"coming and going"* movements, in several directions while rotating the needle.

Classification system currently used to report on cytological diagnosis

Cytological diagnosis (European Guidelines for Quality Assurance in Breast Cancer Screening)
C1: Unsatisfactory
C2: Benign
C3: Atypia probably benign
C4: Suspicious of malignancy
C5: Malignant

Fig. 2.2

The cytological diagnosis is reported according to European Guidelines for Quality Assurance in Breast Cancer Screening, a five-point classification system.

In case of malignant disease, a core needle biopsy (CNB) is recommended, in order to obtain disease biological characteristics (oestrogen receptor [ER]/progesterone receptor [PgR]/Ki67/HER2 status/grade).

An intraoperative frozen tissue sample may be required to assess the margin status. This may guide the appropriate surgical strategy.

Final histological examination of formalin-fixed paraffin-embedded tissue samples provides accurate assessment of the tumour type, grade, hormone receptor status, HER2 amplification/over-expression and proliferation index.

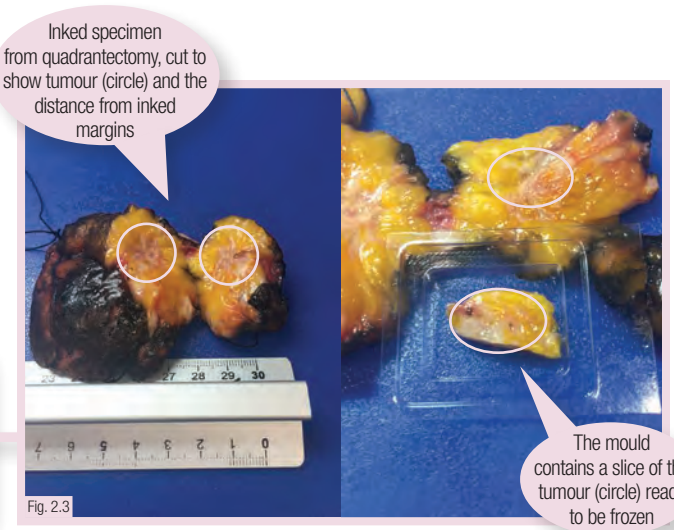


Fig. 2.3

REVISION QUESTIONS

1. The ductulo-lobular unit is lined by a double cell layer. What are the cell types?
2. Which diagnostic categories are used for reporting breast FNAC?
3. Which information is additionally available when a CNB is carried out and what is the proper use of frozen sections during intraoperative diagnosis?

Benign lesions

Papilloma, a benign ductal tumour, appears as a well-defined solid-cystic lesion. It commonly arises in the terminal portion of the lactiferous ducts within the subareolar region of the breast, or as a number of smaller nodules in the central or peripheral gland (papillomatosis).

Histologically, it is composed of branching papillae lined with two layers of cells (luminal and myoepithelial) filling a large and cystically dilated duct.

The luminal cells may undergo proliferative changes, both typical and atypical, and also show malignant changes: *in situ* papillary carcinoma with intracystic and solid variants.

Epithelial cells line the lumina of the papillae which are supported by fibrovascular stroma

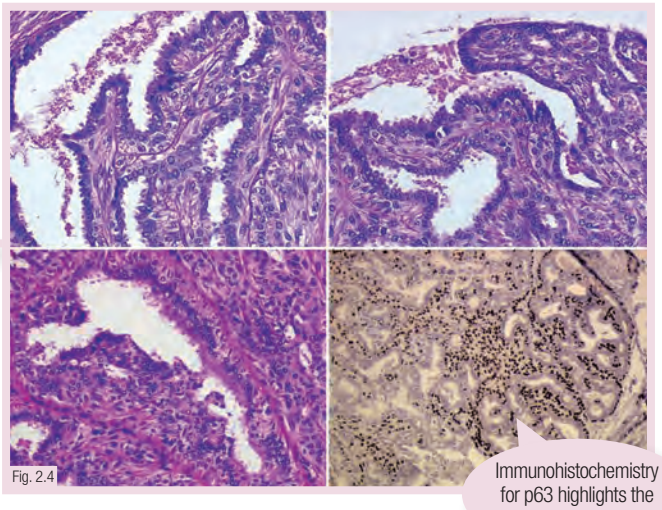


Fig. 2.4

Immunohistochemistry for p63 highlights the myoepithelial cell layer

Fibroadenoma showing stromal proliferation compressing the ducts

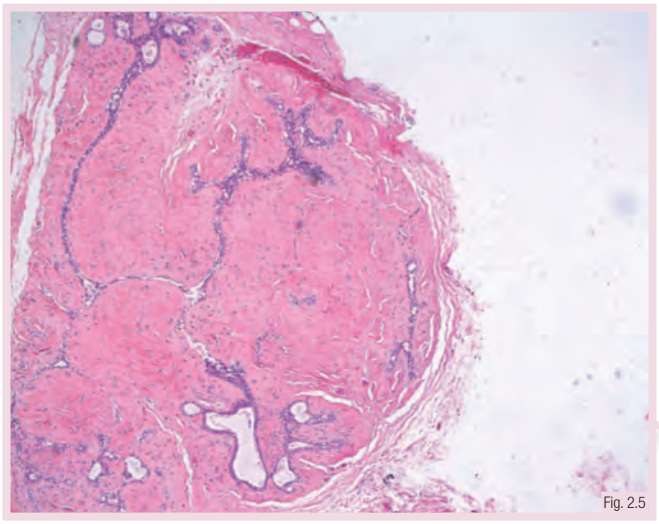


Fig. 2.5

Fibroadenoma is a well-circumscribed benign tumour characterised by a biphasic proliferation of both stromal and epithelial cells. It may be multiple and bilateral.

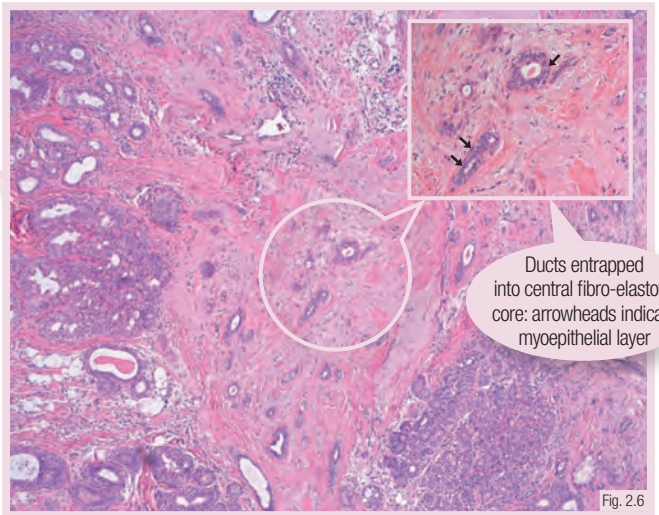
The histological appearance is very typical with loose stroma surrounding ducts with normal appearance (so-called pericanalicular fibroadenoma) or compressing the ducts which appear as slit-like spaces (intracanalicular fibroadenoma).

The "juvenile" variant of fibroadenoma is characterised by a more prominent proliferation of stromal and epithelial cells, raising the problem of the differential diagnosis of a phyllodes tumour.

Radial scar is a benign lesion with clinical and histopathological features similar to invasive carcinoma.

The correct diagnosis rests on the stellate appearance of the lesion, with a central fibro-elastotic core, entrapping radiating glandular structures, lined by luminal and myoepithelial cells that have no or little atypia.

The immunohistochemical identification of myoepithelial cells (using specific markers such as p63, smooth muscle myosin, calponin or caldesmon) may be particularly helpful in differentiating this benign lesion from invasive carcinoma (tubular type).



Ducts entrapped into central fibro-elastotic core: arrowheads indicate myoepithelial layer

Fig. 2.6

REVISION QUESTIONS

1. Is there a malignant variant of papilloma?
2. What are the differences between fibroadenoma and phyllodes tumour?
3. How can we differentiate radial scar from tubular carcinoma?

Intraepithelial neoplasia (DIN or DCIS and LIN or LCIS)

Due to the wide adoption of screening mammography, the detection of atypical, non-invasive proliferative intraepithelial lesions is more common.

The classification of these atypical lesions is still debated. According to their location, they are classified as ductal (DIN) or lobular (LIN). According to their structure, atypia, necrosis and mitoses, they are classified into different grades of malignancy.

The DIN classification has been introduced to unify and simplify the terminology of intraductal neoplastic lesions, avoiding the term "carcinoma".

DIN classification compared with traditional classification of intraductal proliferations

DIN system Ductal intraepithelial neoplasia	
DIN1A	Flat epithelial atypia
DIN1B	Atypical duct hyperplasia (ADH)
DIN1C	Well-differentiated DCIS (G1)
DIN2	Moderately differentiated DCIS (G2)
DIN3	Poorly differentiated DCIS (G3)

Fig. 2.7

DCIS, Ductal carcinoma *in situ*.

ADH: the two ducts show cytological and architectural atypical features similar to low-grade DCIS

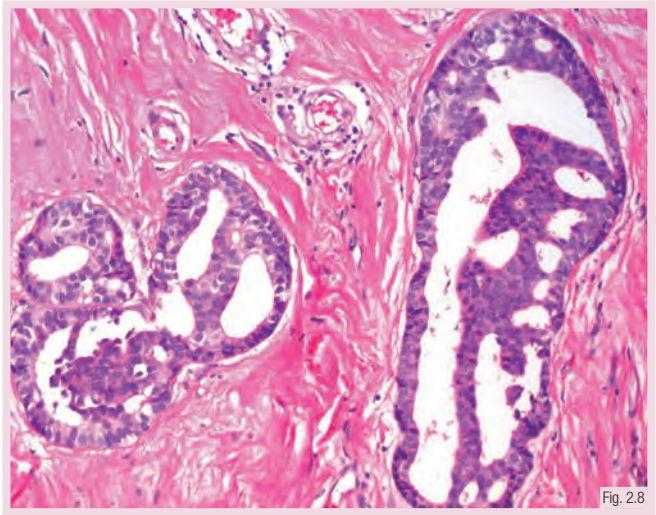


Fig. 2.8

ADH, Atypical ductal hyperplasia; DCIS, ductal carcinoma *in situ*.

DIN1A shows slightly dilated ducts lined by a single or a few layers of epithelial cells, mild atypia and apical snouts with an increased mitotic activity.

DIN1B is a small lesion (less than 2 mm in size), characteristically involving one or few ducts. It is morphologically indistinguishable from a low-grade ductal carcinoma *in situ* (DIN1C).

From a practical point of view, atypical ductal hyperplasia should be considered as a very tiny low-grade ductal carcinoma *in situ* (DCIS), with similar morphology and biological characteristics.

Lobular neoplasia is the proliferation of loosely cohesive epithelial cells within the terminal ductal lobular unit. Traditionally they have been divided into atypical lobular hyperplasia (LIN1) and lobular carcinoma *in situ* (LIN2).

LIN1 and LIN2 have similar cytological features, differing only in the degree of involvement of the lobular space.

LIN3 shows a higher degree of atypia, sometimes with signet-ring cells, and may undergo necrosis, mimicking ductal (DIN3) proliferation, which differ in morphological features.

Morphological differences between LIN3 (left) and DIN3 (right), both of them with central necrosis

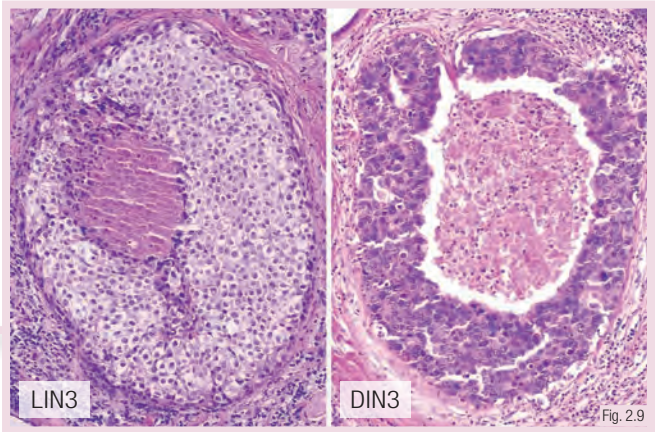


Fig. 2.9

REVISION QUESTIONS

1. Is there a correlation between the DIN terminology and DCIS?
2. What is the difference between DIN1B (ADH) and DIN1C (G1 DCIS)?
3. What is the difference between LIN1 and LIN2? And between them and LIN3?

Report of carcinoma

According to the 2012 edition of the World Health Organization (WHO) Classification, breast carcinomas are divided into invasive carcinomas of no special type, lobular carcinomas, and carcinomas of special type (including 20 different histotypes).

Some of the special types (e.g. tubular, cribriform, mucinous, medullary) when at least 90% pure (i.e. not admixed with different types) have very good prognosis.

On the other hand, some other special types (e.g. carcinoma with central necrosis/fibrosis, metaplastic carcinoma) have the poorest clinical outcome.

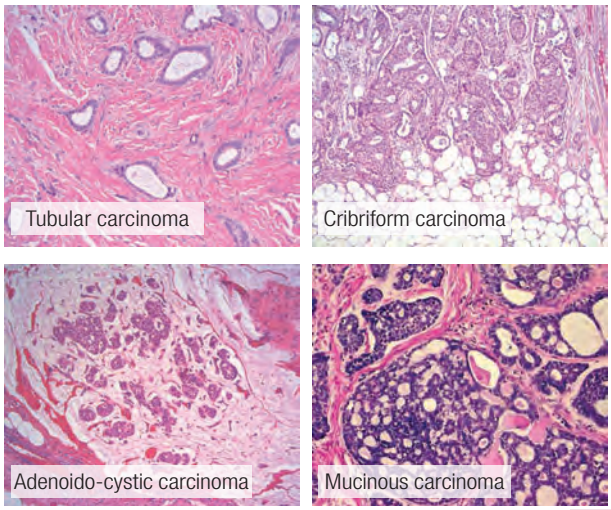


Fig. 2.10

Detail of criteria used to calculate the histological grade of breast carcinoma

Histological assessment of grade	
Glandular (tubular formation)	**Points**
>75% of tumours forming glandular/tubular structures	1
>10% up to 75% of tumours forming glandular/tubular structures	2
<10% of tumours forming glandular/tubular structures	3
Nuclear pleomorphism	
Nuclei small, regular and uniform (similar to normal)	1
Nuclei moderately increased in size and irregular in shape	2
Vesicular nuclei, often nucleoli, marked variation in size/shape	3
Mitotic count: number of mitoses/field area microscope*	
<7 mitoses/10 HPFs	1
8–14 mitoses/10 HPFs	2
>15 mitoses/10 HPFs	3
Overall grade (sum of each feature)	
G1 (well differentiated)	3 up to 5
G2 (moderately differentiated)	6, 7
G3 (poorly differentiated)	8, 9

HPFs, High power fields.
*Power field diameter 0.5 mm

Fig. 2.11

Assessment of histological grade is based on three features of the tumour: tubule formation, nuclear atypia and pleomorphism, and the number of mitoses.

Tumour grade is a faithful mirror of all the biological features and their potential aggressiveness. Therefore, the accurate assessment of tumour grade has an important prognostic value.

Each feature is scored with a 3-tier system, 1 being the best and 3 the worst. The final grade (G1, G2, G3) is determined by adding the individual scores.

Peritumoural vascular invasion, extensive intraductal component within and around the invasive tumour and the regional lymph node status must be reported.

Peritumoural vascular invasion is highly correlated with lymph node metastases. It should be differentiated from artefactual dislocation of neoplastic (or even benign) cells following diagnostic procedures.

Artefactual dislocation is recognisable because the epithelial cells lie in the needle track, or in empty spaces not lined by endothelial cells, and are often intermingled with many red blood cells or inflammatory cells.

Dislocated tumour cells in empty spaces are intermingled with red blood cells and inflammatory cells

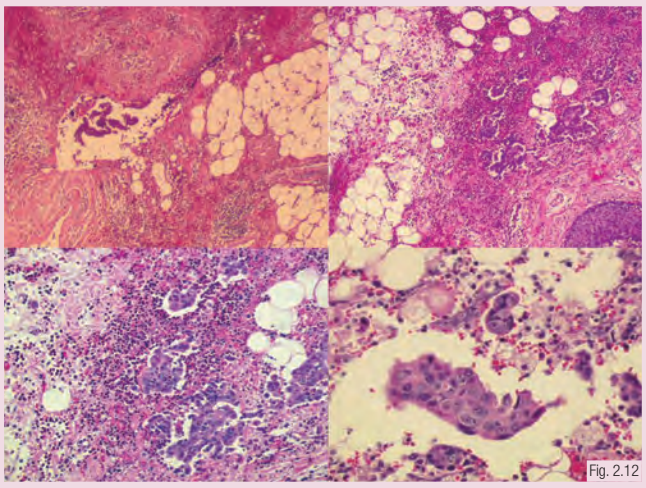


Fig. 2.12

REVISION QUESTIONS

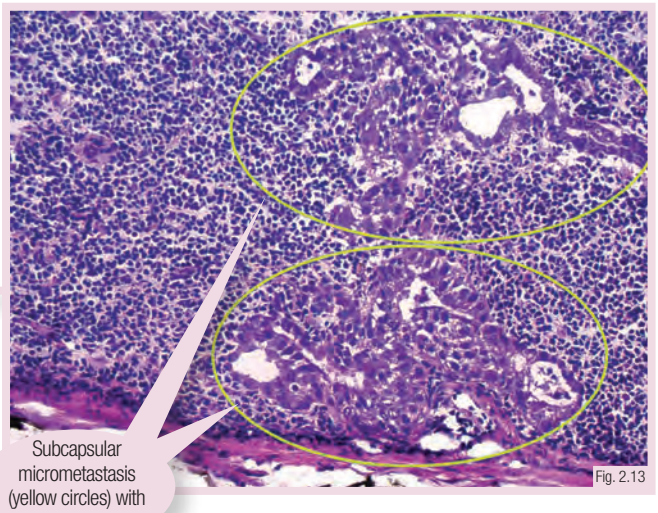
1. What are the special types of breast carcinoma with good prognosis?
2. What are the features to be considered when assessing the grade of breast carcinoma?
3. Why is it important to differentiate true peritumoural vascular invasion from dislocation?

Lymph node status and biological characterisation

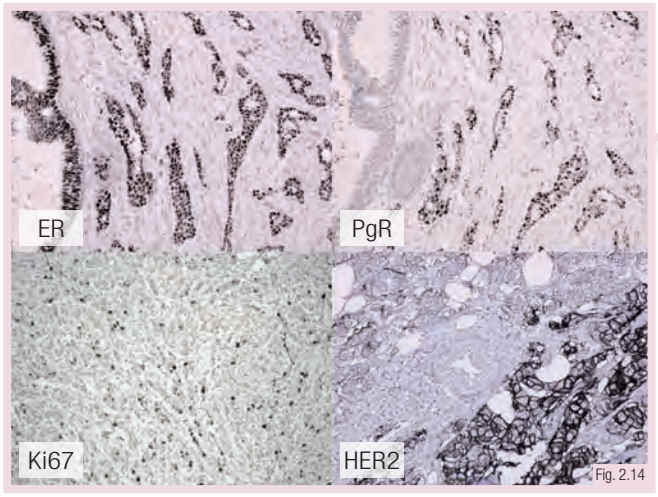
Sentinel lymph node biopsy has proven accurate to assess axillary node status in clinically node-negative disease. It avoids unnecessary axillary clearance and its associated morbidity.

It is important that the entire node is extensively examined by serial sectioning to maximise its predictive value.

According to the size, metastatic deposits are classified as isolated tumour cells (ITC) (<0.2 mm), micro- (up to 2 mm) and macro-metastases (>2 mm).



Biological characterisation of breast carcinoma by immunohistochemistry



ER, Oestrogen receptor; PgR, progesterone receptor.

The pathology report should include the assessment of ER, PgR and HER2 status, and the evaluation of the proliferative fraction (Ki67 labelling index) of the tumour.

ER and PgR are evaluated by immunohistochemistry (IHC) and are usually reported as percentage of invasive tumour cells. Other methods (Allred score or H-score) also take into account the staining intensity, in addition to the percentage of positive cells.

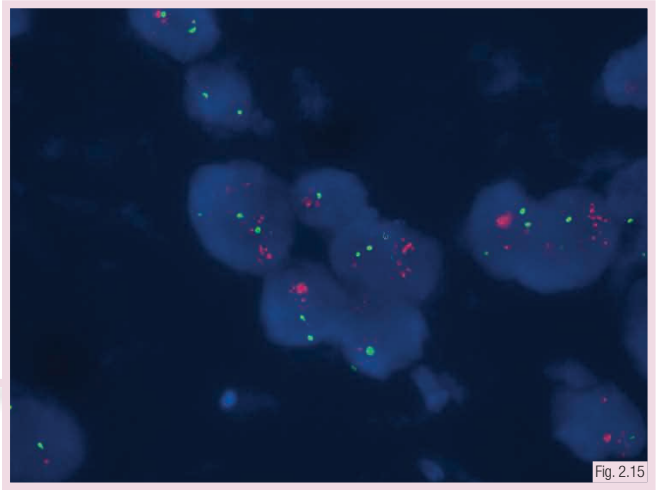
Unfortunately, among pathologists there are interobserver (and sometimes also intraobserver) discrepancies.

Evaluation of HER2 is very important because of its role as a prognostic factor (HER2-positive tumours have poorer prognosis) but, more importantly, its ability to predict the response to anti-HER2 targeted therapies.

IHC is the most widely used testing procedure for HER2, because it is easy to perform, cheap and fast, allowing the correlation of biological features of tumours and their morphological characteristics.

In situ hybridisation assays (fluorescent or chromogenic) are used to assess *HER2* gene amplification in cases with equivocal (2+) IHC results.

Dual colour FISH showing amplification of *HER2* gene (multiple red dots or clusters) and chromosome 17 centromeres (green dots)



FISH, Fluorescence *in situ* hybridisation.

REVISION QUESTIONS

1. Explain how lymph node metastases are classified.
2. What is the most widely used method to evaluate hormone receptor status?
3. What are the two most widely used methods to evaluate HER2 status?

Summary: Pathology (including normal breast) and disease subtypes

- Diagnostic approach
  - cytology is easy, cheap, safe and fast
  - histology provides more accurate assessments for the choice of therapy
- Myoepithelial cells are a marker of benign proliferative lesions
- Some benign lesions can mimic malignant counterparts: ancillary studies are helpful to reach the correct diagnosis
- Ductal intraepithelial neoplasia (DIN) is a modern terminology which avoids the term “carcinoma” for non-invasive tumours
- High-grade lobular neoplasia (LIN3) can be misinterpreted as high-grade ductal intraepithelial neoplasia (DIN3)
- It is important to recognise histologically the so-called special tumour types with good prognosis
- Artefactual dislocation of tumour cells must not be misinterpreted as peritumoural vascular invasion
- There are three classes of lymph node metastatic deposits, according to size
- ER, PgR, Ki67 and HER2 status must be evaluated for making correct treatment decisions

Further Reading

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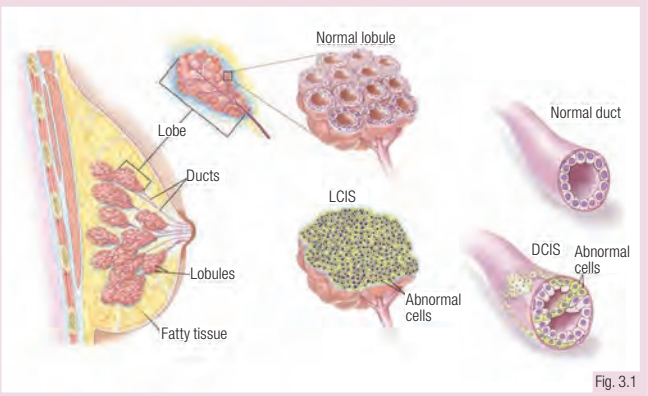
3 Management of carcinoma *in situ*

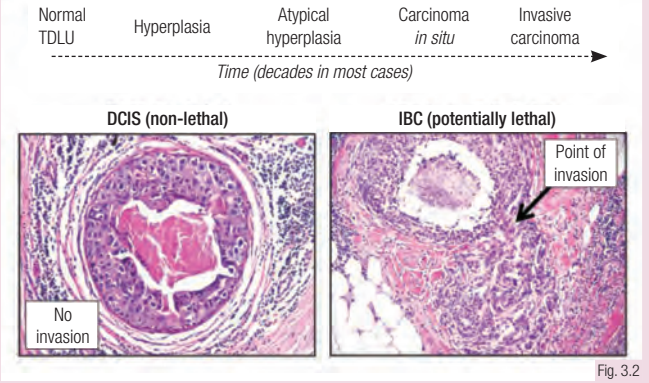
Pathology and biology

Carcinoma *in situ* of the breast can be divided into two categories: ductal carcinoma *in situ* (DCIS), a non-invasive condition of abnormal cells found in the lining of a breast duct, and lobular carcinoma *in situ* (LCIS), a non-invasive lesion that arises from the lobules and terminal ducts of the breast.

LCIS is a risk indicator for the development of subsequent invasive breast cancer (BC) in either breast. It is not considered a pre-cancer; therefore it does not need local treatment.



DCIS, Ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*.



DCIS, Ductal carcinoma *in situ*; IBC, invasive breast cancer; TDLU, terminal duct lobular unit.

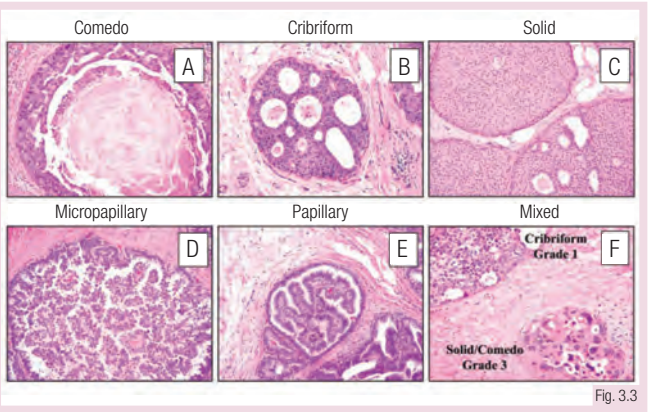
DCIS is the main type of carcinoma *in situ* in the breast (80%–90%) and a late stage of BC evolution.

Since DCIS is a non-invasive lesion, the risk of development of metastases in patients diagnosed with pure DCIS is rare.

The following features characterise DCIS and should be documented in the pathology report: size of the lesion, histological grade, presence of necrosis, architectural pattern and distance to the closest margin.

The histological grade of DCIS is classified as low (well-differentiated), intermediate or high (poorly differentiated).

The different types of DCIS, classified primarily according to their architectural pattern, include the following types: comedo, cribriform, solid, papillary and micropapillary. However, a large proportion of DCIS shows combinations of growth patterns.



REVISION QUESTIONS

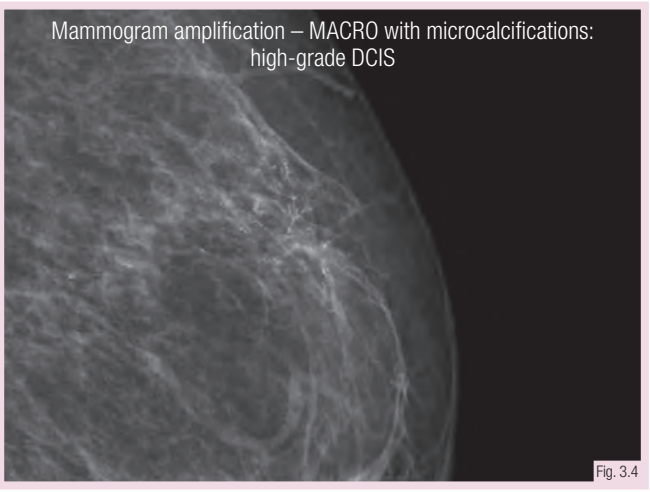
1. What are the different types of carcinoma *in situ*?
2. Describe the most important difference in terms of biology of these types of carcinoma *in situ*.
3. What are the most important features that characterise DCIS?

Diagnosis

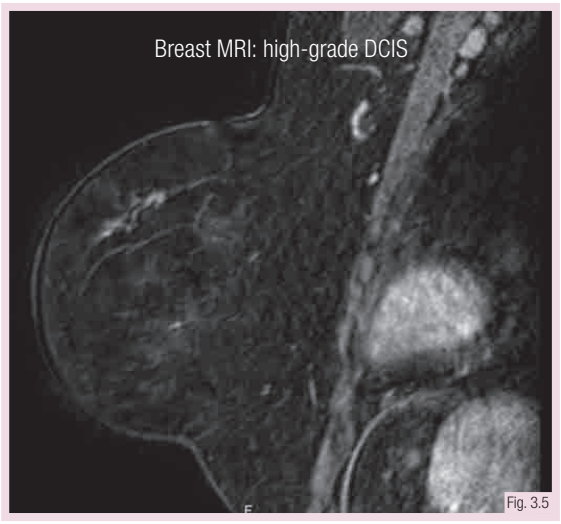
The diagnosis of DCIS has increased significantly with the introduction of BC screening mammography.

Nowadays, DCIS accounts for 20%–30% of all newly diagnosed BCs in populations participating in BC screening.

The majority of patients have microcalcifications on their mammography. Most of these patients do not have any breast-related symptoms.



DCIS, Ductal carcinoma *in situ*.



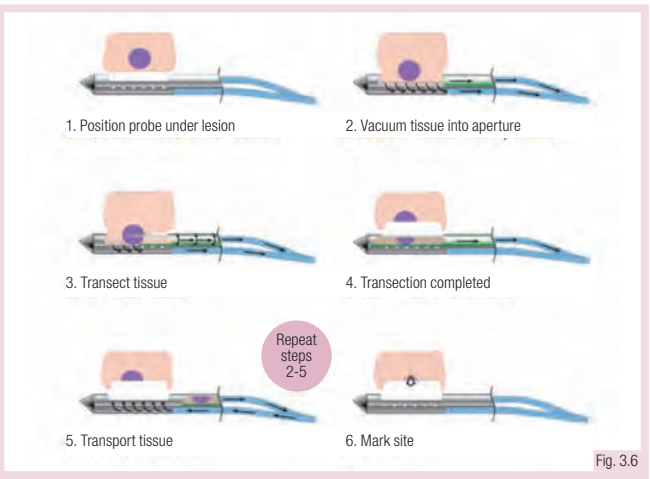
DCIS, Ductal carcinoma in situ; MRI, magnetic resonance imaging.

In order to evaluate the morphology and extent of calcifications, patients should have a diagnostic bilateral mammogram with magnification views. Digital mammography has improved the detection of microcalcifications, and therefore increased the number of women diagnosed with DCIS.

The role of magnetic resonance imaging (MRI) in the evaluation of DCIS is not fully defined, but it assesses the extent of DCIS, if visible, more accurately than mammography. It may also help to determine multicentric disease and synchronous contralateral disease. Its improved sensitivity compared with mammography is particularly robust for high-grade DCIS.

The diagnosis of DCIS is confirmed by a breast biopsy, such as a core biopsy or excisional biopsy. Fine needle aspiration (FNA) is inadequate to distinguish between invasive and *in situ* disease.

Vacuum-assisted biopsy techniques obtain a greater volume of tissue sampling, due to the possibility of obtaining multiple specimens with a single insertion, decreasing the underestimation rate of invasive carcinoma in cases with DCIS. A localising clip is often placed as a marker at the end of the biopsy.



REVISION QUESTIONS

1. Why has the incidence of DCIS diagnosis increased over the last few decades?
2. Describe the role of MRI in the work-up of DCIS.
3. Why is FNA insufficient for the diagnosis of DCIS?

Surgical treatment

The goal of surgical/medical intervention in DCIS is to prevent the future development of invasive carcinoma of the breast.

The surgical treatment of DCIS can be breast-conserving surgery or a mastectomy, depending on the relation between the size of the lesion and the size of the breast, and respecting the patient's preference.

Being a marker of risk and not a real precursor of invasive disease, LCIS has no indication for surgical excision.

Indications for sentinel node biopsy in DCIS
Large area of microcalcifications
Breast mass
Mastectomy

Fig. 3.8

DCIS, Ductal carcinoma *in situ*.

Due to the non-invasive nature of DCIS, sentinel lymph node biopsy (SLNB) is, in general, not indicated.

SLNB can be indicated, however, when there is a high possibility of occult invasive carcinoma, such as the presence of a breast mass or a very large area of microcalcifications.

SLNB for DCIS may also be performed when mastectomy is planned, because subsequent SLNB at a second operation cannot be done if needed.

In multivariate analysis, margin width was not a significant predictor of recurrence among those receiving radiation, even after adjusting for multiple clinical and pathological variables.

Margins should be free of disease, but there is no proven benefit in going further than no lesions on inked margins, especially if radiotherapy is foreseen.

When mastectomy is the option, immediate breast reconstruction should always be offered, and skin-sparing mastectomy is the preferred technique, showing similar results to more radical approaches and a better cosmetic outcome.

Nipple-sparing mastectomies for DCIS

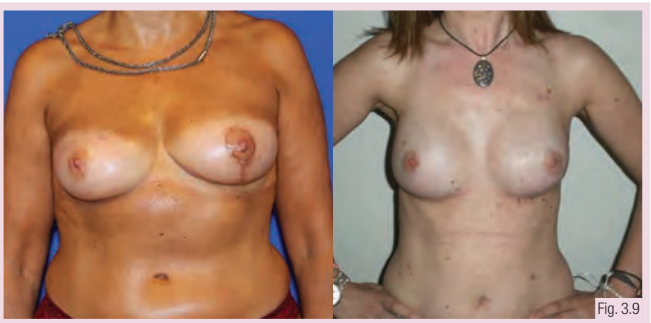


Fig. 3.9

DCIS, Ductal carcinoma *in situ*.

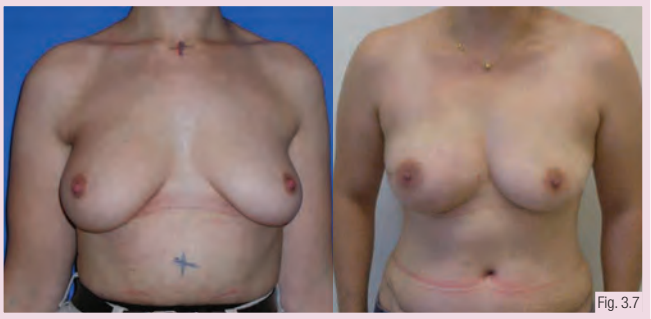


Fig. 3.7

TRAM, Transverse rectus abdominis myocutaneous.

REVISION QUESTIONS

1. Is there a limit in size for performing breast conservation in DCIS?
2. What are the indications for SLNB in DCIS?
3. Is there an ideal margin for DCIS in breast conservation?

Radiotherapy

Radiotherapy is a part of breast-conserving treatment in DCIS. Standard care is adjuvant whole-breast irradiation, delivered in 3 to 5 weeks.

It reduces the 10-year absolute risk of in-breast tumour recurrence by 15% (from 28% to 13%). There is no subgroup that does not benefit from radiotherapy.

This improved local control does not have a significant effect on BC-specific survival or overall survival.

Effect of radiotherapy after breast-conserving surgery

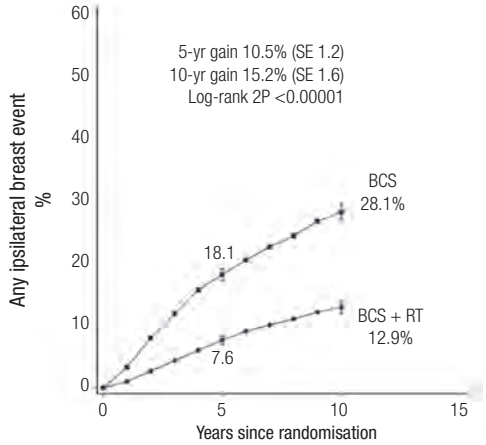
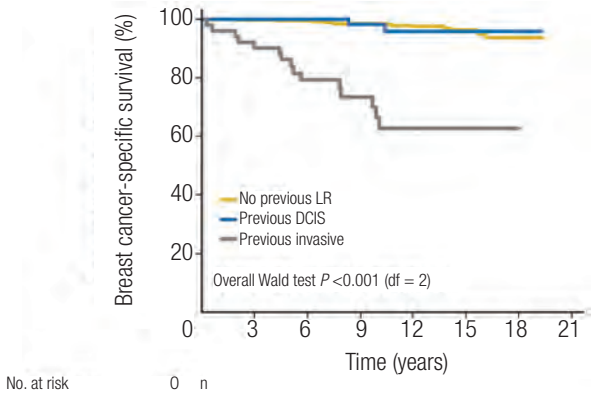


Fig. 3.10

BCS, Breast-conserving surgery; RT, radiotherapy.

Long-term follow-up of patients with DCIS treated in the EORTC 10853 trial. Breast cancer-specific survival for patients without a local recurrence (LR), with a DCIS LR and with an invasive LR



No. at risk	0	n						
No previous LR	18	832	781	668	554	291	101	27
Previous DCIS	2	70	68	63	52	34	14	2
Previous invasive	15	52	46	32	23	10	4	0

Fig. 3.11

DCIS, Ductal carcinoma *in situ*; EORTC, European Organisation for Research and Treatment of Cancer; n, number of patients; O, observed.

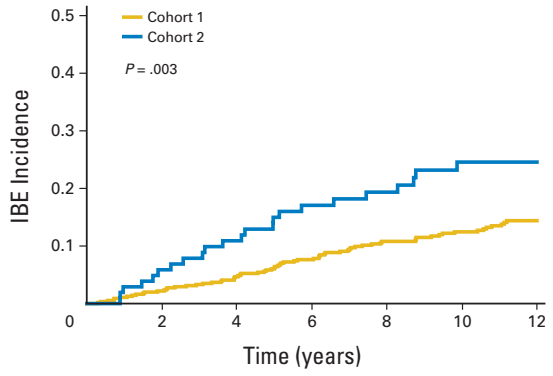
Half of the recurrences are invasive in-breast recurrences and half are *in situ* recurrences. Patients with invasive recurrences experience an increase in BC mortality.

It may be reasonable to omit radiotherapy in selected low-risk patients (with small lesions of low-grade disease resected with tumour-free margins) or in patients with advanced age and extensive comorbidities.

Prospective clinical trials, trying to define the subgroup of low-risk patients that can be treated with breast-conserving surgery only, concluded that for DCIS Grade 1 and 2 diagnosed in postmenopausal patients, the local recurrence rate is around 1% per year (without plateau at long-term follow-up) with local surgery only for lesions smaller than 1 cm, excised with tumour-free margins.

For DCIS Grade 3, the incidence of local recurrence is high if treated with surgery alone, even in very small lesions resected with tumour-free margins.

Ipsilateral breast events (IBEs)



No. at risk							
Cohort 1	561	525	492	449	402	352	206
Cohort 2	104	95	88	78	67	53	34

Cohort 1= low- or intermediate-grade DCIS, tumour size ≤2.5 cm;
Cohort 2= high-grade DCIS, tumour size ≤1.0 cm

Fig. 3.12

REVISION QUESTIONS

1. What is the benefit of postoperative radiotherapy in terms of local control?
2. Why is it important to prevent local recurrences in patients with DCIS?
3. For which patient population could radiotherapy be omitted?

Prevention

Strategies for prevention of BC include lifestyle factors, such as avoidance of obesity, maintaining physical activity and moderation of alcohol intake, as well as surgical and medical therapeutic interventions in cases of high-risk patients such as those with LCIS.

In LCIS, tamoxifen is the most widely accepted selective oestrogen receptor modulator (SERM) for prevention, although its acceptance is low due to a perceived concern about adverse effects and poor ability to identify women at high risk. Aromatase inhibitors (AIs) are being studied in large trials. Newer agents, notably bisphosphonates and metformin, also show promise.

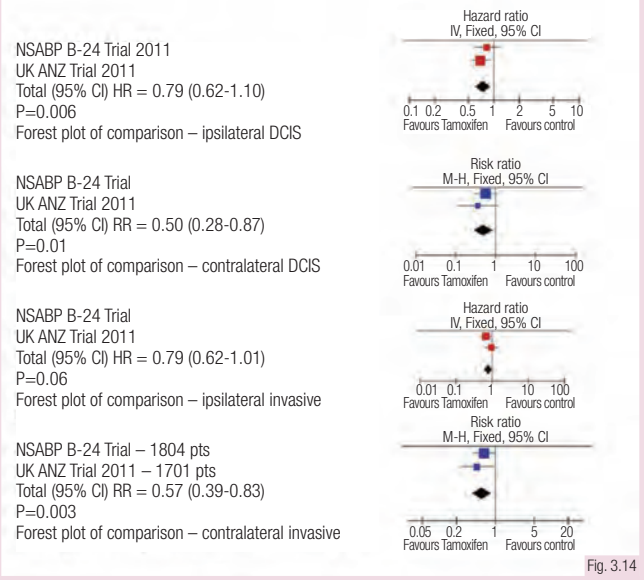


Fig. 3.14

CI, Confidence interval; DCIS, ductal carcinoma *in situ*; HR, hazard ratio; IV, inverse variable; M-H, Mantel-Haenszel; pts, patients; RR, risk ratio.

Factors that may influence non-use of tamoxifen, particularly when local recurrence risk is low, include: ER-negative DCIS and patients with a high risk of subsequent complications such as deep venous thrombosis (especially age >65 years).

Patients receiving breast conservation for DCIS may benefit from radiotherapy + tamoxifen. The use of one or both must be considered in the context of the risks and benefits for the individual case.

Treatment should be discussed in a multidisciplinary team and the patient should be thoroughly informed.

Range of agents considered for breast cancer prevention

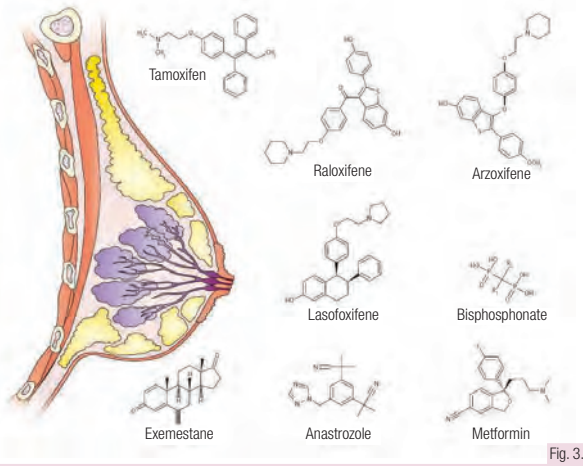


Fig. 3.13

After lumpectomy for DCIS, the benefit of adjuvant tamoxifen was studied in two clinical trials: the UK/ANZ DCIS and the NSABP B-24.

A meta-analysis of both trials showed a reduction in both ipsilateral and contralateral *in situ* recurrences, with no benefit in overall survival with the use of tamoxifen.

The IBIS 2 and NSABP B-35 trials studied anastrozole as another treatment option for postmenopausal women with ER-positive DCIS, which might be more appropriate for some women with contraindications to tamoxifen. But, again, it was without survival benefit.

Ipsilateral invasive local recurrences at 10 years by treatment type

	DCIS cases	Invasive recurrences	Recurrence rate (95% CI)
Conservative surgery	2038	241	11.4 (8.8-14.1)
Conservative surgery + tamoxifen no radiotherapy	567	49	8.6 (6.7-10.6)
Conservative surgery + radiotherapy no tamoxifen	4562	317	7.7 (5.9-9.5)
Conservative surgery + radiotherapy + tamoxifen	937	40	4.3 (3.0-5.6)
TOTAL	**8104**	**647**	

Fig. 3.15

CI, Confidence interval; DCIS, ductal carcinoma *in situ*.

REVISION QUESTIONS

1. What are the known strategies for prevention in high-risk women?
2. What is the benefit of tamoxifen for the reduction of ipsilateral breast recurrences?
3. Are there clear indications for the use of tamoxifen or AIs in women with DCIS?

Summary: Management of carcinoma *in situ*

- The two main types of carcinoma *in situ* are: LCIS, a risk indicator, not needing local treatment, and DCIS, a precursor of invasive cancer, needing local therapy
- The incidence of DCIS has increased with the introduction of mammographic screening
- A breast biopsy is needed for the diagnosis of DCIS. FNA is inadequate to distinguish between invasive and carcinoma *in situ*
- The goal of local therapy is to prevent the future development of invasive carcinoma
- Surgical treatment can consist of breast-conserving therapy or mastectomy (preferable with immediate reconstruction)
- In general, sentinel node biopsy is not indicated
- It is essential to obtain tumour-free margins
- Radiotherapy following breast-conserving surgery decreases the 10-year absolute risk of in-breast recurrences by 15%
- Radiotherapy may be omitted in low-risk patients
- Adjuvant endocrine therapy results in a reduction of ipsilateral and contralateral recurrences in patients with ER-positive DCIS, but without impact on survival

Further Reading

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4 Breast cancer surgery

Breast-conserving surgery and mastectomy

Lumpectomy, tumourectomy, wide excision, quadrantectomy, etc, are mostly synonymous terms for breast-conserving surgery.

The goal is to excise both invasive and intraductal tumour components with clear resection margins and a cosmetic result acceptable for the patient.

Postoperative dents can often be avoided by mobilising residual parenchyma and simple rotation into the defect.

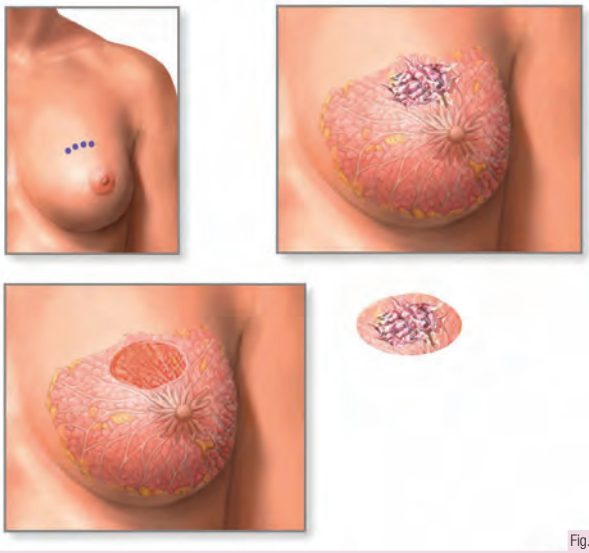


Fig. 4.1

Round-block technique (a) preoperative design with two circular skin markings, (b) lumpectomy and de-epithelialisation, (c) undermining and approximation of nearby breast tissue, and (d) postoperative periareolar scar

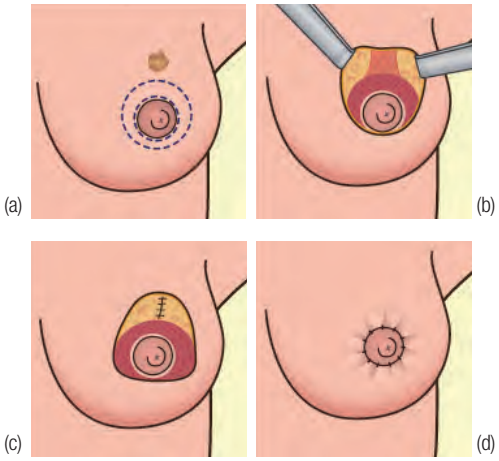


Fig. 4.2

Several techniques (usually derived from cosmetic surgery) are currently used to allow larger resections without causing severe deformities or dents and without compromising oncological results.

These techniques are referred to as oncoplastic surgery and may lead to a decrease in breast size and thus asymmetry, but allow for a natural breast form.

A typical example employed in small to moderate size breasts is the round-block technique (doughnut mastopexy).

The B-Plasty allows the reconstruction of large peripheral defects that include skin removal. Typically, large tumours with skin involvement are good indications for this technique.

In principle, the parenchyma and skin removal is compensated by a circular skin de-epithelialisation and parenchyma rotation into the resection defect.

In large tumours, primary systemic therapy as opposed to complex surgical technique needs to be discussed during interdisciplinary meetings.

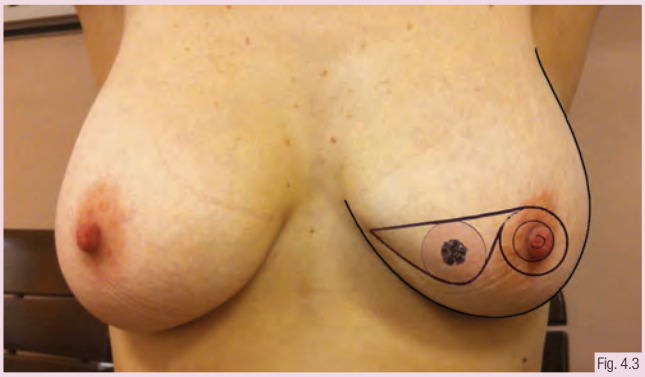


Fig. 4.3

REVISION QUESTIONS

1. What synonymous terms are used for breast-conserving surgery?
2. What is oncoplastic surgery?
3. In large tumours: are there options for “larger” surgery?

Breast-conserving surgery and mastectomy (continued)

Another typical example of oncoplastic surgery is the snowman (Hall-Findlay) technique. This technique allows reduction mammoplasties in small to medium-size breasts.

Up to approximately 800 g of breast tissue can be removed, allowing for the resection of large tumour masses or extensive intraductal components.

Sentinel procedures (see next page) must be carried out before mobilisation of the breast in all oncoplastic techniques.

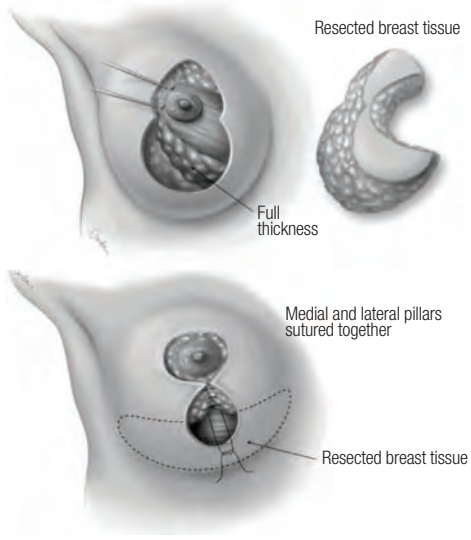


Fig. 4.4

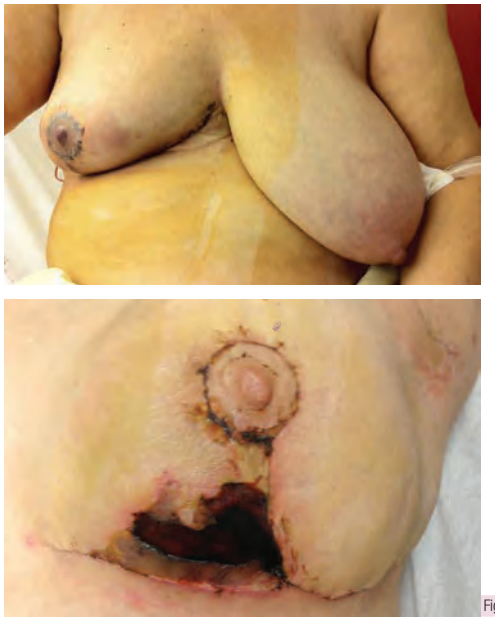


Fig. 4.5

Asymmetry is a common phenomenon after oncoplastic techniques and may lead to contralateral breast surgery at the same time or at a later point in time (e.g. after adjuvant radiotherapy).

Surgical morbidity is clearly increased when oncoplastic techniques are employed. Complications include wound infection, necrosis of displaced parenchyma and skin flaps, and increased seroma formation.

Oncoplastic surgery requires rigorous planning and preoperative markings. Close interdisciplinary work between plastic and oncological surgeons is necessary.

Modified radical mastectomy (MRM, Patey and Dyson 1948) involves the removal of the entire breast and axillary lymph nodes (levels I and II; see next page)

Fusiform incisions depending on tumour location are used. Skin flaps are undermined in a plane between subcutaneous fat and breast tissue. The breast including the pectoralis fascia is removed.

Increasingly skin-sparing modifications of mastectomy are used, which allow primary reconstruction with either prostheses or autologous tissue.

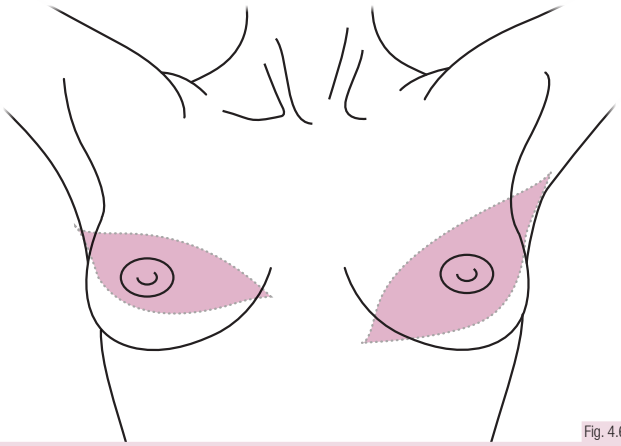


Fig. 4.6

REVISION QUESTIONS

1. In modified radical mastectomy, which structures are removed?
2. What are the requirements for successful oncoplastic surgery?
3. What are the most common side effects associated with oncoplastic surgery?

Surgery of the axilla

The sentinel lymph node (SLN) procedure allows the identification of the first lymph nodes draining the lymphatic system of the breast.

Technetium-labelled colloids and/or blue dye is injected into the breast and accumulated in the draining lymph nodes.

The SLNs are identified and removed via a small axillary incision. In case of metastatic spread to these nodes, axillary dissection should be discussed in some patients.

Sentinel lymph node biopsy

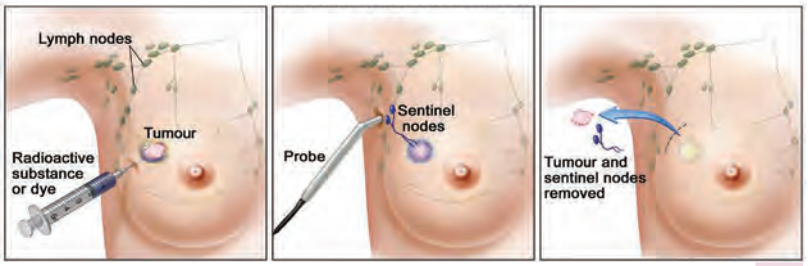


Fig. 4.7

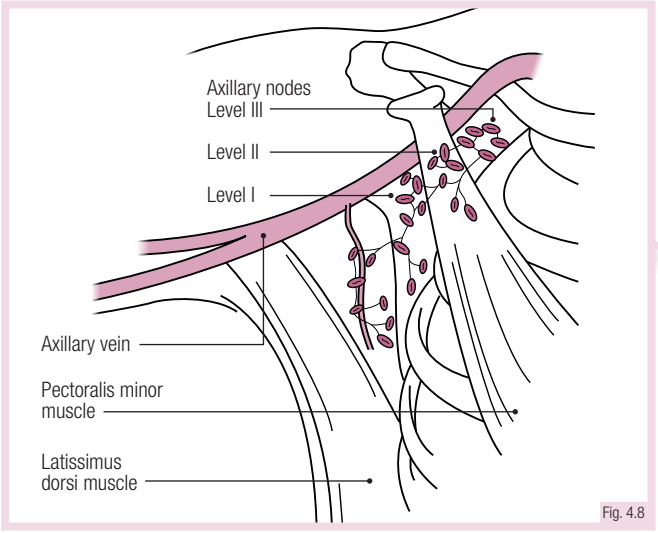


Fig. 4.8

Routine axillary dissection (AD) involves the *en bloc* resection of lymph nodes from levels I and II.

The axillary vein, the long thoracic nerve and the thoracodorsal nerve/vessel bundle must be identified and spared during the dissection.

Recurrent seroma formation and local paraesthesia are frequently associated with AD. Furthermore, lymphoedema can be clinically observed, in up to a quarter of women, one year postoperatively.

SLN is a standard procedure in invasive breast cancer (BC) with clinically negative lymph node status (cN-). cN+ women should undergo primary AD, if not receiving preoperative systemic therapy.

Not all SLN+ women undergo AD. Axillary radiotherapy instead of surgery, or no further local treatment other than whole breast irradiation, are emerging treatment options in selected women. The goal is to minimise morbidity and maximise oncological safety.

Treatment recommendations in SLN+ women are based on (a) prior therapy, (b) tumour stage, (c) planned adjuvant therapy and (d) patient's wishes.

Current treatment options after sentinel lymph node biopsy

Sentinel lymph node negative	→	No further axillary therapy
Sentinel lymph node positive 1-2 nodes positive T1-T2 Breast conservation Whole breast radiotherapy planned No prior systemic therapy	Patient meets all criteria →	No further axillary therapy
Sentinel lymph node positive >2 positive nodes >5 cm tumour size Mastectomy No radiotherapy planned Prior systemic therapy	Patient meets one criterion →	Consider axillary dissection or lymph node irradiation
Sentinel lymph node not identified	→	Consider axillary dissection or lymph node irradiation

Fig. 4.9

REVISION QUESTIONS

1. How is a SLN identified?
2. What are the methods for SLN detection?
3. What are the treatment options for SNL+ cases, and what are they based on?

Breast reconstruction

Breast reconstruction aims to restore the breast, either partially or totally, in order to overcome sequelae of surgical BC treatment.

Breast reconstruction has no documented effect on the survival of BC patients but can help to improve the body image.

Breast reconstruction is performed with implants, autologous tissue or with a combination thereof, depending on the needs of the given patient.

Patient after mastectomy suffering from severe asymmetry

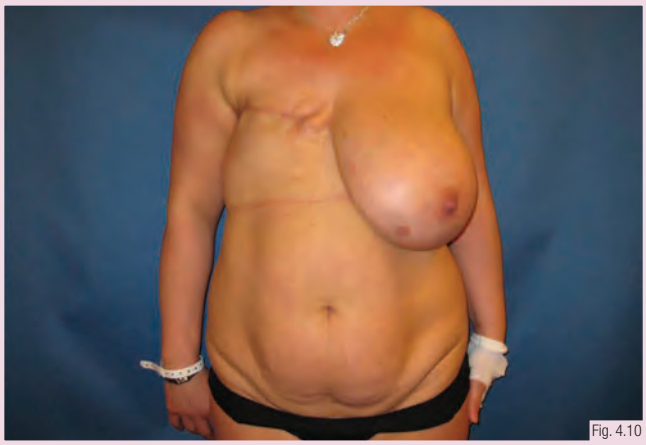


Fig. 4.10

Immediate breast reconstruction with deep inferior epigastric perforator (DIEP)

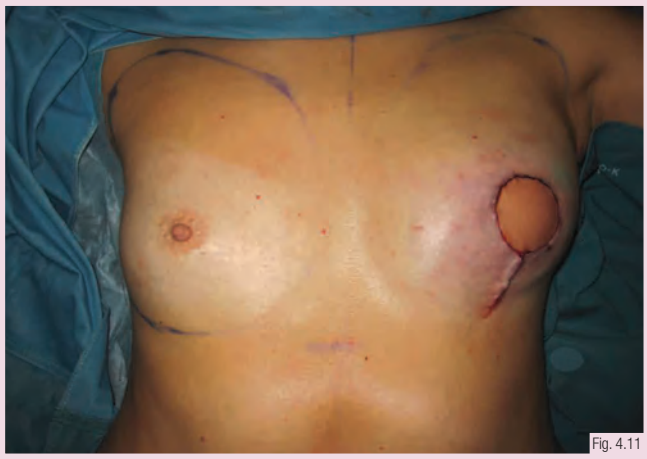


Fig. 4.11

The surgery can either be performed as immediate breast reconstruction (primary reconstruction) or at a later timepoint.

Advantages of immediate breast reconstruction are avoidance of a period without breast, preservation of skin, smaller scars and therefore better cosmetic results.

Delayed breast reconstructions are planned in full knowledge of the oncological situation and fitted into the adjuvant treatment modalities. This also allows more time to discuss the many details of reconstructive surgery.

Implant-based reconstructions are faster procedures than autologous reconstructions, but more prone to asymmetry and secondary revisions.

Prostheses in combination with radiotherapy should be avoided whenever possible, due to more acute and chronic complications, such as capsular contracture.

Implant-based reconstructions can be combined with a pedicled latissimus dorsi flap or with acellular dermal matrix (ADM).

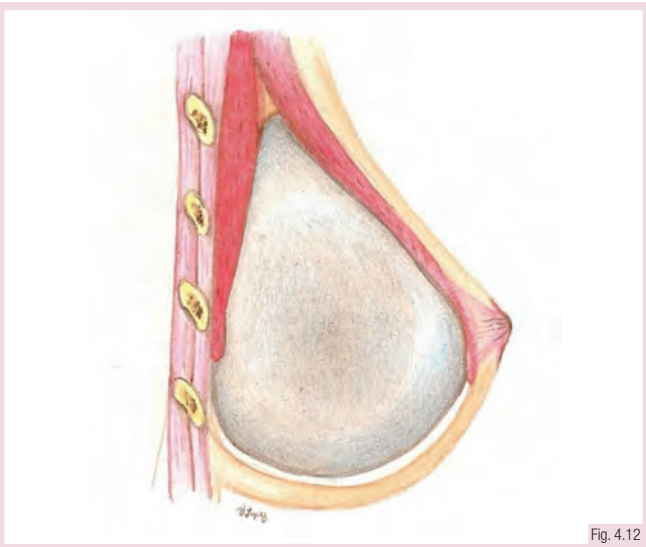


Fig. 4.12

REVISION QUESTIONS

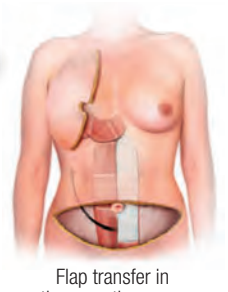
1. What is the advantage of immediate breast reconstruction?
2. Does breast reconstruction have a negative influence on the outcome of BC?
3. Does radiotherapy increase the complications in implant-based reconstructions?

Breast reconstruction (continued)

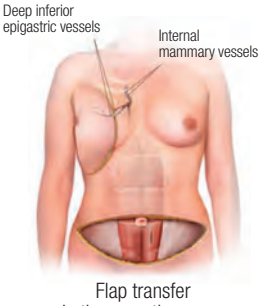
Autologous reconstruction is performed by transplanting suitable tissue from a donor region and transferring it into the recipient area.

Microsurgery is necessary to re-establish blood supply of the tissue, resulting in a longer and more complex surgical procedure.

Recipient vessels of autologous breast reconstruction are either the internal mammary vessels or the thoracodorsal vessels.



Flap transfer in the operating room



Flap transfer in the operating room

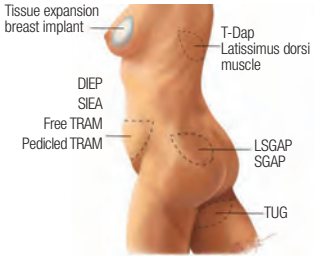


Fig. 4.13

DIEP, Deep inferior epigastric perforator; LSGAP, lateral superior gluteal artery perforator; SGAP, superior gluteal artery perforator; SIEA, superficial inferior epigastric artery; T-DAP, thoracodorsal artery perforator; TRAM, transverse rectus abdominis myocutaneous; TUG, transverse upper gracilis.

Patient after immediate reconstruction with DIEP

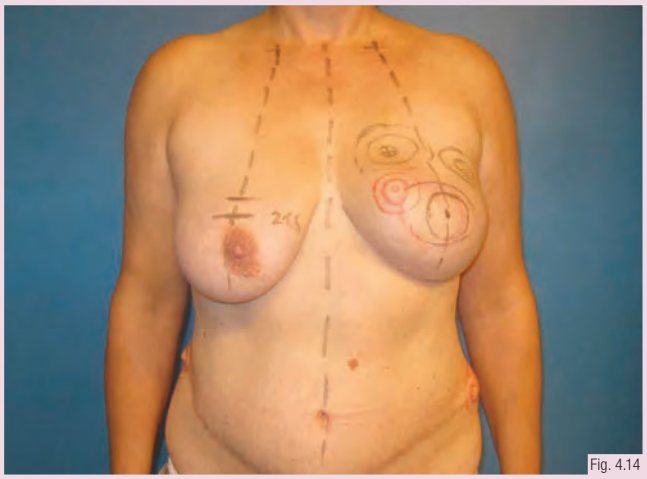


Fig. 4.14

DIEP, Deep inferior epigastric perforator.

Autologous abdominal-based reconstruction can be performed using a pedicled Transverse Rectus Abdominis Myocutaneous (TRAM) flap or a free flap without rectus abdominis muscle (Deep Inferior Epigastric Perforator [DIEP]).

In patients with no excess tissue on the abdomen, the inner thigh (Transverse Myocutaneous [or Upper] Gracilis [TMG or TUG]) or the buttock (Superior or Inferior Gluteal Artery Perforator flaps [S/IGAP]) can be good alternatives for donor sites.

In high-risk patients or after failed breast reconstruction, a pedicled latissimus dorsi flap with or without implant can be a good alternative to free flaps.

In many patients, a contralateral mastopexy is necessary. This can be performed either together with the breast reconstruction or in a second surgery.

Nipple–areola complex reconstruction can be done either with local flaps and tattoo or with skin grafts from the groin in combination with “nipple sharing” from the contralateral side.

Further corrections include lipofilling or liposuction to perfect the cosmetic outcome.

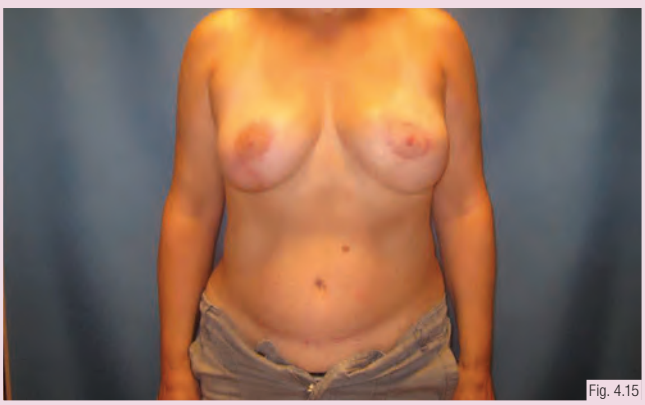


Fig. 4.15

REVISION QUESTIONS

1. Which donor sites can be used for autologous breast reconstruction?
2. How can the nipple–areola complex be reconstructed?
3. What is a good method for autologous breast reconstruction in high-risk patients?

Summary: Breast cancer surgery

- Lumpectomy, tumourectomy, wide excision and quadrantectomy are synonymous terms for breast-conserving surgery
- Oncoplastic surgery allows for a natural breast form without compromising oncological safety
- The SLN procedure allows the identification of the first lymph nodes draining the lymphatic system of the breast and, when negative, a conservative approach to the axilla
- Axillary dissection increases the risk of lymph oedema in the upper limb
- In cN- but SLN+ BC, axillary dissection is not always necessary
- Breast reconstruction has no documented effect on the survival of BC patients
- Breast reconstruction may be performed together with the surgical treatment of cancer, or later in the course of treatment
- Reconstructive surgical techniques are multiple, including implants and autologous tissue
- Radiation therapy is not recommended with prosthetic implants, due to the risk of capsular contracture
- With autologous reconstructions, microsurgery is often necessary to re-establish blood supply to the tissue. The aim of oncoplastic reconstructive BC surgery is to provide the patient with a breast, from autologous tissue as often as possible, without compromising the oncological safety

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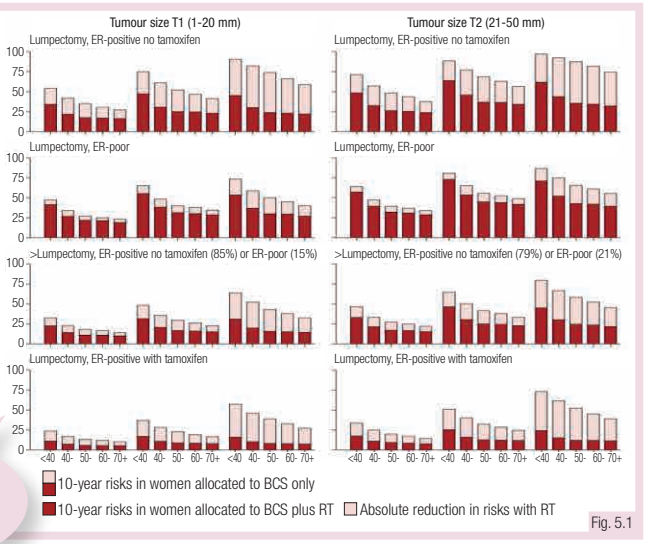
5 Breast cancer radiotherapy

Adjuvant radiotherapy after breast-conserving surgery

All patients should be considered for postoperative 45–50 Gy whole breast radiotherapy (RT) after wide local excision with clear margins.

RT to the conserved breast halves the rate at which the disease recurs and reduces the breast cancer (BC) death rate by about one sixth.

RT following breast-conserving surgery (BCS) of ductal carcinoma *in situ* (DCIS) reduces local recurrence risk by 50%, irrespective of size, margins, age or adjuvant hormone therapy, but has no effect on BC or overall survival (OS).



RT reduces the risk of recurrence by 50% for all levels of risk

Fig. 5.1

BCS, Breast-conserving surgery; RT, radiotherapy.

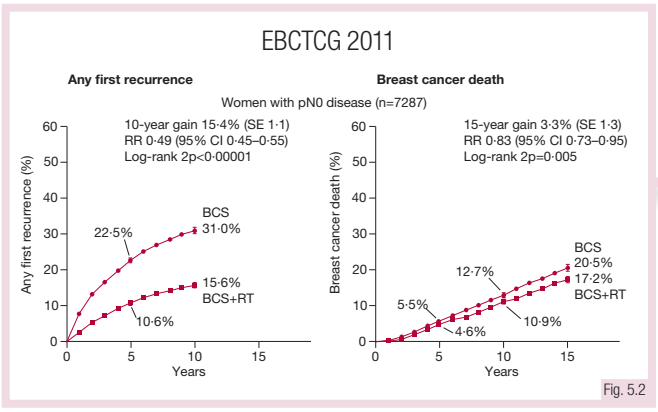


Fig. 5.2

BCS, Breast-conserving surgery; CI, confidence interval; RR, rate ratio; RT, radiotherapy.

Improvements in local control translate into long-term benefit in survival at 15 years in node-negative (pN0) BC.

The Oxford overview shows that for every 4 local recurrences prevented by RT, one BC death is avoided.

There is no subgroup of patients of sufficiently low risk for whom whole-breast RT can be systematically omitted.

Age <40: maximum benefit is in young women

Age >60: there is a small benefit in older women

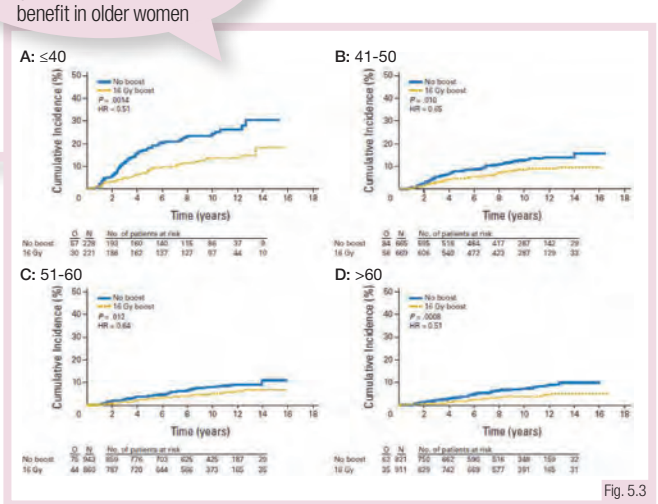


Fig. 5.3

HR, Hazard ratio.

A boost dose (10–16 Gy) to the site of excision after BCS (with clear margins) reduces the risk of local recurrence by a further relative 50%.

10-year follow-up shows that all age groups benefit from a boost. Boost dose should be considered especially if: age <50 years, axillary lymph node-positive disease, tumour Grade 3, vascular invasion and/or close margins.

Shorter fractionation schemes (e.g. 15–16 fractions with 2.5–2.67 Gy single dose; i.e. hypofractionation) have shown similar effectiveness and comparable adverse effects.

REVISION QUESTIONS

1. What is the impact of locoregional RT on OS?
2. Is there any subgroup of patients for whom postoperative RT can be omitted after BCS?
3. What is the impact of local boosting on BC recurrence rate?

Radiotherapy technique

Limits must be set for the volume of the heart and coronary arteries irradiated, especially in left-sided BC, to avoid cardiac toxicity.

3D planning allows beam position to be adjusted, to minimise irradiation of organs at risk, such as lung, heart, coronaries, the glenohumeral joint and the other breast.

Cardiac toxicity may be reduced by using breath holding or respiratory gating techniques.

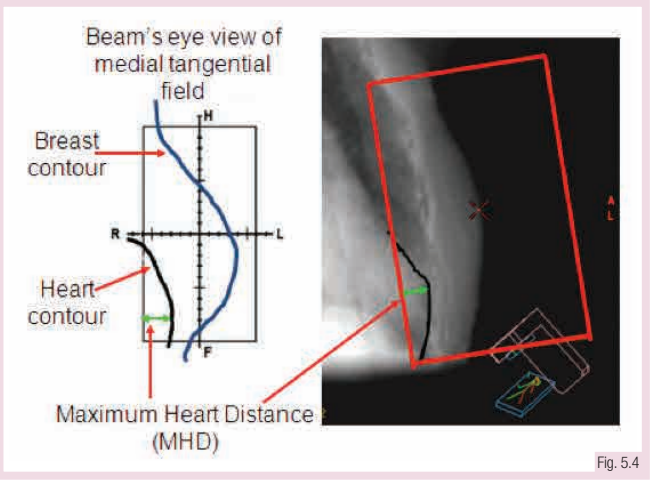


Fig. 5.4

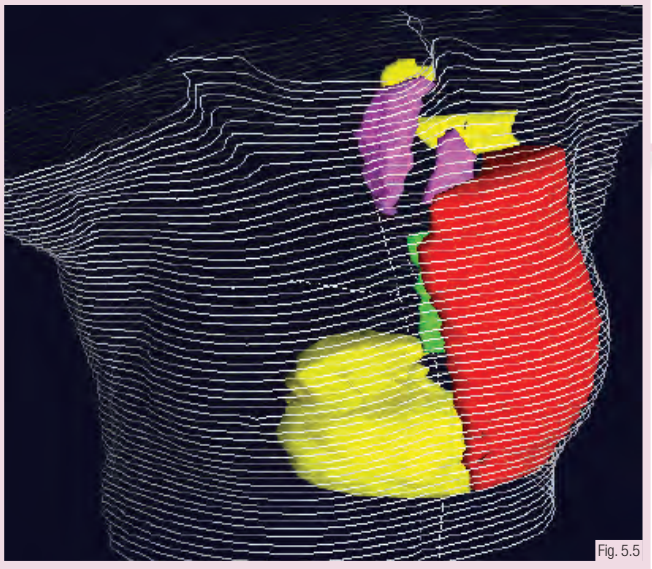


Fig. 5.5

3D computed tomography (CT) planning is recommended for all patients to reduce toxicity while providing optimal chest wall/breast dose distribution.

The optimal dose distribution may be achieved with different techniques, such as intensity modulated RT (IMRT), arc therapy or by using traditional tangential I fields.

After BCS, hypofractionated RT (fewer higher fractions in a shorter treatment period) is the preferred mode of fractionation, allowing for completion of the treatment in 3 weeks instead of 5 weeks with traditional fractionation.

With conventional external beam RT (EBRT), it is more difficult to deliver a homogeneous dose distribution as breast thickness varies in superior–inferior and target volume planes (Figure A).

Hot spots commonly occur at the thinnest parts of the breast, superiorly and inferiorly.

IMRT uses a multileaf collimator to dynamically modify the fluence of the X-ray beam to achieve a more homogeneous dose (Figure B).

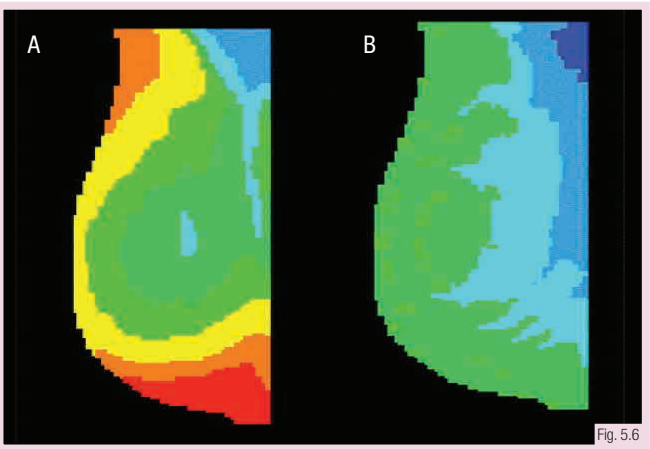


Fig. 5.6

REVISION QUESTIONS

1. What are the main advantages of CT-based RT planning?
2. Where do hot spots occur in the breast with conventional RT?
3. What is the physical advantage of IMRT over conventional RT?

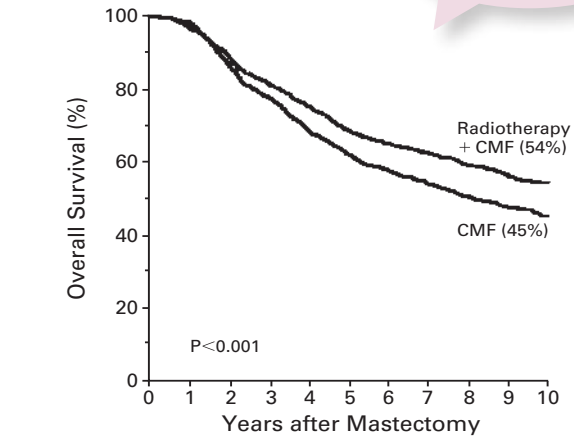
Postmastectomy radiotherapy

Postmastectomy chest wall irradiation has been established as the standard of care for patients with ≥4 pathologically involved axillary nodes.

Current evidence shows that postmastectomy radiotherapy (PMRT) reduces the risks of locoregional failure (LRF), any recurrence and BC mortality, also for patients with T1-2 BC with one to three positive axillary nodes.

However, some of these patients are likely to have such a low risk of LRF that the absolute benefit of PMRT is outweighed by its potential toxicities.

9% survival advantage in premenopausal patients



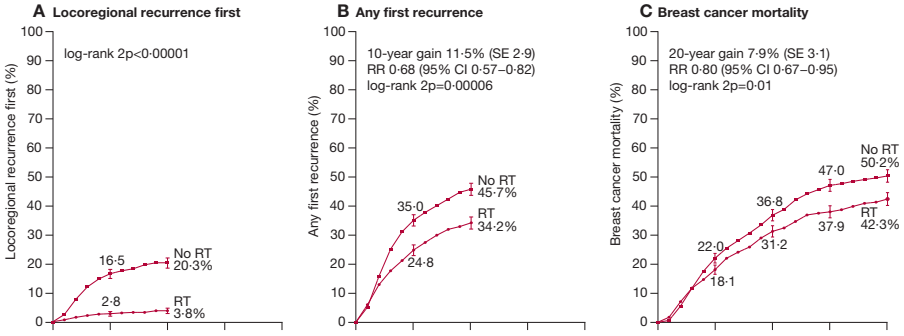
Radiotherapy + CMF	852	755	641	555	392	188
CMF	856	738	587	494	329	163

Fig. 5.7

CMF, Cyclophosphamide/methotrexate/fluorouracil.

EBCTCG 2014

1314 pN1–3 women with Mast+AD



AD, Axillary dissection; CI, confidence interval; Mast, mastectomy; RR, rate ratio; RT, radiotherapy.

Fig. 5.8

Overall survival benefits of PMRT are seen in both pre- and postmenopausal patients.

The benefit of PMRT is independent of the administration of systemic therapy.

PMRT is recommended also in T3-4 node-negative BC.

Doses used for local and/or regional adjuvant irradiation have traditionally been 45–50 Gy, in 25–28 fractions of 1.8–2.0 Gy.

The target volume includes the chest wall, most caudal lymph nodes around the subclavicular arch and the base of the jugular vein, and the surgical scar.

Shorter fractionation schemes (e.g. 15–16 fractions with 2.5–2.67 Gy single dose; i.e. hypofractionation) have shown similar effectiveness and comparable adverse effects.

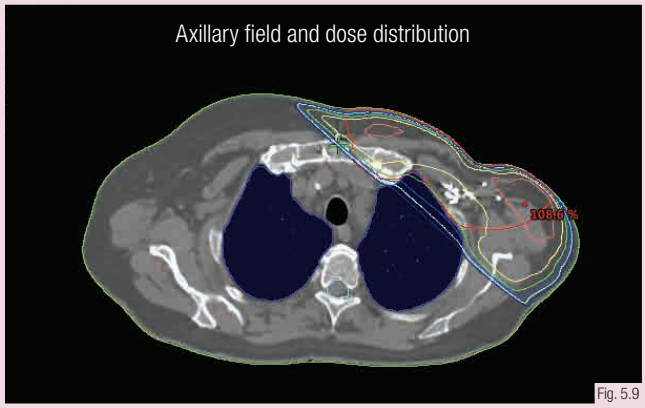


Fig. 5.9

REVISION QUESTIONS

1. For which patients with early BC is postmastectomy RT standard?
2. Should PMRT be standard for patients with 1–3 involved nodes?
3. Is there a survival advantage of PMRT in patients who receive systemic adjuvant therapy?

The role of axillary irradiation

With modern technique and treatment planning, axillary irradiation carries small risks of impaired shoulder movement, pneumonitis and brachial plexopathy.

Sentinel node biopsy is increasingly replacing axillary node clearance with its associated risks of lymphoedema.

There is uncertainty as to which subsets of sentinel node-positive patients should receive axillary irradiation rather than axillary clearance.

RT reduces survival morbidity

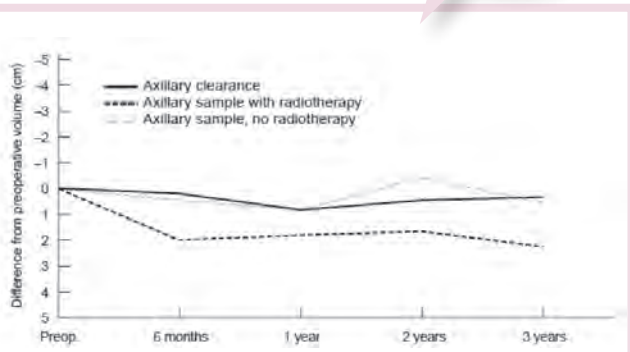


Fig. 5.10

RT, Radiotherapy.

Axillary RT causes little lymphoedema

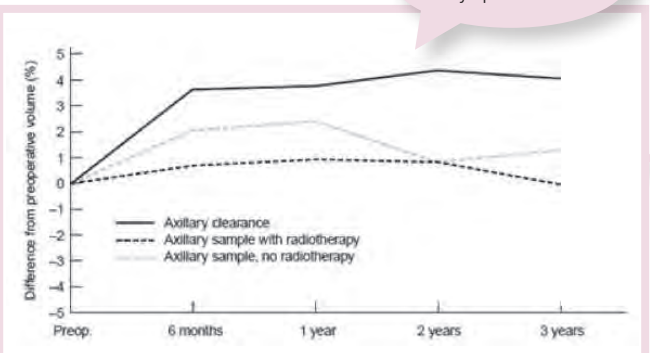


Fig. 5.11

RT, Radiotherapy.

Axillary irradiation causes lower risk of lymphoedema compared with axillary clearance.

Axillary irradiation may restrict shoulder mobility.

After axillary lymph node dissection, the resected part of the axilla should not be irradiated, except in cases of residual disease after surgery.

The EORTC 10981-22023 AMAROS trial compared regional nodal irradiation (RNI) to axillary dissection in patients with a positive sentinel node.

Lymphoedema in the ipsilateral arm was noted significantly more often after axillary lymph node dissection than after axillary RT at 1 year, 3 years and 5 years.

5-year axillary recurrence was 0.43% after axillary lymph node dissection versus 1.19% after axillary RT and there was no difference in disease-free survival (DFS) and OS.

Reduced lymphoedema with axillary RT

	Lymphoedema		
	Axillary lymph node dissection	Axillary radiotherapy	P value
Clinical sign of lymphoedema in the ipsilateral arm			
Baseline	3/655 (<1%)	0/586 (0%)	0.25
1 year	114/410 (28%)	62/410 (15%)	<0.0001
3 years	84/373 (23%)	47/341 (14%)	0.003
5 years	76/328 (23%)	31/286 (11%)	<0.0001
Arm circumference increase ≥10% of the ipsilateral upper or lower arm, or both			
Baseline	33/655 (5%)	24/586 (4%)	0.497
1 year	32/410 (8%)	24/410 (6%)	0.332
3 years	38/373 (10%)	22/341 (6%)	0.080
5 years	43/328 (13%)	16/286 (6%)	0.0009

Data are n/N (%), unless otherwise specified
RT, Radiotherapy.

Fig. 5.12

REVISION QUESTIONS

1. What is the main advantage of axillary irradiation over axillary clearance?
2. What is the main morbidity of axillary RT?
3. What does the AMAROS trial show?

Partial breast irradiation

Partial breast irradiation (PBI) delivers the radiation dose selectively to the site of excision.

Techniques: (a) interstitial implantation, (b) intraoperative intrabeam, and (c) external beam.

PBI is predicated on the observation that most recurrences occur at, or close to, the primary site.

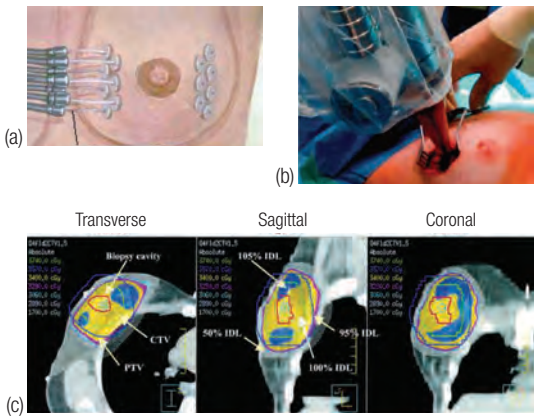


Fig. 5.13

Trials of partial breast irradiation			
Trial	Accrual planned	RT technique	Duration RT
NSABP B-39	4300	Multisource Ir-192	5 days
TARGIT-A	2232	Intraoperative X-rays	1 day
ELIOT	2232	Intraoperative electrons	1 day
RAPID (OCOG)	2128	3D Conformal RT	5-8 days
GEC-ESTRO	1300	Multisource Ir-192, HDR/PDR	2.5-4 days
IMPORT- LOW	1935	External beam IMRT	3 weeks
IRMA	3302	3D Conformal RT	5 days

HDR, High dose rate; IMRT, intensity-modulated radiotherapy; PDR, pulsed dose rate; RT, radiotherapy.

Fig. 5.14

TARGIT-A: Whole breast RT versus intraoperative PBI (intrabeam; figure b above). The 5-year risks for local recurrence for targeted intraoperative RT versus EBRT were 3.3% vs 1.3% (P=0.042).

TARGIT-A: No difference in BC mortality but significantly fewer non-BC deaths in the targeted intraoperative RT group (1.4% vs 3.5%, P=0.0086), attributable to fewer deaths from cardiovascular causes and other cancers.

TARGIT-A: Targeted intraoperative RT concurrent with lumpectomy within a risk-adapted approach, should be considered as an option for eligible patients with BC, as an alternative to postoperative EBRT.

ELIOT: Whole breast RT versus intraoperative PBI (intraoperative electrons). The 5-year event rate for local recurrence was 4.4% in the PBI group and 0.4% in the whole breast RT group; hazard ratio 9.3 [95% confidence interval (CI), 3.3–26.3]. OS did not differ between groups.

ELIOT: Failure of local control was partly attributable to ipsilateral events at sites other than the index quadrant and partly to recurrences around the original tumour.

ELIOT: Skin toxicity adverse effects showed a significant difference in favour of the PBI group; P=0.0002.

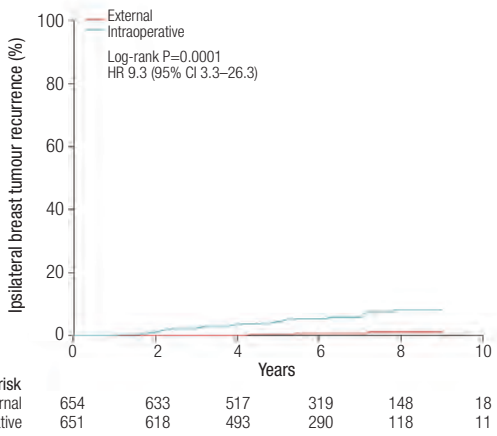


Fig. 5.15

CI, Confidence interval; HR, hazard ratio.

REVISION QUESTIONS

1. Should PBI be standard for any group of patients?
2. What is the rationale for PBI?
3. For partial breast irradiation, what are the pros and cons of intraoperative radiotherapy?

Radiotherapy for locally advanced breast cancer

In most cases, locally advanced disease is treated by neoadjuvant chemotherapy, mastectomy + chest wall irradiation (CWI) to a dose of 45–50 Gy.

In inflammatory BC (T4d): if the inflammatory changes resolve, proceed to mastectomy axillary clearance followed by CWI.

The risk of local recurrence is influenced by pretreatment clinical stage and extent of pathological residual disease after chemotherapy.

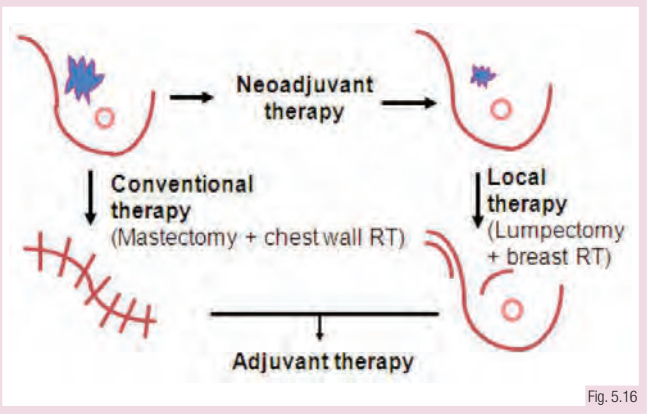


Fig. 5.16

RT, Radiotherapy.

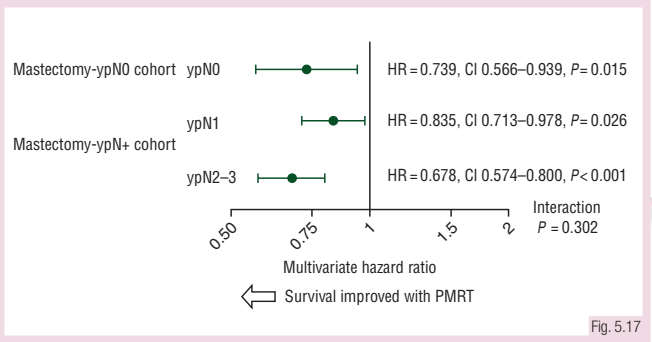


Fig. 5.17

CI, Confidence interval; HR, hazard ratio; PMRT, post-mastectomy radiotherapy.

No randomised data are available for women treated with neoadjuvant chemotherapy (NACT) before surgery to clarify the role of PMRT or the addition of RNI to breast RT in this setting.

In a large cohort study, a consistent OS advantage was observed in cN1 disease treated with PMRT, irrespective of the pathological lymph node response to NACT.

No significant differences in OS were observed after BCS with the addition of RNI to breast RT.

Hyperthermia in combination with radiation can provide useful palliation in patients who have received radical breast/chest wall irradiation as their primary treatment.

An analysis of four randomised controlled trials showed that the odds ratio for a complete response was increased by 2.3-fold (95% CI 1.4–3.8).

Hyperthermia is well tolerated, with superficial or subcutaneous burns and first- and second-degree burns in 5% of cases.

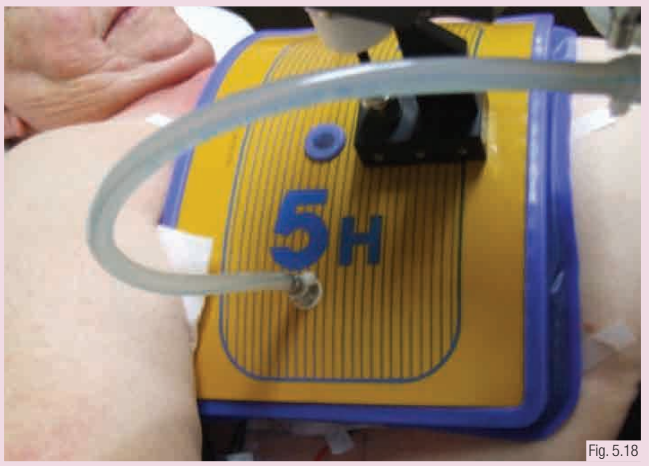


Fig. 5.18

REVISION QUESTIONS

1. If inflammatory changes persist after NACT in inflammatory BC (T4d), should RT precede or follow surgery?
2. Should the chest wall be irradiated after NACT and mastectomy?
3. What is the benefit of hyperthermia for palliation in locally advanced BC after previous radical RT?

Summary: Breast cancer radiotherapy

- Postoperative whole breast RT after wide local excision is standard treatment in invasive early BC
- PMRT is recommended for all cases with four or more positive axillary lymph nodes. Its role when one to three lymph nodes are positive is still open, with data from the EBCTCG suggesting a benefit even when systemic therapy is given
- PMRT reduces the risks of LRF, any recurrence and BC mortality, with the size of benefit depending on the presence of risk factors
- PMRT is advised in all T3 and T4 tumours clinically Stage III, irrespective of the response to NACT
- In patients with a positive sentinel node, RNI instead of axillary dissection results in equal locoregional recurrence rate and less lymphoedema, although the length of follow-up of the AMAROS study is still limited
- PBI may be considered as an option for eligible patients with BC, as an alternative to postoperative EBRT
- Traditional adjuvant irradiation total dose has been 45–50 Gy in 25–28 fractions of 1.8–2.0 Gy
- Hypofractionation, i.e. shorter fractionation schemes, e.g. 15–16 fractions with 2.5–2.67 Gy single dose, has shown similar effectiveness and comparable adverse effects as older schedules with higher number of RT fractions
- Re-irradiation with hyperthermia can provide useful palliation in patients who have received radical breast/chest wall irradiation as part of their primary treatment

Further Reading

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Adjuvant systemic therapies for breast cancer (including follow-up)

6

Risk stratification in early breast cancer

Decisions regarding adjuvant treatment are based on estimations of recurrence risk. Standard criteria include tumour size, nodal status, grade, oestrogen/progesterone receptor (ER/PgR) and human epidermal growth factor receptor 2 (HER2) status.

Assessing tumour biology, e.g. intrinsic subtype, rather than relying solely on standard criteria, can improve the estimation of responsiveness to systemic therapies.

The main intrinsic subtypes – luminal (Lum) A, Lum B, HER2-enriched, and triple-negative (TNBC) – have different prognoses and responses to treatment.

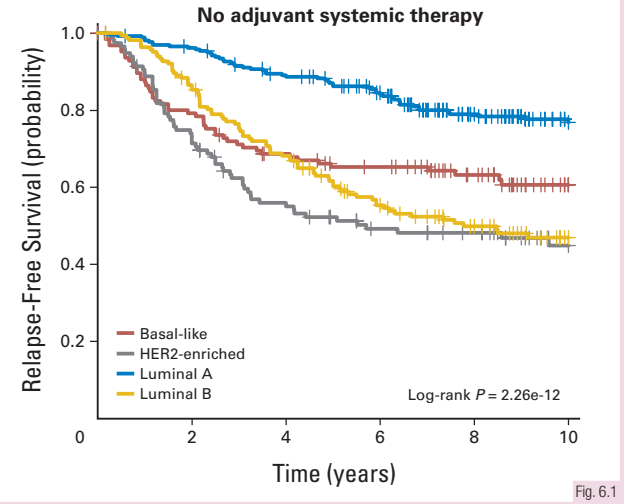


Fig. 6.1

HER2, Human epidermal growth factor receptor 2.

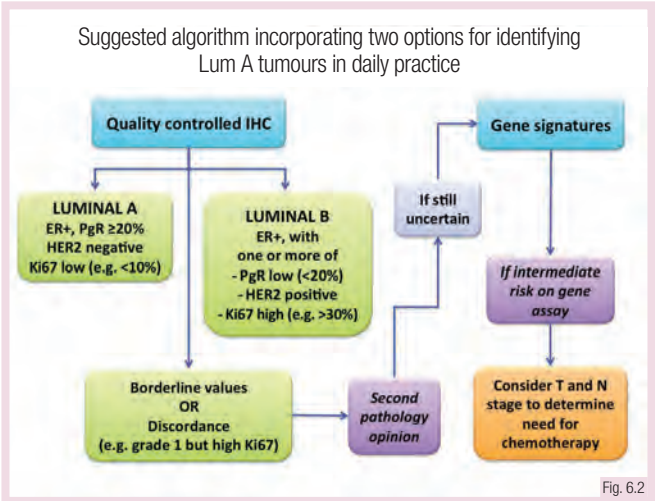


Fig. 6.2

ER, Oestrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PgR, progesterone receptor.

Breast cancer (BC) subtypes can be determined by genomic assays, or with immunohistochemical (IHC) surrogates, which incorporate ER, PgR, HER2 and Ki67.

IHC assessment of Ki67 is subjective, limiting its use in subtype definition. The St Gallen Consensus Guidelines recommend using the criteria of "clearly high" (>30%) and "clearly low" (<10%).

Correlation between IHC and gene assays for clearly low- or high-risk tumours is good. Intermediate or discordant risk on IHC may benefit from genomic tests.

Lum A or Lum A-like (i.e. low-risk on genomic assays) tumours may be less chemosensitive, but more likely to respond well to endocrine therapy (ET).

At present, there is a lack of strong evidence to guide the use of chemotherapy in Lum A disease. The adjacent algorithm may assist with treatment decisions.

Lum B BC has a poorer prognosis, is more aggressive and likely to be more chemosensitive. Chemotherapy is recommended in addition to ET.

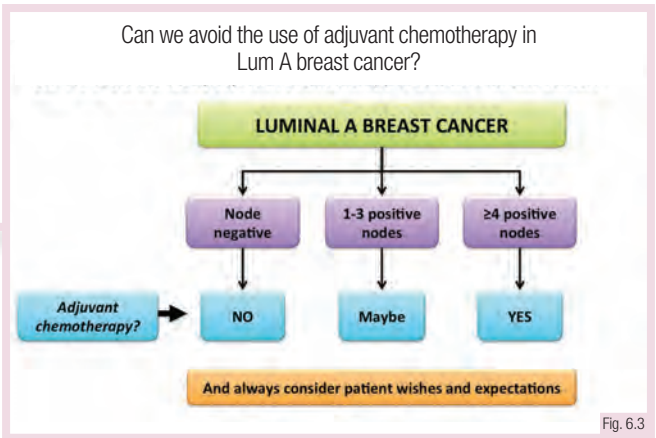


Fig. 6.3

REVISION QUESTIONS

1. What are the four main intrinsic BC subtypes currently used in clinical practice?
2. What is the most commonly used IHC surrogate definition of a Lum B tumour?
3. Which BC subtype is less likely to derive benefit from chemotherapy?

Endocrine therapy for luminal (ER+) breast cancers

The standard duration for ET is at least 5 years; shorter duration has been shown to result in inferior outcomes.

ET options in postmenopausal women include aromatase inhibitors (AIs) and tamoxifen (tam). AIs result in better disease-free survival (DFS) but no meaningful clinical benefit in overall survival (OS). The safety profile of AIs is different from tam.

AIs can be given upfront or after 2–3 years of tam. Tam is still a valid option for selected patients.

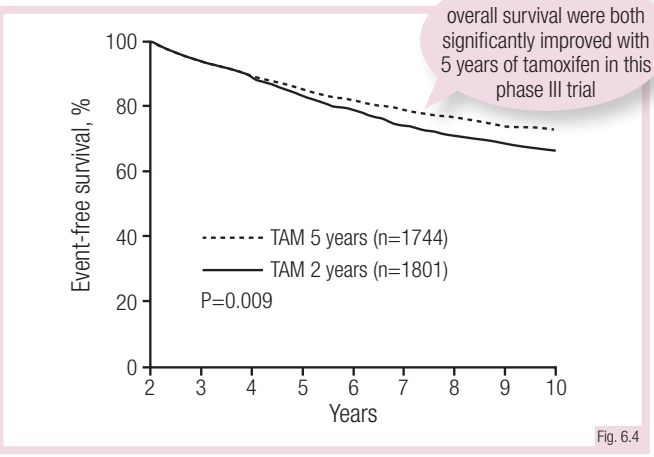


Fig. 6.4

TAM, Tamoxifen.

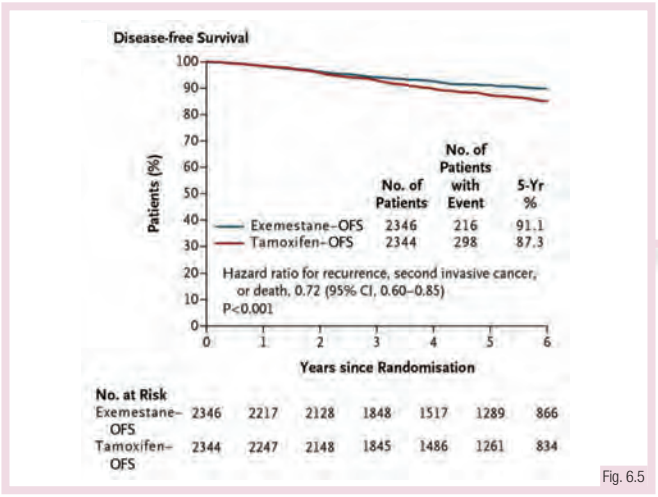


Fig. 6.5

CI, Confidence interval; OFS, ovarian function suppression.

Premenopausal women may be treated with tam alone, tam + ovarian function suppression (OFS), or an AI + OFS, according to level of clinicopathological risk and patient's preference.

The combination of an AI + OFS reduces recurrence compared with tam alone or tam + OFS. However, the addition of OFS to ET increases adverse effects, in particular menopausal and sexual symptoms.

AI + OFS should be considered in higher risk cases, where the absolute benefit over tam +/- OFS is greater. Tam alone is sufficient in low-risk premenopausal patients, where outcomes are good.

Adverse effects of tam include thromboembolism and, rarely, uterine cancer. AIs can cause osteoporosis and arthralgias. All ETs can cause or worsen menopausal symptoms. Monitoring the bone health of women on ET, especially those taking AIs or with OFS, is crucial.

While ET duration is usually 5 years, extending tam to 10 years may be of benefit, with improved outcomes seen in the ATLAS, aTTom, MA.17 and DATA trials, but probably not after initial AIs (IDEAL, NSABP-B42).

Due to the associated adverse effects, and limited *absolute* benefit in low-risk disease, it is more appropriate to reserve extended ET for high-risk disease.

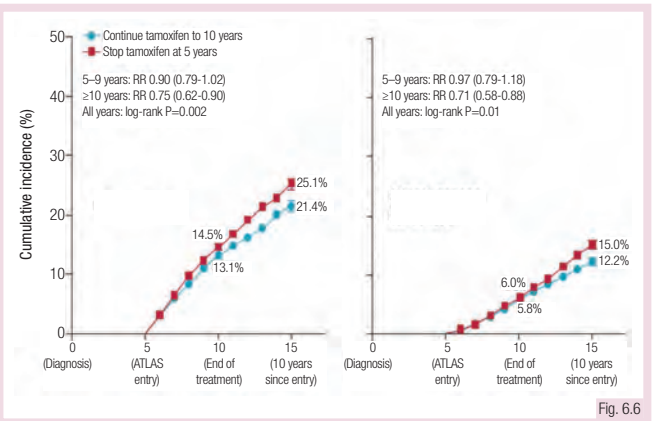


Fig. 6.6

RR, Recurrence rate.

REVISION QUESTIONS

1. Which ET agent(s) would be most appropriate in a premenopausal patient?
2. What are the important adverse effects of tamoxifen and of AIs?
3. What would be the recommended duration of ET for a high-risk ER+ BC?

HER2-positive breast cancer

About 20% of all BCs are HER2-positive (HER2+), and are characterised by aggressive behaviour and poor prognosis.

HER2 positivity is defined by protein overexpression (3+) on IHC, or IHC 2+ with *HER2* gene amplification on *in situ* hybridisation (ISH) testing. Heterogeneity of expression can occur.

Trastuzumab (Tras), a monoclonal antibody against HER2, binds to and prevents activation of the receptor, inhibiting downstream signalling for proliferation. Pertuzumab blocks dimerisation of HER2, and synergises with trastuzumab, improving pathological complete response rates in the neoadjuvant setting. Trials in the adjuvant setting are ongoing (Aphinity).

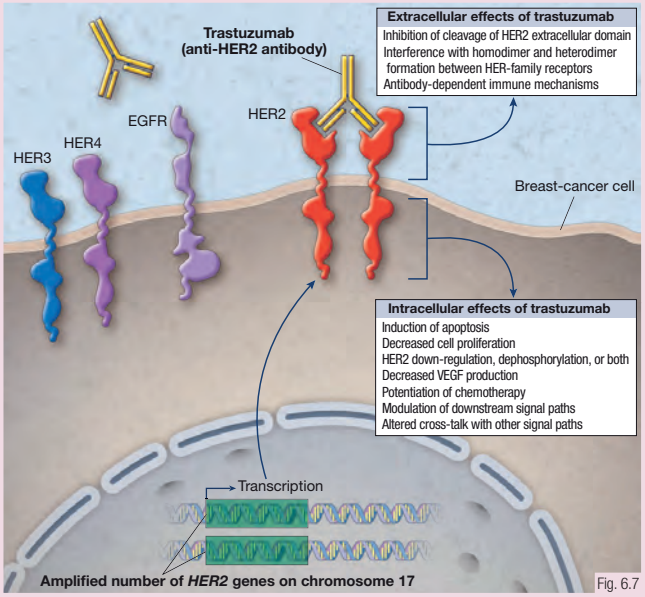


Fig. 6.7

EGFR, Epidermal growth factor receptor; *HER2*, human epidermal growth factor receptor 2; VEGF, vascular endothelial growth factor.

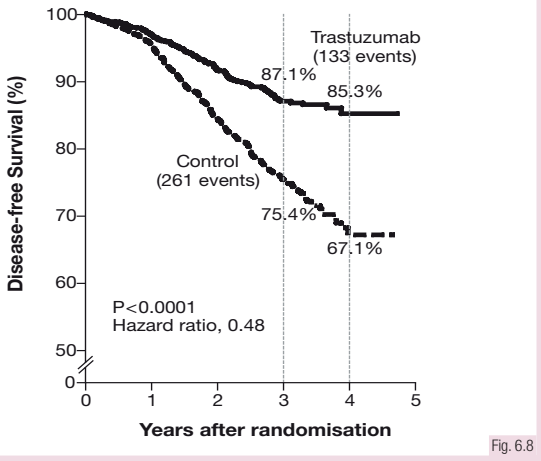


Fig. 6.8

The addition of Tras to adjuvant chemotherapy significantly improves both DFS and OS in HER2+ BC.

Standard accompanying chemotherapy regimens include sequential anthracycline–taxane, with Tras commenced with the taxane. Standard Tras duration is 12 months. Shorter regimens (e.g. FinHER) also showed benefit but 6 months was inferior to 12 months (PHARE trial), and 24 months was not superior to 12 months (HERA trial).

Non-anthracycline regimens include Tras with docetaxel plus carboplatin (TCH), or docetaxel + cyclophosphamide (TC x4). Weekly paclitaxel alone may be a sufficient accompanying regimen for T1a/b, N0 tumours.

Tras can cause decreased left ventricular ejection fraction (LVEF) and, rarely, cardiac failure. It should not be given concurrently with an anthracycline.

Cardiotoxicity is usually asymptomatic, and typically resolves with drug withdrawal. Rechallenge with Tras is feasible. Risk is lower with no prior anthracyclines.

Patients receiving trastuzumab should be monitored with 3-monthly echocardiography/heart scans. In the event of cardiotoxicity, cardiologist input is recommended.

Cardiotoxicity in adjuvant trastuzumab trials

Trial	Chemo regimen	Duration of trastuzumab	No. of patients	Asymptomatic decrease in LVEF	Symptomatic cardiotoxicity
HERA	Any (94% received A)	12 months 24 months	1694 1694	4% 7%	0.8% 1%
NSABP B31/N9831	AC->PH	12 months	1672	14%	4%
BCIRG 006	ACTH TCH	12 months 12 months	1074 1075	19% 9%	2% 0.4%
FinHER	TH or VH->FEC	9 weeks	232	7%	1%

Fig. 6.9

A, Doxorubicin; C, cyclophosphamide; P, paclitaxel; H, trastuzumab; T, docetaxel; V, vinorelbine; F, fluorouracil; E, epirubicin.

REVISION QUESTIONS

1. How is HER2 positivity defined?
2. Tras therapy should be commenced with which standard chemotherapy?
3. How common is symptomatic Tras-induced cardiotoxicity?

Triple-negative breast cancer and chemotherapy regimen by subtype

TNBC is defined by a lack of expression of ER, PgR and HER2. Typically, it is associated with early relapse and poor prognosis.

While most TNBCs are aggressive basal-like (BLBC) subtypes, some rare TNBC subtypes are associated with a good prognosis, e.g. medullary, adenoid cystic.

BRCA1-associated BC is frequently TNBC.
A woman with TNBC and age ≤60 years and/or positive family history may benefit from genetic testing.

Five-year relative survival of triple-negative breast cancers compared with other breast cancers by stage at diagnosis, California, 1999-2003

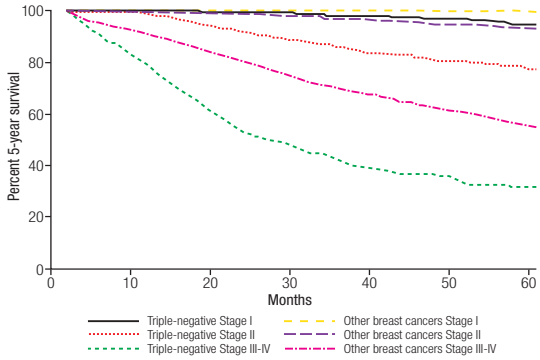


Fig. 6.10

Pathological complete response rate with platinum chemotherapy is sporadic compared with BRCA1 mutation-associated TNBC

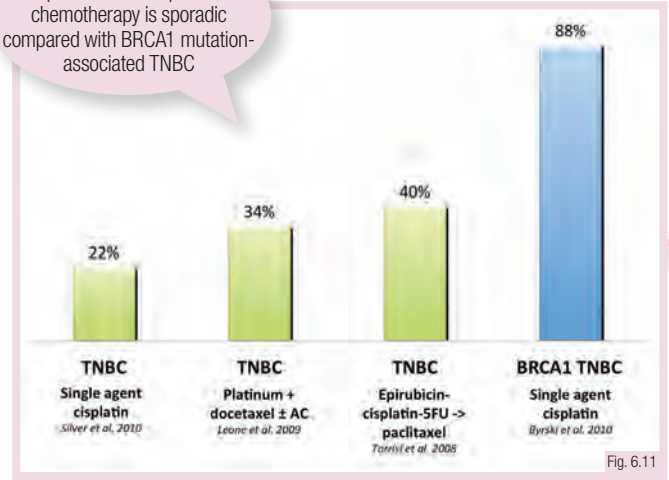


Fig. 6.11

5-FU, 5-Fluorouracil; AC, doxorubicin–cyclophosphamide; TNBC, triple-negative breast cancer.

There are no known effective targeted therapies in TNBC. Treatment is limited to chemotherapy, with lower threshold for sequential anthracycline–taxane.

Incorporation of platinum chemotherapy in TNBC is still under investigation. Some neoadjuvant data have shown particular sensitivity in BRCA-mutated BCs, although this may be simply reflective of overall chemosensitivity.

As results are conflicting, adjuvant platinum use should not be considered as a standard of care, even in BRCA-positive tumours.

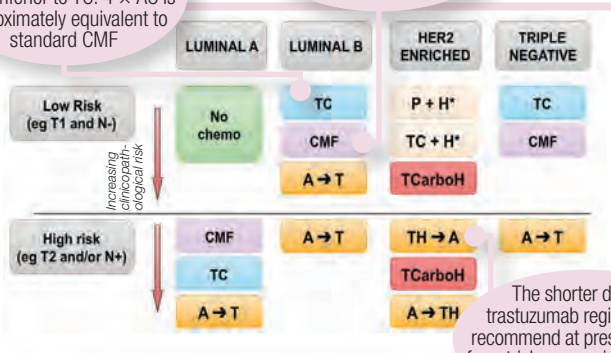
Following a decision to give chemotherapy, consideration should be given to which regimen to use. Data on the best regimen for each subtype is lacking and patient preference must be considered.

A sequential anthracycline → taxane regimen is recommended for patients with high-risk disease (e.g. node-positive Lum B, TNBC, HER2+ tumours).

Less intensive or non-anthracycline-based regimens may be considered in lower risk tumours (e.g. T1, node-negative); however, evidence for this approach is limited.

CMF is a generally outdated regimen, but is valid when an alternative side-effect profile is desired, such as lower risk of alopecia

AC may also be used, although it has been shown to be inferior to TC. 4 × AC is approximately equivalent to standard CMF



The shorter duration trastuzumab regimen is not recommend at present. Results from trials comparing it to longer course are pending

*These regimens have not proven effective in randomised controlled trials and are therefore considered non-standard at present.

AC, Doxorubicin/cyclophosphamide; CMF, cyclophosphamide/methotrexate/fluorouracil; TC, docetaxel/cyclophosphamide; A→T, sequential anthracycline/taxane; TCarboH, docetaxel/carboplatin/trastuzumab; TC+H, docetaxel/cyclophosphamide/trastuzumab; P+H, paclitaxel/trastuzumab; A→TH, sequential anthracycline/taxane+trastuzumab; TH→A, sequential docetaxel+trastuzumab/FEC (FinHER).

N.B. This regimen is one example of a hierarchy of options for adjuvant chemotherapy for increasing clinico-pathological risk. Individual treatment centres may choose not to adopt all regimens.

Fig. 6.12

REVISION QUESTIONS

1. What is the most common type of TNBC?
2. Which chemotherapy agents are generally recommended for treatment of TNBC?
3. What might be some alternative chemotherapy regimens in lower risk BCs?

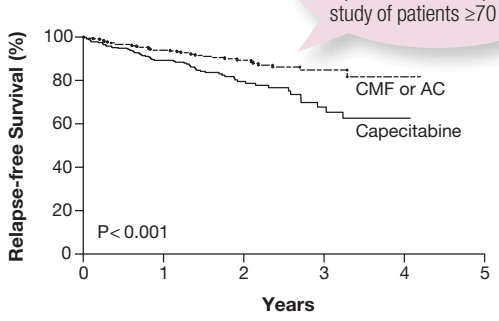
Special considerations and follow-up

Older fit patients (≥70 years) should be offered adjuvant polychemotherapy, as treatment with a single-agent regimen leads to inferior outcomes.

Careful monitoring of adverse effects is critical, as toxicities from chemotherapy increase with age, especially in patients with multiple comorbidities.

Determination of fitness is paramount and geriatric assessment is recommended. Chemotherapy decisions in the elderly require careful balancing of risk and benefit.

Lower relapse rate and improved overall survival were seen with AC or CMF vs capecitabine in this phase III study of patients ≥70 years



No. at Risk

CMF or AC	326	254	124	46	2	0
Capecitabine	307	237	96	29	1	0

Fig. 6.13

AC, Doxorubicin/cyclophosphamide; CMF, cyclophosphamide/methotrexate/fluorouracil.

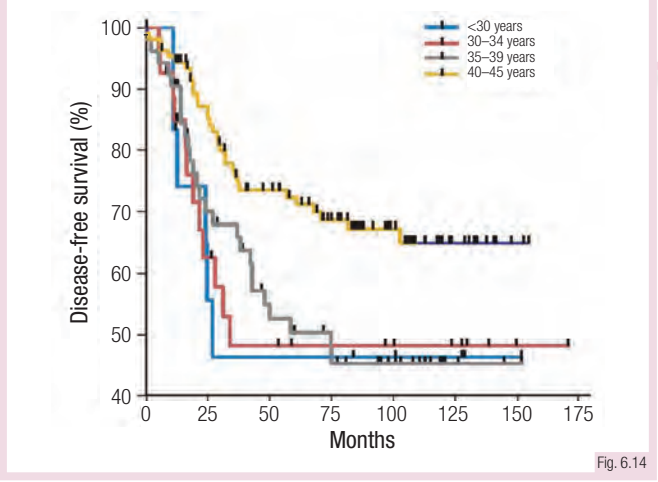


Fig. 6.14

Young age (<35 years) is an independent poor prognostic factor. Referral for genetic testing should be considered, as BRCA-associated BC is more common in young patients.

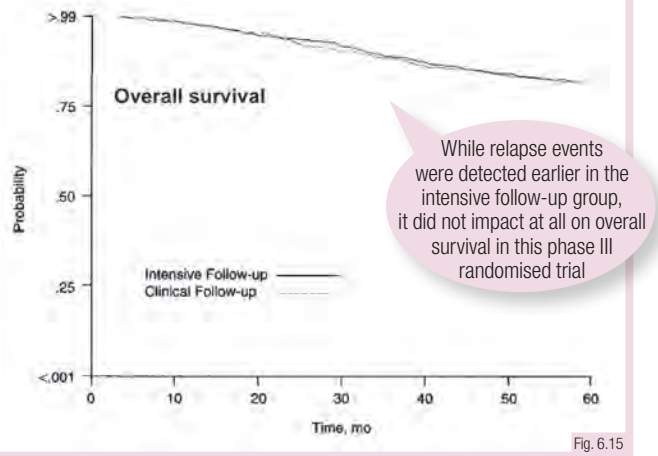
Young patients with ER-low or -negative disease are often treated with anthracycline + taxane. However, strongly ER+ disease can respond very well to ET alone.

Administration of luteinising hormone-releasing hormone (LHRH) agonist during chemotherapy may protect ovarian function. Early referral to a fertility specialist is strongly recommended.

Optimal follow-up for early BC is not established, and may be more relevant for those with a higher risk of relapse. It should be tailored according to individual risk and patient preference.

Regular follow-up may have benefit regardless of the lack of demonstrated survival benefit. This includes ensuring ET compliance, monitoring for adverse events and survivorship issues. Annual or biannual mammography/ultrasonography is relevant for early detection of local relapse.

Intensive follow-up with surveillance computed tomography scans is not recommended, as it does not improve outcomes. Scans should be performed only if there is clinical suspicion of relapse.



While relapse events were detected earlier in the intensive follow-up group, it did not impact at all on overall survival in this phase III randomised trial

Fig. 6.15

REVISION QUESTIONS

1. What is the major determinant of the tolerability of chemotherapy in elderly BC patients?
2. Which young BC patients should be referred to a fertility specialist?
3. How should follow-up be performed?

Summary: Adjuvant systemic therapies for breast cancer (including follow-up)

- Adjuvant therapy decisions are made based on a risk assessment of likelihood of relapse
- In addition to standard clinicopathological criteria, assessment of tumour biology is crucial
- Low-risk Lum A tumours can often be treated with ET alone
- Lum B tumours generally warrant both chemotherapy and ET
- ET should be given for 5 years, and extended to 10 years in high-risk ER+ disease
- HER2+ disease should be treated with adjuvant chemotherapy plus anti-HER2 therapy (trastuzumab). Pertuzumab may be used in the neoadjuvant setting and is being evaluated in the adjuvant setting
- 3-monthly monitoring for cardiotoxicity during trastuzumab therapy is essential
- TNBCs are heterogeneous and generally, but not always, have a poorer prognosis than the other subtypes
- A sequential anthracycline–taxane regimen is usually recommended for high-risk TNBC
- Follow-up after early BC should be individually tailored according to the calculated risk of relapse, keeping in mind that no follow-up programme has been shown to be superior to another. It should include annual or biannual mammography/ultrasound, gynaecological visit and blood tests (especially if on ET)

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Neoadjuvant chemotherapy and management of locally advanced disease

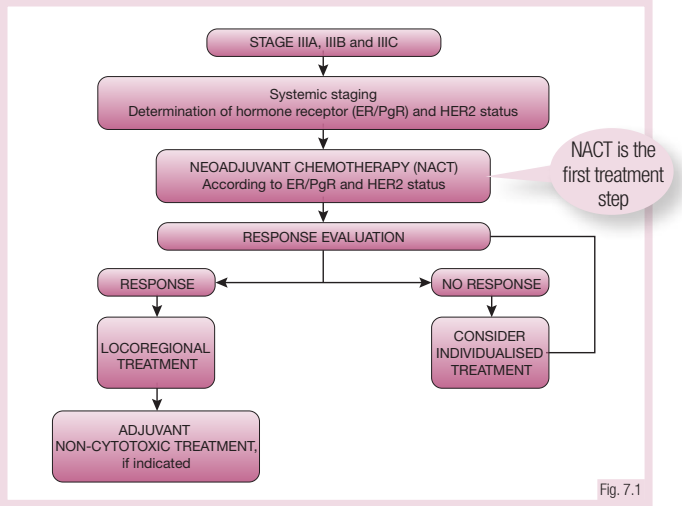
7

Introduction: neoadjuvant and adjuvant therapy

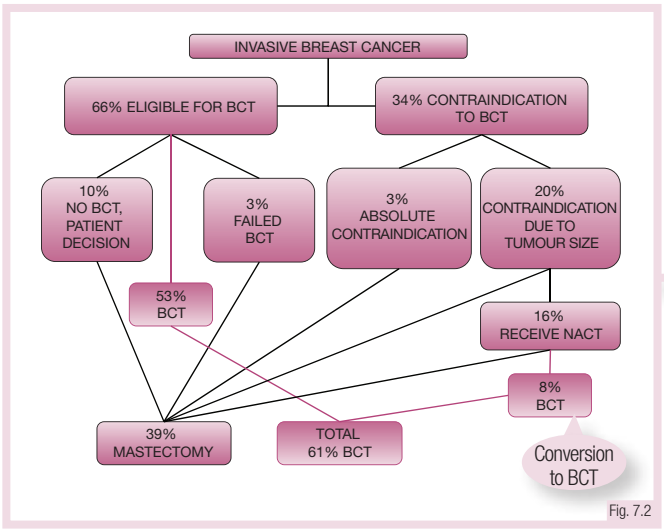
Neoadjuvant chemotherapy (NACT), also called primary systemic therapy, is a treatment option given after diagnosis but before surgery for non-metastatic breast cancer (BC).

Since the 1970s, NACT has been shown to induce tumour response and to facilitate local control before subsequent surgery and radiation.

Traditionally, NACT is considered the first step in the multimodal treatment for locally advanced BC.



ER, Oestrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor.



BCT, Breast-conserving therapy; NACT, neoadjuvant chemotherapy.

Advantages of NACT are:

1. *In vivo* chemosensitivity test: NACT allows for monitoring of response and changing/discontinuing treatment in case of non-responsiveness.

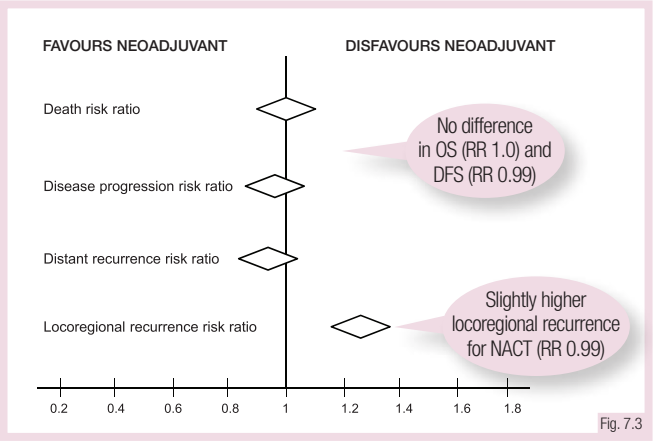
2. Conversion to breast-conserving therapy (BCT) or better planning of surgery, e.g. by having more time for genetic testing, with the option of bilateral mastectomy.

3. Information on prognosis: no residual cancer either in breast or lymph nodes after NACT correlates with a good prognosis.

A meta-analysis showed that NACT is as effective as adjuvant therapy for long-term outcome, even if the locoregional recurrence rate was slightly higher.

NACT is no longer only an option for locally advanced BC patients, but also for any patient who is a candidate for systemic adjuvant therapy.

The same regimens should be used for NACT as for adjuvant therapy. All chemotherapy (ChT) should be provided before surgery, not split into pre- and postoperative.



DFS, Disease-free survival; NACT, neoadjuvant chemotherapy; OS, overall survival; RR, recurrence rate.

REVISION QUESTIONS

1. What does neoadjuvant chemotherapy (NACT) mean?
2. For which BC patients is NACT indicated?
3. What are the main advantages of NACT?

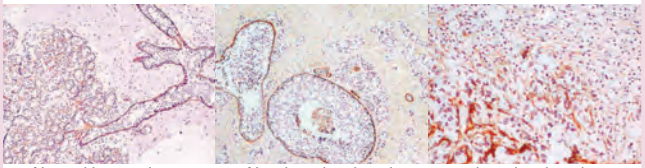
Pathological complete response and long-term outcome

The residual disease is classified using tumour node metastasis (TNM) information, and identified as pathological assessment after NACT with the "yp" prefix.

The absence of any residual cancer cells in the breast and lymph nodes after neoadjuvant therapy is called a pathological complete response (pCR).

pCR is defined as no residual invasive/non-invasive cancer in the breast and nodes (ypT0 ypN0) or no residual invasive cancer in the breast and nodes (ypT0/is ypN0).

Difference between invasive and non-invasive breast cancer



Normal breast tissue | Non-invasive ductal breast cancer | Invasive ductal breast cancer

Fig. 7.4

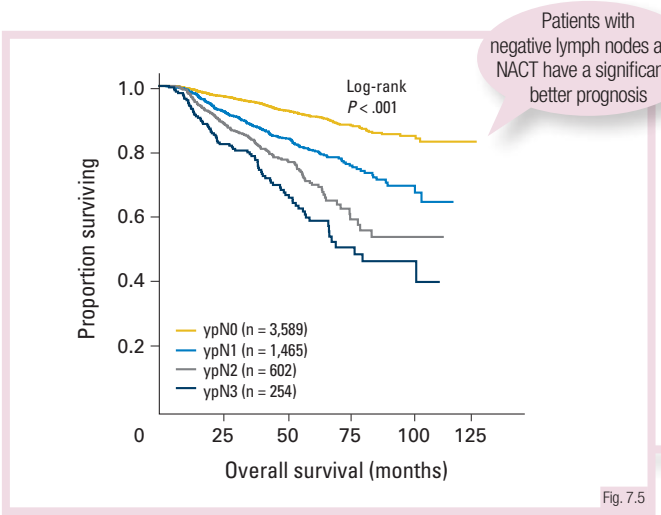


Fig. 7.5

NACT, Neoadjuvant chemotherapy.

In many neoadjuvant trials, patients achieving pCR showed a better long-term outcome, indicating pCR is a powerful prognostic factor, although discussion on the predictive value exists, particularly in hormone receptor-positive disease.

The influence of residual non-invasive disease (ypTis) on prognosis is still unclear, since two large analyses have shown discordant results.

Patients with residual invasive tumour in lymph nodes (ypN+) experienced the worst prognosis in terms of disease-free survival (DFS) and overall survival (OS).

NACT is not recommended when there is uncertainty regarding the appropriateness of ChT. Meticulous patient selection is mandatory.

Patients with triple-negative (TNBC), HER2-positive, or ER/PgR-positive /HER2-negative high-grade (G3) breast tumours, also depending on size, nodal status and age/comorbidity, have the highest probability of benefiting from ChT.

In essence, first select patients who might be candidates for ChT and, second, discuss within the tumour board and with the patient the most optimal timing: either neoadjuvant or adjuvant.

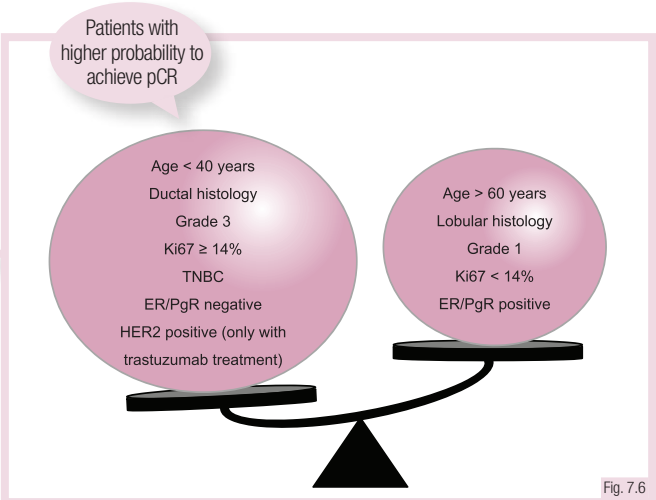


Fig. 7.6

ER, Oestrogen receptor; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; PgR, progesterone receptor; TNBC, triple-negative breast cancer.

REVISION QUESTIONS

1. What does "pCR" mean and how is it defined?
2. Which patients have the worst prognosis after NACT?
3. Which patients are the optimal candidates to receive NACT?

Chemotherapy and targeted therapy

In the early neoadjuvant trials that used an anthracycline-containing ChT, the reported pCR rate was low (4%–29%).

The addition of taxanes led to significantly higher rates of BCT and pCR, especially with taxanes administered sequentially to anthracyclines and cyclophosphamide.

No differences in pCR rate and long-term outcome were observed with the addition of 5-fluorouracil, capecitabine, vinorelbine or gemcitabine.

	Taxane regimen	Relative risk	P-value
pCR	Concomitant	1.04	0.77
	Sequential	1.73	0.013
	Overall	1.22	0.11
BCT	Concomitant	1.27	0.027
	Sequential	1.08	0.095
	Overall	1.11	0.012
DFS	Concomitant	0.85	0.25
	Sequential	0.92	0.24
	Overall	0.91	0.12

BCT, Breast-conserving therapy; DFS, disease-free survival; pCR, pathological complete response.

Fig. 7.7

No difference in DFS for sequential or concomitant administration of taxanes

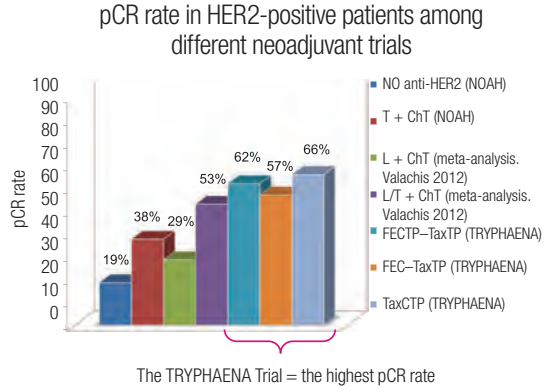


Fig. 7.8

ChT, Chemotherapy; FEC-Tax, 5-flourouracil/epirubicin/cyclophosphamide plus taxotere; HER2, human epidermal growth factor receptor 2; L, lapatinib; P, pertuzumab; pCR, pathological complete response; T, trastuzumab; Tax, taxane.

In the NOAH trial, the addition of trastuzumab (T) to ChT in patients with HER2-positive tumours increased the pCR rate and long-term outcome in comparison with ChT alone.

Lower pCR rates were reported for lapatinib (L) in combination with ChT when compared to trastuzumab plus ChT or T/L plus ChT.

The Tryphaena study showed a pCR rate >60% with T and pertuzumab (P) plus an anthracycline–taxane (FEC-Tax) or a carboplatin–taxane (TaxC) ChT.

Two neoadjuvant trials (GeparQuinto and NSABP B-40) showed a significantly higher pCR rate with the addition of bevacizumab to NACT in HER2-negative BC.

Subgroup analyses showed some benefit from bevacizumab, but this benefit could not be confirmed in adjuvant trials.

The identification of predictive markers to select patients with maximal benefit from new targeted agents is needed urgently.

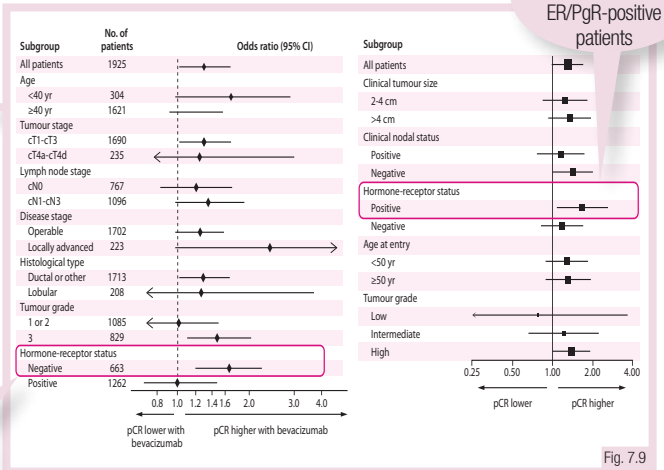


Fig. 7.9

NSABP B40 trial: Greater benefit for ER/PgR-positive patients

GEPARQUINTO trial: Greater benefit for TNBC patients

ER, Oestrogen receptor; pCR, pathological complete response; PgR, progesterone receptor; TNBC, triple-negative breast cancer.

REVISION QUESTIONS

1. What is the optimal ChT combination in the neoadjuvant setting?
2. Which combination achieved the highest pCR rate in HER2-positive patients?
3. What is the role of bevacizumab in the neoadjuvant setting?

Future directions

Assessing tumour response is crucial for patient management. It is achieved by clinical examination and sonographic/radiological measurements.

Breast magnetic resonance imaging (MRI), as well as ultrasound, have been shown to be useful in differentiating early responders from non-responder patients during neoadjuvant therapy.

However, despite improvements in imaging techniques, an accurate prediction of pathological tumour size during neoadjuvant treatment is not yet possible.

A breast magnetic resonance image of a tumour prior to and after neoadjuvant chemotherapy in a patient with partial response

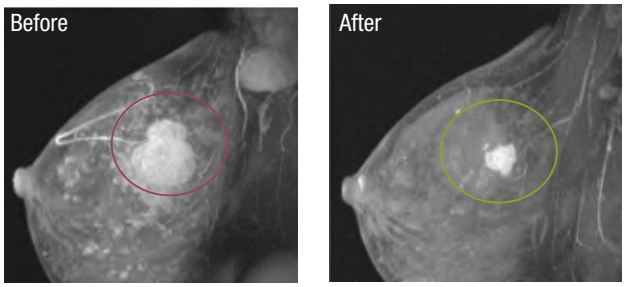


Fig. 7.10

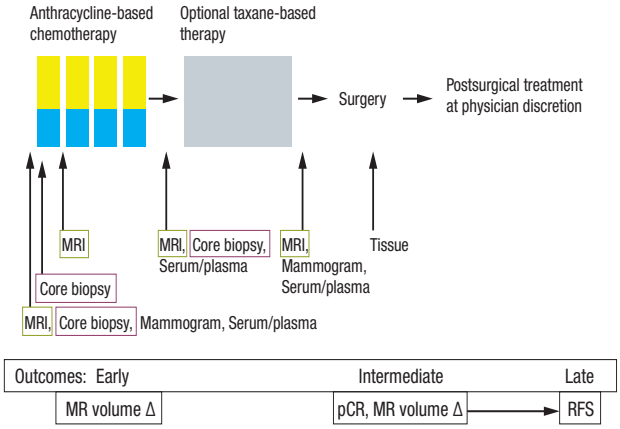


Fig. 7.11

MR, Magnetic resonance; MRI, magnetic resonance imaging; pCR, pathological complete response; RFS, relapse-free survival.

Sequential biopsies could be an option for detecting NACT-induced molecular changes and identifying treatment-response biomarkers in breast tissue.

In the "window-of-opportunity" trial design, a short course of targeted therapy is given prior to ChT or surgical resection, in order to identify early biological changes.

Moreover, a window trial can be used to establish the biologically effective dose of a targeted drug or to identify tumour mechanisms of treatment resistance.

Currently, after NACT and surgery, patients should complete trastuzumab and endocrine treatment, but should not receive further ChT.

In post-neoadjuvant trials, patients with residual invasive BC after NACT are randomised to receive standard adjuvant treatment or a new therapy.

Post-neoadjuvant trials have other advantages: (1) include selected high-risk patients (2) may have smaller sample size due to the high event rate.

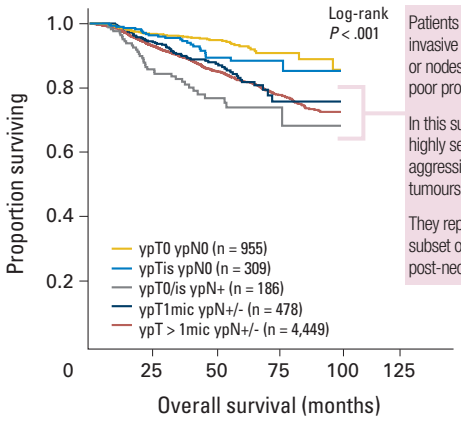


Fig. 7.12

NACT, Neoadjuvant chemotherapy.

REVISION QUESTIONS

1. Is there a validated method to determine early response during NACT?
2. What does "window-of-opportunity" mean?
3. What are the aims of a post-neoadjuvant trial?

Summary: Neoadjuvant chemotherapy and management of locally advanced disease

- NACT is given before surgery and it is the first treatment step in locally advanced disease
- Advantages of NACT: *in vivo* sensitivity test, conversion to BCT, information on prognosis
- Breast MRI and ultrasound are useful in differentiating early responders from non-responders during NACT
- Patients with ypN+ after NACT experience the worst prognosis
- Patients with highly proliferating tumours are more likely to attain pCR with NACT
- Prognostic impact of pCR is higher in patients with TNBC and HER2-positive BC
- In patients with ER/PgR-positive disease, pCR has not been convincingly shown to be of predictive value
- An anthracycline/cyclophosphamide/taxane regimen is the standard of care, also for TNBC; the addition of platinum seems to increase pCR in patients with TNBC, but has not shown DFS/OS benefit when cyclophosphamide was part of the control regimen. Assessing tumour response during NACT is crucial for patient-tailored treatment
- Sequential biopsies could help to identify biomarkers of treatment resistance/response in breast tissue

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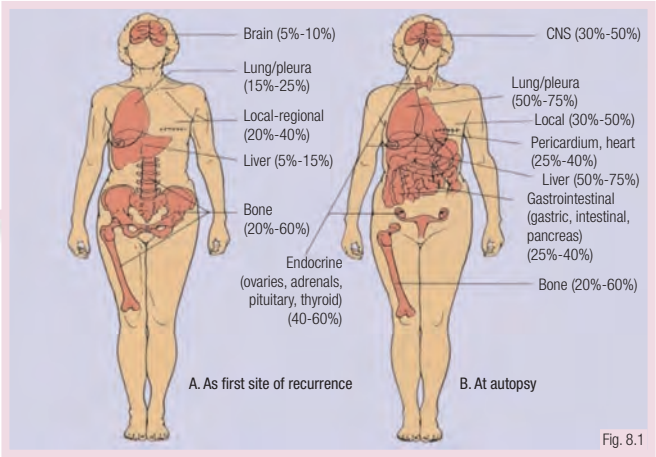
8 Management of metastatic disease (including response assessment)

General considerations

Approximately 20%–30% of early breast cancer patients will develop metastatic breast cancer (MBC). Median survival after MBC diagnosis is approximately 2 to 5 years, depending on the phenotype.

Breast cancer (BC) metastasises preferentially to the bones, liver, lung, brain and distant lymph nodes. Patients frequently develop metastases at multiple sites.

In most patients, MBC is incurable. Thus, the goal of therapy is life prolongation and improvement or preservation of quality of life (QoL), at the cost of minimal toxicity.



CNS, Central nervous system.

Initial assessment includes: history and physical examination, laboratory tests and chest, abdomen and bone imaging. Brain imaging is not necessary if asymptomatic.

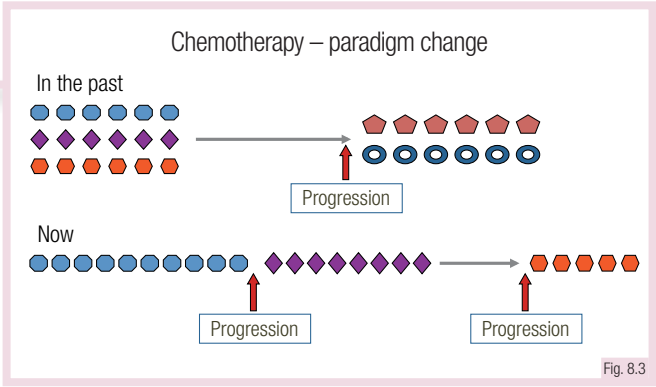
If feasible and potentially impacting treatment choice, biopsy of the metastatic lesion is recommended to confirm distant spread and reassess biomarkers (oestrogen receptor [ER]/progesterone receptor [PgR], human epidermal growth factor receptor 2 [HER2]).

Treatment choice depends on tumour subtype, disease burden and kinetics, previous therapies, need for local treatments, patient-related factors and preferences.

For most of the remaining lifetime, patients undergo active treatments and are exposed to their toxicities. Least toxic treatments (endocrine therapy [ET], single-agent chemotherapy [ChT]) are preferred.

Patients should be invited to participate in treatment decision-making, and offered appropriate psychosocial, supportive and symptom-related care.

Treatment response should be assessed regularly (ChT: every 2–4 cycles, ET: every 2–3 months), preferentially using the same imaging modality. Tumour markers can be used if elevated, but should not alone trigger treatment change.



REVISION QUESTIONS

1. What is the main goal of therapy in MBC patients?
2. What are the most important factors to consider in treatment choice?
3. How should treatment response be assessed?

Luminal HER2-negative breast cancer

Luminal HER2-negative BC, the most common MBC phenotype, is associated with better prognosis. ET is the treatment of choice for most patients.

ET users report better QoL, greater satisfaction with treatment, less treatment-related adverse effects and less activity impairment than patients receiving ChT.

ET options include selective oestrogen receptor modulators (SERM), selective ER degraders (SERD) and aromatase inhibitors (AI), combined with oophorectomy or medical castration by luteinising hormone-releasing hormone (LHRH) analogues in premenopausal patients.

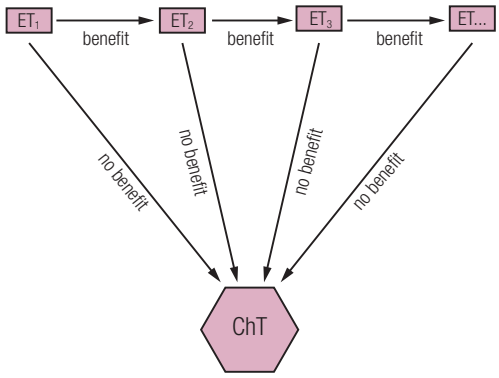


Fig. 8.4

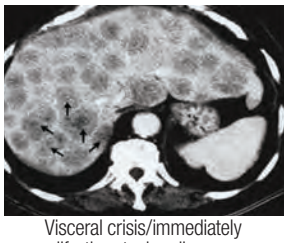
ChT, Chemotherapy; ET, endocrine therapy.

Following effective first-line ET, the next ET should be used at progression. ChT indications include endocrine resistance and need for rapid disease control.

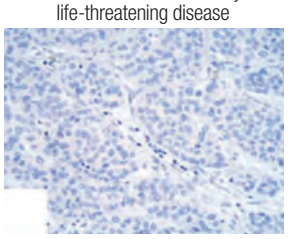
The optimal ET sequence is unknown and depends on menopausal status, prior ET, response duration, drug toxicity profile and availability and patient preferences.

Concomitant ET–ChT does not improve outcome. If ChT is indicated, after achieving disease control, ET can be used as maintenance in ER/PgR-positive disease.

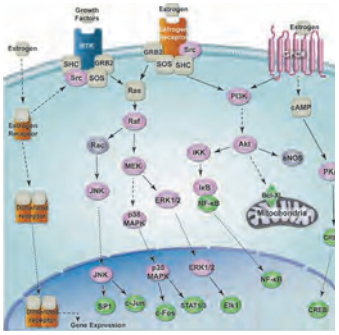
ET contraindications



Visceral crisis/immediately life-threatening disease



ER negativity



ET resistance

Fig. 8.5

ER, Oestrogen receptor; ET, endocrine therapy.

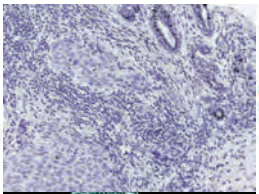
Endocrine resistance can be caused by ER loss, ER gene *(ESR1)* alterations or upregulation of alternative pathways (HER2, PI3K/Akt/mTOR).

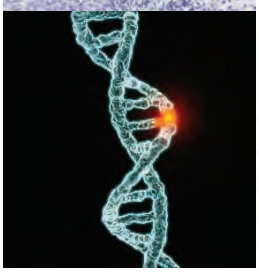
ET resistance may be overcome by therapies targeting dysregulated mechanisms: growth factor receptors, PI3K/Akt/mTOR pathway and cell cycle regulation.

Approved progression-free survival (PFS)-prolonging therapies include the mTOR inhibitor everolimus and the CDK 4/6 inhibitors palbociclib and ribociclib. None of them have demonstrated overall survival (OS) prolongation.

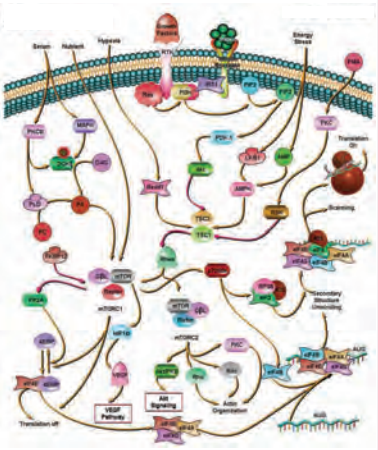
Mechanisms of endocrine resistance

ER loss





ER mutation



Alternative pathway upregulation

Fig. 8.6

ER, Oestrogen receptor.

REVISION QUESTIONS

1. What are the benefits of ET in luminal, HER2-negative MBC?
2. What is the preferred first-line ET option in premenopausal patients ?
3. What are the most frequent mechanisms of endocrine resistance ?

HER2-positive metastatic breast cancer

HER2-directed agents have altered the natural course of HER2-positive BC, and thus are essential components of first and subsequent lines of treatment.

Currently four HER2-directed agents with different activities and mechanisms of action are approved: trastuzumab, lapatinib, pertuzumab and T-DM1.

HER2 blockade is usually combined with ChT or ET. At progression, continued suppression of the HER-2 pathway with the same or an alternative agent is recommended.

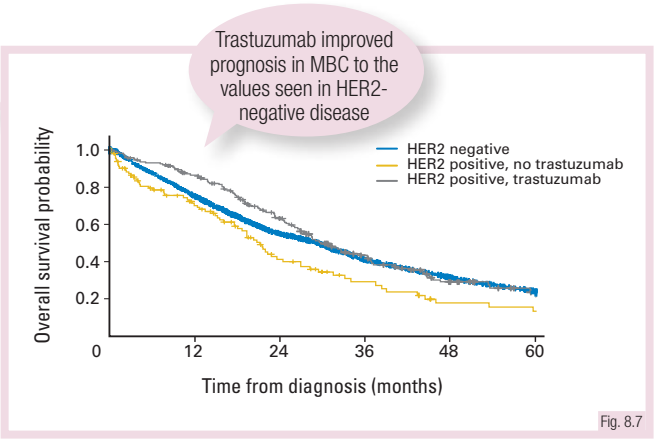


Fig. 8.7

HER2, Human epidermal growth factor receptor 2; MBC, metastatic breast cancer.

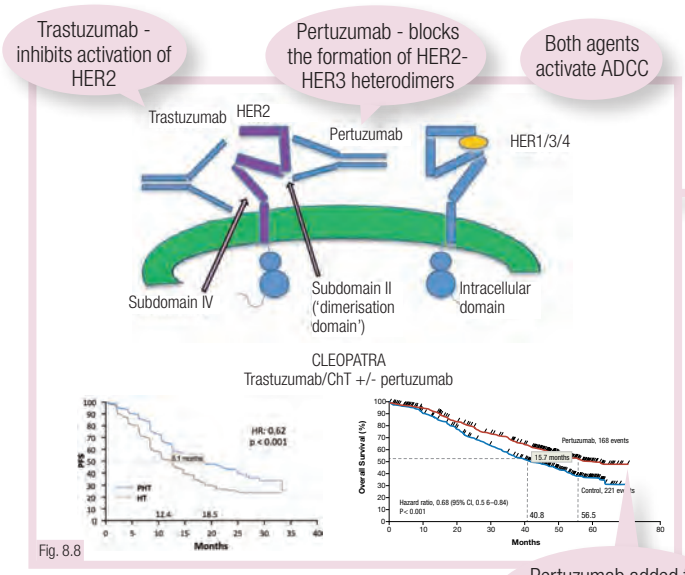


Fig. 8.8

ADCC, Antibody-dependent cell-mediated cytotoxicity; ChT, chemotherapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival.

Pertuzumab added to trastuzumab–ChT provides significant OS benefit and is recommended in the first-line setting, especially for patients not previously treated with trastuzumab. Pertuzumab should not be used beyond progression.

T-DM1 improves OS in second-line and beyond and has a favourable toxicity profile; it is the preferred option. ChT plus lapatinib or trastuzumab is another option.

After achieving disease control with ChT combined with an anti-HER2 agent, maintenance anti-HER2 therapy should be continued until progression.

BC coexpressing hormone receptors and HER2 is a distinct subtype with better prognosis. Limited sensitivity to ET is attributed to ER–HER2 crosstalk.

In luminal HER2-positive BC, anti-HER2 agents can be combined with ET. This approach is less toxic and offers significant PFS, but no OS benefit.

Anti-HER2 agents may cause cardiac toxicity. Pretreatment cardiac assessment and monitoring is mandatory. Cardiotoxicity is usually reversible.

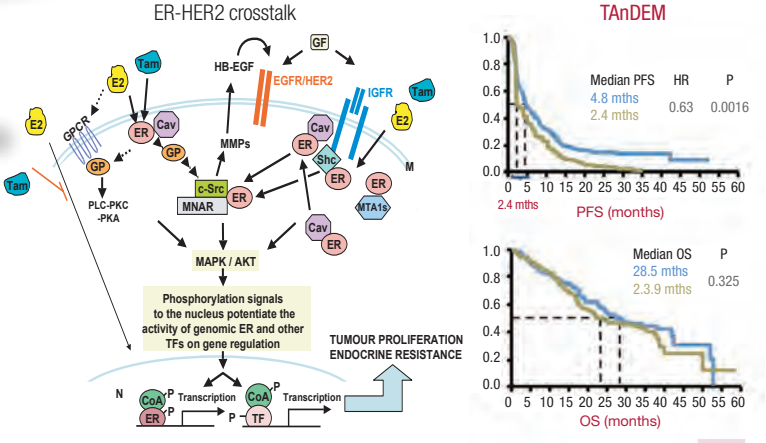


Fig. 8.9

ER, Oestrogen receptor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

REVISION QUESTIONS

1. Which agents can be combined with HER2 blockade?
2. What are second-line treatment options in HER2-positive BC?
3. What is the most important toxicity of anti-HER2 therapy?

Triple-negative breast cancer

Compared with the other BC subtypes, triple-negative breast cancer (TNBC) is associated with shorter time to relapse, higher likelihood of visceral metastases and inferior survival.

TNBC is highly heterogeneous. Mechanisms driving malignant progression of particular subtypes are poorly understood and no targeted therapies are available.

Systemic therapy options are limited to ChT. Most TNBC are highly chemosensitive. No data support specific ChT choices different from those for other BC subtypes.

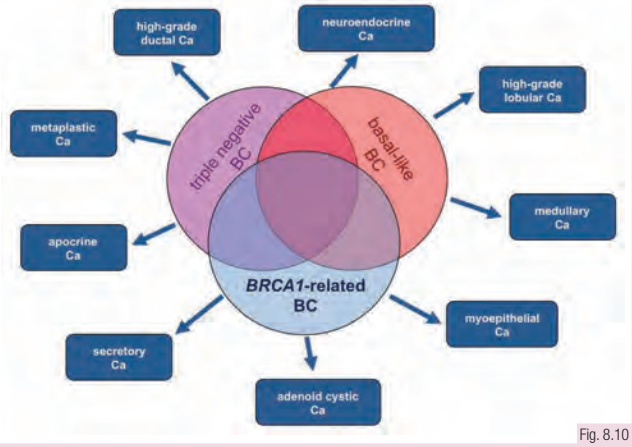


Fig. 8.10

BC, Breast cancer; Ca, carcinoma.

Duration of ChT – overall survival

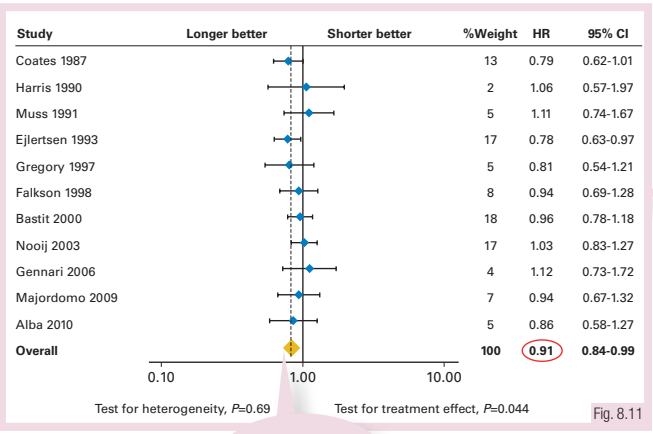


Fig. 8.11

ChT, Chemotherapy.

Improved overall survival with longer chemotherapy

Sequential single-agent monotherapy is preferred. Combination ChT provides a higher response rate and should be given for rapid, symptomatic progression.

Prolonged ChT is associated with extended PFS but has little effect on OS and may compromise QoL. Maintenance single-agent ChT is a reasonable option.

The same ChT rules are also used in other BC patients. The ChT regimen should be adjusted according to toxicities, response achieved and patient preferences.

Platinums cause DNA crosslinks and double-strand breaks, and thus should be particularly effective in homologous-repair-deficient, eg. BRCA-mutant, tumours.

The benefit from carboplatin versus docetaxel in MBC is limited to BRCA mutation carriers. In unselected TNBC, carboplatin may be a less toxic alternative to docetaxel.

Bevacizumab added to ChT has no special properties in TNBC. It only slightly improves PFS, but not OS, causes substantial toxicity, and should not be routinely used.

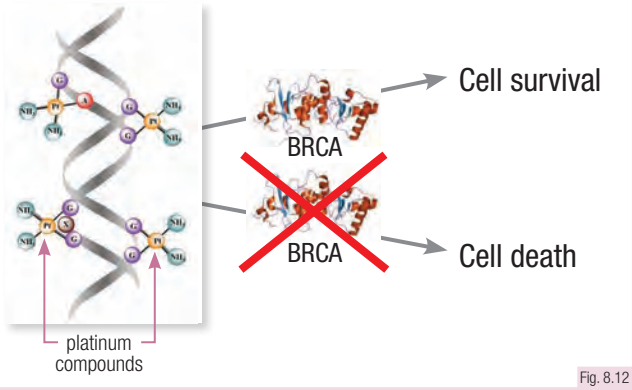


Fig. 8.12

REVISION QUESTIONS

1. What are the clinical features of TNBC?
2. Is combination ChT superior to single-agent ChT in treating TNBC?
3. Should TNBC be treated with a specific drug or regimen?

Local treatment

Local treatments provide palliation, prevent complications and, in selected patients with limited metastatic disease, may prolong survival.

The role of primary tumour resection in MBC is not clear. It improves local control without proven impact on OS, and may be considered in selected patients.

No randomised data support the use of "curative" local therapy for metastatic disease, and encouraging observational studies carry strong selection bias.

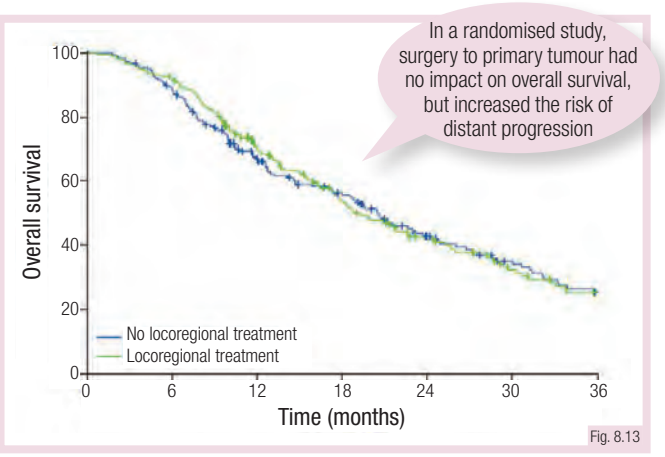


Fig. 8.13

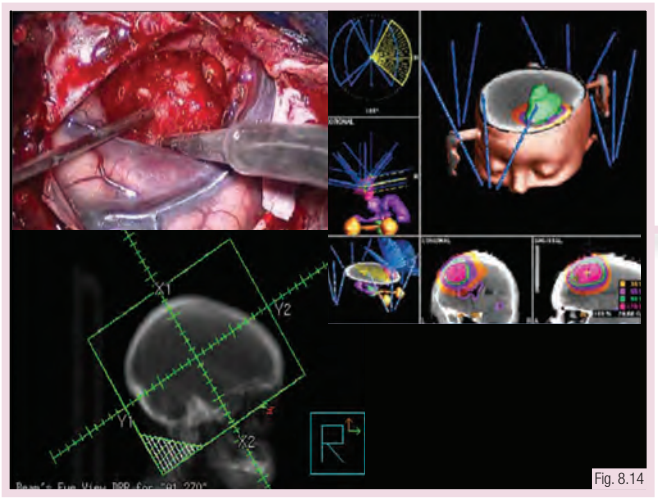


Fig. 8.14

Some BC patients with brain metastases (particularly HER2+) may achieve relatively long survival; less toxic local therapies should be used to avoid late toxicity.

In patients with limited brain metastases, surgery and/or stereotactic radiotherapy (RT) are preferred. If not feasible, whole-brain RT is used. Systemic treatment should not be changed.

Bone metastases cause morbidity and QoL decline. Their treatment includes local therapies (surgery, RT), bone-modifying agents and sometimes radioisotopes.

Single-fraction palliative RT for bone lesions is as effective as multifraction regimens. Radioisotopes are an option, but cause bone marrow toxicity.

Bone-modifying agents delay onset of pain and skeletal-related events, and should be started at the time of diagnosis of bone metastases, unless contraindicated.

Malignant pleural effusion in symptomatic patients can be managed with thoracocentesis and drainage, intrapleural catheter or intrapleural talc or drugs.

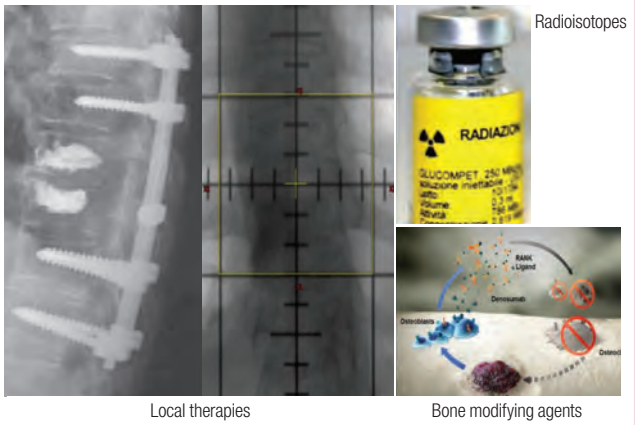


Fig. 8.15

REVISION QUESTIONS

1. Is surgical resection of primary breast tumour in unselected MBC always recommended?
2. What is the preferred local treatment for a single or limited number of brain metastases?
3. What constitutes optimal treatment of bone metastases?

Summary: Management of metastatic disease (including response assessment)

- MBC is an incurable, but treatable condition with 2–5 years median survival depending on subtype
- The main goals of therapy are improvement or preservation of QoL and life prolongation
- Primary tumour resection in MBC may be indicated for local control and QoL reasons
- ET is preferred in most patients with luminal HER2-negative BC
- ET is contraindicated in endocrine resistance and visceral crisis (not visceral metastases)
- Endocrine resistance may be overcome by therapies targeting dysregulated mechanisms
- Sequential anti-HER2 therapy should be used in HER2-positive MBC, unless contraindicated
- ChT is a mainstay in triple-negative BC. Sequential single-agent ChT is preferred
- Efficacy and toxicity of treatment should be monitored regularly
- Local treatments and supportive care are essential in MBC management
- MBC patients should have access to specialised and multidisciplinary care

Further Reading

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B

More advanced knowledge

9 Epidemiology of breast cancer

Distribution and trends

Breast cancer (BC) is the leading cancer in women worldwide. The International Agency for Research on Cancer estimates an incidence of 1.4 million cases per year, 450 000 in European women.

Incidence is higher in Western Europe, Australia, New Zealand and North America, and lower in Africa and Asia. Half of cases now occur in less developed regions.

BC is also the most frequent cause of cancer death in women, accounting for more than 450 000 deaths in the world and 139 000 in Europe.

Estimated age-standardised rates (world) of incident cases, breast cancer, worldwide in 2012

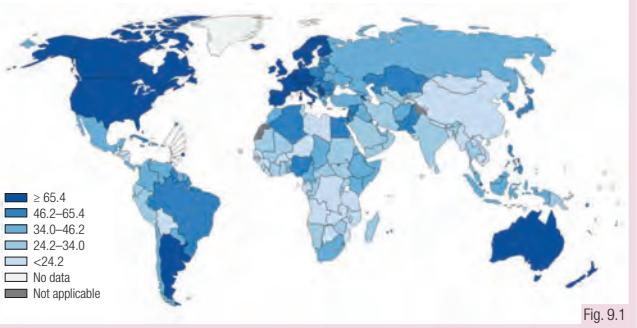

Fig. 9.1

Trends in breast cancer in the USA and Spain

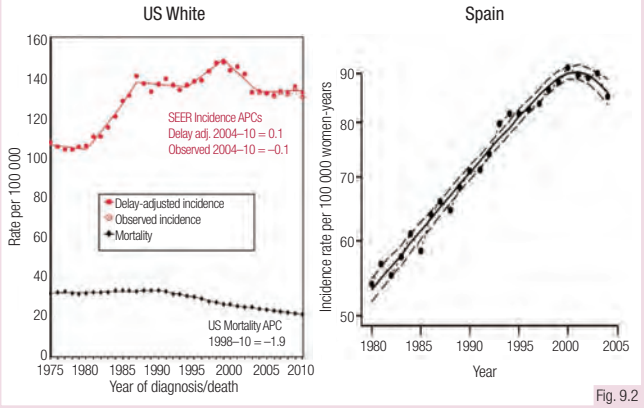

Fig. 9.2

APC, Annual percentage change; SEER, Surveillance, Epidemiology and End Results.

Over the second half of the 20th century, BC incidence rose steadily in most regions. Larger increases were seen in countries with lower rates of incidence.

In white postmenopausal women, a sudden drop in BC rates was seen in many places at the start of the 21st century, but trends stabilised or increased afterwards.

This unexpected downturn was related to a fall in the use of hormonal replacement therapy in some countries (USA) and with screening saturation in others (Spain).

In Europe, even though BC incidence is lower in younger women (<45 years), rates are increasing. This trend may constitute a challenge in the near future.

Regardless of age, BC is 100 times more frequent in women than in men. There are also ethnic differences (lower frequency in Asian and Hispanic women).

While genetic factors also have an independent role, temporal trends and studies in immigrants confirm the influence of environmental factors in the aetiology of this cancer.

Age-standardised BC incidence rates among women aged 20–29 and 30–39 years at diagnosis (1995–2006), pooled European registries

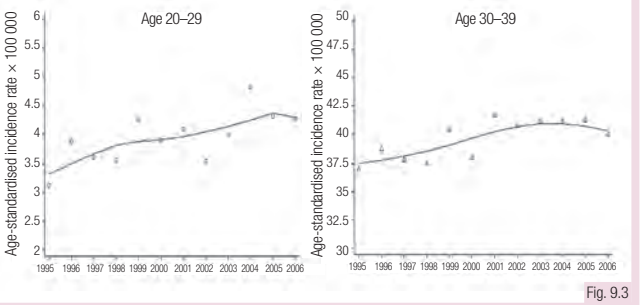

Fig. 9.3

BC, Breast cancer.

REVISION QUESTIONS

1. Why is BC a public health concern?
2. Is BC a disease of wealthy populations?
3. What are the causes of the incidence downturn observed in several developed countries? Do you think the decline will be maintained in the near future?

Main risk factors

BC has a genetic component. Familial history is an important risk factor. The number of relatives affected, particularly first-degree relatives, increases the risk.

Mutations in high-penetrance genes such as *BRCA1/2* and others explain the aggregation of cases in high-risk families and are also linked with other tumours.

In sporadic cases, low-penetrance variants, common in the general population, modulate the risk. Until now, genome-wide association studies have identified more than 70 of these variants.

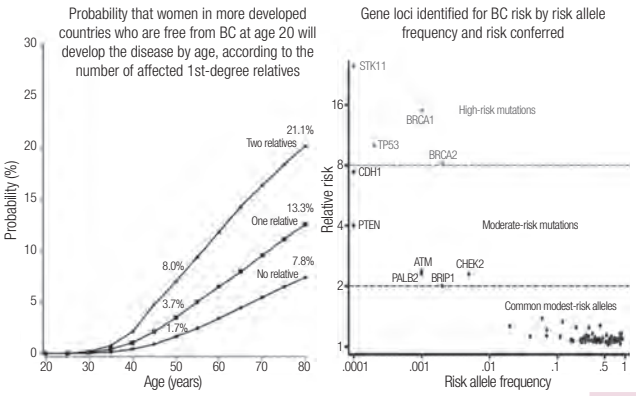

Fig. 9.4

BC, Breast cancer.

Risk factor	Relative risk
Hormonal factors	
Late (age >30 yr) parity or nulliparity	1.2–1.7
Early (age <12 yr) menarche or late menopause (age >55 yr)	1.2–1.3
Combined hormone-replacement therapy (e.g. for 10 or more yr)	1.5

Risk of BC by use of hormone therapy in the Million Women Study

Last reported use of hormone therapy	Years of hormone therapy use	RR (95% CI)
Never user	–	1.00 (0.97 to 1.03)
Past user	3.7	1.08 (1.04 to 1.12)
Current user	7.2	1.68 (1.64 to 1.72)
Oestrogen-only	8.0	1.38 (1.32 to 1.44)
Oestrogen + progestin	6.8	1.96 (1.90 to 2.02)
Tibolone	7.0	1.38 (1.25 to 1.52)
Other/unknown	7.4	1.55 (1.38 to 1.73)

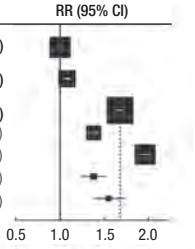

Fig. 9.5

BC, Breast cancer; CI, confidence interval; RR, relative risk.

Hormones play a key role in BC development. Reproductive factors influence BC risk. Late parity, early menarche and late menopause increase the risk for BC. Early pregnancy is a protective factor.

External hormones (oral contraceptives and hormonal replacement) increase BC risk among current users. The excess risk markedly reduces after cessation.

Hormonal replacement therapy is an important risk factor. Combined therapy for periods of ≥5 years entails a higher risk.

Benign breast diseases are associated with an increased risk, particularly proliferative lesions with atypia. Lobular carcinoma *in situ* is considered a risk indicator for invasive carcinoma (risk 4–10-fold).

The amount of dense tissue in the mammogram is a strong determinant of BC risk. Breast density is partly inherited but also influenced by non-genetic factors.

Breast density is used as an intermediate phenotype in BC research. The excess risk persists at least 6–8 years after mammographic exploration.

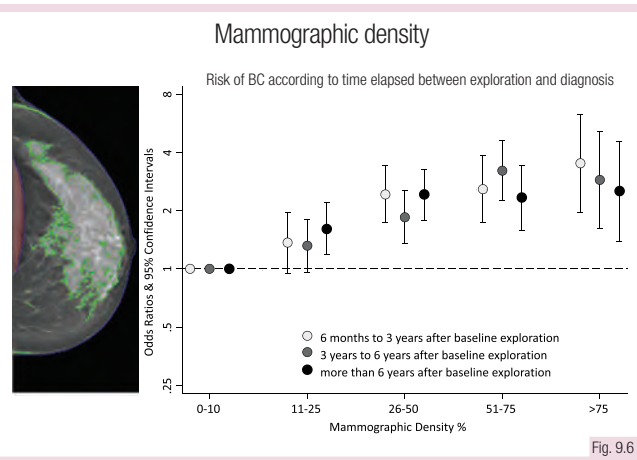

Fig. 9.6

BC, Breast cancer.

REVISION QUESTIONS

1. What kind of genetic variants play a role in BC?
2. Describe the most important reproductive factors and their relation to hormonal exposure and BC.
3. What is mammographic density?

Lifestyle and environmental factors

Obesity, abdominal fatness and adult weight gain are associated with an increased risk of BC after menopause. Obesity is inversely related to premenopausal BC.

There is ample evidence of a lower risk of postmenopausal BC in physically active women. Even moderate activity exerts a protective effect after menopause.

Consumption of alcoholic beverages increases BC incidence in pre- and postmenopausal women, with a clear dose–response trend.

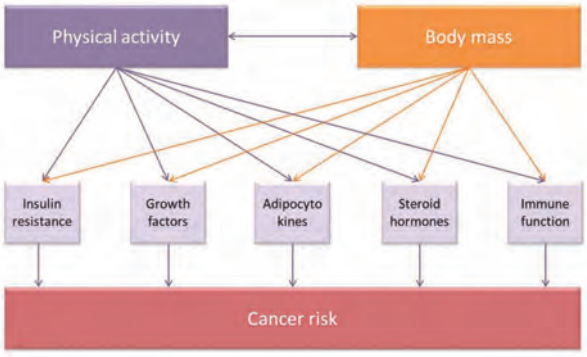

Fig. 9.7

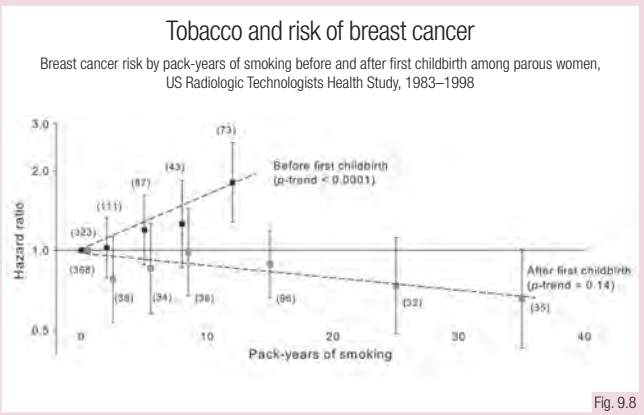

Fig. 9.8

Tobacco influences BC risk, particularly at certain stages of life. Active smoking before a first full-term pregnancy is particularly harmful.

Ionising radiation can induce breast malignancy in exposed women. Carcinogenic sensitivity is higher when exposure occurs in childhood and adolescence.

Available evidence on the influence of other dietary, environmental and occupational factors (i.e. endocrine disruptors, polycyclic aromatic hydrocarbons (PAHs), night-shift) is less conclusive.

Birth size, considered a proxy for prenatal hormonal environment, has been positively associated with BC risk, showing the influence of early-life exposures.

BC risk factors, at critical exposure windows, interplay and interfere with the normal transformation of the breast, either directly or by influencing the hormonal regulatory environment.

Preventive measures include: avoiding obesity, regular practice of exercise, and limitation of (1) alcohol intake, (2) hormone treatments, (3) radiation exposure and (4) tobacco use.

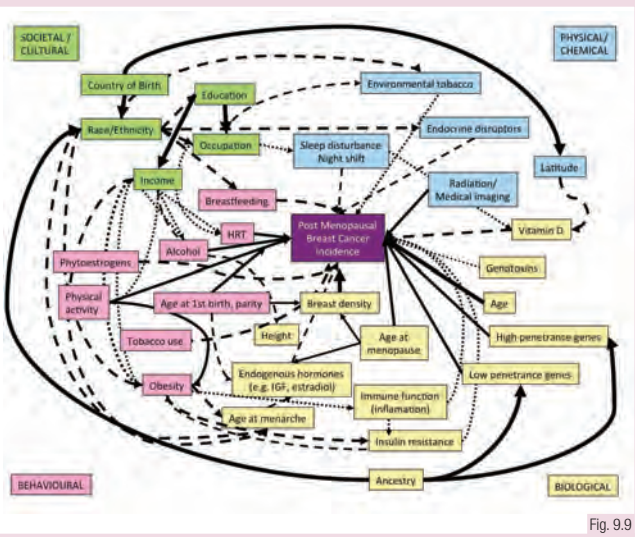

Fig. 9.9

HRT, Hormone replacement therapy; IGF, insulin-like growth factor.

REVISION QUESTIONS

1. What is the hormonal connection between obesity and BC?
2. Why is time of exposure so important for several risk factors?
3. What recommendations related with lifestyle factors can we give to women who want to decrease their BC risk?

Summary: Epidemiology of breast cancer

- BC is the most common malignant tumour in women around the world
- Causes: interplay between genetic and non-genetic factors, usually affecting the hormonal environment that regulates mammary development
- Classical risk factors: age, sex, ethnic origin, reproductive factors (nulliparity and delayed pregnancy) and hormone treatments. Pregnancy at an early age is a protective factor
- Some types of benign breast conditions, specifically those with proliferation and atypia, may be associated with increased risk for BC
- Patients with lobular carcinoma *in situ*, currently depicted as lobular neoplasia *in situ* (LIN), have a 4–10-fold risk of developing an invasive BC
- Mammographic density is considered a phenotypic risk marker
- Well-established dietary determinants: obesity (postmenopausal) and alcohol
- Moderate physical activity is a protective factor
- Smoking before the first full-term pregnancy also increases risk
- Ionising radiation is the best known environmental factor associated with BC
- Correlating the course of life with pathological subtypes will improve understanding of the causes of BC

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10 Screening for breast cancer

History and evolution

The success of mass screening for cervical cancer in reducing mortality supported the early detection approach and resulted in the initiation of a similar approach in breast cancer (BC).

The first screening methods in BC included breast self-examination (BSE) and clinical breast examination (CBE) in addition to mammography.

Neither BSE nor CBE has been proven effective in reducing BC mortality and they are no longer recommended as part of screening programmes.

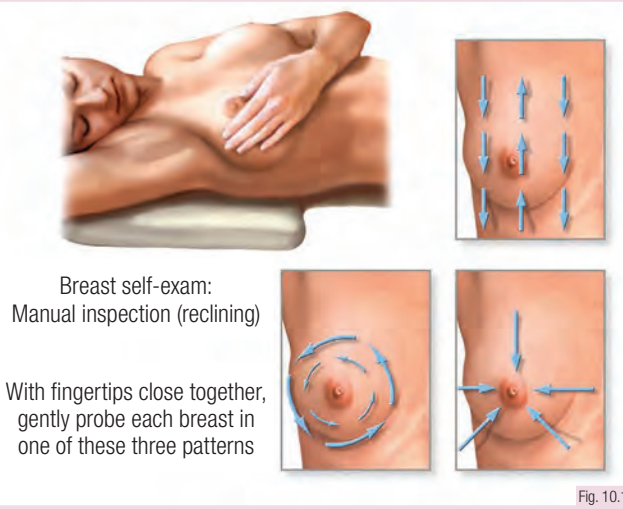


Fig. 10.1

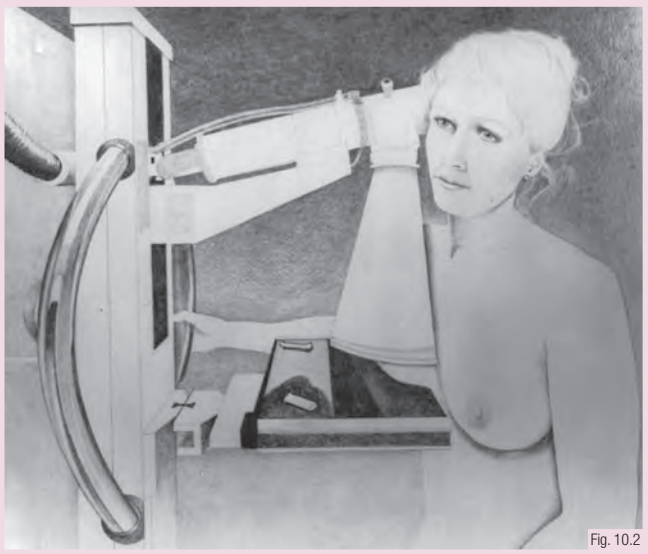


Fig. 10.2

The first mammography systems were available in the mid-1960s and were initially used as diagnostic tools for symptomatic women. Radiation doses in mammography have consistently decreased with time, falling to nearly 1/10 in absorbed dose (mGy) from 1975 to 2015.

The use of mammography as a screening tool evolved together with breast imaging to become a radiology subspecialty.

To obtain scientific evidence for mammography screening, the Health Insurance Plan (HIP) study, a randomised screening trial in the USA, was initiated in 1963.

The HIP study was published in 1972, showing a statistically significant reduction in breast cancer mortality for women randomised to screening.

From 1963 to 1991, eight main randomised controlled trials (RCTs) were completed in different age groups, with varying designs and results.

These RCTs all used film mammography. Since then, the only RCT comparing film to digital mammography showed higher cancer detection and recall rates, but no effect on interval cancer rate.

Trial	Year of initiation
Health Insurance Plan of Greater New York (HIP)	1963
Edinburgh trial	1976
Malmö Mammographic Screening Trial (MMST I and MMST II)	1976
Swedish Two-County Study (Östergotland and Kopparberg)	1977
Canadian National Breast Screening Study 1 and 2 (CNBSS-1, CNBSS-2)	1980
Stockholm trial	1981
Gothenburg trial	1982
United Kingdom Age Trial (Age)	1991

Fig. 10.3

REVISION QUESTIONS

1. What methods of examination were included in the early screening for BC?
2. What and when was the first RCT in mammography screening, and what did it show?
3. How many major RCTs on mammography screening have been performed?

Screening parameters

The most common age range of screening for BC is 50 to 70 years. Screening is common outside this range but it is likely that the effect is small, especially in patients younger than 50 years.

The most common screening interval is two years, which is regarded as optimum for an average-risk woman. Shorter intervals are frequently proposed to improve the effect. However, this includes increased risk for potential harms, too.

No trials have directly compared the effect of different screening intervals. The HIP, Age and Canadian trials used a screening interval of 12 months; the Gothenburg trial 18 months; and the Swedish Two-County trial intervals ranged from 24 to 36 months.

Relationship between pre-diagnosis screening interval, age and percent of women diagnosed with advanced breast cancer (with 95% confidence intervals)

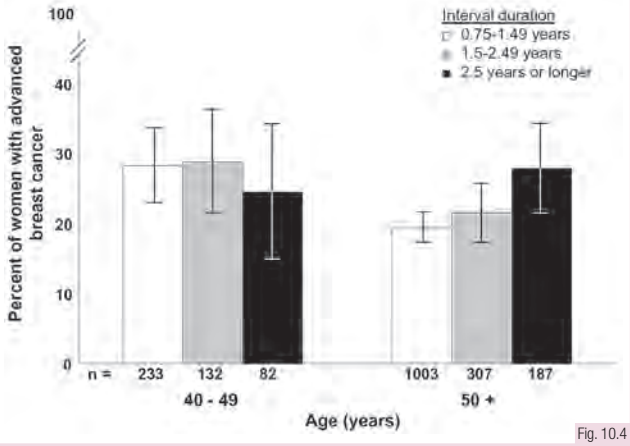


Fig. 10.4

$$\text{Sensitivity} = \frac{\text{Number of true positives}}{\text{Number of true positives + number of false negatives}}$$

$$= \frac{\text{Number of true positives}}{\text{Total number of sick individuals in population}}$$

= Probability of a positive test given that the patient has the disease

$$\text{Specificity} = \frac{\text{Number of true negatives}}{\text{Number of true negatives + number of false positives}}$$

$$= \frac{\text{Number of true negatives}}{\text{Total number of well individuals in population}}$$

= Probability of a negative test given that the patient is well

Fig. 10.5

Improving the sensitivity and specificity of mammography imaging, reading of the images and improving the attendance of women in screening programmes may enhance the net effect.

Rate of detected early cancers in screening, more favourable stage distribution of screen-detected cancers and improved survival are not direct proof of effective screening.

These may show a favourable effect even if the screening was ineffective and thus are biased estimates.

The main effect of interest in screening is the degree of reduction in BC mortality. This is expressed as relative risk reduction (%).

Absolute reduction in risk may be expressed as, for example, the numbers of deaths prevented per 1000 or 10 000 women screened for 10 years.

The effectiveness of mammography screening depends on the population baseline risk of developing BC. In low-risk populations, the effect is negligible, whereas in high-risk populations it may be substantial.

Number of breast cancer deaths in 1000 women

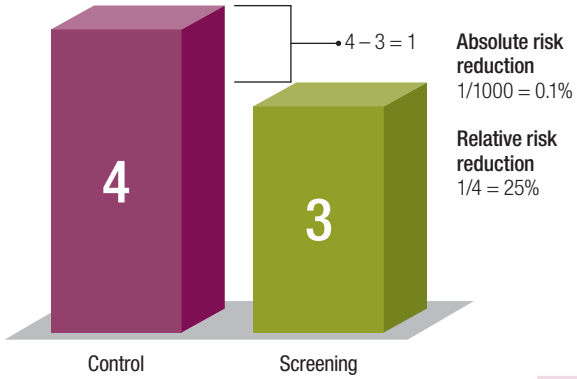


Fig. 10.6

REVISION QUESTIONS

1. What is the most common age range of screening for BC?
2. What is the typical screening interval?
3. Does improved survival provide evidence for successful BC screening?

Benefits and harms of screening

Relative risk reduction in BC mortality from meta-analyses of the aforementioned RCTs showed no difference in women aged 40–49 years, 14% reduction in women aged 50–59 years, and 33% reduction in women aged 60–69 years.

Absolute rates of BC mortality reduction derived from the same meta-analyses were 2.9 for age 40–49, 7.7 for age 50–59, and 21.3 for age 60–69 years, as numbers of BC deaths avoided per 10 000 women screened for 10 years.

Screening reduces the incidence of node-positive and more advanced BC. This may be used as a surrogate marker for improved outcome. However, the association may be biased in several ways (age, comorbidities, treatment).

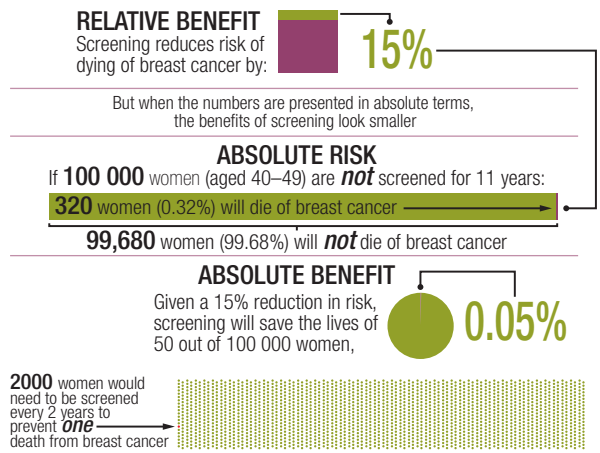


Fig. 10.7

Estimated benefits and harms of mammography screening for 10 000 women who undergo annual screening mammography over a 10-year period

Age, y	No. diagnosed with invasive breast cancer or ductal carcinoma *in situ* during the 10 y of screening[a]	No. of breast cancer deaths in the next 15 y[b]	No. of deaths averted with mammography screening over the next 15 y[c]	No. of breast cancers or ductal carcinomas *in situ* diagnosed during the 10 y that would never become clinically important (overdiagnosis)[d]	No. (95% confidence interval) with ≥1 false-positive results during the 10 y[e]	No. (95% confidence interval) with ≥1 unnecessary biopsy during the 10 y[e]
40	190	27-32	1-16	?-104	6130 (5940-6310)	700 (610-780)
50	302	56-64	3-32	30-137	6130 (5800-6470)	940 (740-1150)
60	438	87-97	5-49	64-194	4970 (4780-5150)	980 (840-1130

Data sources:
[a]Surveillance, Epidemiology, and End Results (SEER) programme.
[b]Surveillance, Epidemiology, and End Results (SEER) programme; Canadian National Breast Screening Study-1 and -2; Swedish 2-County Trial.
[c]Canadian National Breast Screening Study-1 and -2; Swedish 2-County Trial.
[d]Malmö mammographic screening trial; Surveillance, Epidemiology, and End Results (SEER) programme.
[e]National Cancer Institute-funded Breast Cancer Surveillance Consortium.

Fig. 10.8

A false-positive mammography screening result causes anxiety and stress and leads to unnecessary imaging and biopsies. These occur in 1%–7% of mammograms in European screening programmes.

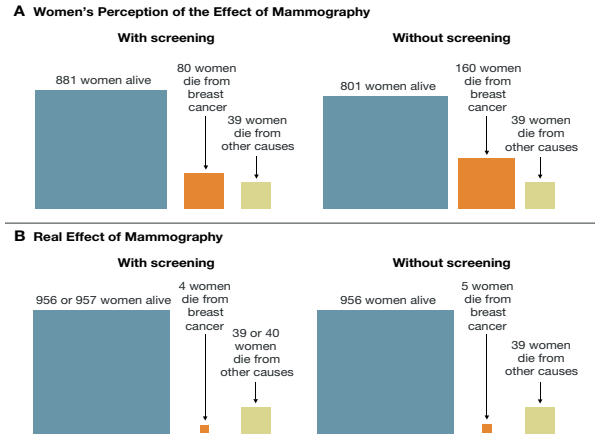
A false-negative mammography screening result is a serious, but relatively rare, harm.

The benefit/harm ratio in mammography screening is generally poorly known by attending women. Information in understandable form and shared decision-making is a must.

Some of the screen-detected cancers would not emerge clinically at all. This results in overdiagnosis, and causes overtreatment, the major harm of BC screening.

The extent of overdiagnosis remains highly uncertain. The estimates range from 0%–54%. Estimating overdiagnosis reliably is difficult and the result depends on study design.

Change from film to digital mammography is likely to increase the rate of overdiagnosis. The incidence of ductal carcinoma *in situ* (DCIS) will most probably increase, as it already has with film mammography screening compared with non-screened.



U.S. Women's Perceptions of the Effects of Mammography Screening on Breast-Cancer Mortality as Compared with the Actual Effects.

Fig. 10.9

REVISION QUESTIONS

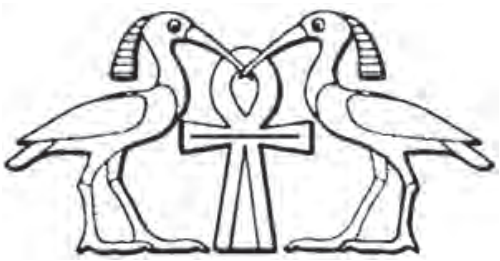
1. What is the magnitude of relative risk reduction in BC mortality according to RCTs?
2. How does this transfer to absolute figures?
3. Why is overdiagnosis a problem in BC screening?

The future

Screening general population averages results in both benefits and harms. Some individuals may gain full benefit, some only harm, and these individuals cannot be identified.

The early screening programmes used age as the only indication of risk for developing BC.

Implementing risk-based screening may improve benefit / harm ratio.



IBIS Breast Cancer Risk Evaluation Tool

The Tyrer-Cuzick model

Fig. 10.10

Application of risk tools, such as the Tyrer-Cuzick model, the Claus model and the Gail model may be helpful.

Family history of BC, hormonal factors, breast tissue density and genetic factors improve predictive accuracy.

More elaborate approaches may include BC risk single nucleotide polymorphisms (SNPs) in addition to risk models.

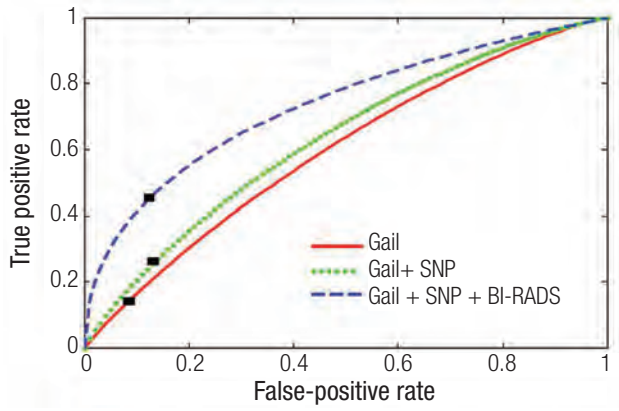


Fig. 10.11

BI-RADS, Breast Imaging–Reporting and Data System; SNP, single nucleotide polymorphism.

Full field digital mammography (FFDM) has largely replaced film-screen technology, being far more sensitive in women below 50 years of age and in those with dense breasts.

Contrast-enhanced magnetic resonance imaging (MRI) has been shown to have higher sensitivity than mammography in women with a strong family history of BC. It is used as an adjunct to mammography in the high-risk population, not the general population.

Digital breast tomosynthesis (DBT) has been tested in several trials and even used for screening in some countries. It is not yet known whether DBT adds to screening benefit over standard mammography.

ESMO recommendations for MRI indications in screening

- *BRCA1* or *BRCA2* gene mutation carrier
- First-degree relative (mother, father, brother, sister, or child) with a *BRCA1* or *BRCA2* gene mutation
- A lifetime risk of breast cancer of 20%–25% or greater, according to risk assessment tools based mainly on family history
- Radiation therapy to the chest for another type of cancer, such as Hodgkin's disease between the ages of 10 and 30 years
- A genetic syndrome such as Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba, or one of these syndromes in first-degree relatives
- **ESMO recommendation:** Annual MRI concomitantly or alternating every 6 months with mammography, starting 10 years younger than the youngest case in the family [LoE: III,A]
- **NOTE! It is not known whether breast cancer mortality is lowered!**

Fig. 10.12

ESMO, European Society for Medical Oncology; LoE, level of evidence; MRI, magnetic resonance imaging.

REVISION QUESTIONS

1. Describe risk-based screening.
2. How is contrast-enhanced MRI used in BC screening?
3. Has DBT been shown more effective than standard mammography?

Summary: Screening for breast cancer

- Early detection for better outcome is the driving idea in cancer screening
- The technical development of mammography equipment in the 1960s enabled the first RCTs in mammography screening, the first results being encouraging (HIP trial)
- The most common age range for screening mammography is 50–70 years, and the most common screening interval is two years
- Rate of detected early cancers in screening, more favourable stage distribution of screen-detected cancers and improved survival are not proof of effective screening
- The risk reduction of BC mortality depends on the age and other baseline risk factors in the screened population
- In the early RCTs, the relative risk reduction varied from nil in the lowest age group (<50 years) to 33% in the 60–69 year age group
- The absolute benefit is described as the number of prevented BC deaths per 10 000 women screened for 10 years, ranging from 3 to 21 in different age groups
- The main harm of mammography screening is overdiagnosis, which leads to overtreatment
- Women attending mammography screening have a poor understanding of the benefits and harms relating to it. Informed consent and shared decision-making need to be enhanced
- Mammography screening developed technically from film mammography into full field digital and is further developing towards tomosynthesis
- Mammography screening has, through its history, been subject to considerable debate. In some countries there have even been plans to abolish population-based mammography screening programmes
- Every woman has the right to a balanced view of the benefits and harms of mammography screening before making her decision to attend or not

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Genetic counselling and testing

Introduction and background

All cancers derive from genetic alterations.

Hereditary and familial cancers are the result of mutations in parental germline cells.

Overall, hereditary *and* familial cancers account for up to 20%–30% of all breast cancers.

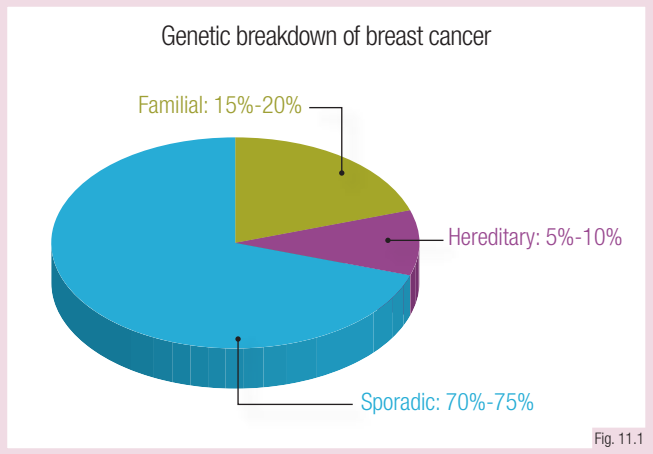

Fig. 11.1

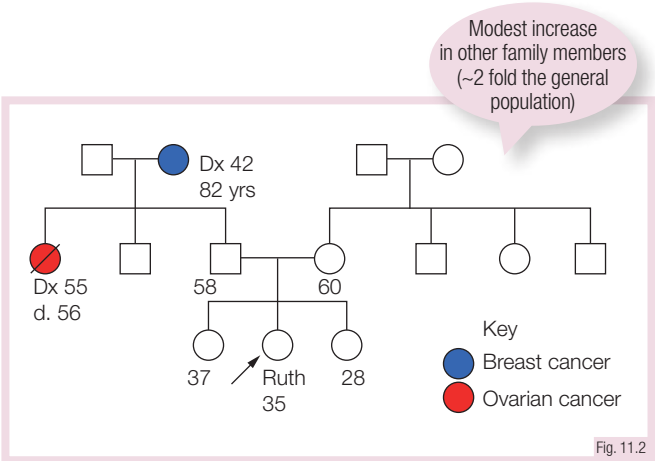

Fig. 11.2

Familial breast cancer (BC) is defined when a person has two or more first- or second-degree relatives with BC.

It normally has later onset in comparison to hereditary BC and is usually unilateral.

The hereditary pattern of familial BC is unclear. Common environmental factors/habits may be influential; weak genetic factors and chance alone could also be important.

Hereditary breast/ovarian cancer is defined when there is a history of multiple cancers in multiple generations of a person's family.

These cancers normally have early onset, and multiple cancers can occur in the same patient.

Specific cancer clusters can be identified in the same family.

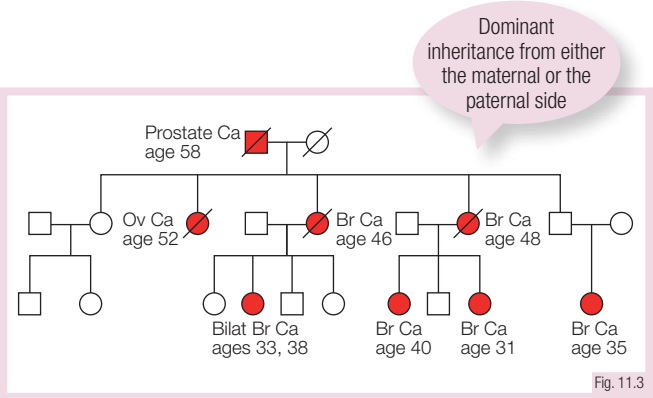

Fig. 11.3

Bilat, Bilateral; Br, breast; Ca, cancer; Ov, ovarian.

REVISION QUESTIONS

1. What is the definition of familial BC?
2. Can familial BC be influenced by changes in lifestyle/habits?
3. Should the family pedigree include both maternal and paternal sides?

Indications and preventive measures

Indications/guidelines for BRCA testing vary in different countries.

Pre- and post-test counselling, delivered by experienced healthcare professionals, is mandatory.

Results will help in planning personalised surveillance to achieve early diagnosis and preventive strategies in all the family, and/or influence the medical/surgical management of the patient.

Individuals for whom BRCA testing is indicated
Individuals with a family member who carries a BRCA mutation
Women with any of the following • Ovarian, Fallopian tube or peritoneal cancer diagnosed ≤45 years • Early-onset breast cancer (diagnosed ≤40 years) • Bilateral breast cancer diagnosed ≤50 years • Breast and ovarian cancer • Triple-negative breast cancer at age 60 or younger • Breast cancer and close relatives with breast cancer, pancreatic cancer, melanomas or aggressive prostate cancers • Breast cancer from an ethnic group with a high mutation frequency (i.e. Ashkenazi Jews)
Men with breast cancer
Individuals without breast cancer but with a family history with features above

Fig. 11.4

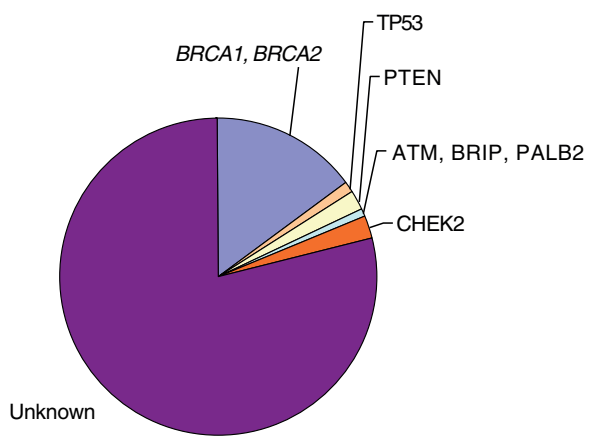

Fig. 11.5

The main genes involved in hereditary BC include:
- High-penetrance genes: *BRCA1–BRCA2, PALB2*
- Low-penetrance genes: *CHEK2/APC*
- TP53 (Li–Fraumeni syndrome)

Approximately 2%–3% and 2%–5% of hereditary BCs are associated with *PALB2 and CHEK2* mutations, respectively.

BRCA1/BRCA2 mutations occur in 1:300-500 individuals in the general population

Some ethnic groups have a very high incidence, e.g. Ashkenazi Jews (1:50). Countries such as Canada, Hungary, Iceland, Sweden, the Netherlands and Italy also have high incidence.

Populations with high incidence usually have founder mutations. Founder mutations are frequently observed in populations that originate from a small ancestral group, geographically or culturally isolated.

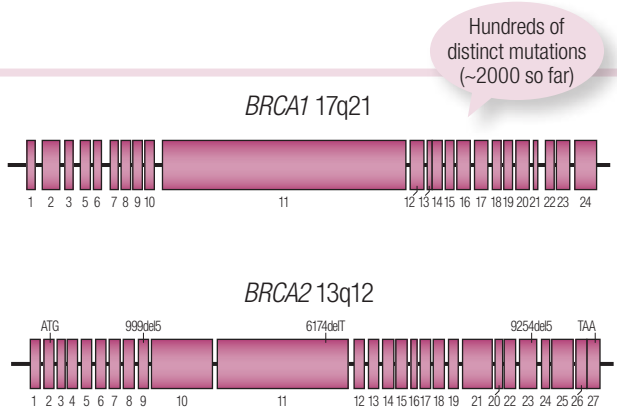

Fig. 11.6

REVISION QUESTIONS

1. Is genetic testing helpful in planning preventive measures and ensuring early diagnosis/treatment in hereditary breast/ovarian cancer families?
2. Should any Ashkenazi Jew be proposed genetic counselling?
3. Are *BRCA1/2* mutations the only genes involved in hereditary BC?

Cancer clinical management

The mean age of BC diagnosis is younger for *BRCA1* carriers than for people who carry the *BRCA2* mutation.

BC patients with *BRCA1/2* mutations also have an increased risk of contralateral BC (~3%/year).

The *BRCA1* mutation is associated with ovarian, peritoneal and Fallopian tube cancers, whereas the *BRCA2* mutation is associated with ovarian, male breast, prostate and pancreatic cancers.

Mean cumulative BC lifespan risk: 57% for *BRCA1*, 49% for *BRCA2* in a high-risk population-based meta-analysis of ten studies

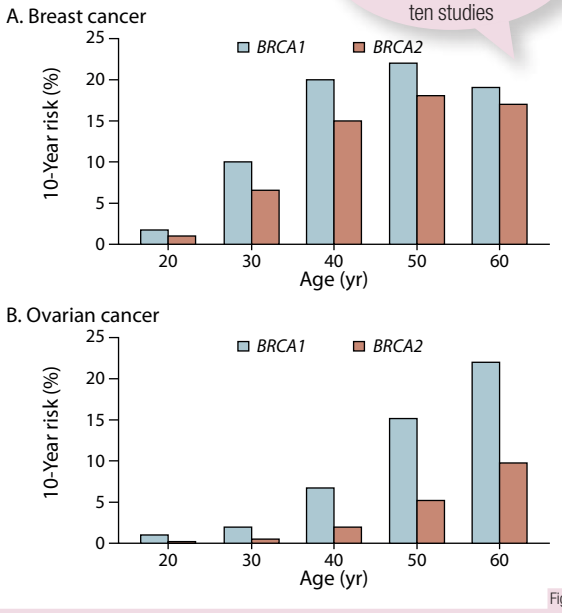

Fig. 11.7

BC, Breast cancer.

Median values (n, %) of different discrete clinicopathological features for sporadic breast cancers, cancers in patients with *BRCA1* and *BRCA2* mutations and in patients with breast cancer who are at different risks of hereditary disease on the basis of family history

	Type	Sporadic (n, %)	Intermediate risk of hereditary disease (n, %)	High risk of hereditary disease (n, %)	Mutations in *BRCA1* (n, %)	Mutations in *BRCA2* (n, %)
Grade	1 2 3	119 (22) 181 (34) 232 (44)	9 (16) 25 (46) 21 (38)	0 (0) 5 (26) 14 (74)	0 (0) 4 (18) 18 (82)	0 (0) 1 (20) 4 (80)
Histological type	Ductal Lobular Medullary Tubular Other	474 (79) 56 (9) 10 (2) 22 (4) 42 (7)	55 (84) 8 (12) 0 (0) 1 (2) 1 (2)	14 (74) 1 (5) 1 (5) 0 (0) 3 (16)	18 (82) 0 (0) 4 (18) 0 (0) 0 (0)	5 (100) 0 (0) 0 (0) 0 (0) 0 (0)
EGFR	Neg Pos	360 (84) 70 (16)	24 (77) 7 (23)	3 (20) 12 (80)	7 (33) 14 (67)	0 (0) 5 (100)
HER2/neu	Neg Pos	374 (87) 55 (13)	52 (88) 7 (12)	15 (83) 3 (17)	17 (81) 4 (19)	3 (75) 1 (25)

EGFR, Epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; Neg, negative; Pos, positive.

Fig. 11.8

BRCA1: ~75% "triple-negative"/basal-like phenotype
BRCA2: heterogeneous group

~1:4 patients with triple-negative BC carry a *BRCA1* mutation. *BRCA2*-related cancers show the same molecular subtypes as sporadic BCs.

Management options for *BRCA1/2* carriers include early surveillance (semiannual). For breast: clinical exam, mammogram and magnetic resonance imaging. For ovary: vaginal ultrasound and CA 125 (controversial). For offspring: consider pre-implantation genetic diagnostics.

Pharmaco-prevention includes tamoxifen and aromatase inhibitors. Surgical prevention includes prophylactic bilateral mastectomy, which reduces the incidence of BC by at least 90%.

Prophylactic salpingo-oophorectomy >35 years, upon completion of child-bearing. Modern oral contraceptives do not increase BC risk and significantly reduce ovarian cancer risk.

The impact of SO on BC risk is greater for *BRCA2* mutation carriers, likely based on the significant proportion of ER-positive tumours in this population

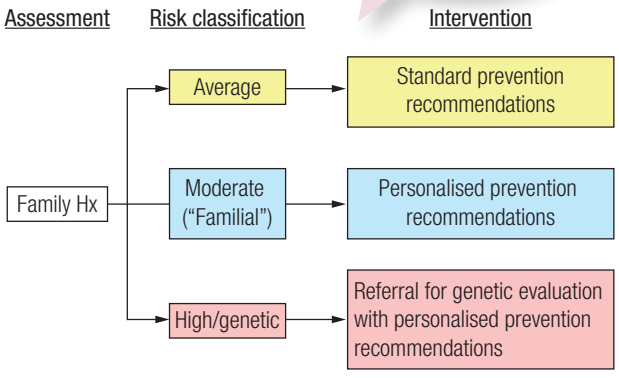

Fig. 11.9

BC, Breast cancer; ER, oestrogen receptor; SO, salpingo-oophorectomy.

REVISION QUESTIONS

1. Should triple-negative BC patients be proposed genetic counselling irrespective of familial history?
2. Do oral contraceptives reduce ovarian cancer risk?
3. Does salpingo-oophorectomy also reduce BC risk?

Summary: Genetic counselling and testing

- Genetic cancer risk assessment and counselling includes several steps
- Calculation of gene mutation probability, discussion of genetic testing cost/benefit ratio and results should be provided by an experienced team
- Individual risk assessment requires personal history and a 3–4 generation family medical history (pedigree)
- Maternal and paternal sides have to be investigated independently, and information about ethnicity and consanguinity is warranted
- Pathological reports should be provided to limit imprecision
- In mutation carriers, surveillance planning, cancer reduction strategies and psychosocial support (i.e. reproductive decision-making, employment/insurance considerations and protection from genetic discrimination) should be provided
- Treatment of early breast and ovarian cancer in individuals with *BRCA1/BRCA2*-related tumours is similar to that for sporadic forms, apart from discussion of prophylactic bilateral mastectomy and salpingo-oophorectomy. Oral PARP inhibitors are indicated in advanced ovarian cancer after standard chemotherapy and have recently proven effective in advanced BC
- Modern oral contraceptives do not increase BC risk and may be used to significantly reduce ovarian cancer risk
- Once a germline *BRCA1/BRCA2* mutation has been identified in an individual, testing of at-risk relatives can identify other members with the family-specific mutation
- Family members, irrespective of mutation status, will benefit from individualised surveillance and early intervention if a cancer is identified

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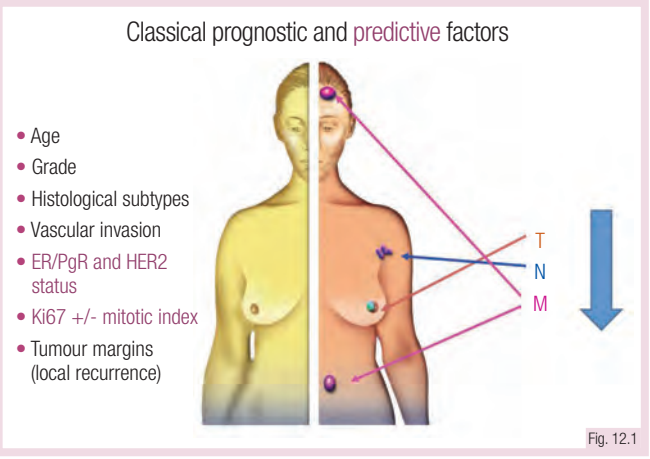
Prognostic and predictive factors

Classical prognostic factors

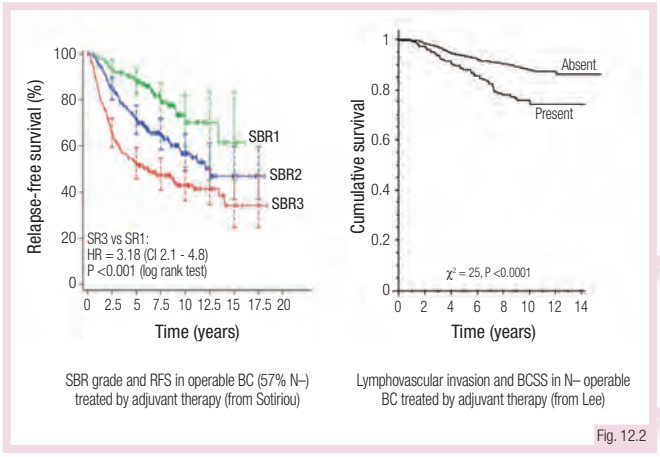
Classical prognostic factors comprise age, stage, tumour grade, tumour type and vascular invasion. Breast cancer (BC) before 35 years old is rare (<5%) and potentially more aggressive.

Tumour node metastasis (TNM) parameters, reflecting tumour burden (tumour size, number and size of lymph node metastasis) and spread are still strong prognostic factors.

Sentinel lymph node biopsy allows the detection of small metastasis deposits (0.2 to 2 mm, micrometastasis, pN1mi [sn]), impacting survival by more than 3% and 5% at 5 and 10 years (distant metastasis), respectively.



ER, Oestrogen receptor; HER2, human epidermal growth factor 2; PgR, progesterone receptor.



SBR grade and RFS in operable BC (57% N–) treated by adjuvant therapy (from Sotiriou)

Lymphovascular invasion and BCSS in N– operable BC treated by adjuvant therapy (from Lee)

BC, Breast cancer; BCSS, breast-cancer-specific survival; HR, hazard ratio; RFS, relapse-free survival; SBR, Scarff-Bloom-Richardson.

With the current extent of mass screening, the stage at diagnosis has decreased. The natural history of BC is modified, thus we have to rely more on tumour biology (type, grade, oestrogen receptor [ER], progesterone receptor [PgR], HER2 status and proliferation).

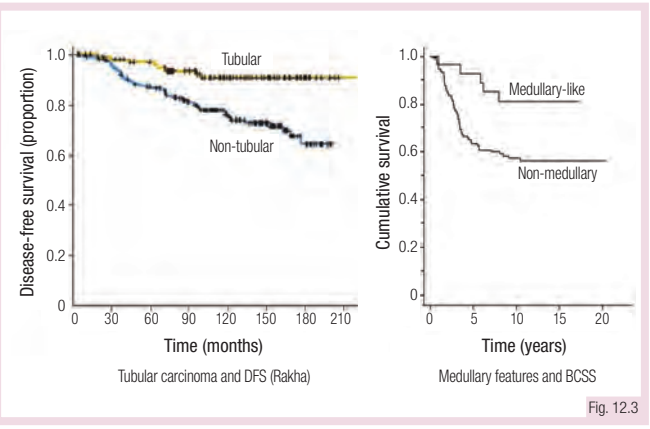
The Scarff–Bloom–Richardson (SBR) grade modified by Elston–Ellis is a powerful prognostic factor. Unfortunately, 50% of patients fall into Grade 2 of intermediate prognosis.

The presence of vascular or lymphatic emboli at the periphery of the tumour is associated with a higher risk of local and distant metastasis.

Among the 20 special types of ER-positive, tubular, mucinous and cribriform BCs show an excellent prognosis, but pleiomorphic lobular BC, a poor one.

The heterogeneous triple-negative (TN) group includes adenoid cystic, juvenile secretory and medullary metaplastic low-grade (good prognosis) tumours.

For the TN and the HER2-positive groups of BC, the presence of many tumour-infiltrating lymphocytes (TILs) is a factor of good prognosis.



Tubular carcinoma and DFS (Rakha)

Medullary features and BCSS

BCSS, Breast-cancer-specific survival; DFS, disease-free survival.

REVISION QUESTIONS

1. What are the classical prognostic factors of BC?
2. What is the prognostic impact of micrometastasis?
3. Which TNBCs have good prognosis?

Predictive markers – intrinsic classification

A positive hormone receptor status, defined by at least 1% of ER-positive cells, is required for hormone therapy (HT). PgR status is a strong prognostic factor, used for the definition of luminal BC.

HER2-positive status (10% complete membrane staining or amplified by *in situ* hybridisation) is mandatory for targeted therapy (TT). Equivocal cases (4–6 copies) are eligible for TT after consideration of other prognostic factors.

Ki67 reflects proliferation and predicts chemosensitivity. It is not standardised and not uniformly recommended, although widely used. The most used cut-off is 20%.

Biomarker	Prognostic	Predictive	Technical validation [LoE/GoR]	Clinical validation
ER	++	+++	YES [I,B]	YES
PgR	+++	+	YES [I,B]	NO
HER2	++	+++	YES [I,B]	YES
Ki67	++	+	NO	NO
Biomarker	**Test and scoring recommendations**			
ER	IHC			
PgR	IHC			
HER2	IHC ≥10% cells with complete membrane staining ISH: number of HER2 gene copies ≥6 or the ratio HER2/chromosome 17 ≥2			
EGFR expression	IHC no final consensus on cutoff around 20% (Ki67 <10% = low; Ki67 >30% = high)			

ER, Oestrogen receptor; GoR, Grade of Recommendation; HER2, human epidermal growth factor 2; IHC, immunohistochemistry; ISH, *in situ* hybridisation; LoE, level of evidence; PgR, progesterone receptor.

Fig. 12.4

OS analysis for the five expression-based tumour intrinsic subtypes, Normal-like being artefactual

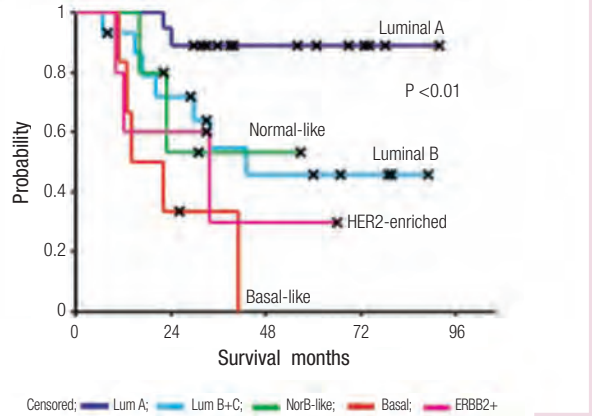


Fig. 12.5

OS, Overall survival.

BC molecular portraits by Perou or intrinsic classification define 4 groups of BC dichotomised by *ESR1* expression and, in the negative group, by *HER2*.

Four categories, luminal A, luminal B, HER2-enriched and basal-like, show radically different prognoses. They express different genes => different therapeutic targets.

"Luminal A-like" tumours by immunohistochemistry (IHC) are ER-positive, HER2-negative, Ki67-low (<20%) and PgR-high (>20%) and/or have low-risk molecular signature (if available) => HT.

"Luminal B-like" tumours (HER2-negative) by IHC are ER-positive, HER2-negative and either Ki67-high or PgR-low, or have high-risk molecular signature (if available).

"HER2-enriched-like" tumours are HER2-positive, ER- and PgR-absent. "Luminal B-like" (HER2-positive) are ER-positive, HER2-positive, any Ki67, and any PgR.

"Basal-like" tumours overlap at 80% with the TN IHC group ER-, PgR- and HER2-negative (including special types with good prognosis). Normal-like is artefactual.

Triple-negative BC by IHC and molecular subtypes: a 80% concordance

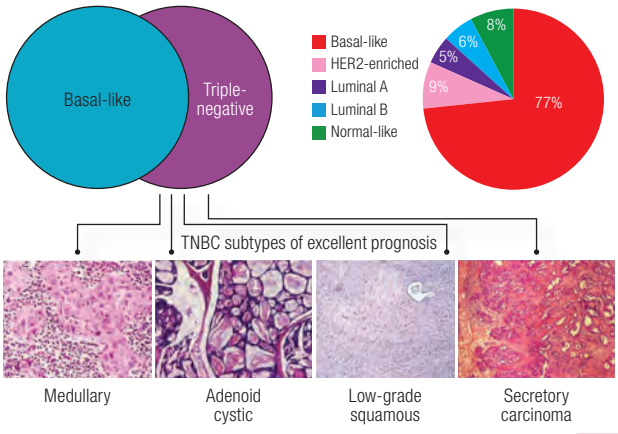


Fig. 12.6

BC, Breast cancer; IHC, immunohistochemistry; TNBC, triple-negative BC.

REVISION QUESTIONS

1. What are the four groups of BC defined in the intrinsic classification?
2. What are the main differences between luminal A-like and luminal B-like (HER2-negative) BC?
3. What are the characteristics of the basal-like group?

Signatures – Other markers

Clinical parameters (age, stage, ER and grade) are integrated into prognostic scoring systems such as the Nottingham Prognostic Index (NPI) and Adjuvant! Online (www.adjuvantonline.com), but HER2 status is missing.

Gene expression profiles (signatures) have been developed to gain additional prognostic information to help physicians in treatment de-escalation/precision.

First-generation gene signatures (Oncotype Dx®, MammaPrint®) are centrally performed. Second-generation signatures can be executed on dedicated instruments.

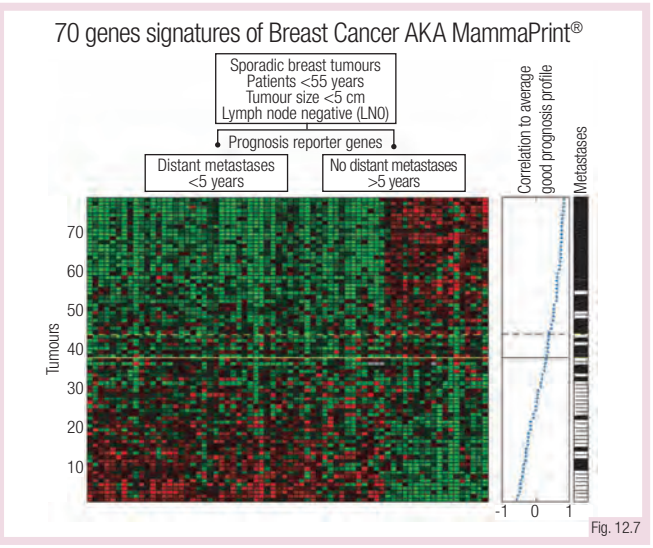


Fig. 12.7

First-generation signatures	Prognostic	Predictive	Technical validation
MammaPrint® All BC, N0, N1-3 70 genes signature 2 categories (low & high risk)	+++	++	YES Gene expression profile Central lab
Oncotype Dx® ER+, HER2- BC, N0, N1-3 21 genes signature Recurrence score RS 3 categories	+++	+++	YES RT-PCR Central lab
Clinical validation			
MammaPrint®: [LoE/GoR: I,A] prospective validation for prognostic value of a low genetic profile in a clinically high risk: 5 yrs DMFS >94% (48% N+) 14% reduction in ChT prescription up to 46% in high clinical risk			
Oncotype Dx®: [LoE/GoR: I,A] prospective validation for RS <11 (prognosis) [LoE/GoR: I,B] validated retrospectively in prospective clinical trials (prediction ChT benefit), prospective clinical validation ongoing for prediction			

Fig. 12.8

BC, Breast cancer; ChT, chemotherapy; DMFS, distant metastasis-free survival; ER, oestrogen receptor; GoR, Grade of Recommendation; LoE, level of evidence; N, node; RS, recurrence score; RT-PCR, recombinant polymerase chain reaction.

MammaPrint®: MINDACT trial, level of evidence (LoE) IA for prognosis (low metastasis (M) risk, high clinical risk, 5-year distant metastasis-free survival [DMFS] >94%) and prediction: high-risk clinical group chemotherapy (ChT) dropped by 46%.

Oncotype Dx®: Level of Evidence (LoE) I, Grade of Recommendation (GoR) B for prognosis and prediction (anthracycline); IA for prognosis of low recurrence score (RS) with HT for ER-positive, HER2-negative BC in TAILORx (5-year distant metastasis-free interval [DMFI] >99.3%).

Prosigna®: [LoE/GoR: I,B] for prognosis and prediction of late recurrence after 5 years for ER-positive, HER2-negative BC treated with HT. Includes intrinsic subtypes categorisation.

Endopredict®: [LoE/GoR: I,B] for prognosis and prediction of late recurrence after 5 years for ER-positive, HER2-negative BC treated with HT.

UPA-PAI-1, a marker of tumour invasiveness, has been validated in prospective clinical trials as a prognostic marker for both node (N)- and N+ BC [LoE/GoR: I,A]. Fresh biopsy is required, thus limiting its use.

Achieving complete pathological response (pCR) after neoadjuvant therapy is highly prognostic for HER2-positive and TNBC. The residual cancer burden (RCB) score is used to standardise quantification of residual disease.

Second-generation signatures	Prognostic	Predictive	Technical validation
Prosigna® ER+, HER2- BC, N0, N1-3 50 genes signature Includes size and N	++	++	YES N-Counter® technology Dedicated instrument
Endopredict® ER+, HER2- BC, N0, N1-3 8 genes signature Includes size and N	++	++	YES RT-PCR Dedicated instrument
Clinical validation			
Prosigna®: [LoE/GoR: I,B] Validated retrospectively in prospective clinical trials of HT Prognosis Late recurrences (after 5 years)			
Endopredict®: [LoE/GoR: I,B] Validated retrospectively in prospective clinical trials of HT Prognosis Late recurrences (after 5 years)			

Fig. 12.9

BC, Breast cancer; ER, oestrogen receptor; GoR, Grade of Recommendation; HER2, human epidermal growth factor receptor 2; LoE, level of evidence; N, node; RT-PCR, recombinant polymerase chain reaction.

REVISION QUESTIONS

1. What are the tools used for prognostic evaluation and their strengths and weaknesses?
2. What are the characteristics of the first-generation signatures?
3. What are the characteristics of the second-generation signatures?

Summary: Prognostic and predictive factors

- The most important prognostic factors in early BC are expression of ER/PgR, HER2 and proliferation markers, number of involved regional lymph nodes, tumour histology and size, grade and presence of peritumoural vascular invasion
- The local recurrence risk is related to the status of the surgical margins
- ER/PgR and HER2 are the only validated predictive factors, allowing for selection of patients for endocrine therapies and anti-HER2 treatments, respectively
- High ER expression is also usually associated with lesser absolute benefit of ChT
- Because of generalised mass screening, the natural history of BC has changed. TNM parameters are less reliable. Tumour biology mirrors the prognosis of BC
- Intrinsic molecular classification reflects the biological properties of tumours. Four distinct classes are recognised: luminal A, luminal B, HER2-enriched and basal-like
- First-generation signatures MammaPrint® and Oncotype Dx® have [LoE/GoR: I,A] for prognosis.
- Second-generation signatures Prosigna® and EndoPredict® have [LoE/GoR: I,B] for prognosis in ER-positive HER2-negative patients treated by HT. They predict late recurrences
- Genomic signatures are best used in combination with traditional prognostic and predictive factors and not in their place
- Despite its [LoE/GoR: I,A] prognostic value in node-negative BC patients, UPA-PAI-1 is not extensively used, probably due to the requirement for a substantial amount of fresh-frozen tissue
- Achieving pCR after neoadjuvant treatment is a strong prognostic factor for HER2-positive and TNBC

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New targets and new drugs for breast cancer

Dissecting pathways in oestrogen receptor-positive breast cancer

The phosphatidylinositol 3-kinase (PI3K) and mechanistic target of rapamycin (mTOR) aberrant signalling pathway plays a critical role in endocrine resistance.

The PI3K–mTOR pathway is the most frequently altered pathway in oestrogen receptor (ER)-positive breast cancer (BC). PI3K and mTOR inhibitors are evaluated alone or in combination trials.

Agents such as pictilisib, alpelisib, buparlisib, taselisib and gedatolisib are under development. Convergent loss of the phosphatase and tensin homologue (PTEN) leads to clinical resistance to a PI(3)K inhibitor.

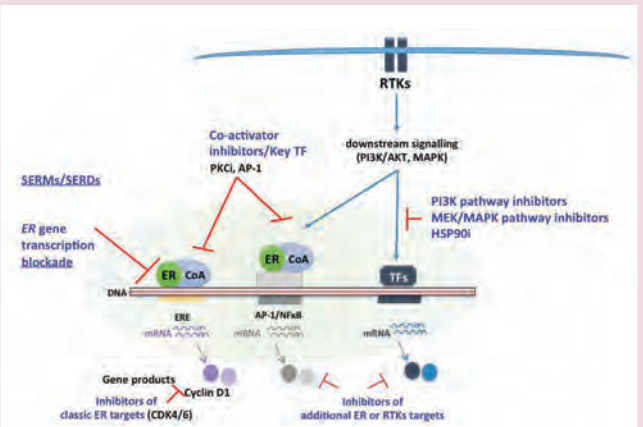

Fig. 13.1

AP-1, Activator protein-1; CDK, cyclin-dependent kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; SERD, selective oestrogen receptor down-regulator; SERM, selective oestrogen receptor modulator.

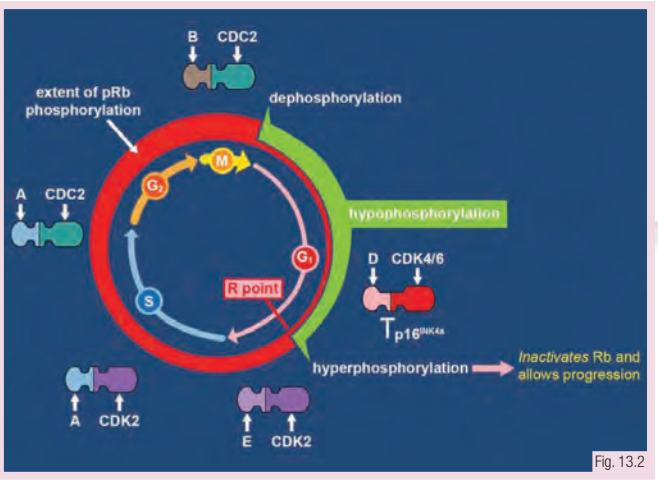

Fig. 13.2

CDK, Cyclin-dependent kinase; pRb, retinoblastoma protein.

Cyclin-dependent kinases (CDKs) are a large family of serine–threonine kinases that play several critical roles in BC cell cycle regulation.

In complex with cyclin D, CDK4 phosphorylates retinoblastoma protein (pRb) and drives cell-cycle progression, a process inhibited by p16.

Several selective CDK 4-6 inhibitors are: US Food & Drug Administration (FDA) and European Medicines Agency (EMA)-approved: palbociclib; or under development in clinical trials: ribociclib and abemaciclib.

Constitutively active mutation in the ER has recently been identified as a recurrent event in ER-positive metastatic BC (MBC). Oestrogen receptor 1 (ESR1) mutation reduces activity of aromatase inhibitors (AIs).

These mutations are observed in the ligand-binding domain and promote the receptors adopting an active conformation, even in the absence of ligand.

New agents are under development in BC to overcome resistance induced by ESR1: LSD102, GDC-0810, AZD9496.

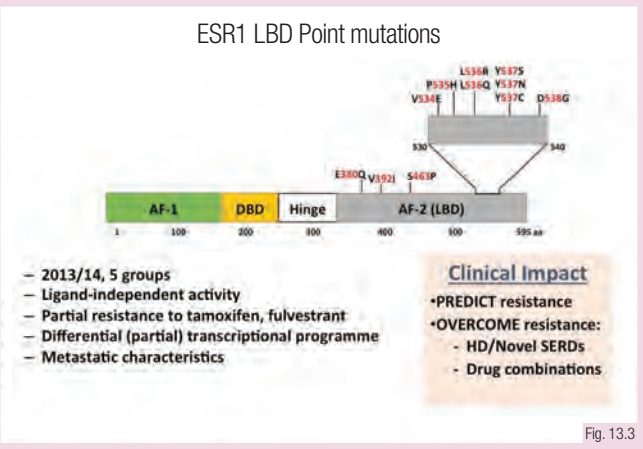

Fig. 13.3

ESR1, Oestrogen receptor 1; HD, high-dose; LBD, ligand binding domain; SERD, selective oestrogen receptor down-regulator.

REVISION QUESTIONS

1. How does PTEN lead to clinical resistance to PI3K inhibitors?
2. Explain cross-talk between CDK4 and pRb.
3. What is the prevalence and clinical significance of ER mutation in patients with MBC?

Dissecting pathways in HER2-positive breast cancer

Substantial research has been performed to explore the pathways responsible for HER2 (human epidermal growth factor receptor 2) signalling.

PI3K/Akt pathway activity has a critical role in predicting response or resistance to anti-HER2 therapy.

PIK3CA mutant/HER2-positive tumours have significantly lower pathological complete response (pCR) rates to neoadjuvant chemotherapy plus dual blockade, compared with wildtype tumours.

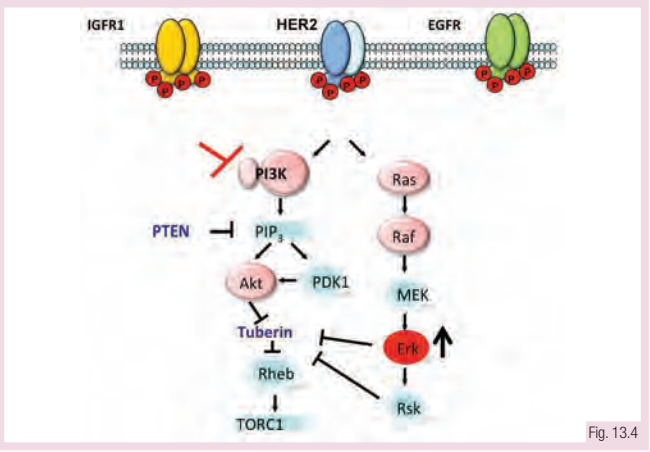

Fig. 13.4

EGFR, Epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IGFR1, insulin-like growth factor receptor-1; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homologue.

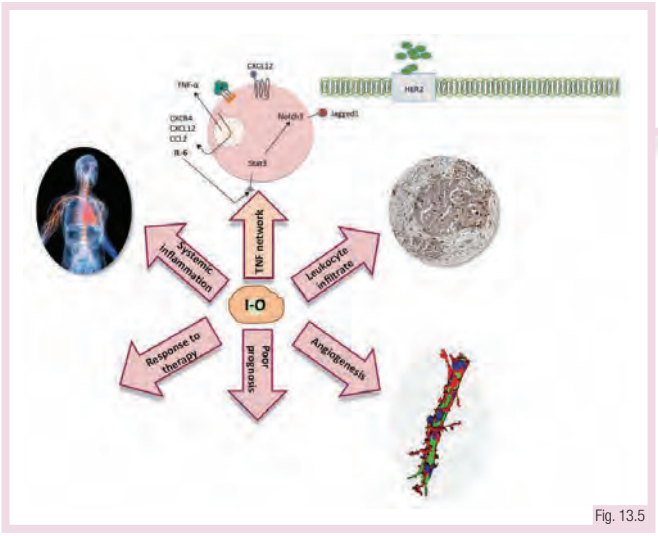

Fig. 13.5

HER2, Human epidermal growth factor receptor 2; I-O, immuno-oncology; TNF, tumour necrosis factor.

The immune system may play a significant role in the therapeutic effects of HER2-targeted agents.

High tumour-infiltrating lymphocyte (TIL) levels in HER2-positive cancers, from patients enrolled in the FinHER adjuvant study, were predictive for benefit from adjuvant trastuzumab therapy.

In the N9831 trial, the presence of TILs was prognostically associated with relapse-free survival (RFS) in patients treated with chemotherapy alone, but not in patients treated with chemotherapy plus trastuzumab.

Several questions remain unanswered in HER2-positive BC:
- What to do at progression?
- Can we omit chemotherapy in ER-positive/ HER2-positive BC?
- What to do for patients with brain metastasis?

Margetuximab is an Fc-optimised monoclonal antibody that targets HER2-positive tumours, enhances antibody-dependent cellular cytotoxicity (ADCC) and improves binding to immune cells.

ONT-380 (tucatinib) is a potent, selective, small-molecule HER2 inhibitor that has shown efficacy in patients with HER2-positive BC.

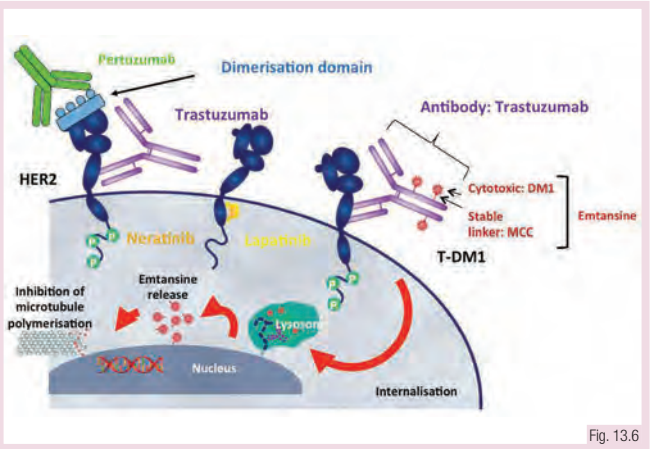

Fig. 13.6

DM1, Emtansine; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine.

REVISION QUESTIONS

1. What is the role of the PIK3 pathway in predictive response to neoadjuvant anti-HER2 therapy?
2. What is the possible role of TILs in HER2-positive BC?
3. Which are the agents under development in HER2-positive BC?

Dissecting pathways in triple-negative breast cancer

Triple-negative breast cancer (TNBC) comprises a highly diverse collection of cancers: the basal-like 1 and 2, immunomodulatory, mesenchymal, stem-like and luminal androgen receptor (AR).

Poly(ADP-ribose) polymerase (PARP) inhibitors demonstrated activity in patients with germline *BRCA1* or *BRCA2* gene mutations. Platinum-derivates may be considered an option in such TNBC subtypes.

Set against the diversity of TNBC, clinical studies of patients with triple-negative disease will need to be focused on molecularly-defined subsets with upfront molecular stratification.

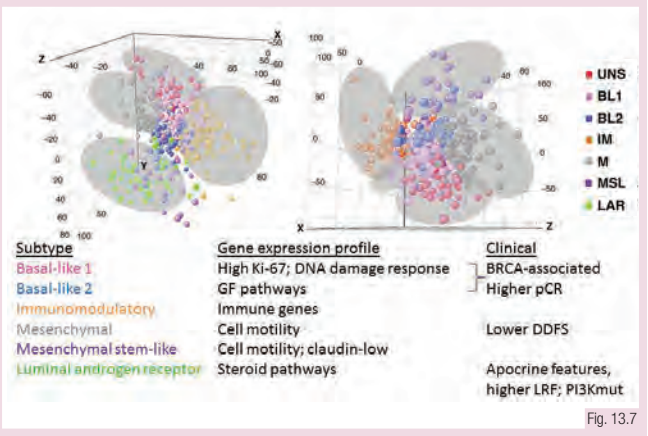

Fig. 13.7

DDFS, Distant disease-free survival; LRF, locoregional failure; pCR, pathological complete response; PI3K, phosphatidylinositol 3-kinase.

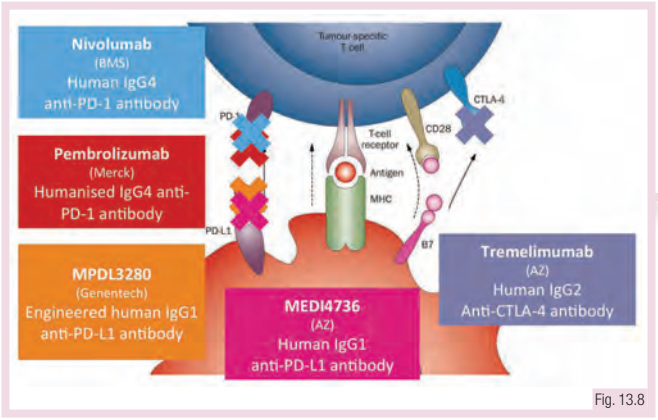

Fig. 13.8

CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; IgG, immunoglobulin G; MHC, major histocompatibility complex; PD-1, programmed death 1; PD-L1, programmed death-ligand 1.

Immune checkpoint inhibition has been demonstrated to be an effective anticancer strategy. Several lines of evidence support the study of immunotherapy in TNBC.

Several immune checkpoint inhibitors are under development in TNBC: pembrolizumab, durvalumab, atezolizumab, nivolumab and tremelimumab.

Immunotherapeutic agents to boost or reactivate the immune system are being extensively studied in TNBC and include antibody conjugates and T-cell approach.

Luminal AR cancers have relatively distinctive gene expression patterns compared with those of other triple-negative subtypes.

This subtype likely overlaps strongly with those TNBCs identified to be AR-positive by immunohistochemistry, which may represent a simple selection strategy.

Several clinical trials have been completed with bicalutamide, enzalutamide and abiraterone in TNBC with AR expression.

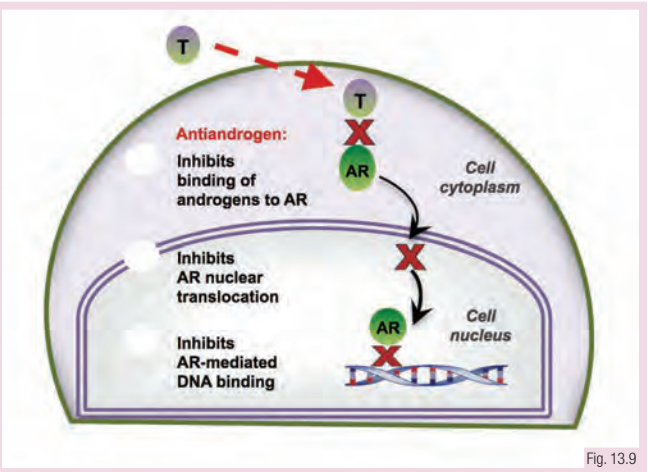

Fig. 13.9

AR, Androgen receptor; T, testosterone.

REVISION QUESTIONS

1. How many subtypes can be distinguished in TNBC?
2. What is the role of immunotherapy in TNBC?
3. What is the role of AR-positivity in luminal AR BC?

Summary: New targets and new drugs for breast cancer

- BC is not a single disease. The identification of functional pathways that are enriched for mutated genes will select subpopulations of patients across ER-positive, HER-positive and triple-negative BC, who will most likely be sensitive to biology-driven targeted agents
- The PI3K-mTOR pathway is the most frequently altered pathway in ER-positive BC
- Many new agents targeting the PI3K–mTOR pathway are under development in ER-positive BC: pictilisib and buparlisib, gedatolisib, alpelisib and taselisib
- CDKs, and dysregulation of this process, is one of the hallmarks of ER-positive BC. Palbociclib is an orally bioavailable, potent CDK4-6 inhibitor, FDA- and EMA-approved. Ribociclib and abemaciclib are under development
- Constitutively active mutation in the ER has been identified as a recurrent event in ER-positive MBC. ESR1 mutation reduces the activity of endocrine therapy
- PIK3CA mutant/HER2-positive disease has had significantly lower pCR rates for neoadjuvant chemotherapy plus dual blockade, compared with wildtype tumours
- Several new HER2-targeting drugs are under development (e.g. margetuximab)
- TNBC comprises a highly diverse collection of cancers: the basal-like 1 and 2, immunomodulatory, mesenchymal, stem-like and luminal AR
- PARP inhibitors and platinum derivatives have demonstrated activity in patients with germline *BRCA1* or *BRCA2* gene mutations
- Immune checkpoint inhibition immunotherapy has shown promise as an anticancer strategy, especially in TNBC
- Luminal AR cancers, potentially targetable with anti-AR agents, have relatively distinctive gene expression patterns compared with those of other triple-negative subtypes

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Organ-specific problems in metastatic breast cancer

14

Bone metastases

Bone is the most common site of metastases in metastatic breast cancer (MBC). Up to 80% of patients, mostly with hormone receptor-positive (HR+) subtype, develop predominantly mixed – osteolytic and osteoblastic – bone metastases (BM).

Nearly half of MBC patients untreated for BM suffer from skeletal-related events (SREs) and/or hypercalcaemia, leading to significant morbidity and mortality.

Standard detection procedures for BM are bone scintigraphy and X-ray or whole body computed tomography (CT) scan. Spinal disease should be evaluated by magnetic resonance imaging (MRI).

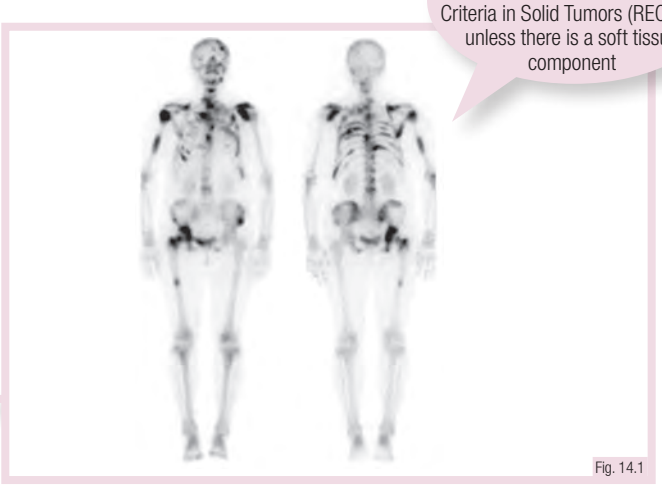


Fig. 14.1

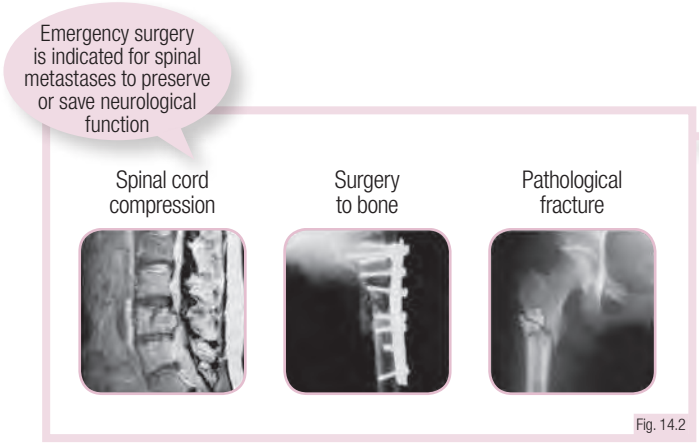


Fig. 14.2

Treatment of BM includes radiotherapy (RT) of painful metastases and those in weight-bearing bones with impending fractures, orthopaedic surgery to prevent or repair fractures and analgesics in addition to systemic therapy.

Bone-seeking radionuclides target BM and may provide temporary pain relief for some patients, though protracted myelosuppression, which can interfere with chemotherapy (ChT), is common. Hence, this is only recommended in the later phase of the disease.

Bone-modifying agents (BMAs), bisphosphonates or denosumab, should be used in combination with systemic therapy and other therapies in order to decrease the rate of SREs.

BMAs delay SREs, relieve symptoms and improve quality of life. One BMA is not recommended over another. Parenteral BMAs are preferred, oral ibandronate might be an alternative for patients with limited BM.

Therapy with BMAs should start at the diagnosis of BM and continue thereafter, even in disease progression. It is suggested to continue BMAs until substantial decline in general performance status (PS) occurs.

BMAs are generally well tolerated; renal toxicity and osteonecrosis of the jaw are uncommon but potentially serious conditions associated with the use of BMAs. Calcium and vitamin D supplements are necessary; invasive dental procedures should be avoided.

Drug name	Method of administration	Recommended dose
Ibandronate	Intravenous/oral	2–6 mg every 3/4 weeks (i.v.); 50 mg per day (p.o.)
Zoledronate	Intravenous	4 mg over no less than 15 minutes every 3-4 weeks*
Denosumab	Subcutaneous	120 mg/4 weeks

*There is evidence that a 12-week schedule is equally effective after 1 year of therapy and is not inferior to a 4-week schedule, even from the start

i.v., Intravenous; p.o., oral.

Fig. 14.3

REVISION QUESTIONS

1. How frequent are BM in patients with MBC?
2. What are the treatment options for BM in patients with MBC?
3. When should treatment with BMA in patients with MBC be started and stopped?

Central nervous system metastases

Breast cancer (BC) is one of the leading causes of leptomeningeal and brain metastases. Central nervous system (CNS) metastases are more frequent in HER2+ and triple-negative breast cancer (TNBC) compared with HR+ subtype (25% vs 10%).

The incidence of CNS metastases is on the rise, most likely due to advances in diagnostics and systemic treatment, with some MBC patients, such as HER2+ patients treated with anti-HER2 therapy, living long enough to develop CNS metastases.

The recommended diagnostic tests are contrast-enhanced CT or MRI; screening for brain metastases is not recommended in asymptomatic patients.

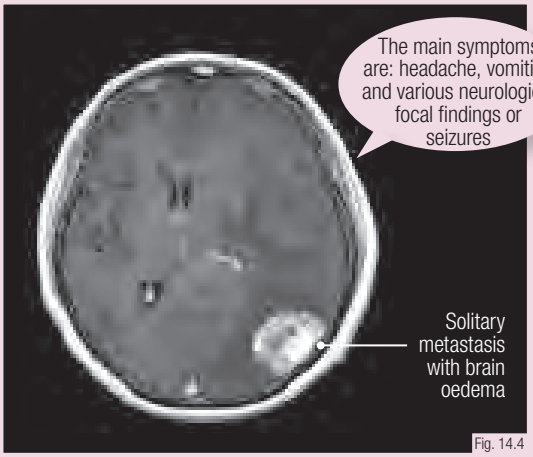


Fig. 14.4

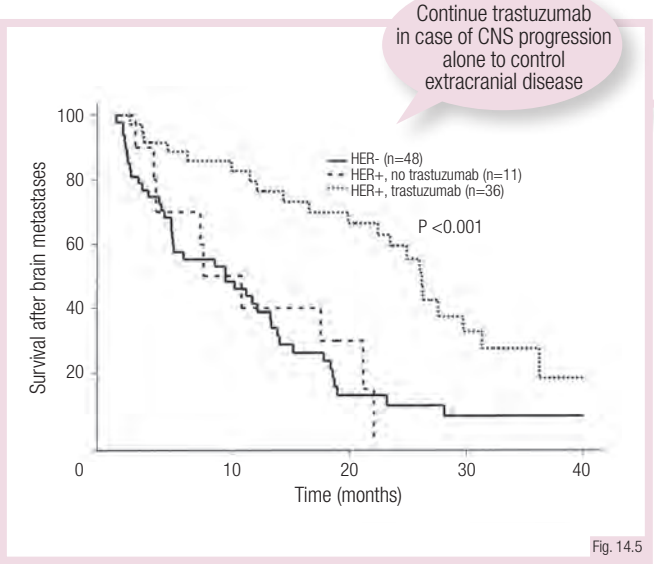


Fig. 14.5

CNS, Central nervous system; HER, human epidermal growth factor receptor.

The median survival rate of patients with CNS metastases is increasing, especially in patients with molecular subtypes for which effective systemic therapy is available.

Corticosteroids represent emergency therapy, providing rapid symptom relief. In MBC patients with progression in CNS alone, systemic therapy should be continued. In addition, in HER2+ patients with newly diagnosed CNS metastases, anti-HER2 therapy should be initiated, if not already provided.

Patients with a single or small number of brain metastases should be treated with stereotactic RT or surgical resection. The role of whole brain radiotherapy (WBRT) after that remains controversial. WBRT remains the preferred option for patients with multiple metastases.

Leptomeningeal metastases occur in approximately 5% of MBC patients, mostly with widespread, heavily pretreated disease. Signs of increased intracranial pressure, cranial or spinal nerve injury and cognitive dysfunction are common.

Treatment is often limited to symptom control. For patients with good PS and controlled extracranial disease, craniospinal RT or inthrathecal ChT (methotrexate, liposomal cytarabine or thiotepa) may be considered, although the latter may not be more effective than systemic ChT.

Intrathecal trastuzumab seems to be a safe and effective option for HER2+ patients with leptomeningeal involvement and controlled extracranial disease.

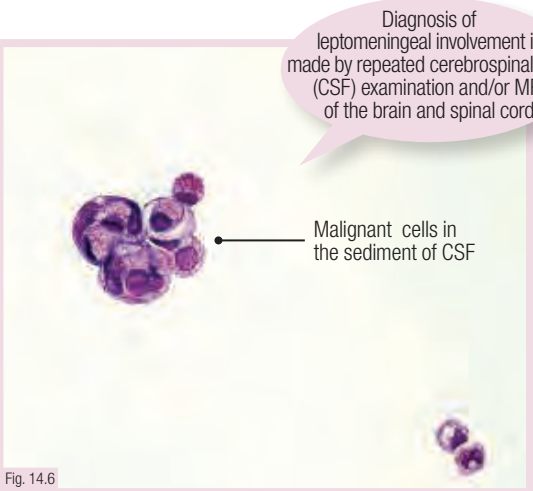


Fig. 14.6

MRI, Magnetic resonance imaging.

REVISION QUESTIONS

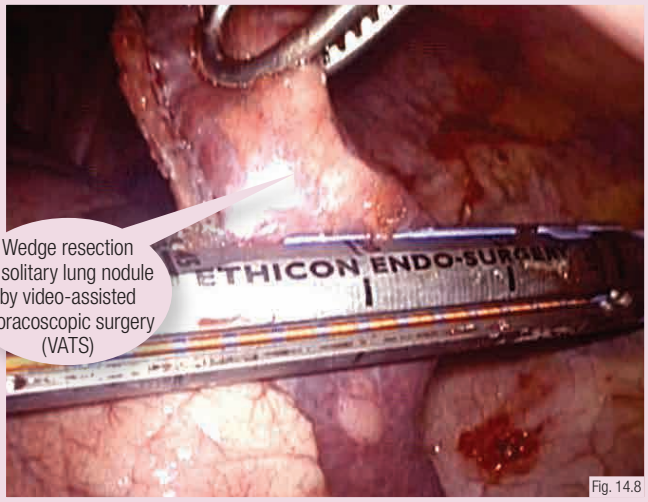
1. Is screening for brain metastases recommended in asymptomatic patients?
2. What is optimal local treatment for solitary brain metastases?
3. Name some of the treatment options for leptomeningeal disease.

Oligometastatic disease

The term oligometastatic disease describes patients with a low-volume metastatic disease, i.e. limited number and size of lesions (up to five and not necessarily in the same organ). Patients with oligometastatic disease represent less than 5% of MBC patients.

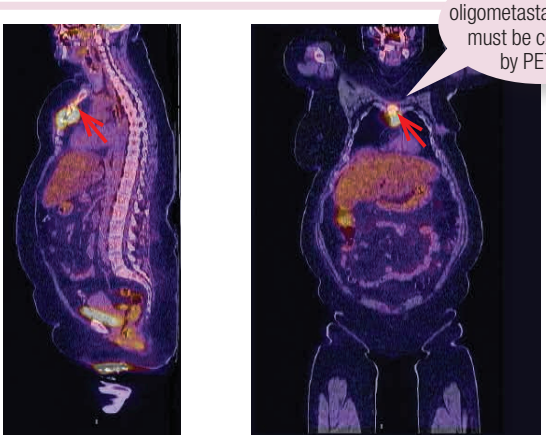
Patients with oligometastatic disease are considered to be potentially amenable to local treatment, aimed at achieving a complete remission status.

Evidence suggests that some patients with oligometastatic MBC treated with multi-modality therapy, i.e. systemic and local therapy, may remain disease-free for over a decade; whether these patients are "cured" depends mainly on competing causes of death.



Wedge resection of solitary lung nodule by video-assisted thoracoscopic surgery (VATS)

Fig. 14.8



Extracranial oligometastatic disease must be confirmed by PET-CT

Fig. 14.7

PET-CT, Positron emission tomography–computed tomography.

Surgical resection in combination with systemic therapy is a potentially curative treatment in patients with oligometastatic BC, with removal of oligometastatic disease in lung, liver, brain or sternum increasingly recommended.

Stereotactic body radiotherapy (SBRT) to oligometastatic lesions in combination with systemic therapy represents a promising new strategy for long-term disease control, with the potential to improve both progression-free and overall survival in oligometastatic BC patients.

There are no firm criteria to select patients who might benefit from multi-modality therapy; long disease-free survival (DFS), low burden of disease, oestrogen receptor or HER2 positivity, completeness of resection and good PS may be helpful.

Approximately 5% of all MBC patients develop liver metastases without extrahepatic disease. Available evidence from series of highly selected patients shows a high survival rate in patients treated with local ablative therapy in addition to systemic therapy.

Since there are no randomised data supporting the effect of local therapy on survival, prospective trials are needed. Local therapy should only be proposed in selected cases of good PS, limited liver involvement and after demonstrated effect of systemic therapy.

Currently, there are no data to select the best local technique for individual patients with oligometastatic liver involvement (surgery, radiofrequency ablation, SBRT, intrahepatic ChT, or other).

Survival outcomes after liver metastases resection in studies with more than 20 patients included

Author	No. patients	Median OS (months)	5 year OS (%)
Adam, 2006	85	46	41
Pocard, 2001	65	ND	46 (4 y)
Elias, 2003	54	34	34
Pocard, 2000	52	42	65 (3 y)
Raab, 1998	34	27	18.4
Sakamoto, 2005	34	36	21
Vlastos, 2004	31	63	61
Yoshimoto, 2000	25	42	33
Thelen, 2008	39	42	NR

OS, Overall survival.

Fig. 14.9

REVISION QUESTIONS

1. How frequent is oligometastatic disease in MBC, and can patients be cured?
2. What is a recommended treatment approach in patients with oligometastatic MBC?
3. What is the preferred treatment of liver metastases in MBC?

Summary: Organ-specific problems in metastatic breast cancer

- Bone is the most common site of metastases in patients with MBC and BM are a frequent cause of disabling SREs, such as pain, pathological bone fractures and spinal cord compression
- In addition to systemic therapy, RT for painful and weight-bearing bones, orthopaedic surgery to prevent or repair fractures, analgesics, and BMAs represent valuable treatment options
- BMAs, bisphosphonates or denosumab, should be started early, if possible before the onset of the first bone event, and should not be discontinued once skeletal events occur, even in the presence of an overall disease progression. These agents should be combined with calcium and vitamin D supplementation
- BC is the second most common cause of CNS metastases and the most common cause of leptomeningeal carcinomatosis among all solid tumours. This is due to improved diagnostic procedures and more effective systemic therapies to control extracranial disease. Both the incidence and survival rates of MBC patients with CNS metastases are increasing
- The mainstay of therapy for treatment of multiple brain metastases remains WBRT, while surgical resection or SBRT are recommended for oligometastatic CNS lesions, in addition to systemic therapy
- Leptomeningeal involvement is a rare condition, developing mostly in heavily pretreated patients in a late phase of MBC; craniospinal RT might be appropriate in selected patients with controlled extracranial disease and good PS in combination with systemic therapy. In patients with HER2+ disease, inthrathecal trastuzumab might be considered
- In a subset of MBC patients with oligometastatic disease, long-term survival can be achieved by multi-modality therapy
- MBC patients with a long disease-free interval, low number of metastases at the involved site, oestrogen receptor positivity, good PS and demonstrated benefit from systemic therapy might benefit from radical local treatment of oligometastatic sites in addition to systemic therapy
- Approximately 3% of all women with MBC develop a solitary pulmonary lesion, but only 35%–40% are breast metastases; therefore, surgical removal is recommended

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Breast cancer in men

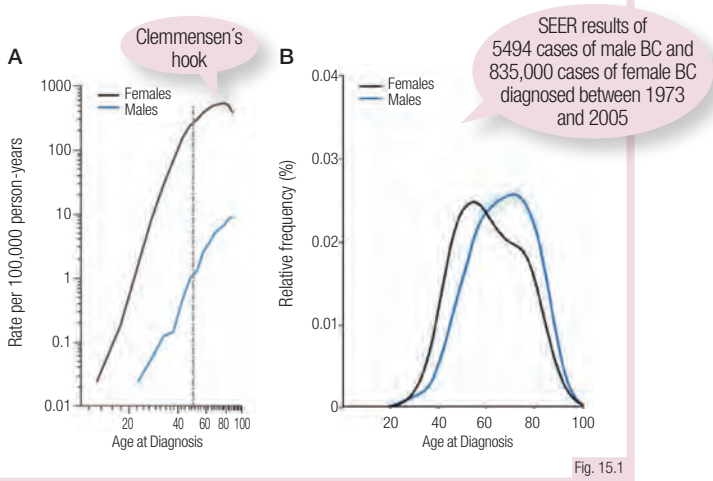
Epidemiology and clinical features

Male breast cancer (BC) accounts for less than 1% of all BC diagnoses worldwide. As with female BC, the incidence rates are higher in North America and Europe and lower in Asia.

According to the SEER database (Surveillance, Epidemiology, and End Results), the mean age at diagnosis is 67 years, six years higher than the average age for women.

15%–20% of male BC patients have a family history of breast or ovarian cancer (relative risk of 2.5).

Male BC incidence increases linearly and steadily with age, with a single peak at around 75 years, in contrast with female BC incidence, with one peak of early-onset disease and a second peak with a later age at onset.



BC, Breast cancer; SEER, Surveillance, Epidemiology and End Results.

Known risk factors

Risk factors for male BC		
Genetics	Endocrine	Other
Klinefelter's	Klinefelter's	Radiation
BRCA2 (less *BRCA1*)	Testicular abnormalities (undescended testis, congenital inguinal hernia, orchidectomy, mumps orchitis)	Ethnic origin (Black men)
Family history	Exogenous oestrogens	History of bone fractures
PTEN (Cowden syndrome)	Liver disease	Alcohol consumption
Androgen receptor	Obesity	Occupational exposures (electromagnetic fields, high temperatures)
p53	Patients treated for prostate cancer	
CHEK2	Hyperprolactinaemia	
CYP17		

Suggestive but not conclusive risk factors

Fig. 15.2

BC, Breast cancer.

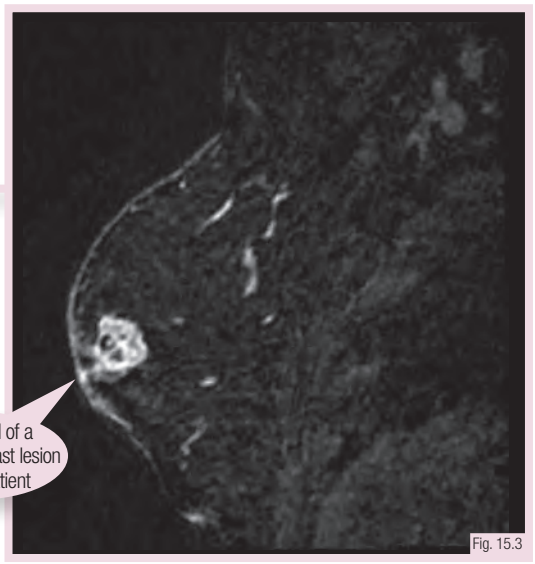
BRCA2 (and few *BRCA1*) mutations contribute to 4%–40% of hereditary BC in men, as opposed to 5%–10% in female BC.

Conditions associated with oestrogen excess and lack of androgens are risk factors for the disease. 3%–7.5% of male BC patients present with Klinefelter's syndrome.

Evaluation of the extent of the disease and stage classification should follow that of female BC guidelines.

Compared with women, male patients have later stage disease, larger tumours, and more frequent nodal involvement, ductal histology, and oestrogen receptor (ER)-positive tumours.

The most common presentation is a painless sub-areolar mass (50%–97%). Clinically suspected axillary nodes are identified in 40%–55% of patients at diagnosis.



MRI, Magnetic resonance imaging.

REVISION QUESTIONS

1. What is the median age at diagnosis of BC in men?
2. What are the known risk factors for BC in men?
3. What are the differential characteristics between male and female BC?

Histopathology, prognosis and local treatment

80%–95% of male BC are invasive ductal carcinomas, 90% are positive for ER and 92%–96% are positive for progesterone receptor (PgR). Data on HER2 status is scarce and inconsistent (HER2 positivity reported in 2%–15% of cases).

New molecular studies suggest that male BC has specific characteristics; e.g. two genomic subgroups: Luminal M1 associated with worse prognosis and Luminal M2 associated with up-regulated immune response and ER signalling.

Molecular subtypes are Luminal A in 83%–98%, Luminal B in 17%, and basal/triple negative in 0%–2%. The International Male BC Program (n=1822) revealed androgen receptor (AR) positivity (88%) and only 25% having high Ki-67 levels (20%–100%). Thus, the majority of male BC is ER+, PgR+ and AR+ and of luminal A subtype, with only 9% being HER2-positive and <1% triple negative.

Overall mortality data in M0 disease from the International Male Breast Cancer Program from 1990 to 2010

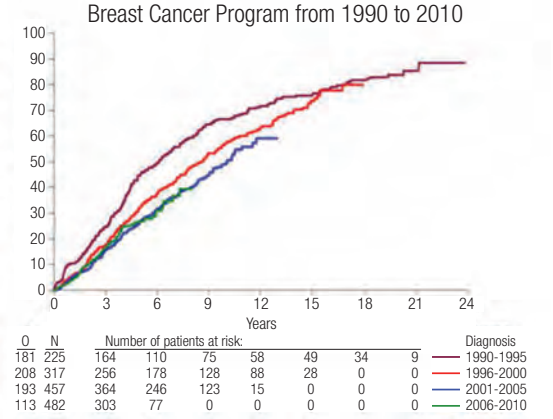


Fig. 15.5

Standard treatment for localised disease includes surgery. Sentinel lymph node biopsy should be performed in clinically node negative disease, as it is feasible in men and associated with less morbidity.

Breast conservative surgery is seldom considered because of the lack of breast tissue and central location of most tumours, but can be performed. Nipple and/or skin-sparing mastectomy may also be considered.

Radiation therapy follows the indications accepted for female BC, but should be balanced against the risk of cardiac complications, as cardiovascular morbidity is frequent in this population.

Overall survival in M0 disease by ER status from the International Male Breast Cancer Program

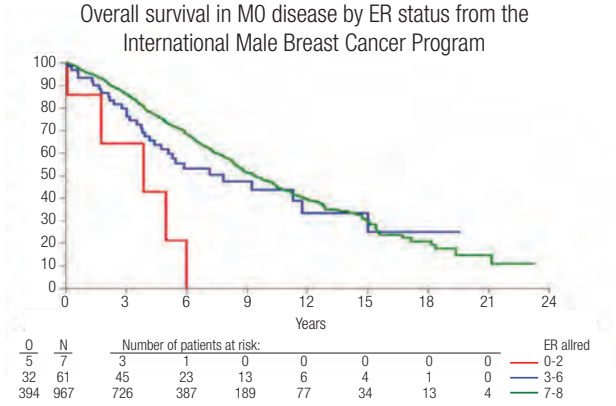


Fig. 15.4

ER, Oestrogen receptor.

The most important prognostic factors of male BC are the stage and lymph node status at diagnosis. The International Male BC Program, which included patients prospectively registered, also confirmed the prognostic value of ER and PgR status (associated with better outcomes).

Based on this registry, there has been a significant improvement in overall survival and BC-specific survival over time.

Studies show worse survival rates for men with BC compared with women, but this could be the result of an older age at diagnosis (comorbid illnesses) and more advanced disease.

Overall survival rates by sex and stage in an international population-based study: 459,846 women and 2,655 men in Denmark, Finland, Geneva, Norway, Singapore and Sweden

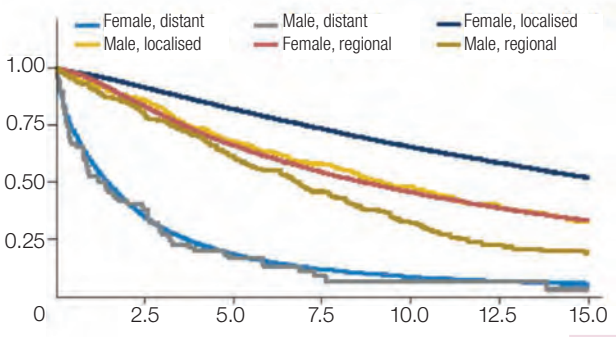


Fig. 15.6

REVISION QUESTIONS

1. What are the main histopathological characteristics of male BC?
2. What are the most important prognostic factors for male BC?
3. How does the prognosis of male BC compare with female BC?

Systemic treatment

In ER-positive disease, tamoxifen is recommended in the adjuvant setting for 5–10 years. Aromatase inhibitors (AIs) should not be used outside clinical trials.

Few data exist on adjuvant trastuzumab in male BC; however, its use should be considered given the therapeutic effect in female HER2-positive BC.

Adjuvant chemotherapy should be considered for men with intermediate- or high-risk disease, mainly in case of ER negativity or involvement of ≥4 lymph nodes.

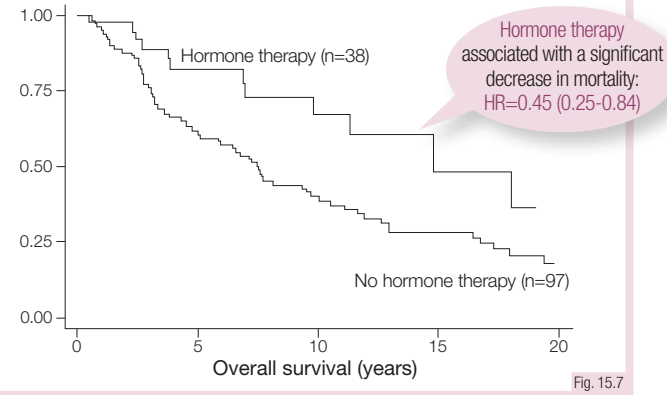


Fig. 15.7

HR, Hazard ratio.

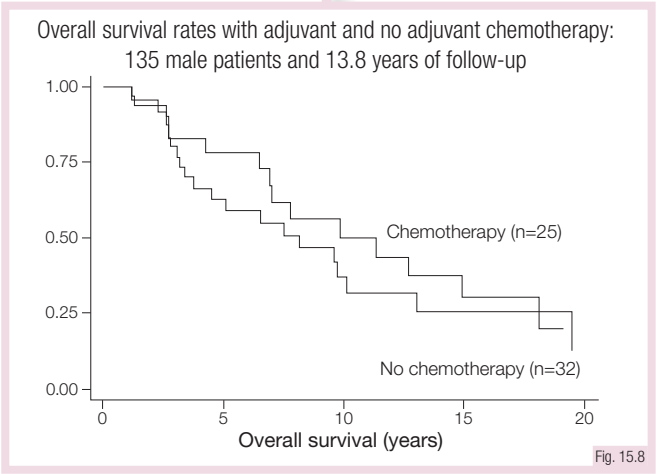


Fig. 15.8

The treatment approach for metastatic disease in men is similar to that of women, with some particularities.

ER positivity predicts response to tamoxifen also in male BC, and it is the preferred treatment in ER+ metastatic disease, where response rates are higher than 80%.

The role of AIs is still unclear, but there is some tendency for their use after progression with tamoxifen. Combination with medical (luteinising hormone-releasing hormone) or surgical orchidectomy should be considered, due to hypothalamic-pituitary negative feedback.

Fulvestrant has shown efficacy for the treatment of metastatic disease (case reports).

Chemotherapy in the metastatic setting should be considered if there is endocrine treatment failure, ER-negative disease and/or life-threatening lesions.

Trastuzumab for HER2-positive disease is recommended in the metastatic setting, based on its efficacy in female patients.

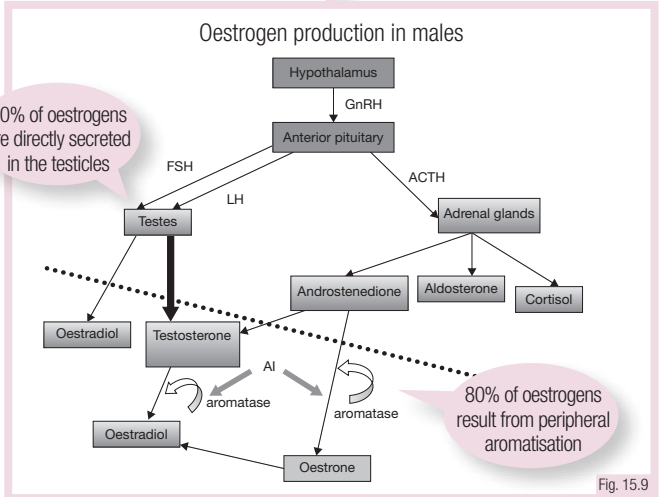


Fig. 15.9

ACTH, Adrenocorticotrophic hormone; AI, aromatase inhibitor; FSH, follicle stimulating hormone; LH, luteinising hormone; GnRH, gonadotropin-releasing hormone.

REVISION QUESTIONS

1. What is the recommended adjuvant treatment for a male patient after modified radical mastectomy in ER+, HER-2 negative, node-positive BC?
2. What is the preferred first-line treatment for a male patient with ER+BC with bone metastases associated with mild pain?
3. When is chemotherapy recommended in the metastatic setting?

Summary: Breast cancer in men

- Epidemiology: <1% of all BC, older age and more advanced disease at diagnosis than in female counterparts
- Histology: majority is invasive ductal carcinoma, ER-positive and HER2-negative
- Survival has improved over time. The reported worse survival rate in men compared with women is probably related to more advanced disease at diagnosis and comorbid illnesses
- The most important prognostic factors are lymph node status, tumour size and ER status
- Surgery: mastectomy and sentinel lymph node biopsy (small tumours and clinically negative axilla) or axillary dissection. Breast-conserving surgery can be considered as well as nipple and/or skin-sparing mastectomy
- Radiation therapy should follow female BC guidelines, but paying more attention to cardiovascular toxicity
- Tamoxifen: mainstay treatment in the adjuvant and metastatic setting, since ER-positive disease is predominant
- AIs: should not be used as adjuvant treatment; are a treatment option in the metastatic setting if progression with tamoxifen, and usually combined with a luteinising hormone-releasing hormone agonist
- Chemotherapy: beneficial in the adjuvant setting if high-risk disease and in the metastatic setting, if failure of hormone treatment, ER-negative and/or life-threatening disease
- Trastuzumab: given the strong benefit in female BC, trastuzumab is also recommended in male HER2-positive early and metastatic BC

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Breast cancer at the extremes of age
Part A: Breast cancer in young women

16

Principles

Breast cancer (BC) is rare in young women, with only 6%–7% of new cases being diagnosed in women under 40 years of age. The risk of BC increases with age.

European cancer registries suggest an increasing trend in BC in young women. BCis a leading cause of death in women under 40 years and diagnosis is often delayed.

There are no effective tools for screening. Mammography is often less effective because young women have higher breast density.

If current age is …	The probability of developing breast cancer in the next 10 years is:	or 1 in …
20	0.1%	1674
30	0.4%	225
40	1.4%	69
50	2.3%	44
60	3.5%	29
70	3.9%	26
Lifetime risk	**12.3%**	**8**

Fig. 16A.1

Predicted probabilities of carrying a *BRCA1* mutation, by age, ER status and grade

Age group	All histologies (%)	ER-positive			ER-negative		
		Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
<30 years	8	1.1	1.6	2.7	14.4	21.0	35.0
30–34 years	5	0.8	1.2	2.0	10.9	15.9	26.5
35–39 years	2	0.2	0.3	0.5	2.7	4.0	6.6
40–44 years	1.5	0.1	0.2	0.3	1.5	2.2	3.7
45–49 years	1	0.1	0.1	0.2	1.0	1.5	2.5
50–59 years	0.3	0.03	0.04	0.07	0.4	0.6	0.9

ER, Oestrogen receptor.

Fig. 16A.2

At diagnosis, breast magnetic resonance imaging (MRI) should be considered if the woman is under 30, or has high breast density or is a *BRCA1/2* mutation carrier.

The main risk factors for BC in young women include a family history and a history of therapeutic radiation to the chest.

Young women are more likely to harbour a mutation in, among others, *BRCA1* or *BRCA2*. Genetic testing should be considered early in patient management.

Young women with BC often have a worse outcome than older women, even after adjusting for stage and subtype, and despite more intensive therapy.

BC in young women has less favourable biological features, including higher histological grade, higher Ki67 and lymphovascular invasion.

Young women are more likely to have triple-negative (TN) subtype. TN subtype in the context of a *BRCA1/2* mutation may warrant tailored treatment in early and advanced disease.

10-year cumulative survival in relation to expected survival by age for Stage IV breast cancer (Fredholm 2009)

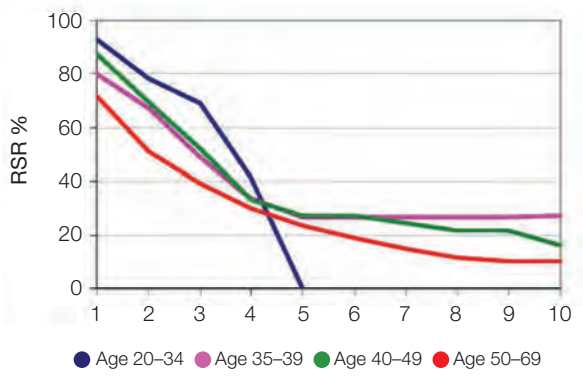

Fig. 16A.3

RSR, Relative survival rate.

REVISION QUESTIONS

1. When is MRI indicated at the time of BC diagnosis?
2. What are the important risk factors for BC in young women?
3. Does the biology of BC in younger women differ to that of older women?

Treatment

Treatment decisions and choice of systemic and local therapy should be driven by biology, stage and subtype, irrespective of young age, at all stages of the disease.

Young age is a risk factor for local recurrence and for contralateral BC. Thus caution with surgical margins and radiation boost after lumpectomy is mandatory.

Mastectomy is not associated with increased survival in young women, and should be performed only if it is medically indicated or is the patient's preference.

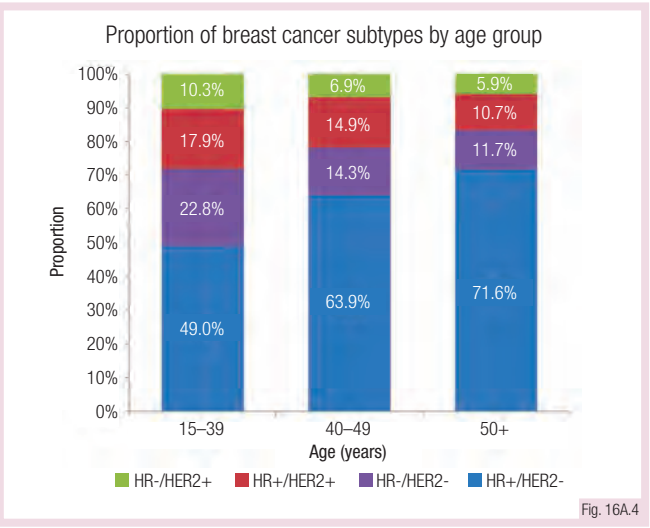

Fig. 16A.4

HR, Hormone receptor; HER2, human epidermal growth factor receptor 2.

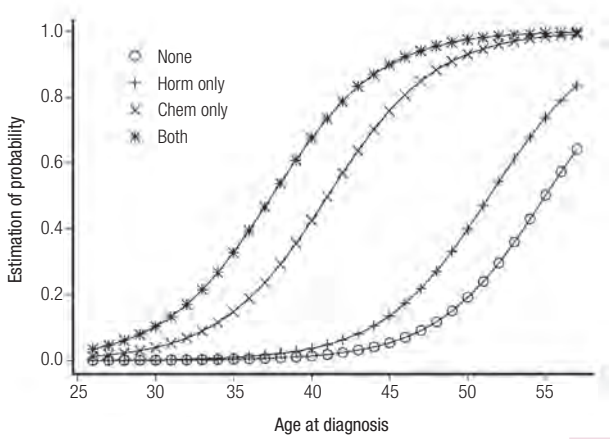

Fig. 16A.5

Options for adjuvant endocrine therapy include tamoxifen or ovarian function suppression (OFS) with either tamoxifen or an aromatase inhibitor.

Adjuvant systemic therapies may adversely affect fertility and result in premature menopause. This is a major cause of anxiety and psychological distress.

Fertility-preservation options should be discussed with all patients prior to therapy. Gonadotrophin-releasing hormone (GnRH) analogues during adjuvant chemotherapy may be considered for ovarian protection.

BC diagnosed during pregnancy is complex and is best managed by a multidisciplinary team. The trimester and timing of labour should be taken into consideration when planning therapy.

Retrospective data on the safety of pregnancy following BC are reassuring and hence it is not contraindicated. Choice and timing of pregnancy is complex for women at high risk of recurrence.

Menopausal symptoms, sexual functioning and psychosocial issues significantly impact quality of life in young women, and must be addressed as part of survivorship care.

Is pregnancy safe after breast cancer?

Study	Pregnant	Non-pregnant	Risk of death/ recurrence
Azim et al (2013)	333	874	Reduced
Cordoba et al (2011)	18	97	Reduced
Azim et al (2011) – M/A	1244	18 145	Reduced
Valachis et al (2010) – M/A	1089	13 051	Reduced
Ives et al (2007)	123	2416	Reduced
Kroman et al (2008)	371	9865	Reduced
Blakely et al (2004)	47	323	No difference
Mueller et al (2003)	438	2775	Reduced
Gelber et al (2001)	94	188	Reduced

M/A, Meta-analysis.

Fig. 16A.6

REVISION QUESTIONS

1. What options exist for adjuvant endocrine therapies in young women?
2. Should young age be the key determinant when deciding on therapy?
3. Is pregnancy after BC contraindicated?

Summary: Breast cancer in young women

- 6%–7% of all new BC cases are diagnosed in women under 40 years of age
- Young women with BC are more likely to harbour a *BRCA1/2* mutation
- No effective screening tools exist, and MRI of the breast may be indicated at diagnosis
- BC in young women has less favourable biological features, and is more often TN disease
- BC in young women has a poorer prognosis and is more likely to have distant and local recurrence
- Treatment decisions should be driven by stage and biology, and not by age
- Numerous options exist for adjuvant endocrine therapy, and OFS may be considered, particularly in higher risk patients
- Adjuvant systemic therapies adversely affect fertility and may result in premature menopause; thus fertility-preservation options should be discussed with all patients
- Pregnancy during BC should be managed by an expert multidisciplinary team
- Pregnancy after BC is not contraindicated but should be carefully planned
- Menopausal symptoms, sexual functioning and psychosocial issues significantly impact quality of life in young women, and must be addressed as part of survivorship care

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16 Breast cancer at the extremes of age
Part B: Breast cancer in the elderly

Principles

Breast cancer (BC) is the most commonly diagnosed female cancer. Its incidence increases with age, and about 25%–30% of BCs in developed countries occur in women aged ≥70 years.

In Northern and Western European women aged 65 years and older, crude BC incidence and BC mortality rates are 295 and 135 per 100 000 women, respectively.

Although BC is a frequent cause of death in older women with BC, a sizeable proportion ultimately die from non-cancer related causes, often related to comorbidities.

Breast cancer mortality in relation to causes of mortality in 14 048 breast cancer patients with median follow-up of 4.7 years

Age	Total deaths	Deaths from breast cancer	%
50–69	1334	933	70
70–74	514	293	57
75–79	696	329	47
≥80	1681	663	39
Total	4225	2218	53

39% of breast cancer patients aged ≥80y who died during follow-up, died because of breast cancer

Fig. 16B.1

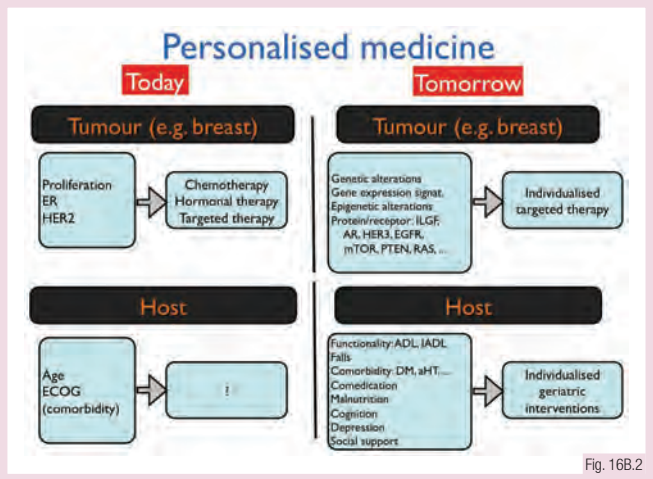

Fig. 16B.2

ADL, Activities of daily living; aHT, arterial hypertension; DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; IADL, instrumental ADL.

BC screening benefit decreases with age and disappears if life expectancy is too short, where it can even become harmful due to increasing risk for overdiagnosis and overtreatment.

Older BC patients are less likely to be treated according to accepted treatment guidelines, and undertreatment can, as a consequence, have a strong negative effect on survival.

General health status can be rated by geriatric assessment, which allows estimation of life expectancy, predicts treatment toxicity, detects multiple health problems and allows directed geriatric interventions and personalised treatment adaptation.

Primary hormone therapy for hormone-sensitive BC in the elderly, instead of surgery, is associated with markedly increased risk of local relapse, but no detriment to overall survival has been demonstrated, so it is mainly an option in frail patients with limited life expectancy.

Breast tumours in older adults are generally more indolent, with higher percentage of hormone sensitivity, lower HER2 overexpression and lower grade, but tumours in the whole range of aggressiveness are seen.

Compliance to hormone therapy can be problematic, and this is most pronounced in older adults.

Relative recurrence and mortality reduction per age group with adjuvant tamoxifen compared with no hormone treatment

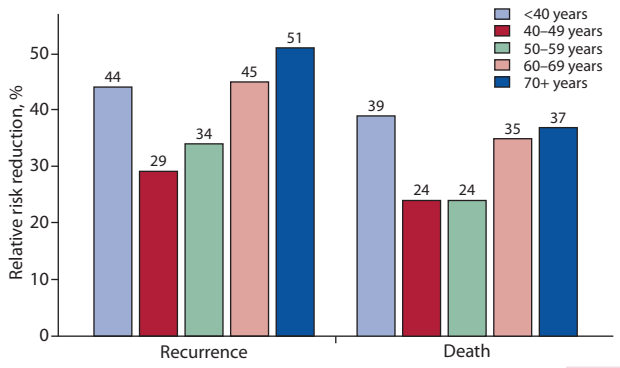

Fig. 16B.3

REVISION QUESTIONS

1. Does the benefit of BC screening increase with age?
2. Does upfront surgery improve overall survival compared with primary hormone therapy in older women?
3. What are the benefits of geriatric assessment in older BC patients?

Treatment

Adjuvant antihormone therapy decreases BC mortality similarly in older and younger patients, but the elderly are more vulnerable to adverse effects of hormone therapy.

Adjuvant breast irradiation after breast-conserving surgery should be considered in all older BC patients, but in lower risk tumours or short life expectancy the absolute benefit can be very limited.

Hypofractionated radiation schedules result in similar locoregional control and adverse effects as standard schedules, while requiring fewer visits. Partial breast irradiation in older patients is still investigational.

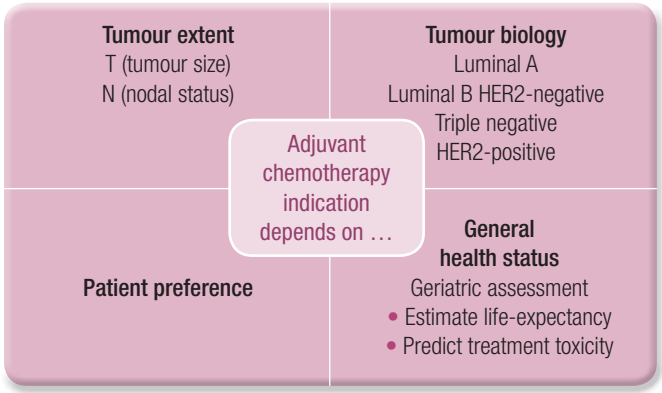

Fig. 16B.4

Indication for adjuvant chemotherapy depends on tumour extent, tumour biology, general health status and patient preference. Older patients with node-positive, hormone-negative disease potentially derive the largest benefit.

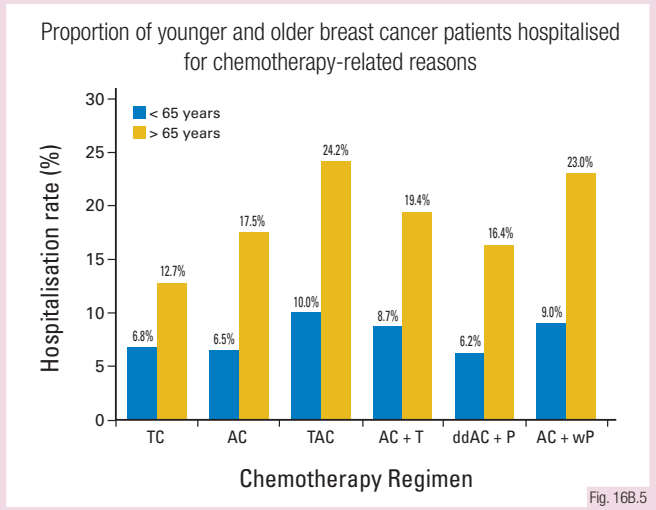

Fig. 16B.5

A, Doxorubicin; C, cyclophosphamide; P, paclitaxel; T, docetaxel; dd, dose-dense; w, weekly.

Adjuvant chemotherapy is generally feasible, but older adults are more sensitive to adverse effects and are more frequently hospitalised for chemotherapy-related complications.

Standard AC (doxorubicin+cyclophosphamide) and CMF (cyclophosphamide, methotrexate and fluorouracil) chemotherapy regimens are better than single-agent capecitabine. Taxanes can be added to anthracyclines in high-risk healthy elderly patients, or replace anthracyclines (e.g. TC regimen, docetaxel+cyclophosphamide) to reduce cardiotoxicity.

Hormone therapy is the treatment of choice for older women with hormone-sensitive metastatic BC, while chemotherapy (mostly single agent) can be used in hormone-resistant or insensitive tumours.

Patients with HER2-positive disease should receive HER2-targeted therapy and chemotherapy. If chemotherapy is contraindicated, anti-HER2 therapy can also be combined with hormone therapy or used alone if hormone-insensitive.

Pharmacology of chemotherapeutic agents can change with increasing age. Dose reductions and schedule modifications are controversial, but should be considered based on known pharmacology and toxicity.

Pharmacokinetic parameters that might change with ageing

Parameter changes	Clinical consequences
Absorption decreased	Oral chemotherapy (e.g. capecitabine) might be less effective in the elderly
Distribution volume decreased	Serum concentrations and toxicity of several chemotherapeutics might increase (e.g. taxanes)
Hepatic metabolism decreased	Not well known, may affect serum concentrations of chemotherapeutics eliminated by hepatic metabolisation (e.g. taxanes, cyclophosphamide, anthracyclines)
Renal excretion decreased	Dosing should be adapted to recommendations in order to avoid excessive serum concentrations and toxicity from renally excreted chemotherapeutics (e.g. carboplatin, methotrexate)

Fig. 16B.6

REVISION QUESTIONS

1. How are breast tumours different in older versus younger women?
2. Should all older BC patients treated with breast-conserving surgery receive adjuvant radiotherapy?
3. Which chemotherapy regimens are preferentially used in older BC patients?

Summary: Breast cancer in the elderly

- About 25%–30% of BCs in developed countries occur in women aged ≥70 years
- A sizeable proportion of older BC patients ultimately die from non-cancer related causes
- Breast tumours are generally more indolent in older women, but tumours in the whole range of aggressiveness are seen
- Older BC patients are less likely to be treated according to accepted treatment guidelines
- Geriatric assessment allows directed geriatric interventions and personalised treatment adaptation
- Primary hormone therapy, instead of surgery, is an option mainly in frail patients but can also be used as a neoadjuvant approach followed by surgery in oestrogen receptor-positive tumours
- Adjuvant hormone therapy improves BC mortality similarly in older and younger patients
- The benefit of breast irradiation after breast-conserving surgery depends on life expectancy and risk of relapse
- Adjuvant chemotherapy is generally feasible, but older adults are more sensitive to adverse effects. Chemotherapy regimens that have been evaluated in the older population should be used preferentially
- Pharmacology of chemotherapeutic agents can change with ageing, sometimes requiring dose modifications

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Locally recurrent disease

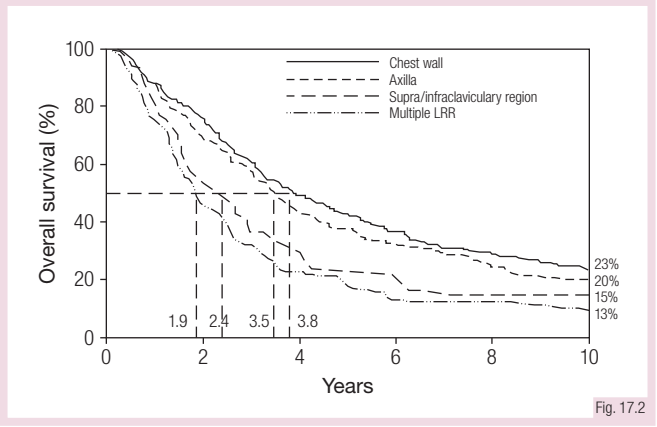
Definition, staging and therapeutic approach

Local recurrence is defined as the reappearance of cancer on the ipsilateral chest wall or remaining breast tissue. Local recurrence can extend outside the original site of the breast.

Regional recurrence denotes tumour involving the regional lymph nodes.

At the time of locoregional recurrence (LRR), re-staging should be done to rule out metastatic disease. Recurrence should be confirmed histologically (including standard prognostic and predictive factors).

Location of recurrence is important for overall survival (OS).

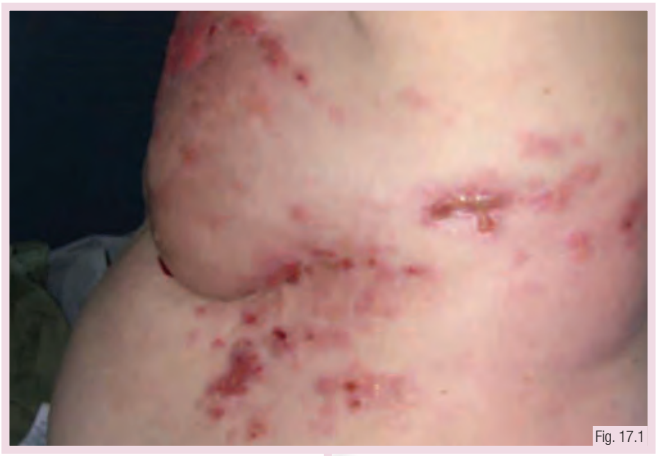


LRR, Locoregional recurrence.

Other factors that were found to be associated with poor OS at the time of LRR include: large primary tumours, multiple macroscopically involved nodes, extracapsular invasion, supra/infraclavicular failures, combined local and nodal LRR and a short interval (<48 months) to first LRR.

Treatment has the potential to provide long-term disease-free survival. Thus, meticulous target volume delineation and RT techniques such as deep inspiration breath hold should be applied to decrease the risk of toxicity, especially in patients who were heavily treated with chemotherapy.

Patients with LRR should also be considered for systemic treatment as part of their treatment management. For this, it can be important to re-determine the receptor status.



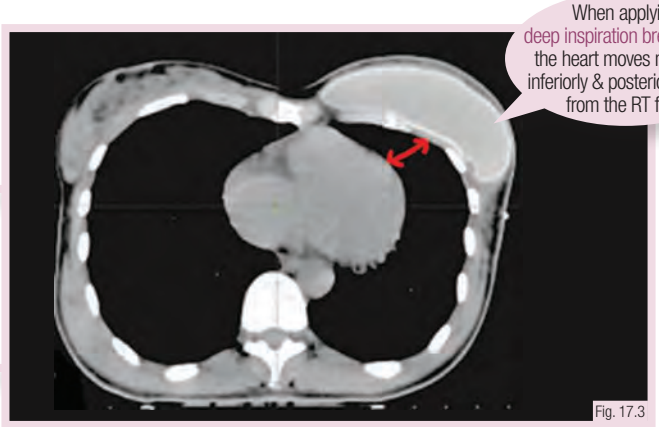
Local treatment may provide palliation even in the presence of metastases.

Salvage treatment depends on the characteristics of the primary and recurrent cancer, previous systemic treatment and the site of recurrence, the extent of disease, the patient's comorbidities and the patient's wishes.

Approximately 5%–17% of patients undergoing mastectomy will have LRR within 10 years, mostly clinically apparent at the chest wall.

For patients who did not undergo immediate post-mastectomy radiation therapy (RT), chest wall and regional lymphatic RT is the standard treatment, followed by a boost to the chest wall after resection of the recurrent disease, with a higher dose in case of residual macroscopic disease.

Limited treatment of the chest wall (RT of chest wall only or part of chest wall), or RT to involved lymph nodes only, increases the risk for future recurrences.



RT, Radiation therapy.

REVISION QUESTIONS

1. Is histological confirmation needed in cases of suspected LRR?
2. Is it necessary to determine receptor status?
3. Can local treatment be offered to patients with disseminated disease?

Locoregional recurrence of breast cancer after mastectomy

Optimal treatment to the chest wall, after primary post-mastectomy chest wall RT, is not well defined, but re-irradiation of the chest wall can be considered.

Re-irradiation can be performed as the primary treatment for gross disease, if surgery is not feasible, or considered in cases at risk of bearing microscopic residual tumour after resection.

The effective re-irradiation dose is generally ≤50 Gy to reduce adverse effects from the accumulated radiation dose. Combining low-dose re-irradiation with hyperthermia results in improved tumour control without adding to toxicity. Hyperthermia must be performed in specialised centres, which at present do not exist in every European country.

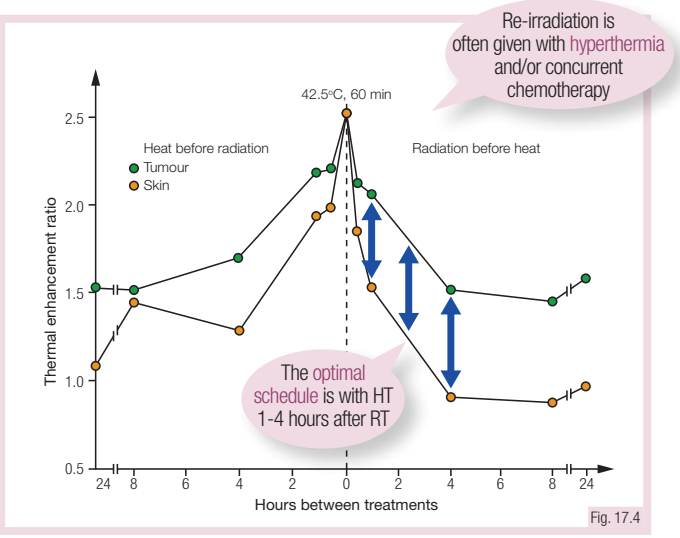


Fig. 17.4

HT, Hyperthermia; RT, radiation therapy.

Thermal enhancement ratio (TER):
TER = RT dose without hyperthermia/RT dose achieving equivalent tumour control with hyperthermia

Maximal effort and techniques should be applied to lower potential long-term toxicity, including active breathing control, superficial type of beams – such as electrons or low-energy photons – and hyperfractionated RT

RT, radiation therapy. Fig. 17.5

Hyperthermia is given once or twice per week for 60 minutes at a target temperature of 42–43°C. Radiosensitisation by hyperthermia is quantified using the thermal enhancement ratio (TER).

Both conventional and hypofractionated RT+hyperthermia schedules are used and hyperthermia is given shortly before or after RT.

The Datta meta-analysis of randomised trials of RT±hyperthermia shows an odds ratio for tumour control of 2.64 in favour of hyperthermia.

After re-irradiation to a total dose of 36 Gy in 12 fractions and hyperthermia treatment twice a week to 42°C, the patient shown in these figures achieved a durable complete response.

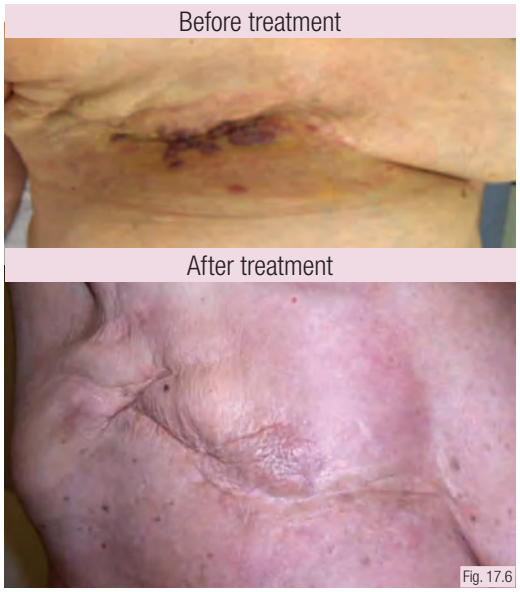


Fig. 17.6

REVISION QUESTIONS

1. Define TER.
2. What is the rationale for combining re-irradiation with hyperthermia?
3. What is the optimal interval and sequence for hyperthermia+RT?

Locoregional recurrence of breast cancer after breast conserving therapy

Based upon a meta-analysis of 17 randomised trials, patients aged >40 years at the time of breast-conserving therapy (BCT) – including surgery and RT – have a LRR rate <3%.

Patients treated with breast-conserving surgery (BCS) alone, without RT, have ~35% risk of LRR. Partial breast irradiation as part of BCT may be associated with higher rates of LRR.

Mastectomy is the standard of care for most patients with local recurrence following breast-conserving therapy

Fig. 17.7

Almost 50% of LRRs after BCT are diagnosed within 5 years. Early LRR (<48 months disease-free interval) is an indicator of a biologically aggressive disease.

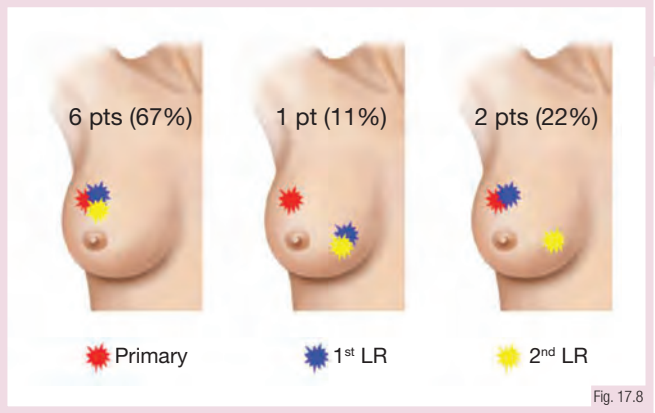


Fig. 17.8

LR, Local recurrence; pt, patient.

Sites of primary tumour in red, first local recurrence (i.e. ipsilateral breast tumour recurrence [IBTR]) in blue and second local recurrence in yellow.

In selected patients who request breast conservation, salvage breast-conserving surgery (SBCS) can be considered even in the case of earlier RT. Careful patient selection is needed.

Considerations such as tumour size (<2 cm), location, disease-free interval, genetics (BRCA) and the patient's preference should be evaluated.

Re-irradiation of the tumour bed after SBCS can be performed in specialised centres via catheter-based interstitial brachytherapy, without significant adverse effects in most patients.

Since there are no guidelines indicating for which patients this approach is appropriate, only patients who have low risk for recurrence and prefer BCS should be considered as potential candidates for such management.

Interstitial brachytherapy after salvage breast-conserving surgery

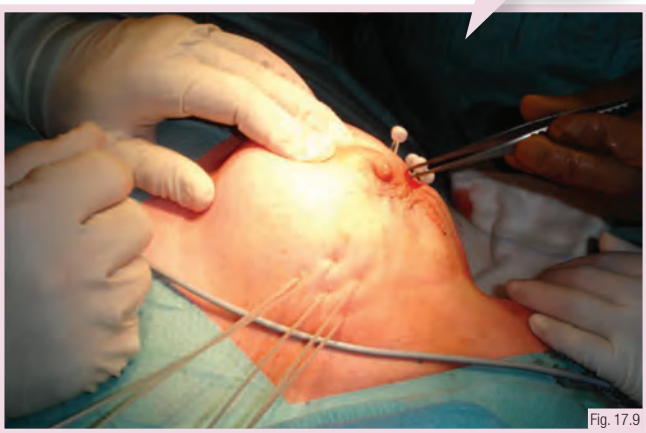


Fig. 17.9

REVISION QUESTIONS

1. What are the rates of LRR after BCT with and without RT?
2. What is the standard treatment of LRR after BCT?
3. Can salvage BCT be offered to patients with LRR after BCT?

Summary: Locally recurrent disease

- At the time of LRR after mastectomy or BCS/BCT, all patients must undergo disease re-staging to rule out synchronous distant metastatic disease
- Any suspected recurrence should be confirmed histologically including standard prognostic and predictive factors
- Patients with LRR represent a heterogeneous group. Salvage treatment depends on the primary local treatment: mastectomy/conservative treatment, axillary lymph node dissection versus sentinel lymph node biopsy, adjuvant RT of chest wall or preserved breast +/- axillary and/or regional lymph nodes, previous systemic treatment, site of recurrence, extent of disease, patient's comorbidities and preferences
- Local treatment may provide palliation even in the presence of disseminated disease
- Management needs to be based on a multidisciplinary assessment. It generally requires combined modality therapy, which should be tailored to the individual's case and take the centre's expertise into account
- Re-irradiation of the tumour bed by catheter-based interstitial brachytherapy after SBCS can be performed in specialised centres
- For LRR of breast cancer in previously irradiated areas, hyperthermia and adapted dose re-irradiation is the treatment of choice. When possible, this should be preceded by surgery
- Durable control depends on the size of the tumour: microscopic > small > extensive
- Maximal effort should be applied to lower the potential long-term toxicity, especially in cases of re-irradiation

NOTE: In addition to surgery and RT, systemic therapy should be considered in most cases to further improve both the local control and the long-term disease control rate. It may consist of chemotherapy, HER2-targeted therapy and/or endocrine therapy, depending on patient and tumour characteristics, taking prior treatments into consideration as well. While endocrine therapy and anti-HER2 therapy should be advised for most ER-positive and HER2-positive cases, respectively, the added benefit of chemotherapy as evaluated in the CALOR trial seems to be more effective for ER-negative cases.

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Appendix 1: WHO Classification of Tumours of the Breast, 4th Edition (2012)

Epithelial tumours
- Microinvasive carcinoma

Invasive breast carcinoma
- Invasive carcinoma of no special type (NST)
  - Pleomorphic carcinoma
  - Carcinoma with osteoclast like stromal giant cells
  - Carcinoma with choriocarcinomatous features
  - Carcinoma with melanotic features
- Invasive lobular carcinoma
  - Classic lobular carcinoma
  - Solid lobular carcinoma
  - Alveolar lobular carcinoma
  - Pleomorphic lobular carcinoma
  - Tubulolobular carcinoma
  - Mixed lobular carcinoma
- Tubular carcinoma
- Cribiform carcinoma
- Mucinous carcinoma
- Carcinoma with medullary features
  - Medullary carcinoma
  - Atypical medullary carcinoma
  - Invasive carcinoma NST with medullary features
- Carcinoma with apocrine differentiation
- Carcinoma with signet ring differentiation
- Invasive micropapillary carcinoma
- Metaplastic carcinoma of no special type
  - Low-grade adenosquamous carcinoma
  - Fibromatosis like metaplastic carcinoma
  - Squamous cell carcinoma
  - Spindle cell carcinoma
  - Metaplastic carcinoma with mesenchymal differentiation
    - Chondroid differentiation
    - Osseous differentiation
    - Other types of mesenchymal differentiation
  - Mixed metaplastic carcinoma
  - Myoepithelial carcinoma
- Rare types
  - Carcinoma with neuroendocrine features
    - Neuroendocrine tumour, well differentiated
    - Neuroendocrine carcinoma, poorly differentiated (small cell carcinoma)
    - Carcinoma with neuroendocrine differentiation
  - Secretory carcinoma
  - Invasive papillary carcinoma
  - Acinic cell carcinoma
  - Mucoepidermoid carcinoma
  - Polymorphous carcinoma
  - Oncocytic carcinoma
  - Lipid rich carcinoma
  - Glycogen rich clear cell carcinoma
  - Sebaceous carcinoma
  - Salivary gland / skin adnexal type tumours
    - Cylindroma
    - Clear cell hidradenoma

Epithelial-myoepithelial tumours
- Pleomorphic adenoma
- Adenomyoepithelioma
  - Adenomyoepithelioma with carcinoma
- Adenoid cystic carcinoma

Precursor lesions
- Ductal carcinoma *in situ*
- Lobular neoplasia
  - Lobular carcinoma *in situ*
    - Classic lobular carcinoma *in situ*
    - Pleomorphic lobular carcinoma *in situ*
  - Atypical lobular hyperplasia

Intraductal proliferative lesions
- Usual ductal hyperplasia
- Columnar cell lesions including flat epithelial atypia
- Atypical ductal hyperplasia

Papillary lesions
- Intraductal papilloma
  - Intraductal papilloma with atypical hyperplasia
  - Intraductal papilloma with ductal carcinoma *in situ*
  - Intraductal papilloma with lobular carcinoma *in situ*
- Intraductal papillary carcinoma
- Encapsulated papillary carcinoma
  - Encapsulated papillary carcinoma with invasion
- Solid papillary carcinoma
  - *In situ*
  - Invasive

Benign epithelial proliferations
- Sclerosing adenosis
- Apocrine adenosis
- Microglandular adenosis
- Radial scar / complex sclerosing lesion
- Adenomas
  - Tubular adenoma
  - Lactating adenoma
  - Apocrine adenoma
  - Ductal adenoma

Mesenchymal tumours
- Nodular fasciitis
- Myofibroblastoma
- Desmoids type fibromatosis
- Inflammatory myofibroblastic tumour
- Benign vascular lesions
  - Haemangioma
  - Angiomatosis
  - Atypical vascular lesions
- Pseudoangiomatous stromal hyperplasia
- Granular cell tumour
- Benign peripheral nerve sheath tumours
  - Neurofibroma
  - Schwannoma
- Lipoma
  - Angiolipoma
- Liposarcoma
- Angiosarcoma
- Rhabdomyosarcoma
- Osteosarcoma
- Leiomyoma
- Leiomyosarcoma

Fibroepithelial tumours
- Fibroadenoma
- Phyllodes tumour
  - Benign
  - Borderline
  - Malignant
  - Periductal stromal tumour, low grade
- Hamartoma

Tumours of the nipple
- Nipple adenoma
- Syringomatous adenoma
- Paget disease of the nipple

Malignant lymphoma
- Diffuse large B cell lymphoma
- Burkitt lymphoma
- T cell lymphoma
  - Anaplastic large cell lymphoma, ALK negative
- Extranodal marginal-zone B cell lymphoma of MALT-type
- Follicular lymphoma

Metastatic tumours

Tumours of the male breast
- Gynaecomastia
- Carcinoma
  - Invasive carcinoma
    - *In situ* carcinoma

Clinical patterns
- Inflammatory carcinoma
- Bilateral breast carcinoma

Appendix 2: TNM Classification of Breast Tumours, 8th Edition (2016)*

TNM Clinical Classification

T Primary tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma *in situ*

Tis (DCIS) Ductal carcinoma *in situ*

Tis (LCIS) Lobular carcinoma *in situ*[a]

Tis (Paget) Paget disease of the nipple not associated with invasive carcinoma and/or carcinoma *in situ* (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.

T1 Tumour 2 cm or less in greatest dimension
- **T1mi** Microinvasion 0.1 cm or less in greatest dimension[b]
- **T1a** More than 0.1 cm but not more than 0.5 cm in greatest dimension
- **T1b** More than 0.5 cm but not more than 1 cm in greatest dimension
- **T1c** More than 1 cm but not more than 2 cm in greatest dimension

T2 Tumour more than 2 cm but not more than 5 cm in greatest dimension

T3 Tumour more than 5 cm in greatest dimension

T4 Tumour of any size with direct extension to chest wall and/or to skin (ulceration or skin nodules)[c]
- **T4a** Extension to chest wall (does not include pectoralis muscle invasion only)
- **T4b** Ulceration, ipsilateral satellite skin nodules, or skin oedema (including peau d'orange)
- **T4c** Both 4a and 4
- **T4d** Inflammatory carcinoma[d]

Note

[a] The AJCC exclude Tis (LCIS).

[b] Microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion. (Do not use the sum of all individual foci.) The presence of multiple foci of microinvasion should be noted, as it is with multiple larger invasive carcinomas.

[c] Invasion of the dermis alone does not qualify as T4. Chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle.

[d] Inflammatory carcinoma of the breast is characterized by diffuse, brawny induration of the skin with an erysipeloid edge, usually with no underlying mass. If the skin biopsy is negative and there is no localized measurable primary cancer, the T category is pTX when pathologically staging a clinical inflammatory carcinoma (T4d). Dimpling of the skin, nipple retraction, or other skin changes, except those in T4b and T4d, may occur in T1, T2, or T3 without affecting the classification.

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed (e.g. previously removed)

N0 No regional lymph node metastasis

N1 Metastasis in movable ipsilateral level I, II axillary lymph node(s)

N2 Metastasis in ipsilateral level I, II axillary lymph node(s) that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary lymph node(s) in the *absence* of clinically evident axillary lymph node metastasis
- **N2a** Metastasis in axillary lymph node(s) fixed to one another (matted) or to other structures
- **N2b** Metastasis only in clinically detected* internal mammary lymph node(s) and in the *absence* of clinically detected axillary lymph node metastasis

N3 Metastasis in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
- **N3a** Metastasis in infraclavicular lymph node(s)
- **N3b** Metastasis in internal mammary and axillary lymph nodes
- **N3c** Metastasis in supraclavicular lymph node(s)

Note

* Clinically detected is defined as detected by clinical examination or by imaging studies (excluding lymphoscintigraphy) and having characteristics highly suspicious for malignancy or a presumed pathological macrometastasis based on fine needle aspiration biopsy with cytological examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with a (f) suffix, e.g. cN3a(f).

Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, e.g. cN1. Pathological classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathological T assignment.

M – Distant Metastasis

M0 No distant metastasis

M1 Distant metastasis

pTNM Pathological Classification

pT – Primary Tumour

The pathological classification requires the examination of the primary carcinoma with no gross tumour at the margins of resection. A case can be classified pT if there is only microscopic tumour in a margin.

The pT categories correspond to the T categories.

Note

When classifying pT the tumour size is a measurement of the invasive component. If there is a large *in situ* component (e.g. 4 cm) and a small invasive component (e.g. 0.5 cm), the tumour is coded pT1a.

pN – Regional Lymph Nodes

The pathological classification requires the resection and examination of at least the low axillary lymph nodes (level I). Such a resection will ordinarily include 6 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

pNX Regional lymph nodes cannot be assessed (e.g. previously removed, or not removed for pathological study)

pN0 No regional lymph node metastasis*

Note

* Isolated tumour cell clusters (ITCs) are single tumour cells or small clusters of cells not more than 0.2 mm in greatest extent that can be detected by routine H and E stains or immunohistochemistry. An additional criterion has been proposed to include a cluster of fewer than 200 cells in a single histological cross section. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification and should be included in the total number of nodes evaluated.

pN1 Micrometastases; or metastases in 1 to 3 axillary ipsilateral lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected*
- **pN1mi** Micrometastases (larger than 0.2 mm and/or more than 200 cells, but none larger than 2.0 mm)
- **pN1a** Metastasis in 1–3 axillary lymph node(s), including at least one larger than 2 mm in greatest dimension
- **pN1b** Internal mammary lymph nodes
- **pN1c** Metastasis in 1–3 axillary lymph nodes and internal mammary lymph nodes

pN2 Metastasis in 4–9 ipsilateral axillary lymph nodes, or in clinically detected* ipsilateral internal mammary lymph node(s) in the absence of axillary lymph node metastasis
- **pN2a** Metastasis in 4–9 axillary lymph nodes, including at least one that is larger than 2 mm
- **pN2b** Metastasis in clinically detected internal mammary lymph node(s), in the absence of axillary lymph node metastasis

pN3
- **pN3a** Metastasis in 10 or more ipsilateral axillary lymph nodes (at least one larger than 2 mm) or metastasis in infraclavicular lymph nodes

*Brierley JD, Gospodarowicz MK, Wittekind C (Eds). TNM Classification of Malignant Tumours, 8th edition. Oxford: John Wiley & Sons, Inc., 2016; pp. 90-96: Breast tumours.

pN3b Metastasis in clinically detected* internal ipsilateral mammary lymph node(s) in the presence of positive axillary lymph node(s); or metastasis in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected

pN3c Metastasis in ipsilateral supraclavicular lymph node(s)

Post-treatment ypN:

- Post-treatment yp 'N' should be evaluated as for clinical (pretreatment) 'N' methods (see Section N – Regional Lymph Nodes). The modifier 'sn' is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed the axillary nodal evaluation was by axillary node dissection.
- The X classification will be used (ypNX) if no yp post-treatment SN or axillary dissection was performed.
- N categories are the same as those used for pN.

Note

*Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathological macrometastasis based on fine needle aspiration biopsy with cytological examination. Not clinically detected is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

G – Histopathological Grading

For histopathological grading of invasive carcinoma the Nottingham Histological Score is recommended.

Stage[a]			
Stage 0	Tis	N0	M0
Stage IA	T1[b]	N0	M0
Stage IB	T0, T1	N1mi	M0
Stage IIA	T0, T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0, T1, T2	N2	M0

Note

[a] The AJCC also publish a prognostic group for breast tumours. [b] T1 includes T1mi.

Image sources

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Chapter 1
Dr Mazen Sudah, Department of Radiology, Kuopio University Hospital, Dr Katja Hukkinen, Department of Radiology, Helsinki University Hospital and Dr Päivi Heikkilä, Department of Pathology, Helsinki University Hospital, for radiological and histopathological photographs.

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BREAST CANCER

ESSENTIALS *for* CLINICIANS

edited by

Fatima Cardoso, Vesa Kataja, Vivianne Tjan-Heijnen

"Breast Cancer: Essentials for Clinicians" was developed for young oncologists and busy oncologists who would like to learn the basics of breast cancer management today. It provides the most important information in a concise, clear and accessible way, with informative figures and tables. Section A, entitled "What every oncologist should know", summarises how diagnosis, staging and treatment of breast cancer (*in situ* to invasive, early to metastatic disease) should be done, highlighting the crucial role of multidisciplinary and specialised care for patients with this malignancy. The respective roles of pathology, surgery, radiation and systemic therapies are detailed. This information is built upon and complemented in section B, that provides more advanced knowledge about prognostic and predictive markers, genetic counselling and testing, new targets and new drugs, and management of specific clinical situations such as young, elderly and male breast cancer patients. Its visual and interactive format enables the reader to easily assimilate the information, and provides a strong backbone of knowledge about the most common type of cancer responsible for half a million deaths per year worldwide.

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