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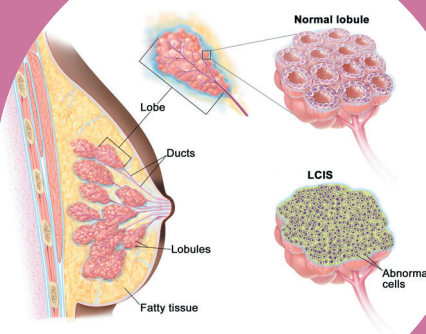
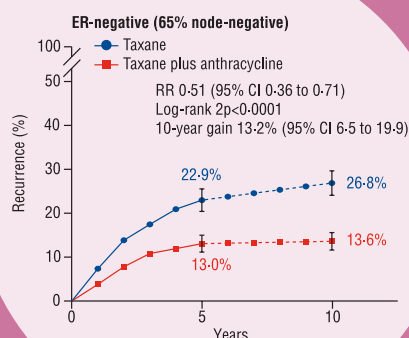
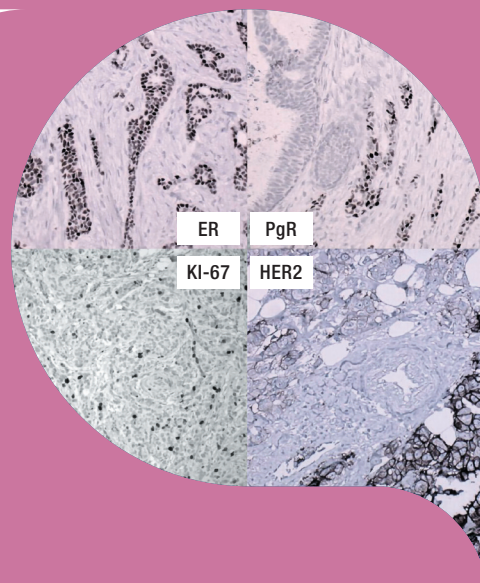
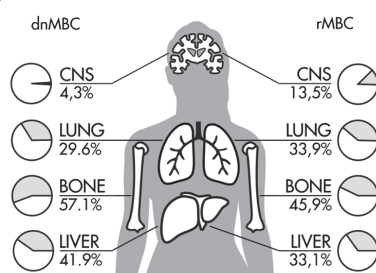
Ivana Božović-Spasojević

Marta Vaz Batista

BREAST CANCER

SECOND EDITION

ESSENTIALS *for* CLINICIANS





Breast Cancer Essentials for Clinicians

Second edition



Breast Cancer Essentials for Clinicians

Second edition

Edited by

Fatima Cardoso

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Preface

It is with great pleasure and a sense of responsibility that we present the second edition of *Breast Cancer: Essentials for Clinicians*. Since the first edition, published 2017, the book has been embraced by physicians in training and clinicians in practice, becoming an invaluable resource in the field of breast cancer management.

The decision to fully revise this book stems from our commitment to provide oncologists with the most current knowledge and practices in the evolving landscape of breast cancer care. As new treatment paradigms emerge, it is crucial for healthcare professionals to stay up to date with these advancements to deliver optimal care to their patients.

Thanks to a team of committed authors, all experts in their respective fields, each chapter reflects the latest standards of care in breast cancer. We have incorporated new insights into diagnosis and treatment, including systemic therapies as well as advancements in surgical and radiation oncology. Additionally, a new chapter on survivorship emphasises the central role of a multidisciplinary approach to high-quality comprehensive patient care.

We hope that this book will serve as a trusted resource for everyone involved in breast cancer care worldwide, helping them to navigate the complexities of this disease in daily practice. We also believe that your engagement, support and feedback will help us shape future editions ensuring that books in ESMO's Essentials for Clinicians series always remain relevant.

Ivana Božović-Spasojević
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On behalf of all editors

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Dr Cardoso is the Director of the Breast Unit of the Champalimaud Clinical Centre (CCC) in Lisbon, Portugal. She is board-certified in medical oncology and internal medicine, having earned her medical degree at the University of Porto, Portugal; she completed fellowships at the Jules Bordet Institute (IJB), Brussels, Belgium and at the MD Anderson Cancer Center, Houston, Texas, USA. She worked for 10 years as Assistant Professor at IJB and returned to Portugal in 2010 to create the Breast Unit of the CCC, the first certified Breast Unit in Portugal.

Her research interests include the biology of breast cancer, prognostic and predictive markers, new anticancer agents and clinical trials. She is also deeply involved in global cancer policy and is the founder and president of the Advanced Breast Cancer (ABC) Global Alliance and the ABC International Consensus Guidelines. She is active in many professional organisations such as the European School of Oncology (ESO), the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), the American Association for Cancer Research (AACR), the European Organisation for Research and Treatment of Cancer (EORTC) and the European Cancer Organisation (ECO), where she serves on several committees, and is the Editor-in-Chief of *The Breast*.

Dr Cardoso has received several educational and research grants, including funding from the European Union and the Bertarelli Rare Cancers Fund, and has authored about 380 publications. She has received several awards, including the prestigious Order of Santiago da Espada for Scientific Merit from the President of Portugal, the 2020 European Breast Cancer Science Award, the 2021 Umberto Veronesi Memorial Award and the 2022 ESMO Women for Oncology Award.



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Professor Tjan-Heijnen obtained her medical degree from Radboud University, Nijmegen, Netherlands. She currently works as a medical oncologist at MUMC+ Comprehensive Cancer Center, Maastricht, Netherlands. Her main field of interest is breast cancer, more specifically focusing on young women with a wish for fertility preservation, and on metastatic breast cancer.

She is the past president of the National Breast Cancer Organisation of the Netherlands and initiated the NABON-Breast Cancer Audit, which annually assesses the quality of breast cancer care in Dutch hospitals. She was chair of the Dutch committee for the assessment of oncological drugs (BOM) and initiator and first director of the Comprehensive Cancer Network South-East Netherlands (OncoZON), involving 11 institutes (2010–2015).

Currently, Professor Tjan-Heijnen chairs the metastatic breast cancer team within OncoZON. Her research focuses on quality of care in daily practice and cost-effective implementation of new treatments. She initiated several Dutch breast cancer studies (Two-to-Six, INTENS, DATA, MIRROR, SONABRE) and is involved in many international studies. She has (co)authored over 300 peer-reviewed full papers and has been the supervisor of 50 PhD students.



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Dr Božović-Spasojević is the Head of the Daily Chemotherapy Hospital at the Institute for Oncology and Radiology, Belgrade, Serbia. She is a European School of Oncology (ESO)-certified breast cancer sub-specialist, with extensive expertise in internal medicine and medical oncology, and holds a Certificate of Competence in Breast Cancer from Ulm University, Ulm, Germany.

She has a background as a former Translational Research Fellow at the Breast International Group (TRANSBIG) and served as a medical advisor and Clinical Research Fellow at the Jules Bordet Institute, Brussels, Belgium. Since 2015, she has been a member of the National Expert Commission for Oncology at the Ministry of Health of the Republic of Serbia, and contributes to the Ethics Committee of Serbia for clinical research and the Medicines and Medical Devices Agency of Serbia for oncology drug registration.

Dr Božović-Spasojević graduated from the European Society for Medical Oncology (ESMO) Leaders Generation Programme in 2018, and is an active leader in oncology communities, serving as co-chair of the ESMO–SIOPE (European Society for Paediatric Oncology) Adolescent and Young Adults Working Group, and as deputy chair of the ESMO Educational Publications Working Group. She is also a member of the steering committee of the Serbian Society of Medical Oncology and serves as a scientific director in the Certificate of Competence in Breast Cancer programme at ESO.



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Dr Vaz Batista is a Medical Oncologist at Hospital Professor Doutor Fernando Fonseca, Amadora, Portugal. She completed her Master's Degree in Medicine at Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal in 2014 and her residency in Medical Oncology in 2021. She has completed postgraduate studies in nutrition in oncology and her areas of interest are breast cancer, gynaecological cancer and clinical trials.

Dr Vaz Batista is passionate about bringing innovation to daily practice, working with special interest in clinical trials focusing on breast cancer, brain metastasis and leptomeningeal carcinomatosis from breast cancer and other solid tumours. She is one of the authors and the medical monitor of the DEBBRAH phase II study, a clinical trial evaluating the role of trastuzumab deruxtecan in patients with HER2-positive or HER2 low-expressing metastatic breast cancer with brain metastases and/or leptomeningeal carcinomatosis. She also collaborates on other clinical trials.

She has been a member of the European Society for Medical Oncology (ESMO) since 2015 and joined the ESMO Educational Publications Working Group in January 2022.

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Abbreviations

¹⁸F-FDG	¹⁸ F-Fluorodeoxyglucose	GnRH	Gonadotropin-releasing hormone
ADC	Antibody–drug conjugate	HBOC	Hereditary breast and ovarian cancer
ADH	Atypical ductal hyperplasia	HER2	Human epidermal growth factor receptor 2
ADM	Acellular dermal matrix	HP	Trastuzumab plus pertuzumab
AFT	Autologous fat transfer	HR	Hazard ratio
AI	Aromatase inhibitor	HRQoL	Health-related quality of life
AJCC	American Joint Committee on Cancer	HT	Hyperthermia
ALH	Atypical lobular hyperplasia	IBR	Implant-based reconstruction
ALND	Axillary lymph node dissection	ICAP	Intercostal artery perforator
AR	Androgen receptor	ICI	Immune checkpoint inhibitor
ASCO	American Society of Clinical Oncology	iDFS	Invasive disease-free survival
A/T	Anthracycline and taxane	IHC	Immunohistochemistry
ATM	Ataxia telangiectasia mutated	IMBCP	International Male Breast Cancer Programme
B	Biopsy	IMN	Internal mammary node
BC	Breast cancer	IMRT	Intensity modulated radiotherapy
BCI®	Breast Cancer Index®	irAE	Immune-related adverse event
BCS	Breast-conserving surgery	ISH	<i>In situ</i> hybridisation
BCT	Breast-conserving therapy	ITC	Isolated tumour cell
BM	Brain metastasis	ITT	Intention to treat
BMA	Bone-modifying agent	LABC	Locally advanced breast cancer
BMI	Body mass index	LB	Liquid biopsy
CAP	College of American Pathologists	LCIS	Lobular carcinoma <i>in situ</i>
CARG-BC	Cancer and Aging Research Group-Breast Cancer	LHRH	Luteinising hormone-releasing hormone
CD	Cardiac dysfunction	LICAP	Lateral intercostal artery perforator
CDH1	Cadherin 1	LMD	Leptomeningeal disease
CDK4/6	Cyclin-dependent kinase 4/6	LN	Lymph node
CDK4/6i	Cyclin-dependent kinase 4/6 inhibitor	LR	Local recurrence
CHEK2	Checkpoint kinase 2	LRR	Locoregional recurrence
ChT	Chemotherapy	Lum	Luminal
CI	Confidence interval	LVEF	Left ventricular ejection fraction
CNB	Core needle biopsy	MBC	Metastatic breast cancer
CNS	Central nervous system	MD	Mammographic density
CPS	Combined positive score	MRI	Magnetic resonance imaging
CR	Complete response	MSI	Microsatellite instability
CT	Computed tomography	mTNBC	Metastatic triple-negative breast cancer
CTS5	Clinical Treatment Score at 5 years	mTOR	Mammalian target of rapamycin
DBCg	Danish Breast Cancer Group	NACT	Neoadjuvant chemotherapy
DCIS	Ductal carcinoma <i>in situ</i>	NAT	Neoadjuvant therapy
DDFS	Distant disease-free survival	NTRK	Neurotrophic tyrosine receptor kinase
DFI	Disease-free interval	OAR	Organs at risk
DFS	Disease-free survival	OFS	Ovarian function suppression
DIEP	Deep inferior epigastric perforator	OMD	Oligometastatic disease
dnMBC	<i>De novo</i> metastatic breast cancer	OS	Overall survival
EBC	Early breast cancer	PALB2	Partner and localiser of BRCA2
EBCTCG	Early Breast Cancer Trialists' Collaborative Group	PARP	Poly (ADP-ribose) polymerase
ECIBC	European Commission Initiative on Breast Cancer	PARPi	Poly (ADP-ribose) polymerase inhibitor
EFS	Event-free survival	PBI	Partial breast irradiation
EMA	European Medicines Agency	pCR	Pathological complete response
EORTC	European Organisation for the Research and Treatment of Cancer	PD-L1	Programmed death-ligand 1
ER	Oestrogen receptor	PET	Positron emission tomography
ESCAT	ESMO Scale for Clinical Actionability of molecular Targets	PFS	Progression-free survival
ESMO	European Society for Medical Oncology	PgR	Progesterone receptor
ESR1	Oestrogen receptor 1	PI3K	Phosphoinositide 3-kinase
ESTRO	European Society for Radiotherapy and Oncology	PMRT	Postmastectomy radiotherapy
ET	Endocrine therapy	PS	Performance status
FDA	Food and Drug Administration	PST	Primary systemic therapy
FNA	Fine needle aspiration	PTEN	Phosphatase and tensin homologue
FNAC	Fine needle aspiration cytology	PV	Pathogenic variant
fx	Fraction	QoL	Quality of life
gBRCA	Germline BRCA	RCB	Residual cancer burden
gBRCAm	Germline BRCA mutation	rMBC	Recurrent metastatic breast cancer
G-CSF	Granulocyte-colony stimulating factor	RR	Regional recurrence
GEC	Groupe Européen de Curiethérapie	RRBSO	Risk-reducing bilateral salpingo-oophorectomy
GES	Gene expression signature	RRM	Risk-reducing mastectomy
		RT	Radiotherapy
		RTOG	Radiation Therapy Oncology Group

SBRT	Stereotactic body radiotherapy
SCP	Survivorship care plan
SEER	Surveillance, Epidemiology, and End Results
SERD	Selective oestrogen receptor degrader
SERM	Selective oestrogen receptor modulator
SG	Sacituzumab govitecan
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy
SRE	Skeletal-related event
TAD	Targeted axillary dissection
TAM	Tamoxifen
TC	Tumour cell
TDLU	Terminal duct lobular unit
T-DM1	Trastuzumab emtansine
T-DXd	Trastuzumab deruxtecan
TE	Tissue expander
TER	Thermal enhancement ratio
THP	Trastuzumab, pertuzumab and paclitaxel
TIL	Tumour-infiltrating lymphocyte
TKI	Tyrosine kinase inhibitor
TNBC	Triple-negative breast cancer
TNM	Tumour, node, metastasis
TRK	Tropomyosin receptor kinase
Trop-2	Trophoblast cell surface antigen 2
UICC	Union for International Cancer Control
US	Ultrasound
VAB	Vacuum-assisted biopsy
WBRT	Whole-brain radiotherapy
WHO	World Health Organization
wt	Wild type

Acknowledgements

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Fatima Cardoso, Vivianne Tjan-Heijnen, Ivana Božović-Spasojević, Marta Vaz Batista

What every oncologist should know

Screening, diagnosis & 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 changes in breast size or shape. Skin rash, ulceration, erythema and eczema of the nipple-areola complex may also occur.

A lump in the axilla or the supraclavicular fossa may indicate regional lymph node (LN) metastases. Skeletal or abdominal pain, cough, breathlessness or neurological signs or symptoms may suggest **metastatic cancer**.

Physical changes to the breast that may be cancer-related

Change in the size and shape of the breast

A breast lump with skin ulceration



Fig. 1.1

Inflammatory cancer in the left breast



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 punch biopsy** can provide 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.

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

Paget 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 disease.

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

Paget disease



Fig. 1.3

REVISION QUESTIONS

1. What proportion of BCs are local or locoregional at the time of 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 a breast tumour in mammography screening are key **histories** 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).

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).

Breast palpation and position of patient

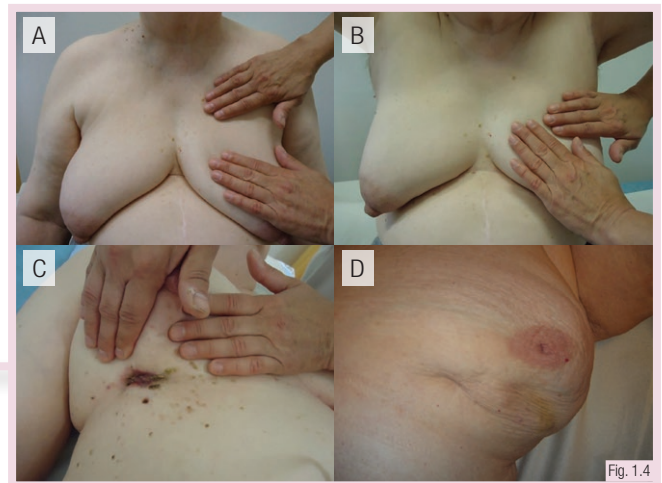


Fig. 1.4

The triple test approach to diagnosis

I Clinical examination

- History
- Inspection and palpation

II Breast imaging

- Mammography
- Breast and axillary ultrasound
- Breast magnetic resonance imaging

III Core needle biopsies from suspicious lesions

Fig. 1.5

The triple diagnostic approach consists of breast inspection and palpation, breast imaging usually with mammography and US, and core needle biopsies (CNBs) of suspicious breast lesion(s).

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 US examination of the breast and the axilla.

Typical findings suggestive of cancer on 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 on US.

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.

Mammography findings

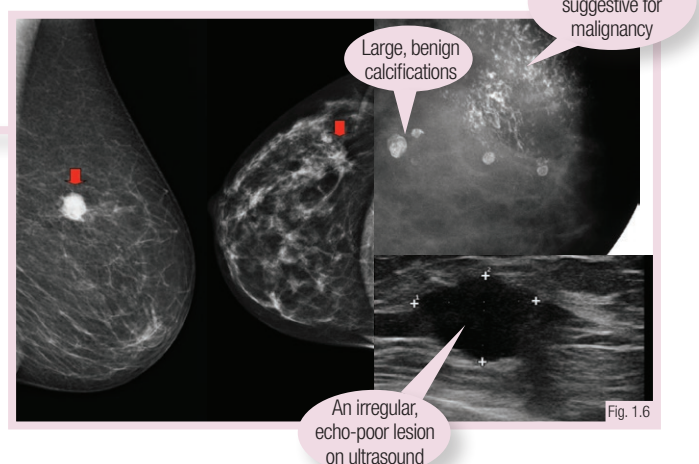


Fig. 1.6

REVISION QUESTIONS

1. What are the key points to note in the patient's history?
2. What components are included in the triple diagnostic approach?
3. What are the findings typical of BC on mammography?

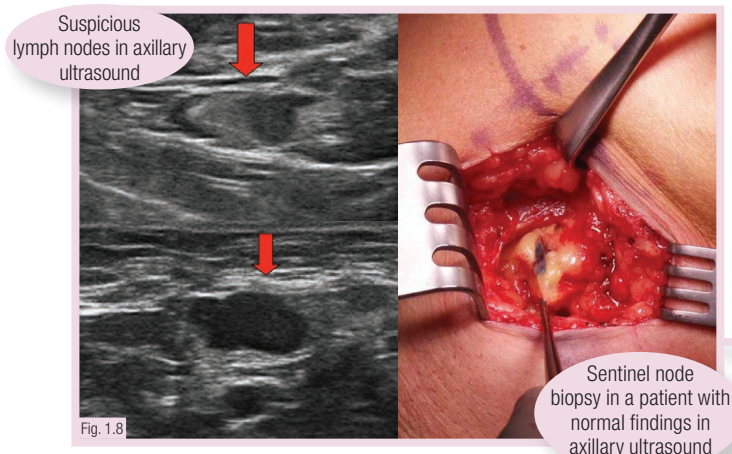
Percutaneous needle biopsy and axillary staging

A **CNB** or a **vacuum-assisted biopsy (VAB)** is taken from the breast. The biopsy is frequently guided by US, sometimes by stereotactic mammography or magnetic resonance imaging (MRI). Sensitivity of biopsies exceeds 98% and false-positive findings are rare.

The tissue material obtained with **CNB** and **VAB** usually allows detection of invasive tumour growth, histological classification of cancer and the completion of assays for biological features such as hormone receptor status, human epidermal growth factor receptor 2 (HER2) status and Ki-67 expression.

The diagnostic accuracy of **fine needle aspiration cytology (FNAC)** is lower than that of CNB and depends on the skill of the investigator. FNAC may be used to detect LN metastases and is also useful in the diagnosis and treatment of breast cysts.

Axillary ultrasound and sentinel lymph node biopsy

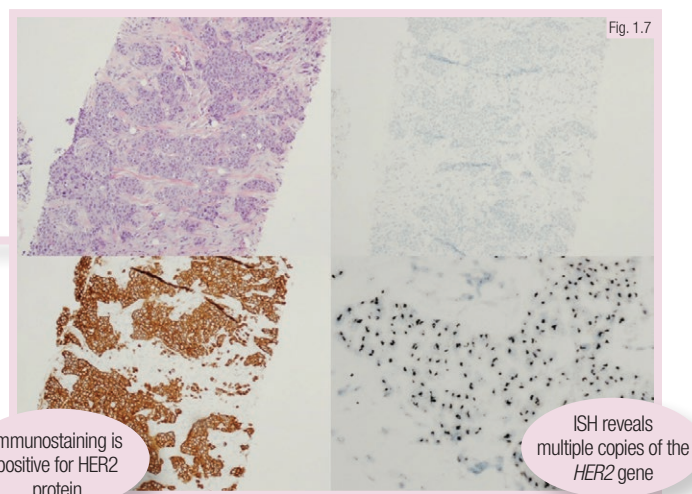


The **sentinel node** is the first node to receive lymph drainage from the tumour site in the breast. SLNB is currently the gold standard in nodal staging of patients without metastases at axillary US.

Sentinel nodes are usually detected following injection of a **radioactive tracer** and/or a **blue dye** into the breast.

Patients with axillary node metastases, detected before surgery, undergo **axillary LN dissection** or may be offered neoadjuvant treatment, and, if clinically downstaged, may undergo SLNB or targeted axillary dissection to confirm pathological staging.

Histopathological assays from core needle biopsy. A core needle biopsy shows grade 3 invasive ductal carcinoma with negative ER staining



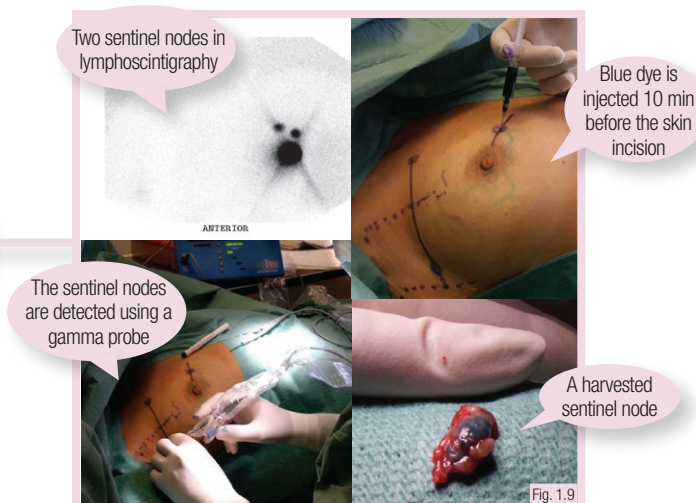
ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; ISH, in situ hybridisation.

The **axillary nodal status** is considered the most important single prognostic factor and may help in the selection of patients for (neo)adjuvant systemic treatments and radiotherapy (RT).

Axillary US is performed prior to starting cancer treatment. A needle biopsy is taken from the nodes suspected to be cancerous on US.

A **sentinel lymph node biopsy (SLNB)** is carried out when metastases are not detected at axillary US.

Sentinel node detection and dissection



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?

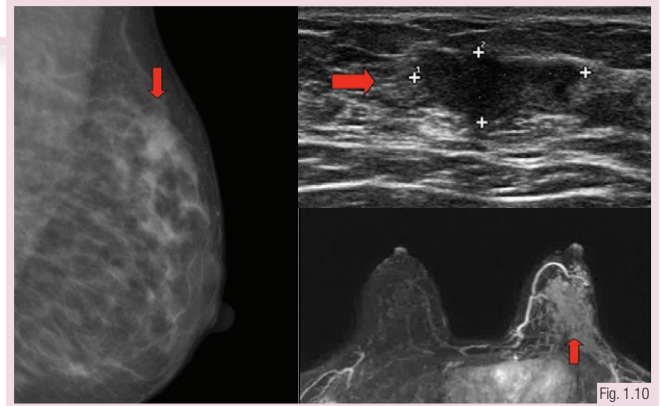
Other staging examinations

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

MRI has **high sensitivity**, but **false-positive** findings occur in 5%–10% of patients. A biopsy should be considered when a lesion is visible only on MRI.

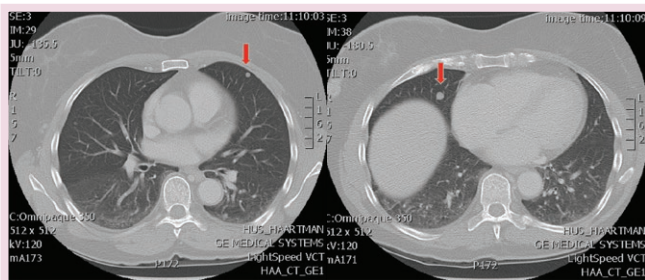
When assessing **response to neoadjuvant chemotherapy**, and screening **women who are susceptible to BC**, MRI is superior to other imaging methods, although US may be equally useful for response assessment. It is also useful in the detection of **occult BC** in a patient with overt axillary metastases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

An example of MRI in assessment of cancer size. A 29-year-old woman with a small breast tumour on mammography and ultrasound, but cancer encompasses almost the entire breast on MRI



MRI, magnetic resonance imaging.

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



CT, computed tomography.

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

For patients at **high and intermediate risk** of distant relapses, **imaging of the chest, abdomen and bone** is recommended prior to administration of systemic treatments.

If clinical signs or laboratory values suggest the presence of **metastases**, imaging exams are mandatory.

^{18}F -Fluorodeoxyglucose-**positron emission tomography** (^{18}F -FDG-PET) or PET combined with computed tomography (PET-CT) are not usually 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. ^{18}F -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 on standard imaging are unclear.

An example of FDG-PET in BC staging. BC metastases in lumbar vertebrae III, IV and V and the sacrum in an FDG-PET scan. The metastases were not visible on CT



BC, breast cancer; 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. Advanced 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 experienced in the care of patients with BC are essential team members.

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

A multidisciplinary team meeting



Fig. 1.13

Example of pathology report

Meeting date: <u>8.9</u>		Specimen: Weight: <u>88</u> g	
Number: <u>2013 - 12345-6</u>		Dimensions: <u>5</u> x <u>5</u> x <u>2.9</u> cm	
NAME: _____			
Margins Cran: <u>13</u> mm Med: <u>7/09</u> mm Ant: <u>2</u> mm Caud: <u>8</u> mm Lat: <u>19</u> mm Post: <u>4</u> mm		Tumour Type: <u>Ductal</u> Grade: <u>3</u> Size (mm): <u>2.2</u> DCIS: <u>comedo</u> <u>3</u> <u>5%</u> Multifoc.: <u>No</u> LVI: <u>No</u>	
		% +/++/+++ ER: <u>0</u> - SN 1: <u>0/1</u> PR: <u>0</u> - SN 2: <u>0/1</u> MIB-1: <u>20</u> ++ SN 3: _____ c-erbB2: <u>100</u> +++ SN 4: _____ c-erbB2 IISH: _____ NSN: _____ All nodes: <u>0/3</u> Metastasis size: _____ mm ECE: _____	
Additional information			

Fig. 1.14

DCIS, ductal carcinoma in situ.

The **pathology report** should include the dimensions of the tumour(s) and the width of the surgical margins in millimetres. Cancer histological type and grade and presence of lymphovascular invasion are also reported.

The number of examined **regional LNs**, LNs 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 testing for oestrogen receptor (ER), progesterone receptor (PgR), HER2 and Ki-67. **Gene expression arrays** and other genetic tests may assist in decision-making for adjuvant therapy.

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

The fluent flow and the exact documentation of information from all parties are essential for **successful multidisciplinary teamwork**.

Personalised sequence of treatments

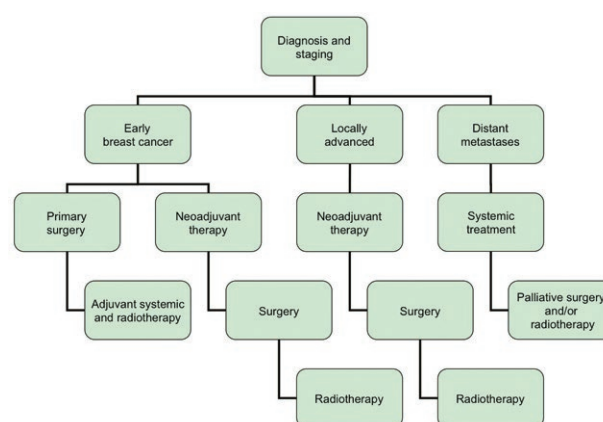


Fig. 1.15

REVISION QUESTIONS

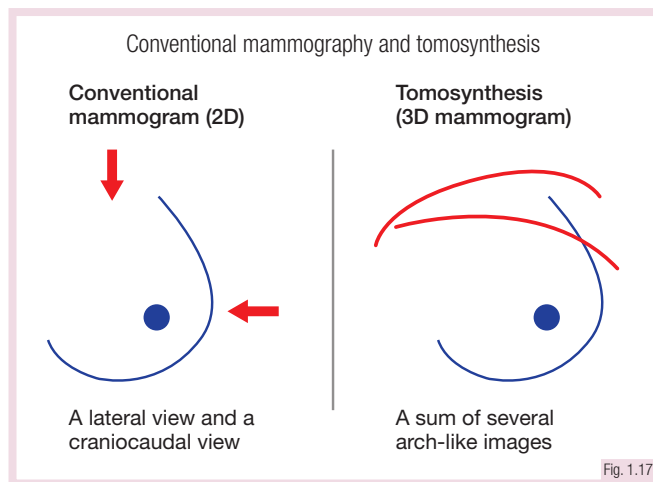
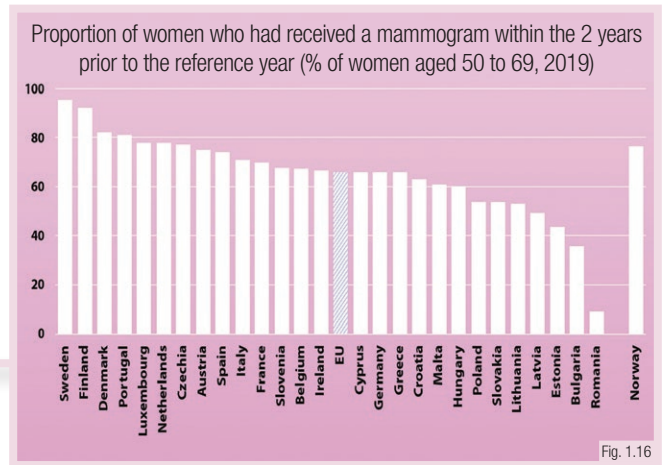
1. What are the goals of a multidisciplinary team meeting?
2. Which healthcare professionals should be included in the core team?
3. What information should be available in the pathology laboratory report?

Breast cancer screening

The European Commission Initiative on Breast Cancer (ECIBC) Guidelines Development Group strongly recommends **organised mammography screening** for asymptomatic women aged 50–69, and conditionally for women aged 45–49 or 70–74.

The ECIBC suggests mammography screening every 2 to 3 years for women aged 45–49, **every 2 years at age 50–69**, every 3 years at age 70–74.

According to EuroStat, about **two thirds of women aged 50–69 had received a mammogram within two years in the European Union in 2019**.



In organised mammography screening, mammograms are recommended to be read independently by two radiologists (**double screening**) to increase cancer detection rate.

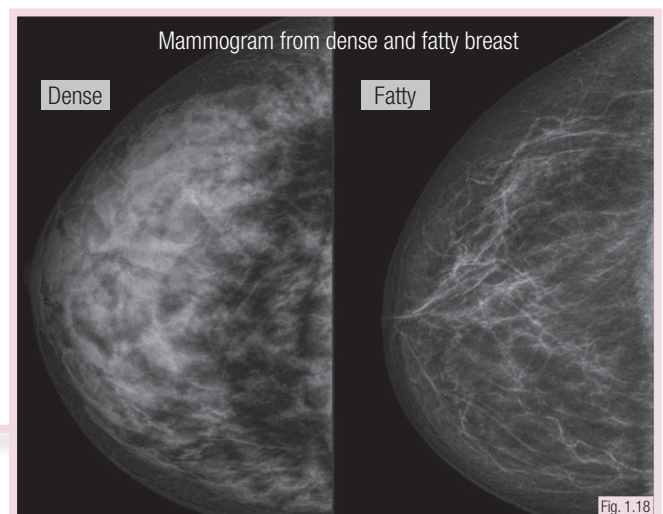
The ECIBC suggests using either **digital mammography** or **digital breast tomosynthesis** (a pseudo-3D imaging technique).

Detection of cancer is more difficult when **the breast density** is high. When high breast density is found at the first imaging, digital breast tomosynthesis may be the preferred technique for the next screening rounds.

BC screening **allows detection of asymptomatic cancers when tumour size is still small**. This may allow less extensive surgery and abolish the need for (neo)adjuvant treatments.

The **exact efficacy of mammography screening on BC mortality reduction rate is unknown**, as the estimates vary. In the 50–69-years age group, the estimated relative BC mortality reduction rate is about 20%.

The **estimated BC mortality reduction rate is probably slightly inferior in the age group 45–49 years**, due to greater breast density.



REVISION QUESTIONS

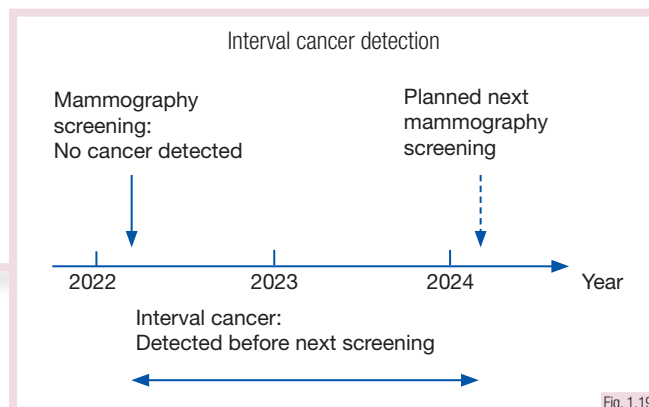
1. At what age is organised mammography screening strongly recommended?
2. What is digital breast tomosynthesis?
3. By how much, as a percentage, does mammography screening reduce BC mortality?

Breast cancer screening (continued)

In general, screening-detected BCs are associated with a **favourable prognosis**.

Prognosis of screening-detected cancers is favourable even when compared with non-screening-detected cancers of a **similar size**.

Interval cancers that are detected between the screening rounds tend to have a less favourable prognosis compared with screening-detected cancers.



US-guided breast biopsy



US, ultrasound.

The benefits of BC screening need to be **balanced with its potential harms**. Screening is associated with a small radiation hazard.

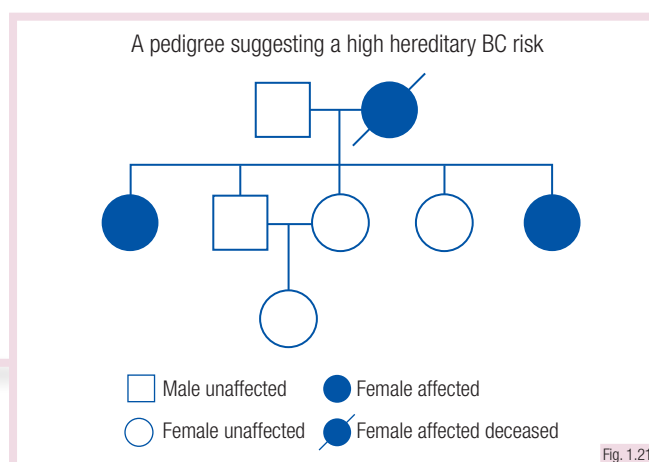
False-positive findings may lead to re-imaging and a breast biopsy. Some screening-detected ductal *in situ* carcinomas and small cancers (about 10%) are over-diagnosed, unlikely to threaten life, leading to overtreatment.

Screening carries a risk for **false-negative findings** (about 20%), which may lead to unsubstantiated feeling of security and cancer detection as interval cancer.

Annual screening with MRI of the breast and US or mammography is recommended for women with a **high familial BC risk**, when risk-reducing mastectomy is not the preferred option.

When the familial risk is high, intensified **screening including MRI detects BC earlier** compared with mammography screening alone.

When a germline pathogenic variant of *BRCA1*, *BRCA2* or *PALB2* is present, intensified screening should start **at age 30, or 5 years younger** than the age at which the youngest relative was diagnosed with BC.



BC, breast cancer.

REVISION QUESTIONS

1. Is the prognosis of interval cancers comparable to that of screening-detected cancers?
2. What are the potential harms associated with mammography screening?
3. What imaging modalities should be used when familial BC risk is high?

Summary: Screening, diagnosis & 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 statuses can be determined from CNB
- 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 predisposition for BC
- Axillary US with needle biopsy from suspicious nodes is an essential part of the diagnostic procedure
- SLNB is the gold standard in patients without evidence of axillary nodal metastases in the pre-treatment US examination of the axilla
- Staging by imaging to detect distant metastases is considered for high-risk patients
- The main goal of the multidisciplinary team meeting is to optimise the treatment for each patient. It is mandatory for all patients with BC
- Organised BC screening is strongly recommended for asymptomatic women aged 50–69, and conditionally recommended for women aged 45–49 or 70–74
- Screening reduces mortality from BC; the effect is best documented for postmenopausal women

Further Reading

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Image sources: The authors thank 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. **Fig. 1.15.** courtesy of M. Leidenius; **1.16.** European Union, Eurostat; **1.17.** courtesy of H. Joensuu; **1.19, 1.20, 1.21.** courtesy of the authors.

Normal breast and diagnostic approach

The **mammary gland** is a modified tubulo-alveolar sweat gland, with ~12 lobes surrounded by fibrous tissue and abundant fatty tissue.

Terminal duct lobular units (TDLUs) are the essential components, lined by a double layer of cells: the luminal epithelial cells and the peripheral **myoepithelial cells**.

TDLUs also represent the main **anatomical source** of most breast cancer (BC) precursors and BCs, both in men and women, although male BC is rare.

Low magnification of a normal breast histology with lobules and ducts

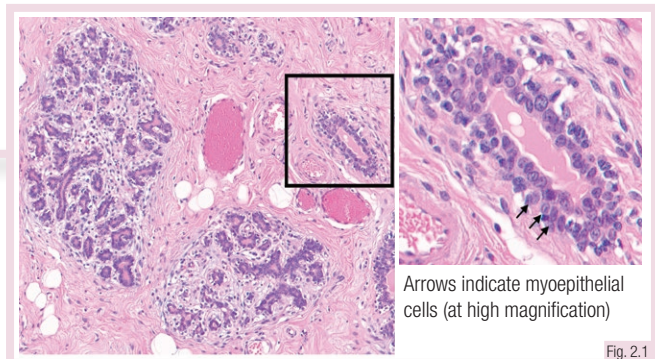


Fig. 2.1

Core biopsy reporting categories	
B1	Normal breast tissue
B2	Benign lesion
B3	Lesion of uncertain malignant potential
B4	Suspicious
B5	Malignant (B5a: <i>in situ</i> ; B5b: invasive)

Fig. 2.2

B, biopsy.

If breast disease is suspected, it is mandatory to obtain a representative **sample (cytohistological)** of the lesion as this will determine subsequent management.

Cytology is a rapid, cheap, safe and easy technique; core biopsy, however, provides **more details** to guide clinical decisions.

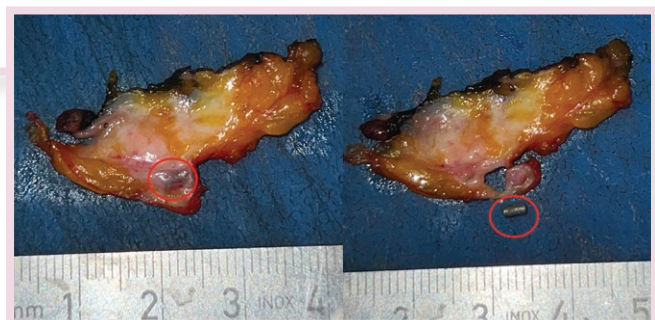
As with cytology reporting, core biopsy results are also reported in **five categories** described by the letter B (for biopsy), followed by a number (1–5).

After core biopsy, a **clip** should be placed to mark the suspicious area and to make it easier to locate during the gross pathological examination of the eventual surgical specimen. In tumours that will be subject to neoadjuvant systemic therapy, it can also guide surgery in the event of pathological complete response (pCR).

During recent years, the role of pathologists in the BC field has dramatically evolved, from a purely diagnostic responsibility to the provision of essential **prognostic and predictive factors**.

Alongside traditional techniques (i.e. haematoxylin and eosin staining, immunohistochemistry [IHC], *in situ* hybridisation [ISH]), pathologists should be ready to implement **new assays** (genomic and genetic testing, liquid biopsy and digital imaging).

Slice of BCS specimen showing clip inside the tissue (left) and after removal (right)



BCS, breast-conserving surgery.

Fig. 2.3

REVISION QUESTIONS

1. What is the morphological characteristic of TDLUs?
2. What does B(1–5) stand for in a pre-surgical breast biopsy pathology report?
3. Why should a clip be placed in the breast lesion after the biopsy procedure?

Intraductal proliferative lesions and lobular neoplasia

Due to the wide adoption of mammography screening programmes the detection of **atypical**, non-invasive proliferative lesions, both of ducts and lobules, is more common.

The current terminology used to identify these atypical lesions depends on **their location and on their morphology** and some of them are considered just precursors.

All of them, except ductal carcinoma *in situ* [DCIS] and lobular carcinoma *in situ* [LCIS] pleomorphic type, are considered **lesions of uncertain malignant potential** and are categorised as B3.

List of terms allowed for intraductal and lobular proliferations according to the 5th edition WHO Classification of Breast Tumours (2019)

Proliferative lesions and precursors	
Ductal	Lobular
Columnar cell lesions, including flat epithelial atypia (FEA)	Atypical lobular hyperplasia (ALH)
Atypical ductal hyperplasia (ADH)	Lobular carcinoma <i>in situ</i> (LCIS), classic type
Ductal carcinoma <i>in situ</i> (DCIS, G1,2,3)	Lobular carcinoma <i>in situ</i> (LCIS), florid type
	Lobular carcinoma <i>in situ</i> (LCIS), pleomorphic type

Fig. 2.4

WHO, World Health Organization.

Invasive focus of breast carcinoma cells <1 mm in size

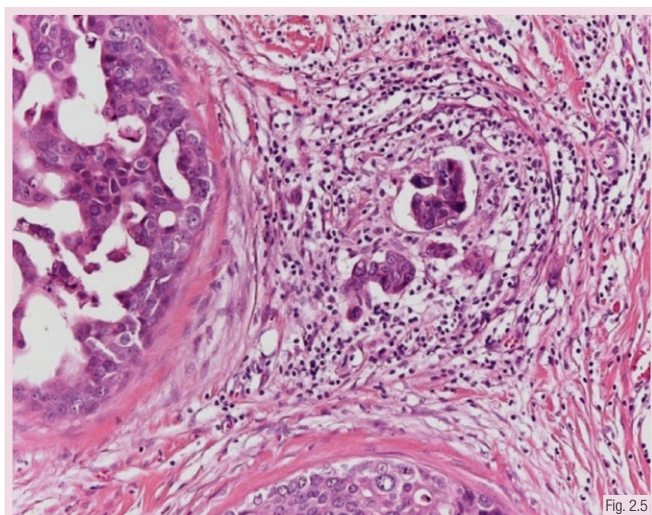


Fig. 2.5

Atypical ductal hyperplasia is a small lesion (<2 mm in size) with some, but not all, of the characteristics of a low-grade DCIS (DCIS G1).

DCIS is characterised by the presence of fully neoplastic cells growing within, and **confined to**, the ducts without any invasion through the basal membrane.

Extensive microscopic examination should be performed in case of large DCIS lesions, to identify even tiny foci of **microinvasion** that would change the stage to pT1mi.

Atypical lobular hyperplasia and LCIS are characterised by **loosely cohesive** cells, differing only in the extent of acinar involvement: in the former, <50% of the acini of the lobular unit are filled by atypical cells.

LCIS pleomorphic type is often associated with invasive lobular carcinoma, and it is considered a **malignant lesion**. It should be classified as B5a.

Unlike ductal, all lobular lesions share the same feature of loss of membranous **E-cadherin expression** when tested by IHC.

Immunostaining for E-cadherin decorates the normal luminal (ductal) cells but not the neoplastic population of lobular cells

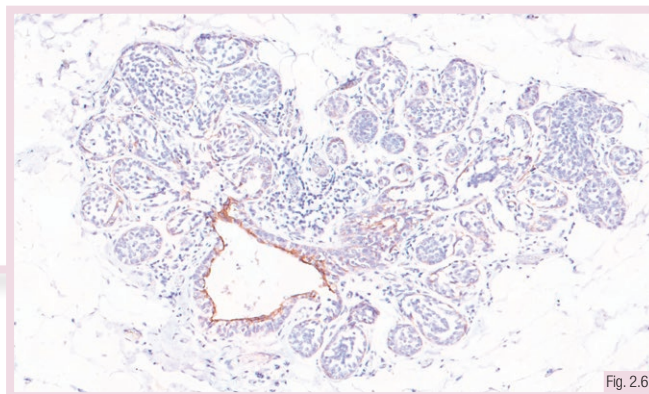


Fig. 2.6

REVISION QUESTIONS

1. Can ductal and lobular non-invasive proliferations be identified by a simple and uniform terminology?
2. What are the clinical implications of a pure DCIS and of a microinvasive carcinoma within a large DCIS?
3. How can we definitively differentiate between ductal and lobular lesions?

Pathology report: morphological section

The pathology report must contain some **morphological characteristics** such as tumour size, histological type (according to World Health Organization classification) and grading.

When the tumours show peculiar morphology in >90% of the neoplastic cells, they are called **special type** and they may have a better or worse prognosis compared with tumours of no special type.

Assessment of histological **grade** is based on three features of the tumour: tubule formation, nuclear atypia and pleomorphism and the number of mitoses. Each feature is scored from 1 to 3, the sum of which gives a number between 3 and 9 to indicate the grade, G1: 3–5; G2: 6, 7; G3: 8, 9.

Special types of breast carcinoma

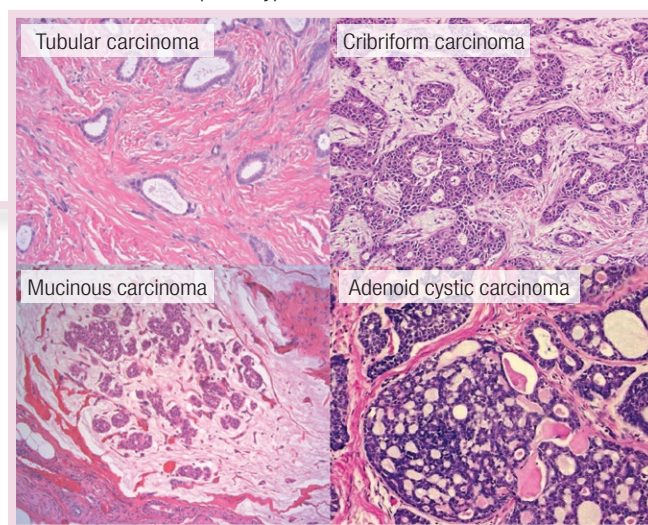
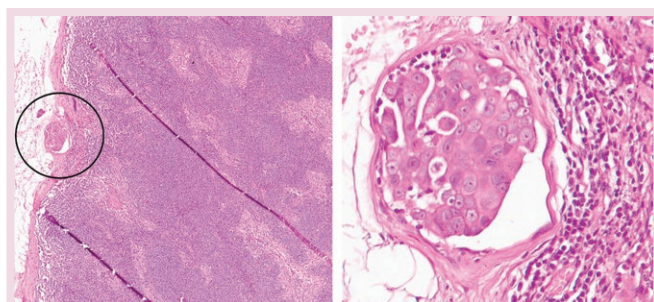


Fig. 2.7

Micrometastasis in a SLN



SLN, sentinel lymph node.

Fig. 2.8

Peritumoral vascular invasion correlates with lymph node (LN) status, which is an essential **prognostic factor** for patients with BC.

Accurate sentinel LN (SLN) histological examination avoids **unnecessary axillary clearance** and its associated morbidity in clinically node-negative disease.

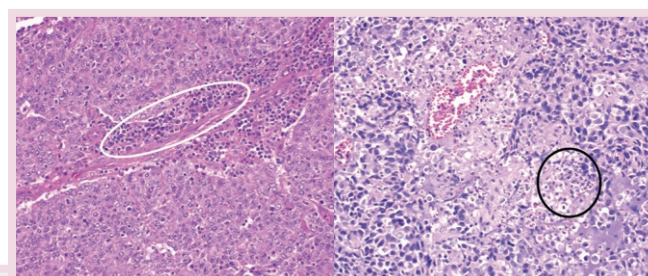
According to their **size**, LN metastases are classified as isolated tumour cells (ITCs; <0.2 mm), micrometastases (0.2–2 mm) and macrometastases (>2 mm).

Tumour infiltrating lymphocytes (TILs) correlate with a patient's immune response and with a better prognosis in some tumour types.

The presence of TILs may be **predictive of response** to immunotherapy, but its evaluation needs to be standardised.

Usually, the TILs are in the stroma, but sometimes they are also within the cancer cells: intraepithelial TILs. Reflecting the growing significance of TILs evaluation in daily practice, the TILs Working Group provides a **web-based training tool** (tilsinbreastcancer.org).

TILs within the cancer cells



TIL, tumour infiltrating lymphocyte.

Fig. 2.9

REVISION QUESTIONS

1. Is there a correlation between histological features and prognosis?
2. Based on the size of LN metastases, how many classes exist?
3. Why could including the TILs evaluation in the pathology report be useful?

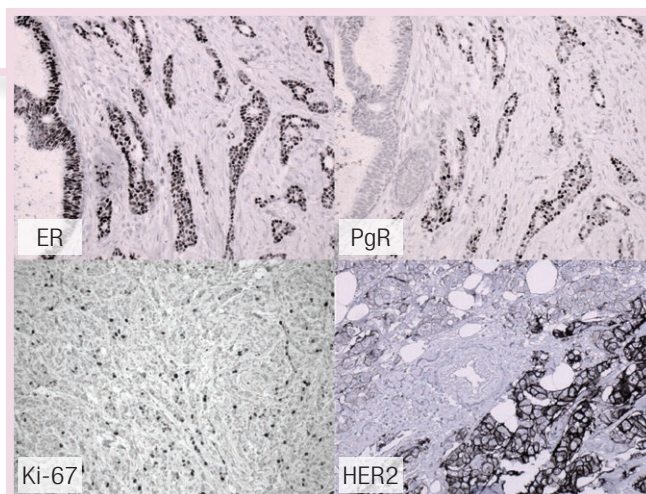
Pathology report: immunohistochemical section and surrogate molecular classification

Reliable assessment of oestrogen receptor (ER), progesterone receptor (PgR), Ki-67 and human epidermal growth factor receptor 2 (HER2) status informs the **systemic treatment** in the (neo)adjuvant and advanced tumour settings.

ER and PgR are evaluated by IHC and are usually reported as a percentage of invasive tumour cells. They are considered **positive** if $\geq 1\%$ of tumour cells are immunostained.

Tumour proliferation fraction is assessed by the **Ki-67 labelling index**, which is expressed in the nuclei of proliferating cells but not in the resting ones. In the metastatic setting, programmed death-ligand 1 (PD-L1) testing is recommended in patients with triple-negative BC due to therapeutic implications.

IHC staining for ER, PgR, Ki-67 and HER2



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

Fig. 2.10

Pathological surrogate definitions according to the 13th St Gallen IBCC 2013

Luminal A-like	ER/PgR-positive (high) HER2-negative Ki-67-low
Luminal B-like (HER2-negative)	ER-positive HER2-negative PgR-negative/low or Ki-67-high
Luminal B-like (HER2-positive)	ER-positive HER2-positive (overexpressed or amplified) PgR and Ki-67 any
HER2-positive	HER2-positive (overexpressed or amplified) ER/PgR-negative
Triple-negative	ER/PgR-negative HER2-negative

Fig. 2.11

ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; IBCC, International Breast Cancer Conference; PgR, progesterone receptor.

HER2 status plays a crucial role both as a **prognostic** factor (promoting proliferation and motility of neoplastic cells) and as a **predictive** factor of response to HER2-targeted therapies.

HER2 protein overexpression is usually evaluated by IHC, while **HER2 gene amplification** by ISH, according to American Society of Clinical Oncology/College of American Pathologists guidelines.

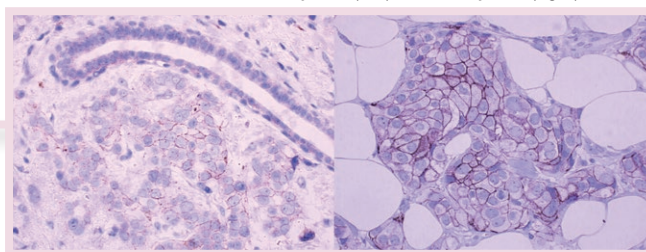
Standardisation of biomarker assessment aims to reduce **discrepancies** among pathologists and provides a surrogate for the molecular classification of BC.

Although breast tumours have been traditionally categorised as HER2-positive and HER2-negative, **HER2 expression is a continuous variable**.

Tumours with an IHC score of 1+ or 2+ in the absence of gene amplification have recently been reconsidered and categorised as **HER2-low** BCs.

For these HER2-low tumours, novel anti-HER2 **antibody-drug conjugates** have demonstrated compelling clinical activity in the advanced setting.

HER2-low tumours: 1+ by IHC (left) and 2+ by IHC (right)



HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

Fig. 2.12

REVISION QUESTIONS

1. Is there a cut-off that defines positive hormone receptor status?
2. How do a tumour's immunohistochemical features correlate with its molecular classification?
3. What is the definition of HER2-low BC?

Neoadjuvant setting

Originally introduced for inoperable BCs, preoperative (neoadjuvant) therapies (NATs) are now increasingly offered for **de-escalating** surgery, assessing tumour response to systemic treatments and for determining post-surgery therapy.

Pathologists play a major role in both the pre- and post-surgical phases by providing a complete **biological characterisation** of the tumour.

pCR is highly correlated with **long-term survival** and is defined as the absence of invasive tumour cells in both the breast and all removed axillary LNs.

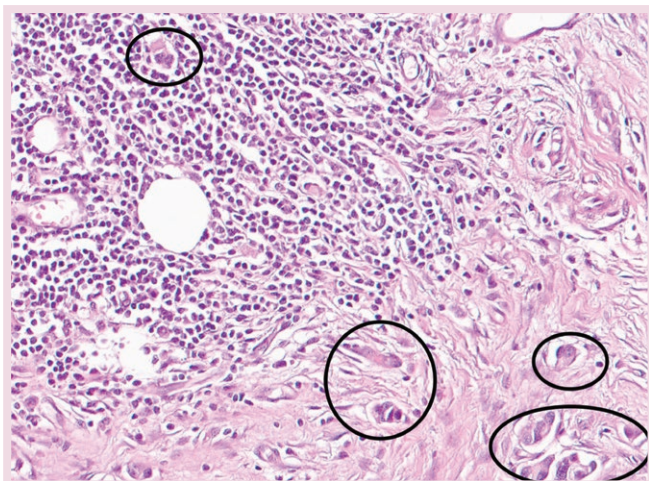
Definition of pCR according to the FDA

T	N
No tumour (nor invasive/nor <i>in situ</i>) => ypT0	No metastatic tumour at all => pN0
Allowed presence of <i>in situ</i> component => ypTis	No metastatic tumour at all => pN0 Presence of isolated tumour cells ≠ pCR

FDA, Food and Drug Administration; pCR, pathological complete response; N, node; T, tumour.

Fig. 2.13

Isolated tumour cells in a post-NAT SLN: ypN0(i+) does not qualify as pCR



NAT, Neoadjuvant therapy; pCR, pathological complete response; SLN, sentinel lymph node.

Fig. 2.14

Clinicians should provide **pretreatment information** such as site, size, stage, hormone receptor and HER2 status of the tumour, type of NAT and clinical response.

Pathologists should accurately perform gross examination of the surgical specimens and appropriate sampling of the **tumour bed**, mapping the samples to ensure measurement of any residual tumour.

SLN biopsy achieves an acceptable false-negative rate if three LNs are removed and extensively scrutinised histologically.

The **pathology report** in case of residual tumour must include tumour size and cellularity, presence of *in situ* carcinoma and assessment of ER/PgR/Ki-67/HER2 status.

The N (node) parameter must include the number of positive nodes and total nodes removed, the size of the largest metastatic deposit and the presence of extracapsular extension and **fibrosis**.

Along with the tumour, node, metastasis (TNM) stage, according to the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), it is recommended to calculate the residual cancer burden (**RCB**) score and the **RCB class**.

Morphological parameters required for RCB assessment: macroscopic and microscopic pathological evaluation of the primary tumour (T) and the lymph nodes (N)

T	N	→ RCB
Primary tumour bed area (mm x mm)	Number of positive lymph nodes	RCB (absolute value)
Percentage of cancer cellularity in the tumour bed (0, 1%, 5%, 10%, 20%, ..., 90%)		
Percentage of cancer that is carcinoma <i>in situ</i> (0, 1%, 5%, 10%, 20%, ..., 100%)	Maximum diameter of metastasis	RCB Class (pCR, I, II, III)

An RCB calculator can be found online: MD Anderson Cancer Center. www3.mdanderson.org/app/medcalc

N, node; pCR; pathological complete response; RCB, residual cancer burden; T, tumour.

Fig. 2.15

REVISION QUESTIONS

1. What is pCR and how is it defined?
2. How can clinicians help pathologists accurately evaluate the post-NAT surgical specimen?
3. What should be included in the pathology report of surgical specimens post-NAT?

Summary: Pathology (including normal breast) and disease subtypes

- The primary diagnostic approach to a breast lesion should preferably be made by histology (core biopsy) and the findings should be classified as a B category (1–5)
- A clip is placed after a core biopsy to assist surgeons and pathologists to locate the lesion
- Intraductal and lobular proliferations are mostly considered lesions of uncertain malignant potential, except for DCIS and LCIS pleomorphic type, which are considered malignant lesions
- E-cadherin expression is a helpful tool for distinguishing ductal from lobular proliferations
- Morphological assessment of the so-called ‘good prognosis special types’ must be supported by immunophenotypic expression
- There are three classes of LN metastatic deposits according to their size
- The clinical success of immune checkpoint inhibitors has called attention to TILs
- Assessment of ER, PgR, Ki-67 and HER2 is a surrogate for the molecular classification of BC
- HER2 expression is no longer categorised as a binary variable
- As NAT is increasingly adopted, clinicians and pathologists should collaborate to best assess tumour response

Further Reading

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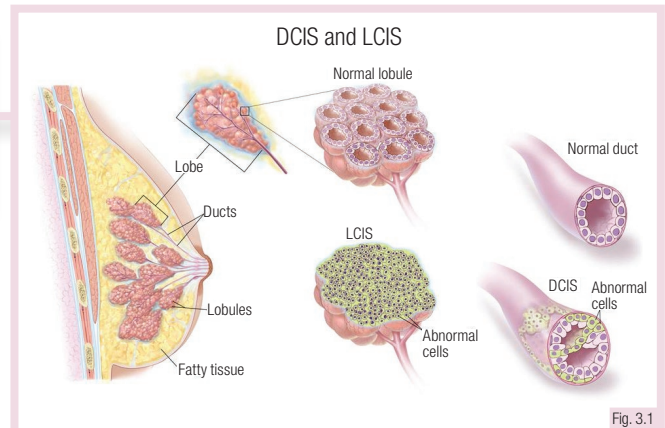
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Pathology and biology

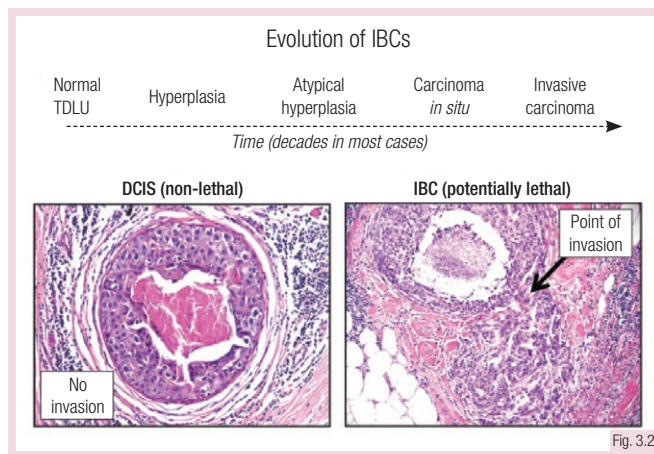
Carcinoma *in situ* of the breast can be divided into two categories: ductal carcinoma *in situ* (DCIS), a non-invasive condition of abnormal cells found in the lining of a breast duct, and lobular carcinoma *in situ* (LCIS), a non-invasive lesion that arises from the lobules and terminal ducts of the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

LCIS is a risk indicator for the development of subsequent invasive breast cancer (BC) in either breast.

LCIS is not considered a pre-cancer and therefore does not require 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% of cases) and an initial stage of BC evolution.

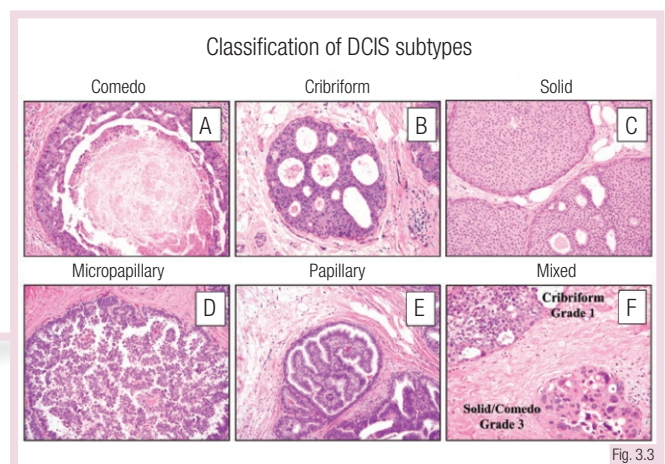
Since DCIS is a non-invasive lesion, there is no risk of development of metastases in patients diagnosed with pure DCIS.

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. Immunohistochemistry is usually limited to the detection of oestrogen receptor (ER) expression as oestrogen is the only actionable target in DCIS.

The histological grade of DCIS is classified as low or grade 1 (well differentiated), intermediate or grade 2 (moderately differentiated), or high or grade 3 (poorly differentiated).

The histological subtypes of DCIS, classified primarily according to their architectural pattern, include: comedo, cribriform, solid, papillary and micropapillary type.

However, a large proportion of DCIS show combinations of growth patterns.



DCIS, ductal carcinoma in situ.

REVISION QUESTIONS

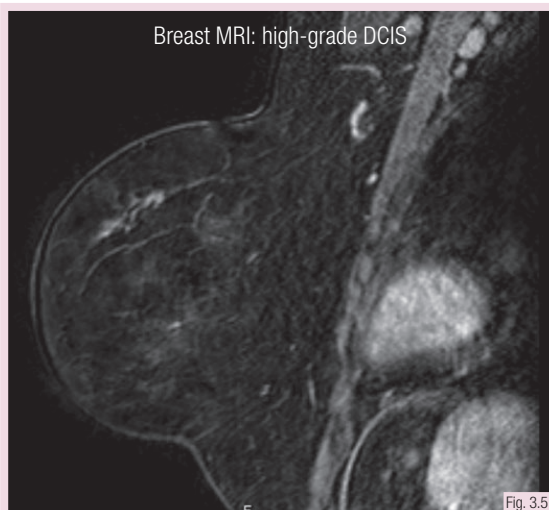
1. What are the different subtypes of carcinoma *in situ*?
2. Describe the most important biological differences between these subtypes of carcinoma *in situ*.
3. What are the most important features that characterise DCIS?

Diagnosis

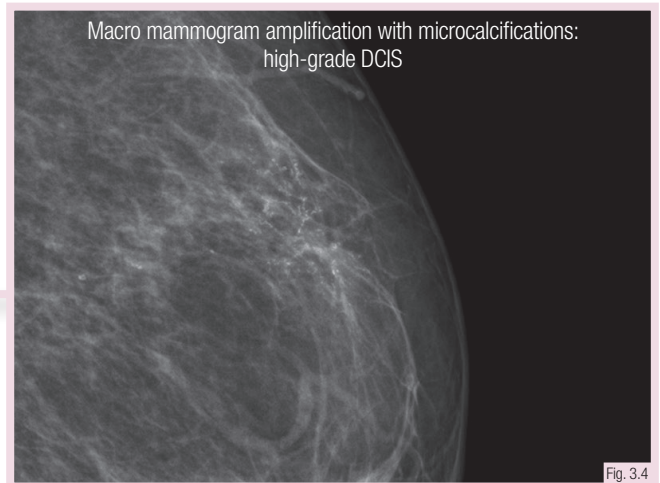
The frequency of diagnosis of DCIS has increased significantly with the introduction of BC (mammographic) screening.

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

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; MRI, magnetic resonance imaging.



DCIS, ductal carcinoma in situ.

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.

Breast MRI 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. 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, which reduces the underestimation rate of invasive carcinoma in cases with DCIS.

A localising clip is often placed at the end of the biopsy.

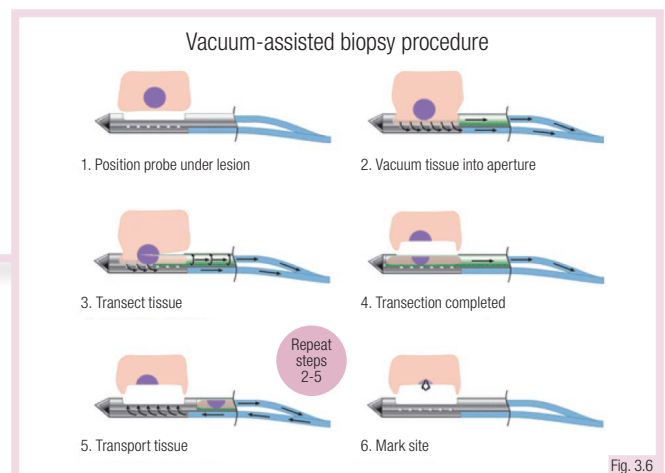


Fig. 3.6

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.

Depending on the size of the lesion in relation to the size of the breast and taking the patient's preference into account, treatment options may include breast-conserving surgery (BCS) or a mastectomy.

LCIS has no indication for surgical excision; it is a marker of risk and not a real precursor of invasive disease.

Breast conservation (left) and autologous reconstruction with abdominal flap (right)



Possible indications for SLNB in DCIS

Large area of microcalcifications

Breast mass

Mastectomy

Fig. 3.8

DCIS, ductal carcinoma in situ; SLNB, sentinel lymph node biopsy.

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 be considered when mastectomy is planned, because post-mastectomy SLNB is unreliable.

In a multivariate analysis, margin width was not a significant predictor of recurrence among those receiving radiotherapy (RT), 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 2 mm, especially if RT is foreseen.

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

Nipple-sparing mastectomies for DCIS



DCIS, ductal carcinoma in situ.

REVISION QUESTIONS

1. What factors determine patient suitability for BCS in DCIS?
2. What are the indications for SLNB in DCIS?
3. Is there an ideal margin for DCIS in BCS?

Radiotherapy

RT is a part of breast-conserving treatment in DCIS. Standard care is postoperative hypofractionated whole-breast RT, delivered over a period of 1–3 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 RT.

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

Long-term follow-up of patients with DCIS treated in the EORTC 10853 trial

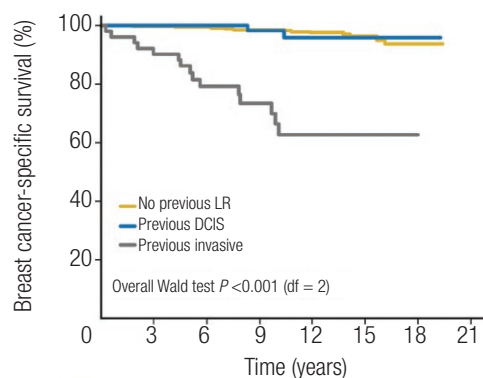


Fig. 3.11

DCIS, ductal carcinoma in situ; EORTC, European Organisation for Research and Treatment of Cancer; LR, local recurrence; n, number of patients; O, observed.

Prospective clinical trials have tried to define a subgroup of low-risk patients that can be treated with BCS only. These concluded that for DCIS grade 1 and 2 diagnosed in postmenopausal patients, the local recurrence rate is ~1% per year (without plateau at long-term follow-up) with local surgery only for lesions <1 cm, excised with tumour-free margins.

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

In patients with resected non-low-risk DCIS, a radiation boost to the tumour bed after whole-breast RT might further improve local control.

Effect of RT after BCS

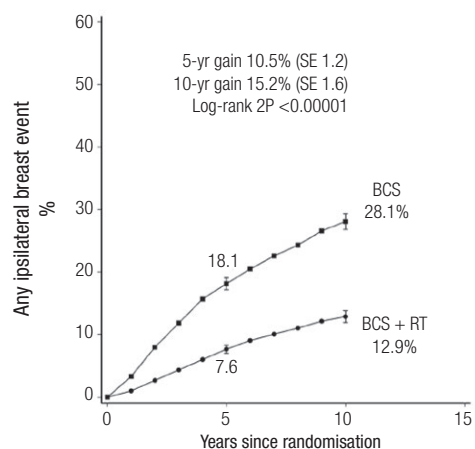


Fig. 3.10

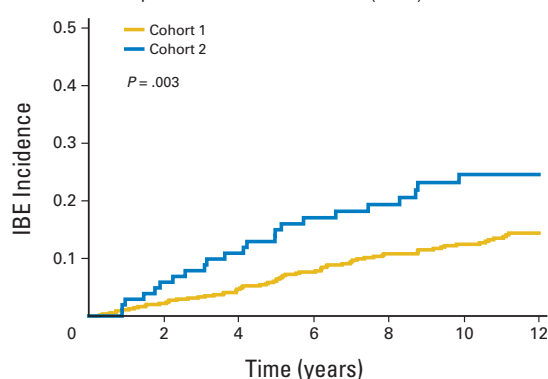
BCS, breast-conserving surgery; RT, radiotherapy; SE, standard error.

Half of all local 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 de-escalate RT in selected low-risk patients (with small lesions of low-grade disease resected with tumour-free margins), or in patients of advanced age with extensive comorbidities.

Hypofractionated (1–3 weeks) whole-breast RT is the standard of care and partial-breast RT can be considered in selected low-risk patients.

Ipsilateral breast events (IBE)



No. at risk	0	2	4	6	8	10	12
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

DCIS, ductal carcinoma in situ.

REVISION QUESTIONS

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

Prevention of recurrence

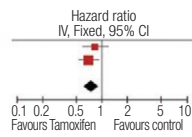
BC prevention strategies include lifestyle factors, such as avoidance of obesity, maintaining physical activity and moderation of alcohol intake, as well as surgical and medical therapeutic interventions, in case of high-risk patients such as those with germline mutations.

In DCIS, **tamoxifen** is the most widely accepted selective ER modulator for prevention, although its acceptance is low due to a perceived concern about adverse effects and poor ability to identify women at high risk.

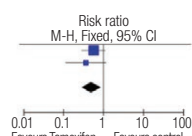
Aromatase inhibitors (AIs) have been being studied in large trials. Newer agents, notably **bisphosphonates**, also show promise.

Forest plots of NSABP B-24 and UK/ANZ DCIS trials 2011

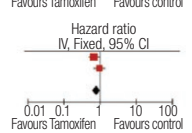
NSABP B-24 Trial 2011
UK/ANZ DCIS Trial 2011
Total (95% CI) HR = 0.79 (0.62-1.01)
P=0.006
Forest plot of comparison – ipsilateral DCIS



NSABP B-24 Trial 2011
UK/ANZ DCIS Trial 2011
Total (95% CI) RR = 0.50 (0.28-0.87)
P=0.01
Forest plot of comparison – contralateral DCIS



NSABP B-24 Trial 2011
UK/ANZ DCIS Trial 2011
Total (95% CI) HR = 0.79 (0.62-1.01)
P=0.06
Forest plot of comparison – ipsilateral invasive



NSABP B-24 Trial 2011 – 1804 pts
UK/ANZ DCIS Trial 2011 – 1701 pts
Total (95% CI) RR = 0.57 (0.39-0.83)
P=0.003
Forest plot of comparison – contralateral invasive

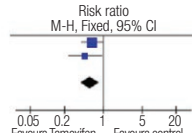


Fig. 3.14

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** include patients with ER-negative DCIS and patients with a high risk of subsequent complications such as deep venous thrombosis (especially age >65 years), particularly when risk of local recurrence is low.

Patients receiving BCS for DCIS may benefit from **RT + 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 BC prevention

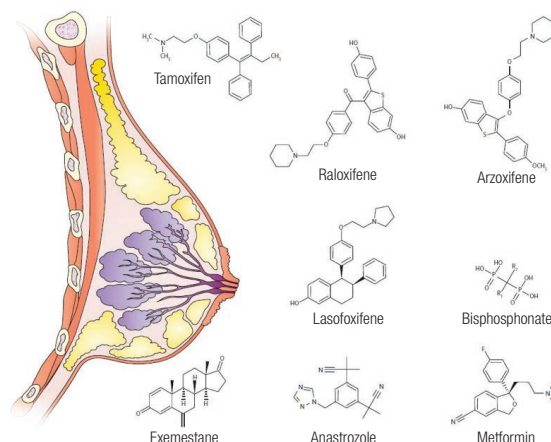


Fig. 3.13

BC, breast cancer.

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

A **meta-analysis** of both trials showed a reduction in both ipsilateral and contralateral *in situ* recurrences, with no benefit in OS. Low-dose tamoxifen (5 mg/day for 2–3 years) significantly reduced recurrences with lower rates of side effects than the standard dose (20 mg/day for 5 years).

The IBIS-II and NSABP B-35 trials studied **anastrozole** as alternative treatment for postmenopausal women with ER-positive DCIS, which may be more appropriate for some women with contraindications to tamoxifen, but again, there was no survival benefit.

Ipsilateral invasive local recurrences at 10 years by treatment type

	DCIS cases	Invasive recurrences	Recurrence rate (95% CI)
BCS alone	2038	241	11.4% (8.8–14.1)
BCS + tamoxifen	567	49	8.6% (6.7–10.6)
BCS + RT	4562	317	7.7% (5.9–9.5)
BCS + RT + tamoxifen	937	40	4.3% (3.0–5.6)
TOTAL	8104	647	

Fig. 3.15

BCS, breast-conserving surgery; CI, confidence interval; DCIS, ductal carcinoma in situ; RT, radiotherapy.

REVISION QUESTIONS

1. What are the known strategies for DCIS prevention in high-risk women?
2. What is the benefit of tamoxifen for the reduction of ipsilateral recurrence?
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 requiring local treatment, and DCIS, a precursor of invasive cancer and requiring local therapy
- The incidence of DCIS has increased with the introduction of population-based screening
- A breast biopsy is needed for the diagnosis of DCIS. Vacuum-assisted biopsy techniques obtain a greater volume of tissue sampling than FNA, which is important to distinguish between invasive and *in situ* carcinoma
- The goal of local therapy is to prevent the future development of invasive carcinoma
- Surgical treatment can be either BCS or mastectomy (the latter preferably with immediate reconstruction)
- In general, SLNB is not indicated
- It is essential to obtain tumour-free margins
- RT following BCS decreases the 10-year absolute risk of in-breast recurrences by 15%
- RT may be de-escalated 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

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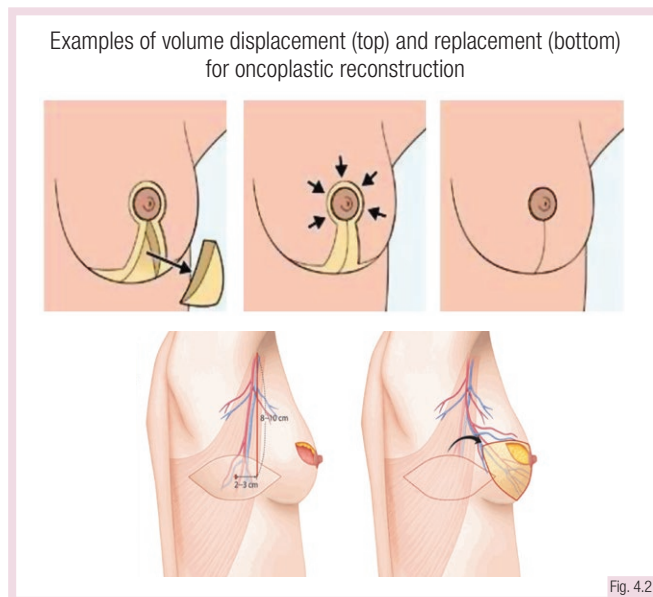
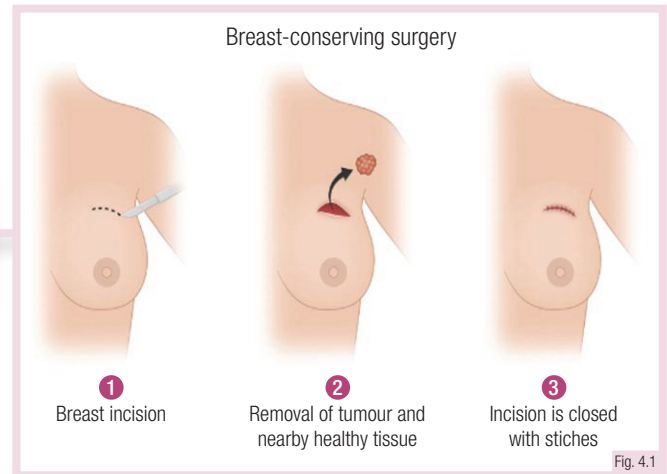
Image sources: Fig. 3.1. www.cancer.gov ©2012 Terese Winslow LCC, U.S. Govt has certain rights; 3.2, 3.3. Allred DC. *J Natl Cancer Inst Monogr* 2010;2010:134-138; 3.6. <http://www.medsurge.in/products/mammotome-biopsy-system.html> (date last accessed 10 October 2024); 3.10. Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Correa C et al. *J Natl Cancer Inst Monogr* 2010;2010:162-177; 3.11. Donker M, et al. *J Clin Oncol* 2013;31:4054-4059; 3.12. Solin LJ, et al. *J Clin Oncol* 2015;33:3938-3944; 3.13. Cuzick J, et al. *Lancet Oncol* 2011;12:496-503; 3.14. adapted from Staley H, et al. *Breast* 2014;23:546-551. All other figures courtesy of the authors.

Breast cancer surgery

Breast cancer (BC) surgery aims to remove invasive and non-invasive BC with **clear margins**. It can be performed as **standard breast-conserving surgery (BCS)**, **oncoplastic BCS** or **mastectomy** with or without reconstruction.

BCS, also known as lumpectomy, tumourectomy or wide local excision, can be chosen when breast size allows a **cosmetically acceptable resection**, and is often combined with **partial or whole-breast radiotherapy (RT)**.

The preferred locations of the incision are **periareolar** or in the **inframammary fold** for a superior cosmetic outcome.



Oncoplastic BCS is often performed when an excision of **>20%** of breast tissue is needed; the two main procedures are **volume displacement** or **replacement**.

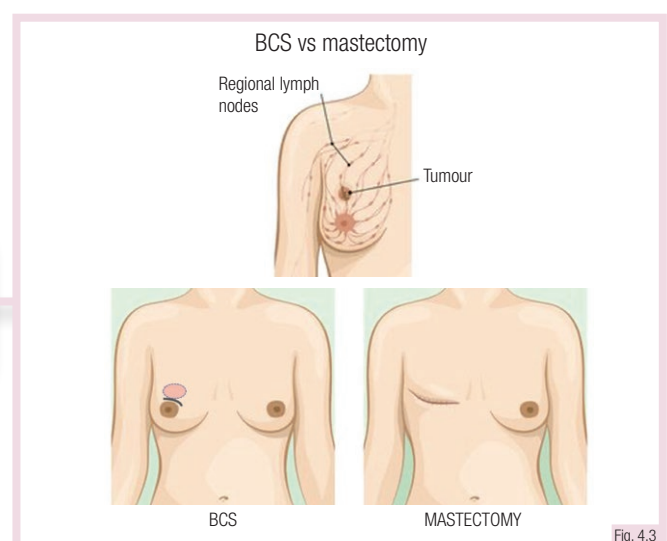
In volume displacement, remaining **breast tissue** is used to fill the defect, whereas in the case of replacement, surrounding **autologous tissue** is used.

Options depend on the **patient's wishes**, **posture**, **breast size** and **size and location** of the tumour. Examples of both techniques include the round block technique, Wise pattern reconstruction and reconstruction using (lateral) intercostal artery perforator ([L]ICAP) flaps.

Mastectomy aims to remove **all breast tissue** and is performed depending on **patient preference**, **gene mutations**, or when **tumour size** or **multicentricity** makes BCS impossible.

The **borders of the resection** are the parasternal region, the inframammary fold, the latissimus dorsi muscle on the lateral and the clavicular region on the cranial side.

To prevent **seroma**, a **common complication**, various techniques are used such as drains and quilting.



BCS, breast-conserving surgery.

REVISION QUESTIONS

1. BCS is well known by various other terms. Can you name them?
2. Which techniques are used in oncoplastic BCS?
3. What are considered good reasons for a mastectomy?

Breast cancer surgery (continued)

Mastectomy with reconstruction can be performed depending on BC characteristics and the patient's wishes, posture and comorbidity.

Options are skin-saving or nipple-sparing mastectomy, with immediate or delayed reconstruction with prosthesis, autologous tissue or fat transplantation.

In the case of chest wall RT, direct reconstruction with autologous tissue or prosthesis may be considered, but discussion on the impact of RT on morbidity and cosmetic outcome is ongoing. Alternatively, delayed reconstruction with autologous tissue or prosthesis and latissimus dorsi flap can be performed.

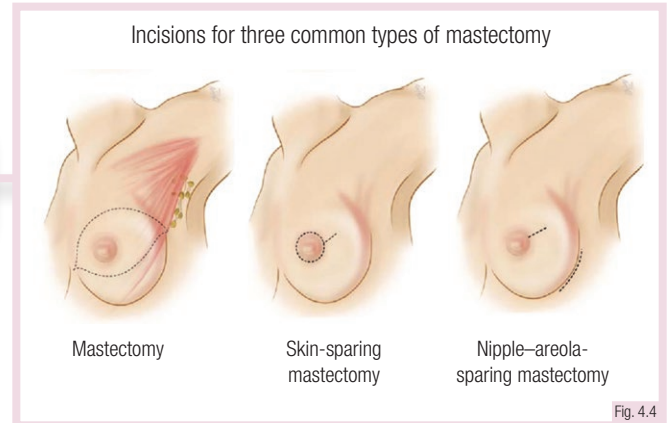


Fig. 4.4

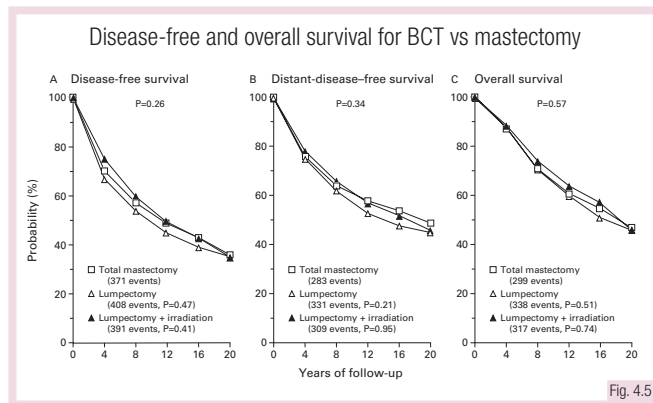


Fig. 4.5

BCT, breast-conserving therapy.

BCS with RT (breast-conserving therapy [BCT]) vs mastectomy? Recently, several articles have tried to show the superiority of BCT; however, this is difficult to prove since these were cohort studies and patient selection cannot be excluded.

Therefore, the conclusion remains that BCT and mastectomy, with or without reconstruction, are equal in terms of oncological safety outcomes such as recurrence and survival.

If a patient has a choice between BCT and mastectomy, a number of aspects need to be considered such as the future look and feel of the breast or chest wall scar, the chances of irradiability and RT and its potential consequences, such as impact on quality of life (QoL).

Breast surgery is often performed upfront, followed by RT and/or systemic treatment if indicated. Primary systemic therapy (PST) is applied increasingly frequently, especially in triple-negative and human epidermal growth factor receptor (HER2)-positive BC, often resulting in pathological complete response of the tumour in the breast and axilla. This can guide adjuvant systemic therapy.

After PST, surgery of the breast and axilla can be tailored to the response, often de-escalating surgery to BCS and targeted axillary dissection (TAD). Patient's expectations need to be managed depending on BC subtype and PST.

Complications can include seroma, necrosis, rebleeding and lymphoedema.

Example of skin necrosis after mastectomy and immediate breast reconstruction



Fig. 4.6

REVISION QUESTIONS

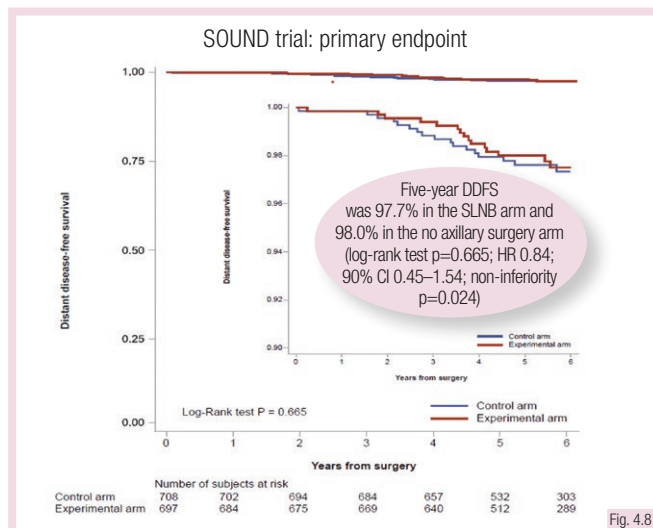
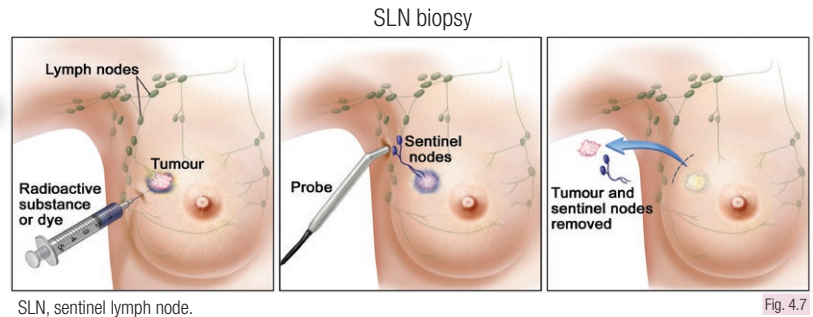
1. What factors are important in the decision-making process for mastectomy with reconstruction?
2. What can you say about the oncological safety of BCT vs mastectomy?
3. Which BC subtypes have high response rates to PST?

Surgery of the axilla

In clinically node-negative (cN0) BC, the sentinel lymph node (SLN, the first draining lymph node [LN]) is identified in the axilla using periareolar-injected technetium and/or blue or green dye.

In case of pN0 or pNmi BC, no further regional treatment such as axillary lymph node dissection (ALND) or RT is indicated.

In cN1 BC, one can consider omission of complementary regional treatment (according to the ACOSOG Z0011 trial), RT (level 1–2 or 1–4 according to the AMAROS trial) or ALND. Any decision should consider the patient's wishes, age and comorbidity.



CI, confidence interval; DDFS, distant disease-free survival; HR, hazard ratio; SLNB, sentinel lymph node biopsy.

In clinically node-positive BC (cN1/2/3) and primary surgery, ALND is often indicated. All level I and II axillary LNs are removed, while carefully preserving the long thoracic nerve and the thoracodorsal nerve/vessel bundle. However, use of PST is becoming more common here.

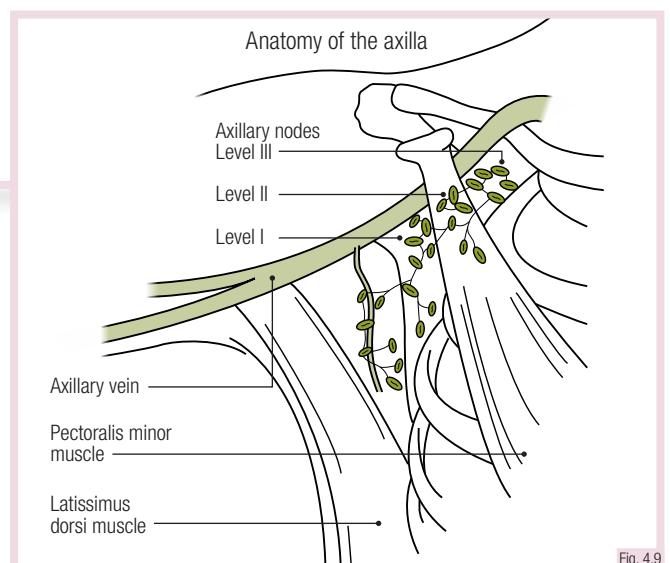
In case of PST, removal of a pre-PST marked metastatic LN and SLN, after finishing PST (so-called TAD), provides the most accurate information on remaining axillary disease. This can guide further axillary treatment (omission of further axillary treatment, RT, ALND or a combination) and systemic treatment.

Removal of the pre-PST marked metastatic LN or SLN is an alternative staging procedure after PST.

Various studies have explored the impact of the omission of the SLN biopsy (SLNB) in patients with cT1–2N0 BC treated with whole-breast RT: the Italian SOUND study, the German INSEMA and the Dutch BOOG 2013-08 study.

A preoperative axillary ultrasound was performed in all patients.

The SOUND study showed that omission of the SLNB is non-inferior to performing the SLNB in cT1N0 BC, in terms of administered systemic treatment and distant disease-free survival and overall survival.



REVISION QUESTIONS

1. How is a SLNB performed?
2. What can you say about the oncological safety of omission of the SLNB in cT1N0 BC?
3. Name the anatomical structures that need to be preserved in ALND?

Breast reconstruction

Breast **reconstruction** aims to restore the breast, either partially or totally, and has been shown to improve patients' health-related QoL.

Breast reconstruction does not influence **oncological outcomes**. The choice for a reconstruction and which type is considered in a shared decision-making process with the patient.

Reconstruction can be performed with **implants**, **autologous tissue** or a **combination** of both, depending on the patient's characteristics and preferences. Reconstruction can be preceded by a **tissue expander** when too much skin is lost during mastectomy or when the patient would like more breast volume than currently possible.

Severe asymmetry after a unilateral mastectomy without reconstruction



Bilateral DIEP flap reconstruction (abdominal tissue) with nipple reconstruction



Scar positioning of an immediate reconstruction (right breast) and a delayed reconstruction (left breast)
DIEP, deep inferior epigastric perforator.

Reconstruction can be performed immediately following mastectomy, either during the same procedure (**primary/immediate reconstruction**) or as a consecutive procedure (**secondary/delayed reconstruction**).

In the case of immediate breast reconstruction, a period without a breast can be avoided and more skin can be preserved, leading to smaller scars and therefore a better **aesthetic result**.

Delayed breast reconstructions are often due to oncological safety or upcoming RT. **Tertiary reconstructions** are those replacing a previous reconstruction, which can be for various reasons.

Implant-based reconstruction (IBR) has a shorter operating time than free flap surgery, but asymmetry and secondary **revisions** are more frequent.

If RT of the thoracic region is recommended, **IBR should be avoided**, due to higher rates of acute and chronic complications.

IBR can be combined with **pedicled latissimus dorsi flaps** or with **acellular dermal matrix (ADM)** to obtain better implant coverage.

Breast reconstructed with a temporary TE (left and centre).
TE replaced by a definitive implant-based breast reconstruction (right)

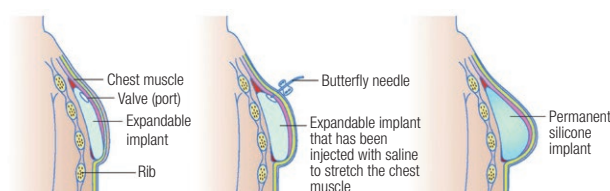


Fig. 4.12

TE, tissue expander.

REVISION QUESTIONS

1. What are the main types of reconstruction?
2. When should IBR be avoided?
3. What are the advantages of immediate breast reconstruction?

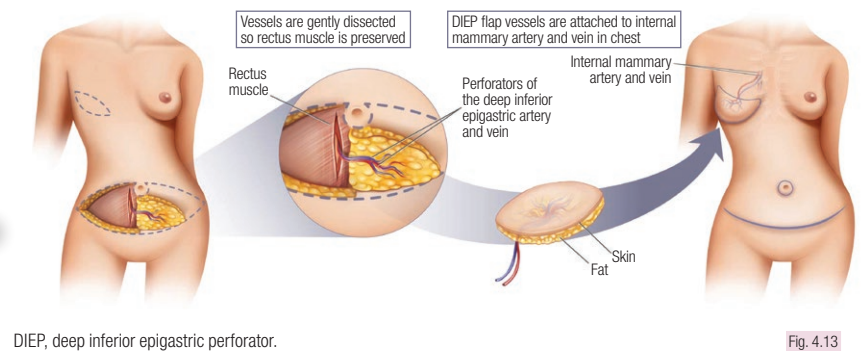
Breast reconstruction (continued)

In autologous free flap reconstruction, **skin and fat are harvested together with the supplying artery and vein** (and sometimes nerve) from a donor site and connected to the intercostal blood vessels and nerve to create a new breast.

The use of autologous tissue leads to a more **natural and softer feel** to the breast, compared with implant reconstruction. The most commonly used donor site is the abdomen (deep inferior epigastric perforator [DIEP] flap).

Coaptation of a sensory nerve from the donor site to the breast leads to better outcomes in sensation and QoL compared with non-innervated breast reconstruction.

Surgical procedure of the DIEP flap breast reconstruction



Replacement of a failed TE reconstruction by a tertiary LTP reconstruction



Failed TE reconstruction after explantation of the TE (top left); LTP flap reconstruction with preserved nipple (top right); LTP donor site – lateral thigh; front view (bottom left); LTP donor site – lateral thigh; rear view (bottom right).

LTP, lateral thigh perforator; TE, tissue expander.

Alternative donor sites to the abdomen can be used if the patient has too little abdominal tissue or has abdominal scars which can influence postoperative flap viability.

Examples of alternative donor sites include the **flanks, lower back, inner thighs, outer thighs or buttocks**.

Autologous breast reconstructions often require **secondary correction** to correct asymmetry or imperfections due to unpredictable postoperative changes to the reconstruction.

In **autologous fat transfer (AFT)**, fat is harvested through liposuction from a donor site (e.g. thighs, abdomen or flank), then processed and injected into the breast.

AFT can be used to correct deformities after reconstruction and as a standalone breast reconstruction method, with or without **pre-expansion** using an external vacuum device.

Most patients require **multiple sessions** (mean of four surgeries) to obtain a final and total breast reconstruction. Overnight hospitalisation is not usually needed after each session.

Patient after bilateral nipple-sparing mastectomy (left); patient after four sessions of bilateral AFT reconstruction (right)



AFT, autologous fat transfer.

REVISION QUESTIONS

1. What are the advantages of nerve coaptation in autologous breast reconstruction?
2. How many sessions are usually required to obtain total breast reconstruction with AFT?
3. When would a plastic surgeon consider an alternative donor site to the abdomen for autologous breast reconstructions?

Summary: Breast cancer surgery

- BC surgery can be performed as BCS, oncoplastic BCS or mastectomy with or without reconstruction
- Options depend on patient's wishes, posture, breast size and size and location of the tumour
- BCT is equal to mastectomy in oncological safety outcomes. BCS scores higher in the long term for QoL
- Complications of BC surgery can include seroma, necrosis, rebleeding and lymphoedema
- In cN0 BC, SLNB is the standard procedure for axillary staging
- In case of PST, axillary staging consists mostly of targeted axillary dissection, or removal of the pre-PST marked LN or SLN
- Breast reconstruction after mastectomy positively influences QoL
- Breast reconstruction can be performed using implants, autologous tissue or a combination of both
- The timing of the reconstruction is dependent on oncological safety or upcoming RT. Autologous breast reconstruction leads to a more natural feel and touch to the breast than IBR
- A nerve coaptation accompanying a free flap breast reconstruction can enhance recovery of breast sensation compared with similar reconstructions without a nerve coaptation
- Various donor sites can be utilised for harvesting flaps for free flap breast reconstruction, depending on the patient and the location of tissue surplus
- AFT can be used, often requiring one single surgery, to correct deformities after reconstruction, but also as a standalone breast reconstruction method, though this requires multiple surgeries

Further Reading

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van Loevezijn AA, van der Noordaa MEM, Stokkel MPM, et al. Three-year follow-up of de-escalated axillary treatment after neoadjuvant systemic therapy in clinically node-positive breast cancer: the MARI-protocol. *Breast Cancer Res Treat* 2022; 193:37–48.

Image sources: Fig. 4.1. www.gleneagles.com.sg (date last accessed 17 October 2024); 4.2. Rainsbury, RM. *Nat Clin Pract Oncol* 2007;4:657-664 (top); Kim JB, et al. *Arch Plast Surg* 2018;45:29-36 (bottom); 4.3. adapted from logika600/PIXTA, pixtastock.com; 4.4. Djohan R, et al. *Cleve Clin J Med* 2008;75:S10-S16; 4.5. Fisher B, et al. *N Engl J Med* 2002;347:1233-1241; 4.6. Yun MH, et al. *Arch Plast Surg* 2017;44:509-515; 4.7. www.cancer.gov ©2010 Terese Winslow, U.S. Govt has certain rights; 4.8. courtesy of Oreste D. Gentilini; 4.10. Bachleitner K, et al. *J Clin Med* 2020;9:3030; 4.12. Potter S, et al. *BMJ* 2018;362:k2607; 4.13. courtesy of Joshua L. Levine, M.D., Center for Breast Reconstruction, NY, NY USA. All other figures courtesy of the authors.

Adjuvant radiotherapy after breast-conserving surgery for early breast cancer

Adjuvant radiotherapy (RT) after breast-conserving surgery (BCS) significantly **lowers the risk of local, regional and distant failure and improves overall survival (OS)**.

In patients with **node-negative breast cancer (BC)**, RT has shown to halve the average annual recurrence rate and reduce BC deaths by about a sixth.

In patients with **node-positive BC**, RT has shown a five-fold reduction in the 1-year recurrence risk and a moderate additional effect over the next few years, but little further effect after 5 years.

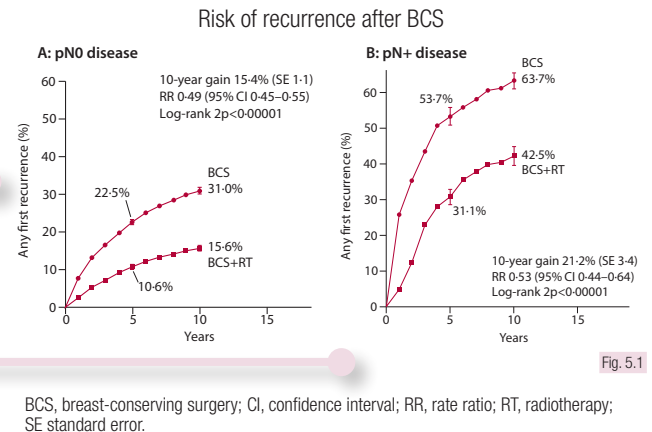


Fig. 5.1

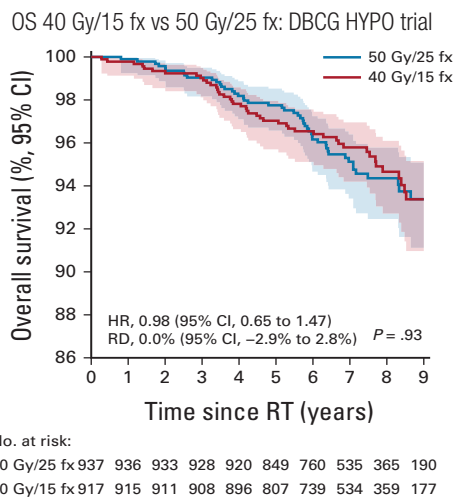


Fig. 5.2

CI, confidence interval; DBCG, Danish Breast Cancer Group; fx, fractions; HR, hazard ratio; OS, overall survival; RD, risk difference; RT, radiotherapy.

After BCS, a **boost** to the tumour bed reduces the 10-year risk of ipsilateral BC recurrence for all age groups, with the highest absolute benefit in young women.

The use of a boost dose (10–16 Gy) should be considered depending on the risk factors, **e.g. young age, close margins, node-positive disease, grade 3 tumour and vascular invasion**.

Important risk factors that can contribute to a **worse cosmetic outcome after boost** irradiation are photon boost instead of electron boost, high boost dose, boost volume and adjuvant chemotherapy (ChT).

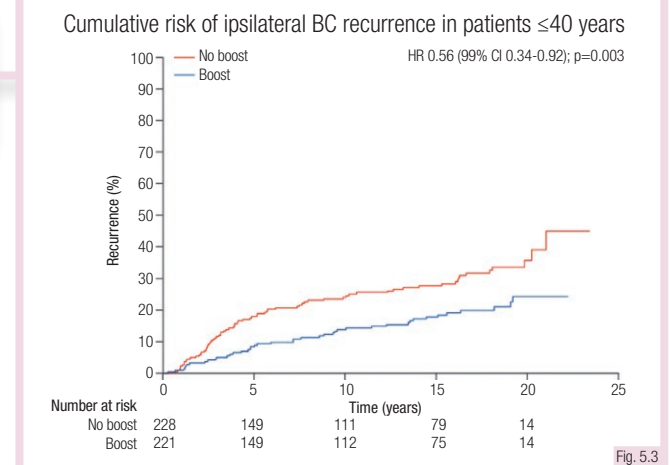


Fig. 5.3

BC, breast cancer; CI, confidence interval; HR, hazard ratio.

REVISION QUESTIONS

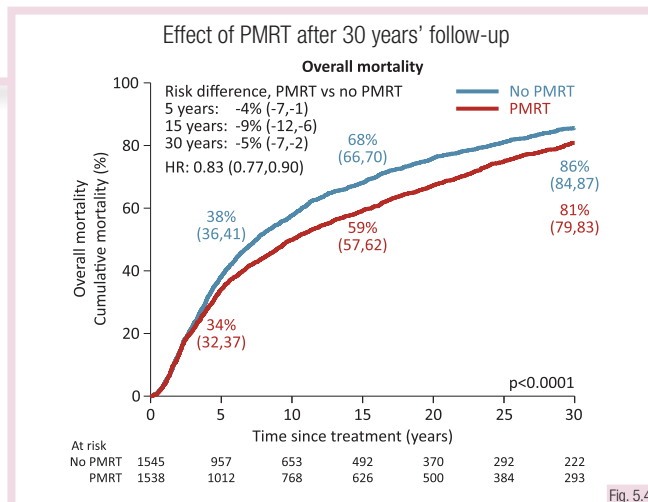
1. What is the impact of RT after BCS?
2. Is hypofractionation comparable with normofractionation according to morbidity?
3. What is the impact of a boost on BC recurrence rate?

Adjuvant RT after mastectomy for early BC

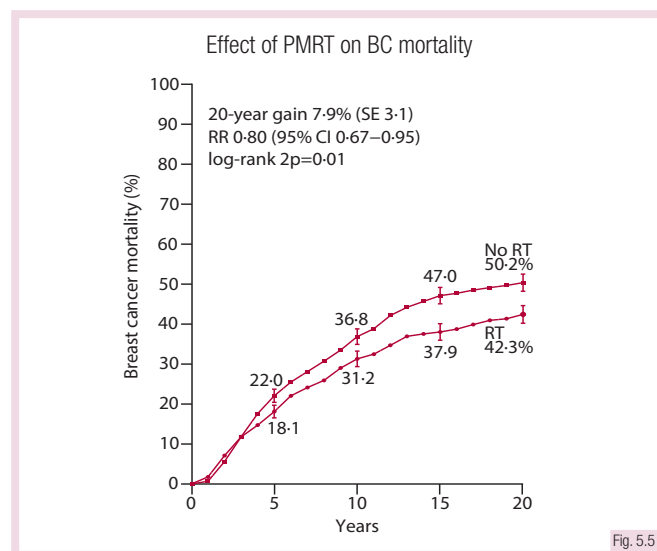
Postmastectomy RT (PMRT) reduces the 30-year risk of locoregional recurrence and **improves OS** in patients with node-positive BC. This improvement starts at 5 years after PMRT.

The OS benefit of PMRT is documented in both **pre- and postmenopausal** patients also treated with systemic therapy.

PMRT should be considered in patients with **node-positive** disease and in patients with locally advanced BC, irrespective of nodal status.



HR, hazard ratio; PMRT, postmastectomy radiotherapy.

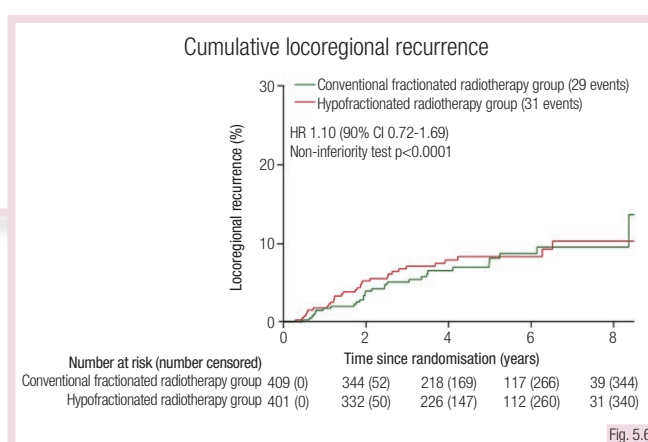


BC, breast cancer; CI, confidence interval; PMRT, postmastectomy radiotherapy; RR, rate ratio; RT, radiotherapy; SE standard error.

PMRT was previously delivered with 50 Gy in 25 fx; however, several trials have investigated if hypofractionation is non-inferior compared with conventional RT.

In a Chinese randomised study of high-risk patients receiving **hypofractionated or conventional PMRT**, the results reported for the 5-year risk of locoregional recurrence were comparable.

In the **Skagen Trial 1** (NCT02384733) and the **HypoG-01 trial** (NCT03127995) moderate hypofractionation and conventional RT are being compared; results are expected in 2025.



CI, confidence interval; HR, hazard ratio.

REVISION QUESTIONS

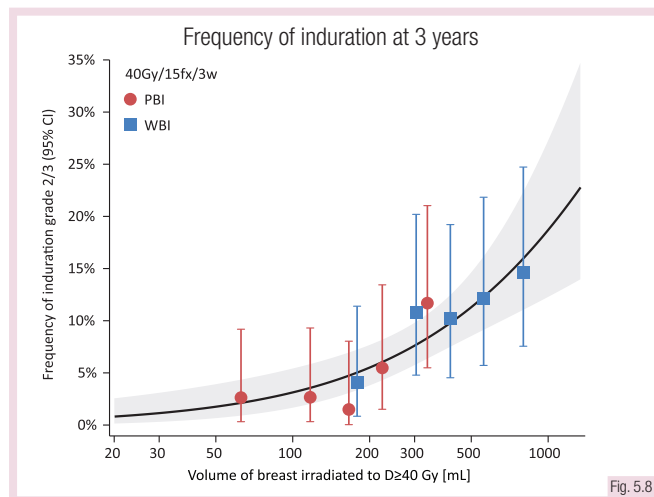
1. Is there a long-term survival gain from PMRT?
2. Which patients benefit from PMRT?
3. What is the evidence to support hypofractionated PMRT?

Partial breast irradiation

Partial breast irradiation (PBI) for selected patients is **non-inferior** in terms of local recurrence and late morbidity compared with whole-breast irradiation.

PBI is recommended after BCS in a selected subgroup of patients with **low risk of recurrence** (age >50 years, small tumour size, node-negative, oestrogen receptor [ER]-positive and human epidermal growth factor receptor 2 [HER2]-negative).

The rationale for PBI is based on the **low risk of recurrence** and the fact that most ipsilateral recurrences occur close to the primary tumour bed.

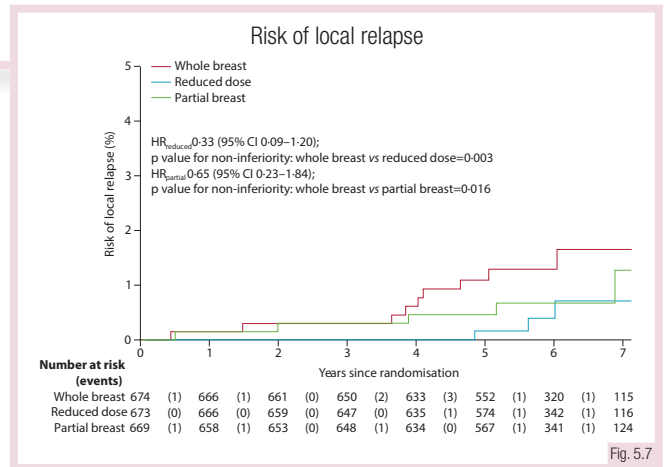


CI, confidence interval; D, dose; fx, fractions; PBI, partial breast irradiation; w, weeks; WBI, whole-breast irradiation.

External beam RT. **Advantages:** safe and effective, simple technique, non-invasive. **Disadvantages:** 1–3 weeks treatment, higher dose to organs at risk (OAR) compared with brachytherapy and intraoperative RT.

Brachytherapy. **Advantages:** dosimetric advantages, sparing of OAR. **Disadvantages:** invasive procedure, technically complex.

Intraoperative irradiation. **Advantages:** direct visualisation of target, single-dose treatment, short treatment length. **Disadvantages:** lack of pathological information, short range of dose leading to inferior outcome.

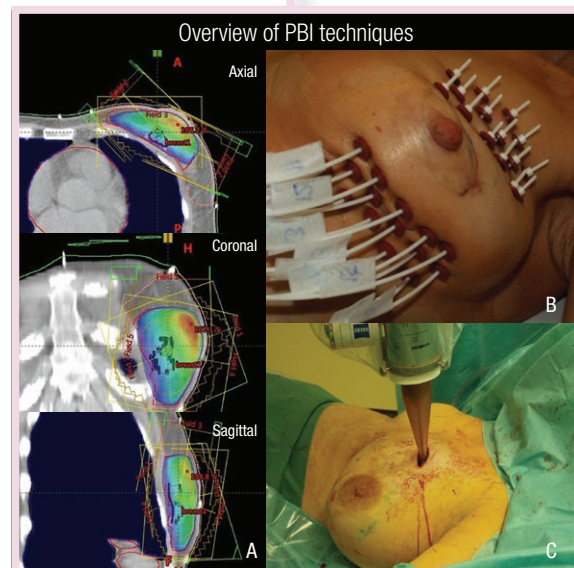


CI, confidence interval; HR, hazard ratio.

PBI delivers the RT dose **confined to the primary tumour bed**.

The risk of **breast induration** increases significantly with the volume of breast tissue irradiated, strongly favouring small volumes and PBI.

Techniques: External beam RT (A) is the most frequently used technique. Other techniques include interstitial brachytherapy (B) and intraoperative irradiation (C).



REVISION QUESTIONS

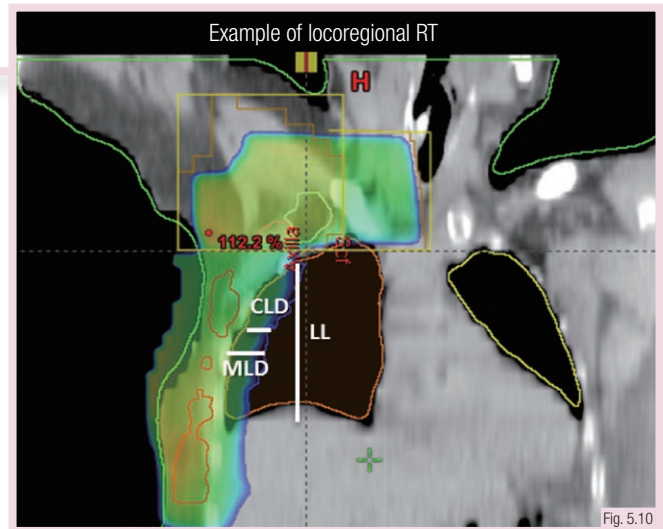
1. Should PBI be recommended to a subgroup of patients with BC?
2. Does the volume of irradiated breast reflect the risk of induration?
3. What are the advantages and disadvantages of the different PBI techniques?

The role of axillary irradiation

For patients **without indication for preoperative systemic treatment**, locoregional RT is recommended in node-positive disease.

For patients who have received **preoperative systemic treatment for cN1 disease**, locoregional RT should be considered. For patients who have received preoperative systemic treatment for cN2–N3 disease, locoregional RT is recommended.

Several centres **omit axillary lymph node dissection (ALND)** if the patient has **macrometastasis** in 1–2 sentinel lymph nodes (SLNs). However, **in clinically node-positive disease**, ALND may be indicated followed by locoregional RT.



CLD, central lung distance; LL, left lung; MLD, mean lung distance; RT, radiotherapy.

The European Organisation for the Research and Treatment of Cancer (EORTC) 10981-22023 **AMAROS** trial compared ALND with regional irradiation in patients with cT1–2 disease, no palpable lymph node (LN) but a positive SLN.

After 5-year follow-up, axillary control was high and comparable in the two arms and significantly less morbidity was observed after irradiation.

After 10-year follow-up, axillary control was still high and no difference was observed in OS, disease-free survival (DFS) or locoregional control. Furthermore, RT was associated with less lymphoedema.

Risk of 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 (5%)	0.0009

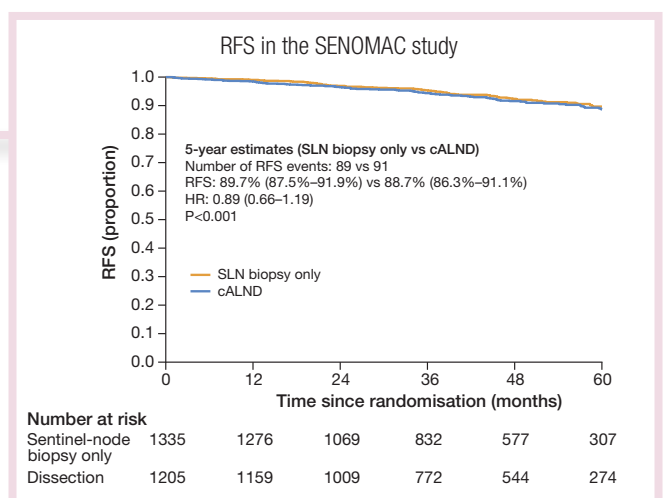
Data are n/N (%), unless otherwise specified.

Fig. 5.11

In the **SENOMAC trial**, patients with clinically node-negative BC (T1–T3) and 1–2 SLN macrometastases were randomised 1:1 to ALND vs regional RT.

In total, **2766 patients were randomised** between January 2015 and December 2021. The median follow-up was 3.9 years.

First results were presented at the San Antonio Breast Cancer Symposium 2023 and showed **no significant difference in 5-year recurrence-free survival** between the two arms.



cALND, completion axillary lymph node dissection; HR, hazard ratio; RFS, recurrence-free survival; SLN, sentinel lymph node.

Fig. 5.12

REVISION QUESTIONS

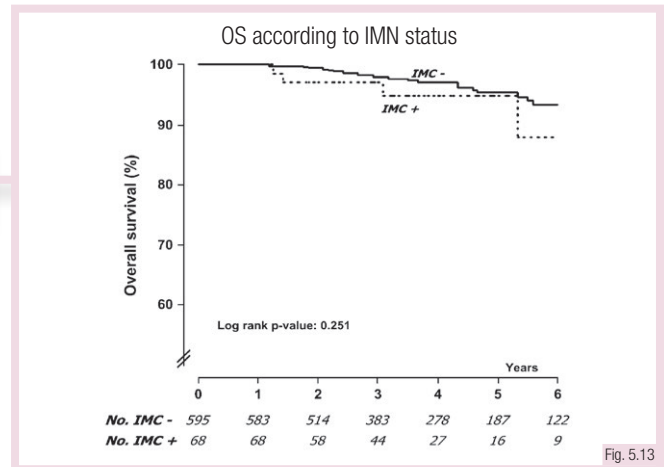
1. When is locoregional RT recommended?
2. What does the AMAROS trial show?
3. What do the first results of the SENOMAC trial show?

The role of internal mammary node irradiation

The incidence of metastatic involvement of the internal mammary nodes (IMNs) varies between 4% and 9% in node-negative patients and 16%–65% in node-positive.

An overview of older trials did not show survival benefit from IMN irradiation (IMN-RT), despite fewer locoregional recurrences.

An overview of randomised trials after BC surgery indicated a higher risk of cardiac mortality in patients who had received RT compared with those who had not.



IMC, internal mammary chain; IMN, internal mammary node; OS, overall survival.

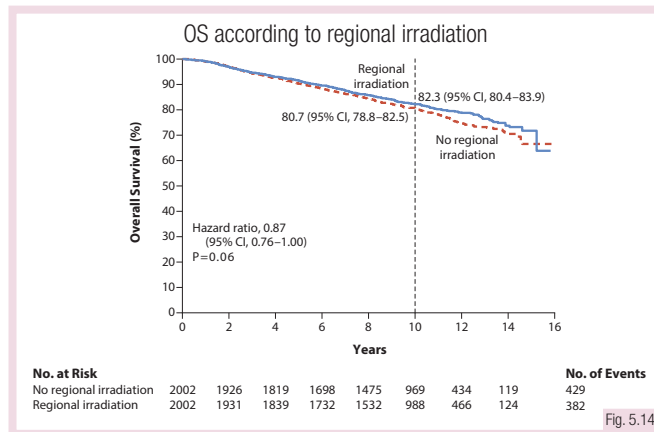


Fig. 5.14

CI, confidence interval; OS, overall survival.

The EORTC initiated a randomised trial investigating the effects of IMN and medial supraclavicular node RT.

Irradiation of regional LNs had no significant effect on OS. DFS and distant DFS were improved, and BC mortality was significantly reduced.

At 10-year follow-up, 3% of the patients had pulmonary fibrosis (4.4% in the nodal-irradiation group vs 1.7% in the control group) and 6% had cardiac disease (6.5% vs 5.6%, respectively).

In a prospective cohort study (the Danish Breast Cancer Group [DBCG] IMN study), 1412 patients with axillary LN-positive disease received IMN-RT (right-sided BC) whereas 1598 patients received no IMN-RT (left-sided BC).

At 15-year follow-up, the OS rate was 60.1% in patients who received IMN-RT compared with 55.4% without IMN-RT.

IMN-RT did not lead to a higher risk of death from ischaemic heart disease.

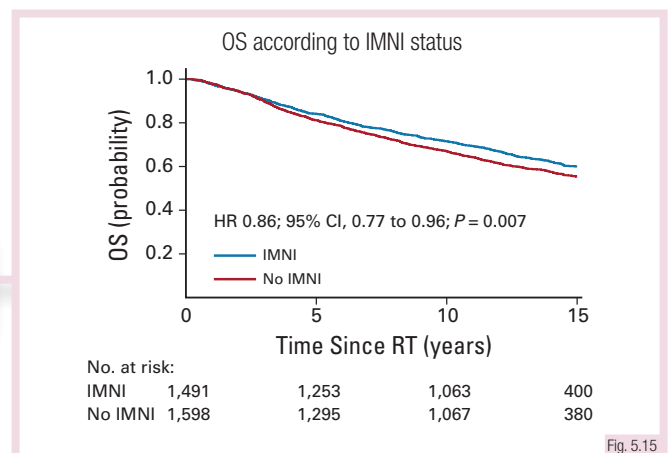


Fig. 5.15

CI, confidence interval; HR, hazard ratio; IMN, internal mammary node; IMNI, IMN irradiation; OS, overall survival; RT, radiotherapy.

REVISION QUESTIONS

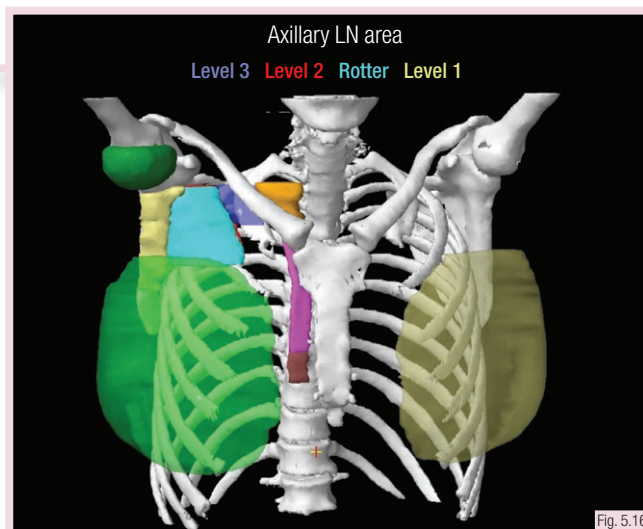
1. Historically, what impact did IMN-RT have on survival?
2. What was the impact of IMN-RT in the EORTC study?
3. What was the impact of IMN-RT in the DBCG IMN study?

Target delineation and RT technique

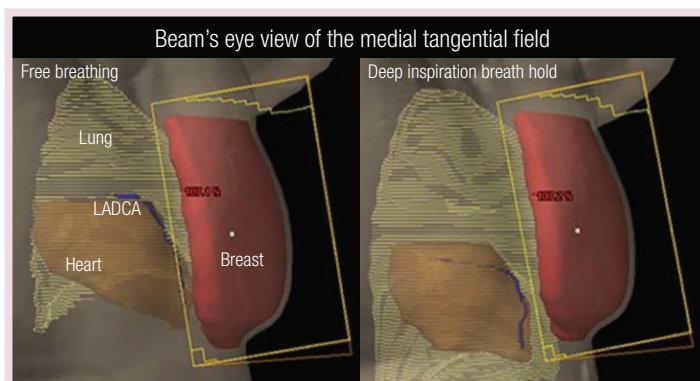
Target and OAR are delineated according to the European Society for Radiotherapy and Oncology consensus guidelines.

For locoregional disease, the LN target area depends on N-stage and surgical procedure.

Depending on RT technique, the following OAR should be considered: heart, ipsi- and contralateral lung, spinal cord, plexus brachialis, humeral head, oesophagus and thyroid gland.



Level 1: axilla level 1; Level 2: axilla level 2; Level 3: axilla level 3; Rotter: Interpectoral nodes. LN, lymph node.



LADCA, left anterior descending coronary artery.

Fig. 5.17

3D computed tomography (CT) planning is recommended for all patients with BC to reduce toxicity while providing optimal target-dose distribution.

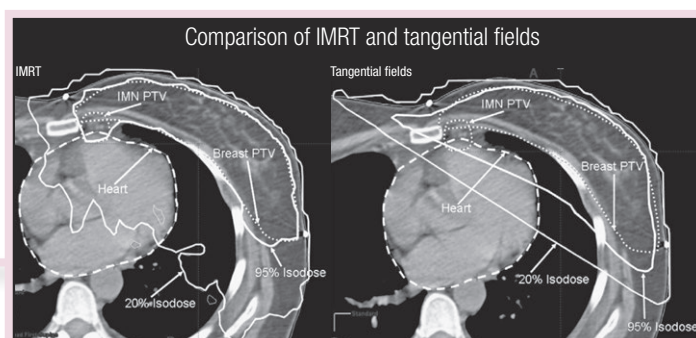
Tangential RT is considered the most common and effective method in BC RT to minimise radiation dose to OAR.

Cardiac and pulmonary complications are a potential risk in breast RT. Dose to heart and lung may be reduced by breath hold or respiratory gating techniques.

Optimal dose distribution may be achieved with different techniques such as standard tangential fields, intensity modulated RT (IMRT) or arc therapy.

IMRT and arc therapy may improve conformity and homogeneity of the dose distribution to residual breast tissue compared with tangential RT.

IMRT and arc therapy reduce the volume of OAR receiving a high RT dose but increase the volume that receives a low-dose bath.



IMN, internal mammary node; IMRT, intensity modulated radiotherapy; PTV, planning target volume.

Fig. 5.18

REVISION QUESTIONS

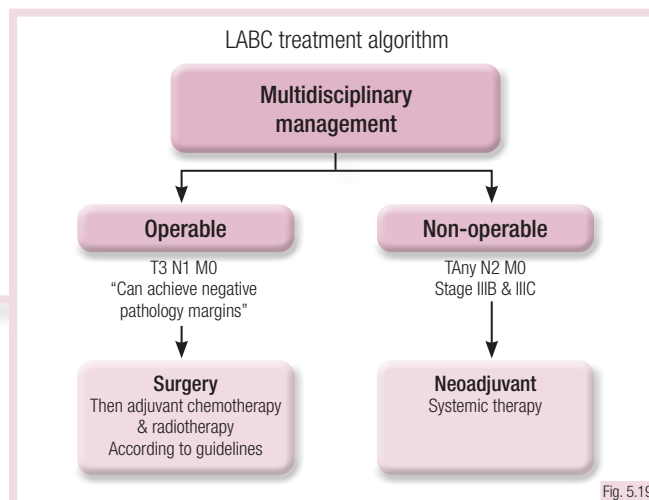
1. How are target and OAR defined in BC RT?
2. What are the main advantages of CT-based RT planning?
3. What are the advantages and disadvantages of IMRT and tangential fields?

RT for locally advanced BC

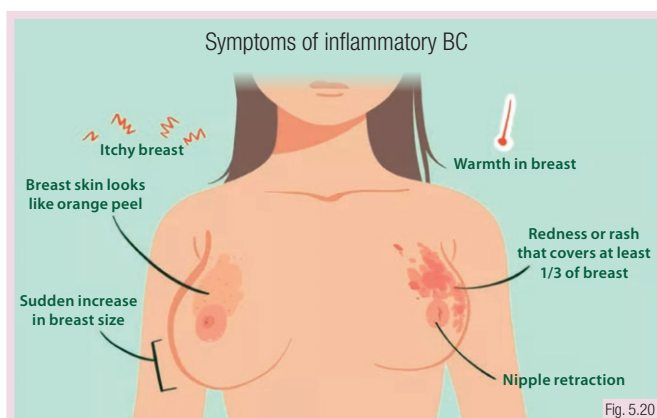
Locally advanced BC (LABC) is more common in younger patients and survival is strongly related to BC subtype.

Outcomes in patients with LABC are strongly related to access to the best available care (medicines, multidisciplinary care, guidelines, high-quality pathology, imaging, surgery and RT).

LABC is normally treated with a combination of ChT, often given preoperatively (neoadjuvant ChT [NACT]), surgery and RT.



LABC, locally advanced breast cancer; M, metastases; N, node; T, tumour.



BC, breast cancer.

BCS is an option for some patients with LABC after NACT, as long as there are no signs of inflammatory BC. For these patients, RT is recommended.

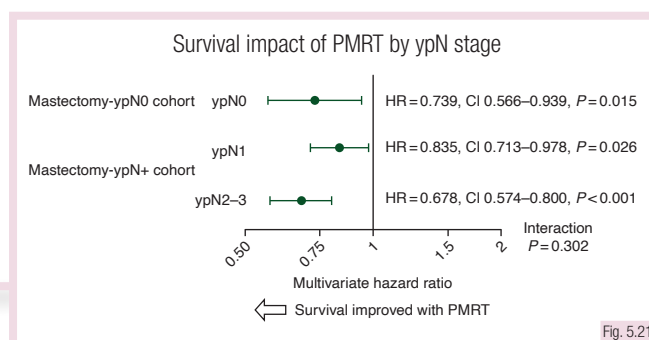
RT is recommended following NACT and mastectomy (PMRT) for T4 and/or node-positive disease.

In patients with inflammatory BC, a mastectomy is generally recommended, even if the cancer has responded well to NACT. PMRT to the chest wall and LNs is strongly recommended.

The LN target for RT depends on the preoperative clinical tumour, node, metastases (TNM) stage.

No randomised data is available for patients treated with NACT to clarify the impact of PMRT or the addition of regional node irradiation to breast RT.

In a large cohort study of patients with clinically node-positive BC treated with NACT, PMRT was associated with improved OS (hazard ratio [HR] ~0.75) irrespective of pathological LN status.



CI, confidence interval; HR, hazard ratio; PMRT, post-mastectomy radiotherapy; ypN, post-chemotherapy pathological lymph node.

REVISION QUESTIONS

1. What are the best treatment options for LABC?
2. Is RT recommended after surgery following NACT?
3. Is there an OS gain from RT after mastectomy following NACT?

Summary: Breast cancer radiotherapy

- Adjuvant RT after BCS reduces the risk of recurrence and improves OS. Thus, RT is recommended for all patients after BCS
- PBI should be considered after BCS in a subgroup of patients with low risk of recurrence
- A boost to the tumour bed reduces the risk of recurrence for all age groups; however, the higher dose results in increased toxicity. Therefore, a boost should be considered, especially in young patients
- Moderate hypofractionation in both pN0 and pN+ patients has shown non-inferiority regarding morbidity, locoregional control and mortality compared with normofractionation
- PMRT reduces the risk of recurrence and improves OS. PMRT should be considered in patients with node-positive disease and locally advanced node-negative disease
- The AMAROS trial showed that axillary irradiation compared with axillary dissection results in an equal locoregional recurrence rate but less lymphoedema in patients with positive SLNs
- Worldwide, there is no consensus whether a BC patient with a positive SLN should receive axillary irradiation rather than axillary clearance, though there is a trend towards omitting axillary surgery and favouring irradiation
- RT of the IMNs is recommended in node-positive patients as it improves DFS and OS
- For locoregional disease the LN target depends on N-stage and surgical procedure
- Treatment of LABC is complex and needs multidisciplinary care

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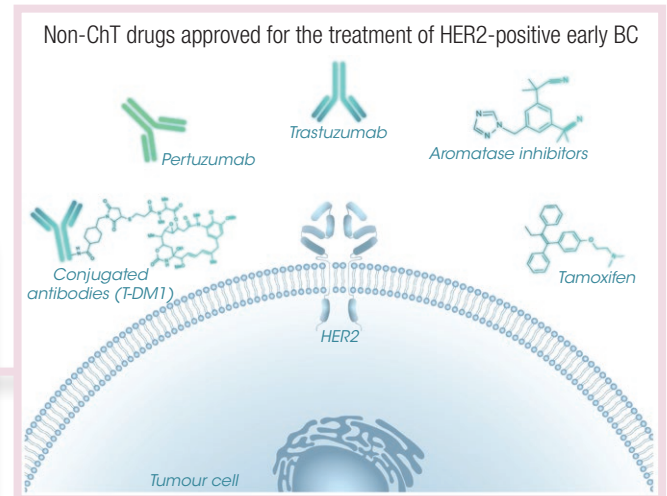
Image sources: **Fig. 5.1.** EBCTCG (Early Breast Cancer Trialists' Collaborative Group), et al. *Lancet* 2011;378:1707-1716; **5.2.** Offersen BV, et al. *J Clin Oncol* 2020;38:3615-36; **5.3.** Bartelink H, et al. *Lancet Oncol* 2015;16:47-56; **5.4.** Overgaard M, et al. *Radiother Oncol* 2022;170:4-13; **5.5.** EBCTCG (Early Breast Cancer Trialists' Collaborative Group), et al. *Lancet* 2014;383:2127-2135; **5.6.** Wang SL, et al. *Lancet Oncol* 2019;20:352-360; **5.7.** Coles EC, et al. *Lancet* 2017;390:1048-1060; **5.8.** Thomsen MS, et al. *Radiother Oncol* 2022;177:231-235; **5.9.** Sirák I, et al. *Transl Cancer Res* 2020;9:S29-S36; **5.10.** adapted from Onal C, et al. *J Breast Cancer* 2012;15:320-328; **5.11.** Donker M, et al. *Lancet Oncol* 2014;15:1303-1310; **5.12.** de Boniface J, et al. *N Engl J Med* 2024;390:1163-1175; **5.13.** Veronesi U, et al. *Ann Oncol* 2008;19:1553-1560; **5.14.** Poortmans PM, et al. *N Engl J Med* 2015;373:317-327; **5.15.** Thorsen LBJ, et al. *J Clin Oncol* 2022;40:4198-4206; **5.16.** Offersen BV, et al. *Radiother Oncol* 2015;114:3-10; **5.17.** Vikström J, et al. *Acta Oncol* 2011;50:42-50; **5.18.** Becham WA, et al. *Int J Radiat Oncol Biol Phys* 2007;69:918-924; **5.19.** courtesy of the authors; **5.20.** <https://www.verywellhealth.com/ibc-inflammatory-breast-cancer-430621>; **5.21.** Rusthoven CG, et al. *Ann Oncol* 2016;27:818-827.

Neoadjuvant chemotherapy and HER2 blockade

Since the 2017 St. Gallen International Consensus Conference, **preoperative chemotherapy** (ChT) is preferred for treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (BC), to enable postoperative treatment to be tailored to the pathological response of the tumour.

Standard ChT is a sequential regimen of **anthracyclines**, such as epirubicin combined with cyclophosphamide, followed by **taxanes**.

Endocrine therapy (if oestrogen-receptor [ER]-positive) and **HER2-blocking antibodies** (trastuzumab, pertuzumab) or **antibody–drug conjugates (ADCs)**, such as trastuzumab emtansine (T-DM1) are also part of standard treatment if residual disease is present.



BC, breast cancer; ChT, chemotherapy; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine. Fig. 6.1

Benefits of adding trastuzumab to ChT for all patients with early HER2-positive BC (EBCTCG meta-analysis)

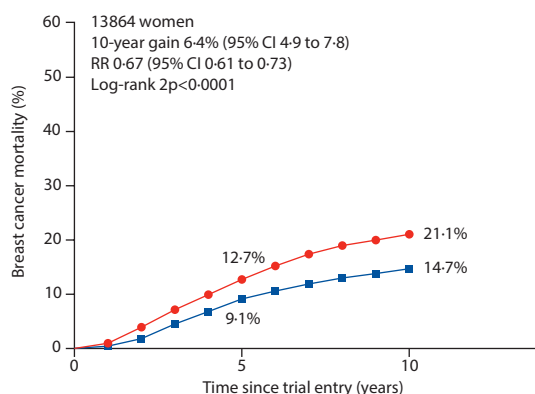


Fig. 6.2

BC, breast cancer; ChT, chemotherapy; CI, confidence interval; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; HER2, human epidermal growth factor receptor 2; RR, rate ratio.

After surgery, **adding pertuzumab** to trastuzumab showed a 5% improvement in 6-year invasive DFS (iDFS) in the node-positive cohort.

In patients **without lymph node** (LN) involvement, there was **no benefit** from the addition of pertuzumab to trastuzumab plus ChT (95% of 6-year iDFS for each group).

Improvement in **overall survival** (OS) has **not yet** been demonstrated, but mature data from the APHINITY trial are awaited at the time of publication.

In a meta-analysis of the EBCTCG (Early Breast Cancer Trialists' Collaborative Group) trial, adding **trastuzumab** to ChT improved 10-year disease-free survival (DFS) by 9% and reduced cancer-related mortality by 6%.

In most trials, trastuzumab is given every 3 weeks for 1 year, **after** 3 to 4 cycles of **anthracycline-based ChT** (thus during the taxane portion of ChT) or after the completion of ChT.

In 2010, the **NOAH trial** showed that 1 year of adjuvant trastuzumab (given as neoadjuvant and adjuvant treatment) improved 3-year event-free survival (EFS) by 15% compared with neoadjuvant ChT (NACT) alone.

Benefits of adjuvant pertuzumab for patients with node-positive early HER2-positive BC (APHINITY trial)

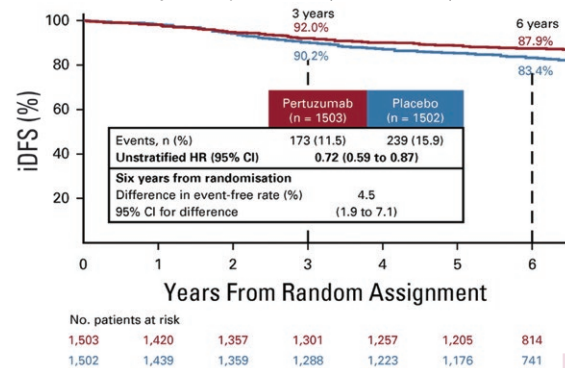


Fig. 6.3

BC, breast cancer; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; iDFS, invasive disease-free survival.

REVISION QUESTIONS

1. Why is neoadjuvant therapy recommended in patients with early HER2-positive BC?
2. What is the proven benefit associated with adjuvant trastuzumab?
3. What is the proven benefit associated with pertuzumab and for which patient group?

Adjuvant therapy is tailored to the pathological response to neoadjuvant therapy

Meta-analyses have shown that after ChT, patients whose tumours achieved pathological complete response (pCR) have a **better** 5-year EFS (86%) and **5-year OS** (95%) than those without pCR (63% and 76%, respectively).

Adjuvant ChT does **not** modify the prognosis of patients with pCR.

pCR constitutes therefore a rational **basis** for **personalising** therapeutic escalation or de-escalation decisions.

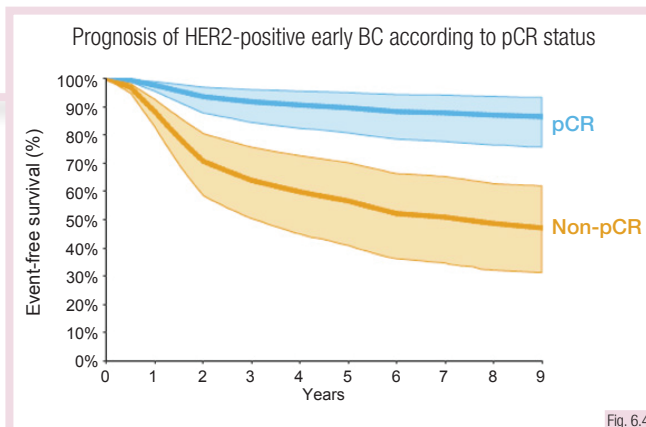


Fig. 6.4

BC, breast cancer; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response.

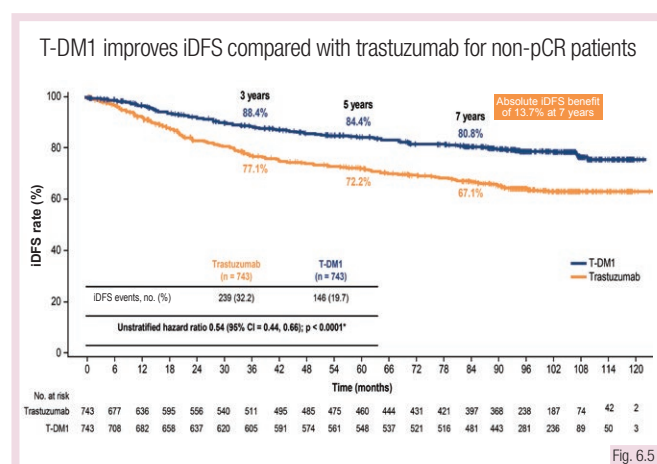


Fig. 6.5

CI, confidence interval; iDFS, invasive disease-free survival; pCR, pathological complete response; T-DM1, trastuzumab emtansine.

T-DM1 for 1 year improved 7-year iDFS by 13.7% compared with trastuzumab alone in patients without pCR who had received NACT administered with trastuzumab in the KATHERINE trial.

T-DM1 was associated with 25.7% of grade 3 side effects (15.4% in the trastuzumab group), the most frequent of which was **thrombocytopenia** (5.7%).

In the KRISTINE trial, as the combination of T-DM1 with **pertuzumab worsened EFS**, it cannot replace the taxane, platinum, trastuzumab and pertuzumab combination in the neoadjuvant setting.

The PERSEPHONE trial showed the **non-inferiority** of **6 vs 12 months of trastuzumab**, with fewer cardiac events at 1 year (5% vs 8%, respectively) in patients without pCR.

However, as results from **other non-inferiority trials** are **negative**, 1 year of trastuzumab (with pertuzumab if nodal involvement) remains recommended for patients with pCR.

Six months of trastuzumab, vs 12, is an option for **selected cases**, inspired from tumour characteristics in PERSEPHONE (69% ER-positive, 92% T1 or T2, 59% N0, 90% anthracycline).

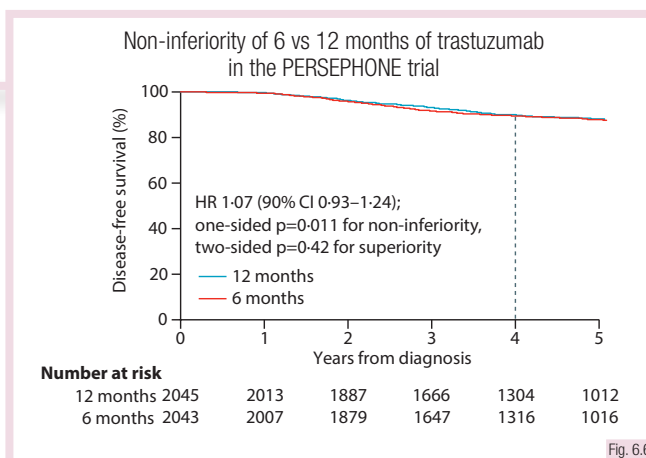


Fig. 6.6

CI, confidence interval; HR, hazard ratio.

REVISION QUESTIONS

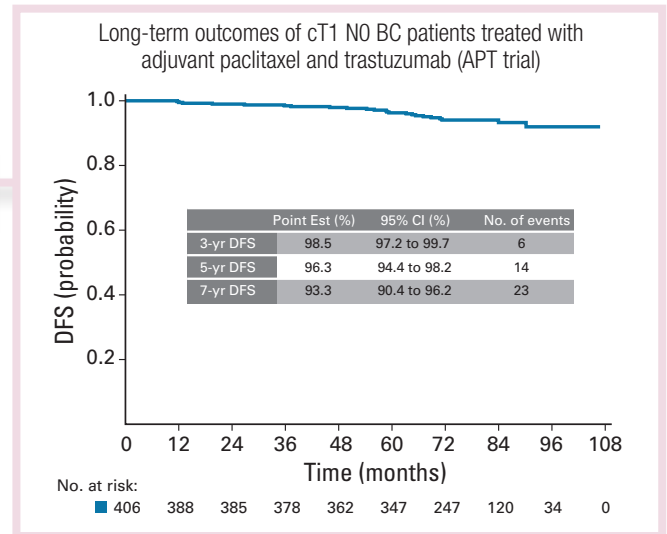
1. Which characteristic guides the decision to escalate or de-escalate adjuvant treatment for early HER2-positive BC?
2. What is (regimen and duration) the optimal adjuvant treatment for patients who did not achieve pCR?
3. What is (regimen and duration) the optimal adjuvant treatment for patients with pCR?

Neoadjuvant and adjuvant de-escalation strategies

The APT phase II trial evaluated primary surgery and adjuvant paclitaxel combined with trastuzumab in node-negative HER2-positive BC with tumour size ≤ 2 cm.

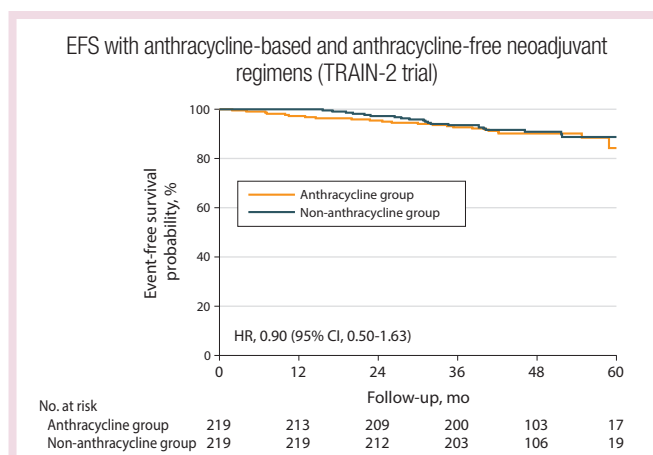
The 7-year DFS was 93% and 7-year OS 95%. As 64% of tumours were also ER-positive, longer follow-up is needed.

cT1 N0 patients can be treated with primary surgery, followed by 12 weeks of weekly paclitaxel and trastuzumab every 3 weeks for 1 year.



BC, breast cancer; CI, confidence interval; DFS, disease-free survival.

Fig. 6.7



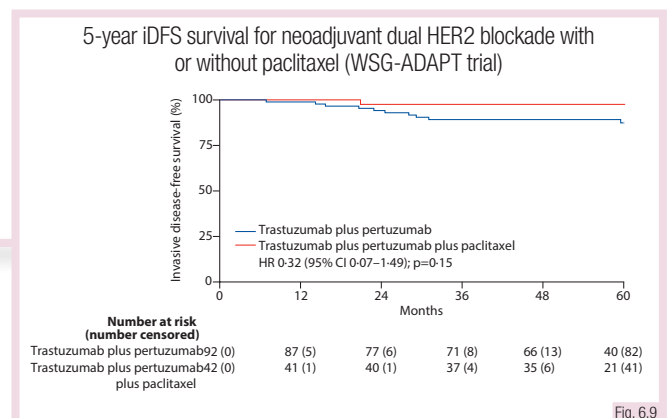
CI, confidence interval; EFS, event-free survival; HR, hazard ratio.

Fig. 6.8

In the WSG-ADAPT trial, pCR was 40% for trastuzumab plus pertuzumab (HP) and 90% for the trastuzumab, pertuzumab and paclitaxel (THP) regimen.

The 5-year iDFS rates were 98% in the THP group and 87% in the HP group.

However, 43% of patients with pCR after HP received adjuvant epirubicin and cyclophosphamide-based ChT, thus further data are needed before sparing NACT.



CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; iDFS, invasive disease-free survival.

Fig. 6.9

REVISION QUESTIONS

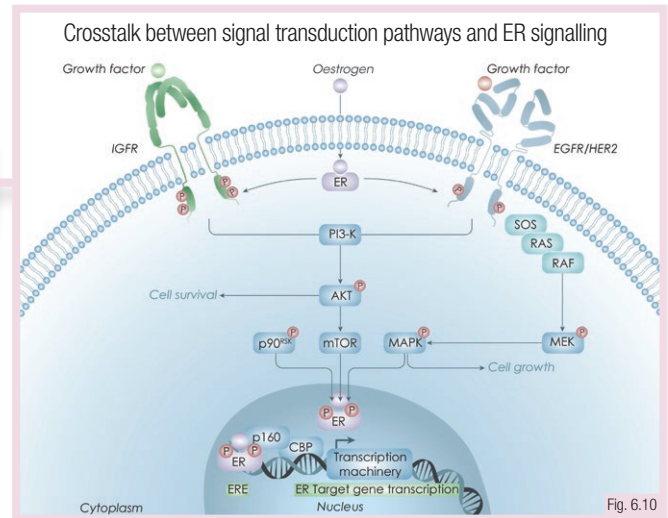
1. For which patients can NACT be omitted?
2. What is the adjuvant ChT regimen for patients not treated with NACT?
3. What is the current alternative to anthracycline-based ChT and in which cases is it justified?

Specificities of early ER-positive, HER2-positive BC and future perspectives

For early triple-positive BC, adjuvant **hormone therapy** is recommended and follows the same rules as for ER-positive, HER2-negative BC.

A complex molecular bidirectional **crosstalk between the ER and HER2** pathways constitutes one of the key mechanisms of drug resistance in this BC subtype.

ChT-free regimens have **not yet been validated** but treatment de-escalation remains an important issue for low-risk tumours.

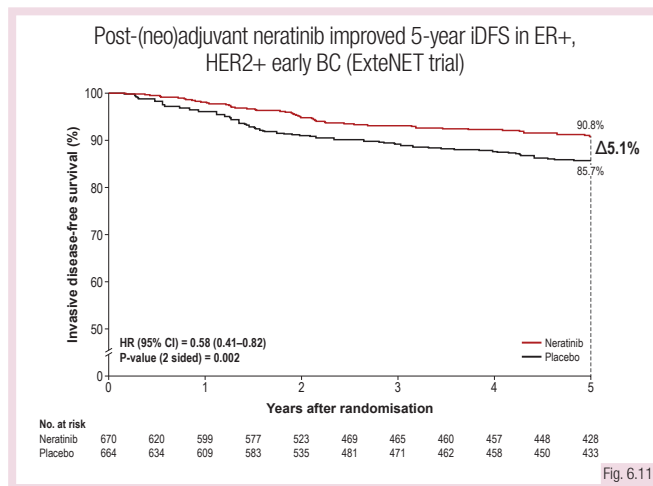


EGFR, endothelial growth factor receptor; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; IGF, insulin-like growth factor receptor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase.

The ExteNET trial evaluated the benefit of the tyrosine kinase inhibitor **neratinib** for 12 months after (neo)adjuvant ChT and trastuzumab.

Neratinib improved 5-year iDFS by 5.1% and 8-year OS by 2.1% (7.4% and 9.1%, respectively if no pCR), only for ER-positive, HER2-positive tumours.

Neratinib was associated with important toxicities, mainly clinically impactful **diarrhoea** (55% grade 1–2 and 39% grade 3), and its place **remains to be defined** since patients did not receive pertuzumab or T-DM1 in case of no pCR.

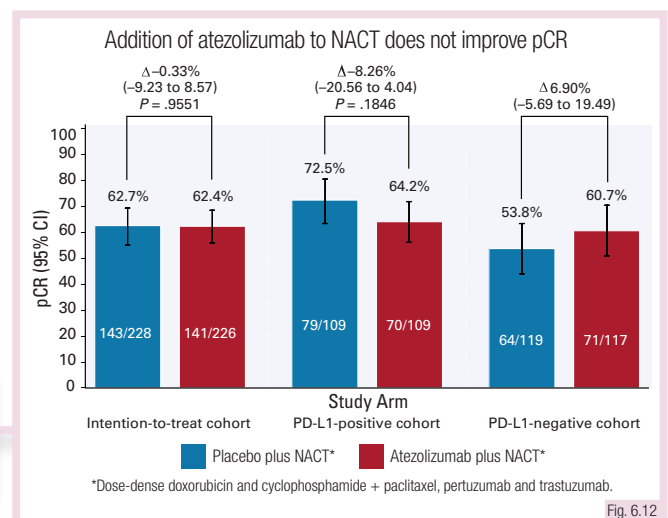


BC, breast cancer; CI, confidence interval; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; iDFS, invasive disease-free survival.

The DESTINY-Breast11 trial is evaluating the new ADC **trastuzumab deruxtecan** (T-DXd) alone or followed by THP, vs standard ChT.

The DESTINY-Breast05 trial is currently comparing **T-DXd vs T-DM1 adjuvant treatment** for patients with residual invasive disease in breast and/or axillary LNs after neoadjuvant therapy.

The first phase III study (IMpassion050) evaluating **immune checkpoint inhibitors** was **negative** because it did not improve the pCR rate, but future survival data should be evaluated.



CI, confidence interval; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; PD-L1, programmed death-ligand 1.

REVISION QUESTIONS

1. What are the specificities of the care of ER-positive, HER2-positive early BC patients?
2. For which category of patients has neratinib proven effective?
3. What are the possible strategies to improve the current treatment of early HER2-positive BC?

Cardiotoxicity of systemic treatments for early HER2-positive BC

In the TRAIN-2 trial, left ventricular ejection fraction (LVEF) <50% or a decrease of >10% from baseline was more frequent in the anthracycline group (7.7%) than in the control group (3.2%).

Discontinuation of anthracyclines is required in case of severe symptomatic cardiac dysfunction (CD), and temporary interruption for moderate symptomatic CD.

Temporary interruption of anthracyclines is recommended for moderate/severe asymptomatic CD. Heart failure drugs should be prescribed for symptomatic CD.

Management of anthracycline-related cardiotoxicity (ESC guidelines)	
Anthracycline-related cardiac dysfunction	Management
Severe symptomatic (hospitalisation)	- Discontinuation of anthracycline - HF treatment (angiotensin inhibitor, beta-blocker, SGLT2 inhibitor, mineralocorticoid receptor antagonist)
Moderate symptomatic (intensification of HF therapy is needed)	- Temporary interruption of anthracycline - HF treatment
Moderate to severe asymptomatic (LVEF ↓ ≥10% or any new ↓ LVEF AND new ↓ in GLS by 15% from baseline OR new rise in cardiac biomarkers)	- Temporary interruption of anthracycline - HF treatment

Fig. 6.13

ESC, European Society of Cardiology; GLS, global longitudinal strain; HF, heart failure; LVEF, left ventricular ejection fraction; SGLT2, sodium-glucose cotransporter-2.

Management of anti-HER2 therapy-related cardiotoxicity (ESC guidelines)	
HER2-targeted therapy-related cardiac dysfunction	Management
Severe symptomatic (hospitalisation)	- Temporary interruption of HER2-targeted therapies - HF treatment
Moderate symptomatic (intensification of HF therapy is needed)	- Temporary interruption of HER2-targeted therapies - HF treatment
Moderate to severe asymptomatic (LVEF ↓ ≥10% or any new ↓ LVEF AND new ↓ in GLS by 15% from baseline OR new rise in cardiac biomarkers)	- Temporary interruption of HER2-targeted therapies - HF treatment

Fig. 6.14

ESC, European Society of Cardiology; GLS, global longitudinal strain; HER2, human epidermal growth factor receptor 2; HF, heart failure; LVEF, left ventricular ejection fraction.

In the HERA study, 4.4% of secondary cardiac endpoints were observed in the 1-year trastuzumab arm and 0.9% in the observation arm.

Adding pertuzumab to trastuzumab did **not appear to increase** the occurrence of cardiac events in the APHINITY trial.

Temporary interruption of anti-HER2 therapy is recommended for severe and moderate symptomatic and asymptomatic CD. After improvement in LVEF and/or resolution of symptoms, the decision to restart can be discussed within a multidisciplinary team.

It is recommended that an **echocardiography** and measurement of **natriuretic peptides** and **troponin levels** are performed at baseline (after 2 cycles in high-risk patients), every 3 months during the treatment, and at 3 and 12 months after the end of treatment.

Cardioprotective drugs could be considered in patients with high- and very high-risk factors before they receive anthracyclines and/or anti-HER2 therapies.

These drugs could also be considered for **asymptomatic patients** with a significant fall in global longitudinal strain or elevation of troponin/natriuretic peptides levels.

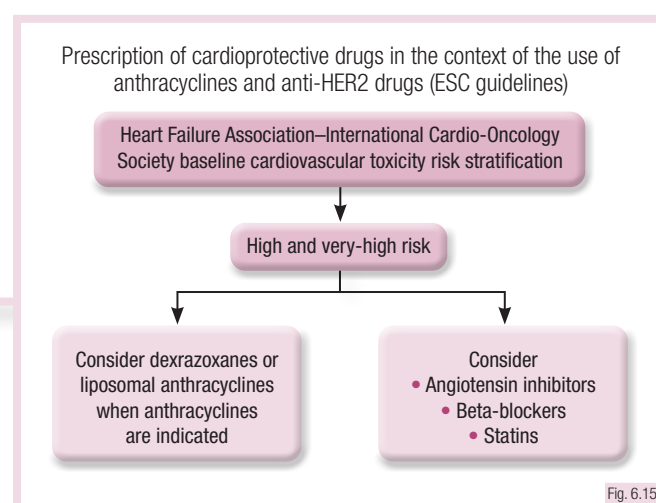


Fig. 6.15

ESC, European Society of Cardiology; HER2, human epidermal growth factor receptor 2.

REVISION QUESTIONS

1. How common is cardiotoxicity from anthracyclines and when should they be discontinued/interrupted?
2. How common is cardiotoxicity from HER2-targeted therapies and when should they be discontinued/interrupted?
3. What imaging follow-up is recommended and when should cardioprotective drugs be prescribed?

Summary: Early HER2-positive breast cancer: systemic therapy

- cT1 N0 patients can be treated by primary surgery followed by 12 weeks of weekly paclitaxel and 1 year of trastuzumab every 3 weeks
- For all other patients, standard NACT is 4 cycles of epirubicin or doxorubicin plus cyclophosphamide followed by taxanes (docetaxel or paclitaxel)
- Trastuzumab should be added to ChT after anthracyclines for all patients because it substantially improves both DFS and OS
- Adding pertuzumab to trastuzumab for patients with node-positive disease is an option because it improves 6-year iDFS by 5%
- Adjuvant therapy is tailored to pathological response and based on trastuzumab for 1 year (possibly with pertuzumab in case of LN involvement)
- Patients with residual disease should be treated with T-DM1 every 3 weeks for 1 year because it improves both iDFS and OS compared with trastuzumab
- Nine cycles of paclitaxel and carboplatin is an alternative to anthracyclines when contraindicated, but is not the standard of care
- For triple-positive tumours, adjuvant hormone therapy should be prescribed following the same guidelines as for ER-positive, HER2-negative BC
- Cardiac monitoring before and during systemic treatment, prescription of cardioprotective drugs and management of anthracyclines/HER2-targeted therapies should follow European Society of Cardiology guidelines
- New agents are being evaluated in the post-neoadjuvant setting, for patients whose tumours have not achieved pCR

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Image sources: Fig. 6.1. courtesy of the authors; 6.2. EBCTCG, *Lancet Oncol* 2021;22:1139-1150; 6.3. Piccart M, et al. *J Clin Oncol* 2021;39:1448-1457; 6.4. Spring LM, et al. *Clin Cancer Res* 2020;26:2838-2848; 6.5. courtesy of S. Loibl; 6.6. Earl HM, et al. *Lancet* 2019;393:2599-2612; 6.7. Tolaney SM, et al. *J Clin Oncol* 2019;37:1868-1875; 6.8. van der Voort A, et al. *JAMA Oncol* 2021;7:978-984; 6.9. Nitz U, et al. *Lancet Oncol* 2022;23:625-635; 6.10. adapted from Johnston SRD. *Clin Cancer Res* 2010;16:1979-1987; 6.11. Chan A, et al. *Clin Breast Cancer* 2021;21:80-91.e7; 6.12. Huober J, et al. *J Clin Oncol* 2022; 40:2946-2956; 6.13, 6.14, 6.15. adapted from Lyon AR, et al. *Eur Heart J* 2022;43:4229-4361.

Presentation, prevalence and prognosis

Triple-negative breast cancer (TNBC) is defined by a lack of oestrogen receptor (ER) and progesterone receptor (PgR) expression and a lack of human epidermal growth factor receptor 2 (HER2) overexpression.

TNBC is often high-grade and the most common histology is invasive carcinoma of no special type, also called infiltrating ductal carcinoma.

ER-low-positive breast cancer (BC), as defined by 1%–10% ER expression by immunohistochemistry, often has gene expression profiles similar to TNBC.

Germline genetic alterations associated with ER-negative BC

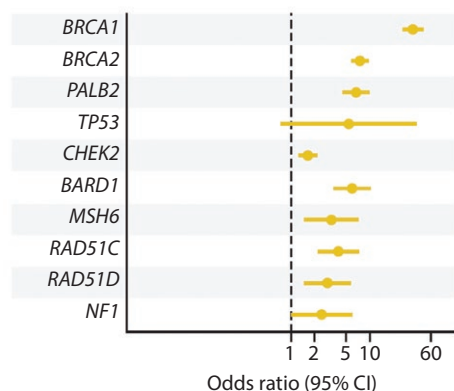


Fig. 7.2

BARD1, BRCA1-associated RING domain protein 1; BC, breast cancer; CHEK2, checkpoint kinase 2; CI, confidence interval; ER, oestrogen receptor; MSH6, mutS homologue 6; NF1, neurofibromin 1; PALB2, partner and localiser of BRCA2; TP53, tumour protein 53.

Prognosis of TNBC is poor with a lower 5-year survival rate compared with other BCs diagnosed at the same stage.

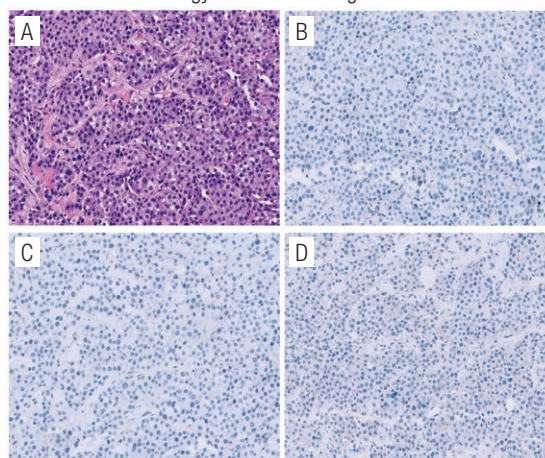
TNBC carries a higher risk of recurrence and commonly involves visceral sites and the central nervous system at relapse.

In TNBC, tumours with a high level of tumour-infiltrating lymphocytes (TILs) have been shown to have a better long-term prognosis as well as short-term outcomes, including a higher rate of pathological complete response (pCR) to treatment.

REVISION QUESTIONS

1. What is the typical presentation of TNBC?
2. What are the risk factors associated with TNBC?
3. What is the typical pattern of relapse for TNBC?

Histology and IHC staining of TNBC



(A), H&E; 20× magnification. Invasive carcinoma of no special type comprising solid trabeculae of moderately atypical cells (B), Immunohistochemistry for ER; 20× magnification. Carcinoma cells are negative for ER (C), Immunohistochemistry for PgR; 20× magnification. Carcinoma cells are negative for PgR (D), Immunohistochemistry for HER2; 20× magnification. Carcinoma cells are negative for HER2

Fig. 7.1

ER, oestrogen receptor; H&E, haematoxylin and eosin; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PgR, progesterone receptor; TNBC, triple-negative breast cancer.

TNBC accounts for 15%–20% of all cases of BC diagnosed worldwide.

Risk factors associated with TNBC include younger age, African American ethnicity and germline *BRCA* mutation (g*BRCAm*), in particular *BRCA1*.

Genetic testing is particularly important in patients with TNBC as it impacts choice of therapy and has implications for personal risk management and familial predictive testing.

5-year relative survival: TNBC compared with other BCs by stage at diagnosis

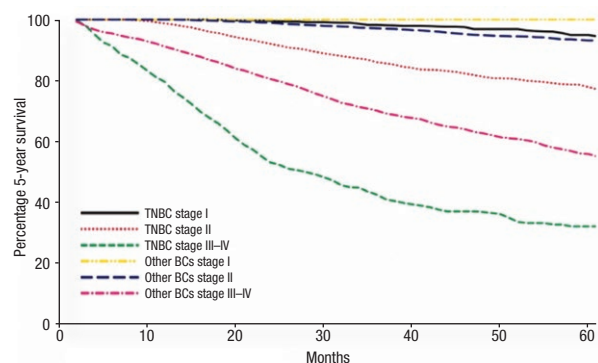


Fig. 7.3

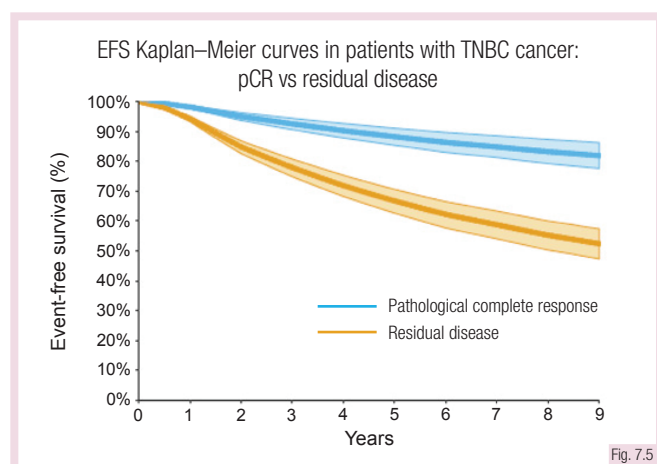
BC, breast cancer; TNBC, triple-negative breast cancer.

Selecting a treatment approach – neoadjuvant vs adjuvant

TNBC is associated with earlier systemic dissemination of disease, warranting a **lower threshold** and early initiation of (neo)adjuvant **systemic therapy**.

Neoadjuvant therapy has numerous advantages over adjuvant therapy.

Neoadjuvant chemotherapy (NACT) is the preferred approach supported by international guidelines for TNBCs that are **cT1c and above** in tumour size **and/or** with **positive regional lymph nodes (LNs)**.



EFS, event-free survival; pCR, pathological complete response; TNBC, triple-negative breast cancer.

pCR is an accepted surrogate endpoint in early TNBC and efforts to intensify neoadjuvant therapy have focused on improving pCR rates.

Patients with **residual disease** after NACT represent a **group at high risk of disease relapse**.

This patient group is the focus of investigations into **novel therapies and adjuvant strategies to improve survival outcomes**.

REVISION QUESTIONS

1. What are the advantages of NACT in the management of early TNBC?
2. When should NACT be considered in patients with non-metastatic TNBC?
3. What is the significance of pCR in TNBC?

Neoadjuvant treatment approach	
Advantages	Disadvantages
• Early treatment of micrometastatic disease • Observation of <i>in situ</i> tumour response • Intensification of treatment to increase the probability of achieving a pCR • Tailoring of treatment based on the presence/absence of a pCR • Prognostication based on the presence/absence of a pCR • Downstaging of tumour and nodes with facilitation of breast-conserving surgery • Allows time for germline genetic results and surgical planning	• Adverse events from neoadjuvant chemotherapy or immunotherapy that delay or preclude surgery • Overtreatment of small tumours due to incomplete staging • Less precise nodal staging which may impact on adjuvant radiotherapy decisions

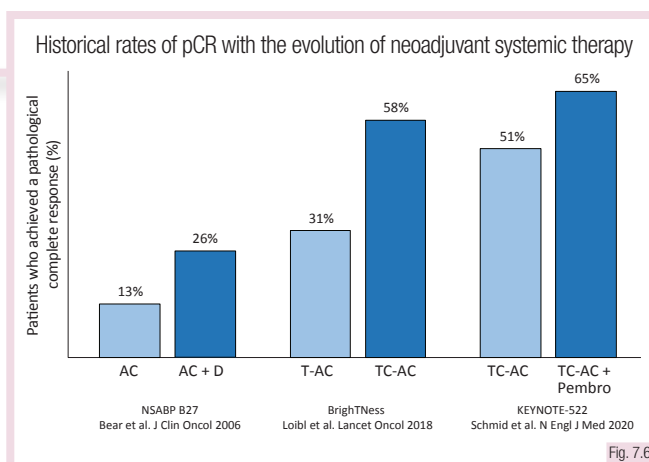
Fig. 7.4

pCR, pathological complete response.

pCR is defined as the **absence of any invasive disease** in both the breast (**ypT0 or ypTis**) and the LNs (**ypN0**).

Studies have shown a **strong correlation between pCR and long-term event-free survival (EFS) and overall survival (OS) in patients with TNBC**.

Failure to achieve a pCR or residual disease following neoadjuvant therapy predicts a worse long-term outcome and prognosis.



AC, doxorubicin and cyclophosphamide; D, docetaxel; pCR, pathological complete response; Pembro, pembrolizumab; T, paclitaxel; TC, paclitaxel and carboplatin.

Optimising neoadjuvant systemic therapy in early TNBC

The optimal **NACT backbone** in TNBC includes an **anthracycline** (doxorubicin or epirubicin) and a **taxane** (paclitaxel, docetaxel or nab-paclitaxel) chemotherapy (ChT) agent.

For taxanes, acceptable options include weekly **paclitaxel**, dose-dense paclitaxel every 2 weeks, every **3 weeks docetaxel** or nab-paclitaxel in cases of hypersensitivity reaction or other medical contraindications.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis showed that **dose-dense administration of ChT** reduces the 10-year BC recurrence risk, BC mortality and all-cause mortality.

Platinum-containing ChT compared to ChT without platinum in neoadjuvant therapy for early TNBC			
Outcomes	Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)
DFS at 2 years	HR 0.63 (0.53–0.75)	1966 (8 RCTs)	⊕⊕⊕⊕ High
DFS at 5 years	HR 0.63 (0.53–0.75)	1966 (8 RCTs)	⊕⊕⊕⊕ High
OS at 2 years	HR 0.69 (0.55–0.86)	1973 (8 RCTs)	⊕⊕⊕⊕ High
OS at 5 years	HR 0.69 (0.55–0.86)	1973 (8 RCTs)	⊕⊕⊕⊕ High
Pathological complete response	RR 1.44 (1.31–1.59)	3083 (15 RCTs)	⊕⊕⊕⊕ High

ChT, chemotherapy; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; RCT, randomised controlled trial; RR, risk ratio; TNBC, triple-negative breast cancer. Fig. 7.8

Multiple trials have looked at the addition of **immunotherapy** to NACT to improve pCR rates and survival.

The phase III KEYNOTE-522 trial showed improvements in pCR rates (64.8% vs 51.2%) and EFS (hazard ratio [HR] 0.63, 95% CI 0.49–0.81) with the addition of pembrolizumab to ChT (anthracycline-based plus carboplatin and paclitaxel).

The addition of **pembrolizumab** should be discussed with patients with cT1c, cN1–2 or cT2–4, cN0–2 (**stage II or III**) TNBC, along with the potential for serious immune-related adverse events (irAEs).

Exploratory subset analysis of TNBC patients from the ABC trials

Status	4-Year IDFS (%)		4-Year IDFS Δ (%)	Proportional benefit by risk HR (95% CI)
	TaxAC	TC		
Hormone receptor-negative				
Node negative	89.5	87.0	2.5	1.31 (0.86 to 1.99)
1–3 positive nodes	85.5	74.6	10.9	1.58 (0.90 to 2.79)
≥4 positive nodes	71.8	60.8	11.0	1.34 (0.62 to 2.91)

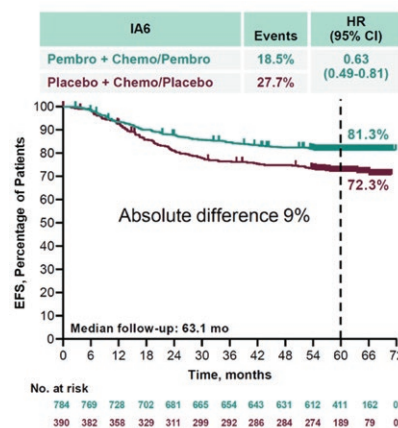
ABC, Anthracyclines in Early Breast Cancer; CI, confidence interval; HR, hazard ratio; IDFS, invasive disease-free survival; TaxAC, taxane, doxorubicin and cyclophosphamide; TC, docetaxel and cyclophosphamide; TNBC, triple negative breast cancer. Fig. 7.7

Multiple randomised controlled trials have evaluated the **addition of platinum ChT to NACT** and demonstrated **increased pCR rates**; however, the effects on long-term survival outcomes were less consistent.

A Cochrane review in 2023 found that **platinum-containing NACT improved disease-free survival (DFS) at 5 years, OS at 5 years and pCR rates** when compared with NACT without platinum.

The main toxicity associated with the addition of platinum ChT is **haematological toxicity** resulting in **more ChT delays** (risk ratio 2.23, 95% confidence interval [CI] 1.70–2.94) and **dose reductions** (risk ratio 1.77, 95% CI 1.56–2.02), but this can be managed with the above measures or with granulocyte-colony stimulating factor (G-CSF) prophylaxis to **avoid compromising taxane dosing**.

EFS benefit with the addition of pembrolizumab in the KEYNOTE-522 trial



CI, confidence interval; EFS, event-free survival; HR, hazard ratio; IA6, interim analysis 6; mo, months; Pembro, pembrolizumab. Fig. 7.9

REVISION QUESTIONS

1. What is the ideal NACT backbone in TNBC treatment?
2. What are the benefits of adding platinum ChT to standard treatment?
3. What are the benefits of pembrolizumab and what toxicities need to be considered?

Postoperative management of patients who received neoadjuvant therapy

For patients who received neoadjuvant pembrolizumab and achieved pCR, pembrolizumab should be continued for 9 cycles postoperatively, as per KEYNOTE-522.

Trials are underway to evaluate the role of adjuvant immune checkpoint inhibitor therapy in patients with residual disease who did not receive preoperative pembrolizumab.

Postoperative radiotherapy (RT) indications are based on the clinical stage of the disease and remain the same regardless of the presence or absence of pCR.

Trial name	Population	Comparison	Primary endpoint	Estimated study completion date
A-BRAVE phase III NCT02926196	TNBC Stratum A: Primary surgery with pN2, any T OR pN1, pT >2 cm OR pN0, pT >5 cm Stratum B: Post neoadjuvant chemotherapy and surgery with residual disease	Avelumab × 1 year vs observation	Co-primary endpoints of DFS in: a) all patients b) Stratum B patient	October 2025
NRG-BR006 phase III NCT02954874	TNBC ≥1 cm residual invasive cancer OR residual lymph node macrometastases (ypN1mi, ypN1, ypN2, ypN3)	Pembrolizumab × 1 year vs observation	Dual primary endpoint of iDFS in: a) all randomised patients b) PD-L1 positive patients	May 2026

DFS, disease free survival; ICI, immune checkpoint inhibitor; iDFS, invasive disease-free survival; PD-L1, programmed death-ligand 1; TNBC, triple-negative breast cancer.

Fig. 7.10

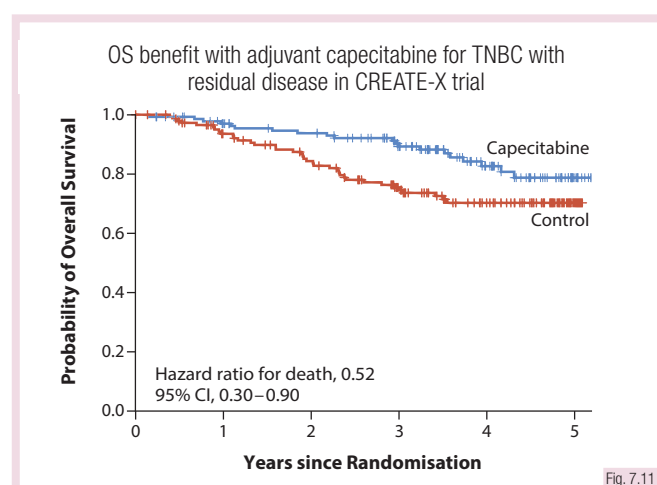


Fig. 7.11

CI, confidence interval; OS, overall survival; TNBC, triple-negative breast cancer.

In patients **without a gBRCAm** who have postoperative residual disease, pembrolizumab should be continued for a total of 1 year if given in the neoadjuvant setting.

Based on the OS and DFS benefit seen in the CREATE-X trial, in the absence of gBRCAm, 6–8 cycles of adjuvant capecitabine can be considered for residual disease post NACT in TNBC.

There is currently **no prospective evidence** to support treating residual disease with both pembrolizumab and capecitabine in those who have received neoadjuvant pembrolizumab, but there is safety data regarding the combination of capecitabine and pembrolizumab.

In patients with a gBRCAm and residual disease, adjuvant olaparib has shown both DFS and OS benefit when compared with placebo, as evidenced in the phase III OlympiA trial.

For patients who have not received pembrolizumab, adjuvant olaparib for 1 year is the preferred option.

However, in patients who received neoadjuvant pembrolizumab, there is controversy regarding whether pembrolizumab should be continued, switched to, or combined with adjuvant olaparib.

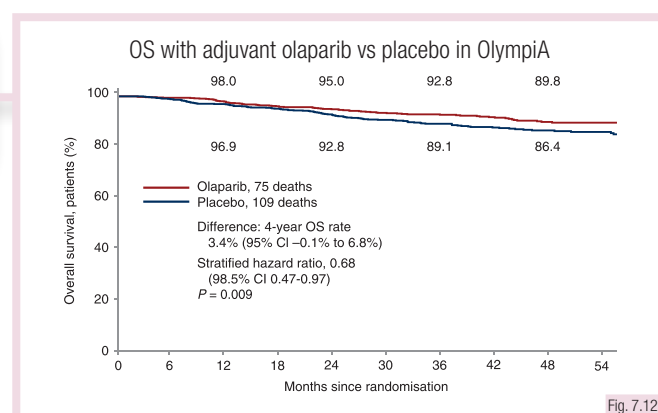


Fig. 7.12

CI, confidence interval; OS, overall survival.

REVISION QUESTIONS

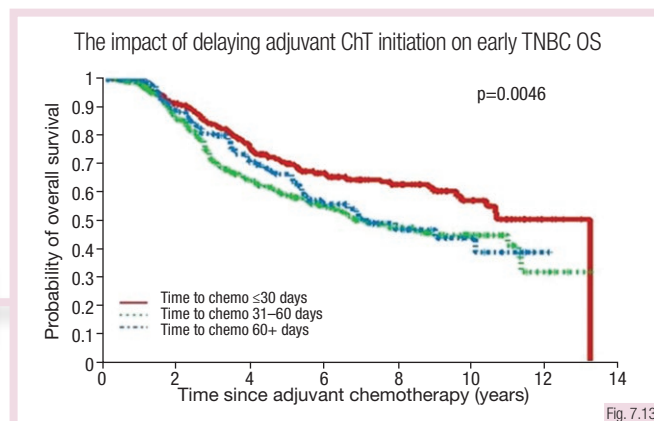
1. How should patients with pCR be managed postoperatively?
2. How should RT decisions be made for a patient who has received NACT?
3. What are the options for postoperative systemic therapy in patients with residual disease?

Adjuvant management of patients who have undergone upfront surgery

For patients with small primary tumours ≤ 1 cm and clinically negative LNs, upfront surgery is preferred for accurate pathological staging.

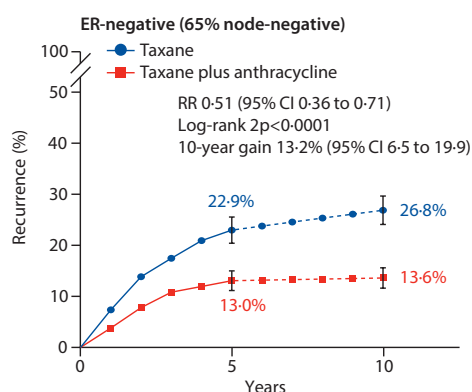
Adjuvant therapy is indicated for patients with a primary tumour >0.5 cm or with pathologically node-positive tumours.

Adjuvant ChT should ideally start within 4 weeks following surgery, in those whom it is indicated, as delays are associated with poorer survival outcomes.



ChT, chemotherapy; OS, overall survival; TNBC, triple-negative breast cancer.

BC recurrence: adjuvant taxane-anthracycline vs taxane-only regimens in ER-poor/negative early BC



BC, breast cancer; CI, confidence interval; ER, oestrogen receptor; RR, rate ratio.

Similar to the neoadjuvant setting, anthracyclines and taxanes form the preferred ChT backbone in the adjuvant setting.

There is currently no role for the addition of platinum ChT and/or immunotherapy to standard anthracycline/taxane ChT in the management of patients who have undergone upfront surgery.

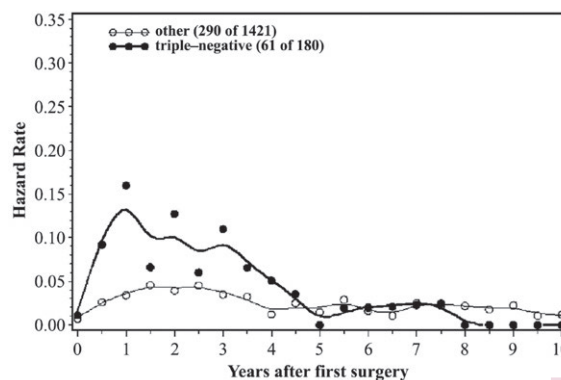
For patients with low-risk node-negative disease <1.0 cm, or in whom anthracyclines are contraindicated, taxane-based regimens such as docetaxel and cyclophosphamide or paclitaxel and carboplatin may be considered.

TNBC has a high tendency to recur within 3 years, with most recurrences occurring in the 5 years following diagnosis and definitive treatment.

This pattern of relapse differs slightly from that of hormone-positive BCs, in which the risk of recurrence plateaus but continues to persist beyond 5 years.

Clinical surveillance principles for TNBC mirror that of other receptor subtypes but with closer surveillance for the first 3 years and a low threshold for investigating new symptoms is recommended.

Rates of distant recurrences following surgery in TNBC and other BCs



BC, breast cancer; TNBC, triple-negative breast cancer.

REVISION QUESTIONS

1. What are the indications for adjuvant ChT in patients who have undergone upfront surgery?
2. What are the roles of adjuvant carboplatin and immunotherapy in early TNBC?
3. How does the relapse pattern of TNBC differ from that of hormone-positive disease?

Summary: Early triple-negative breast cancer: systemic therapy

- TNBC is an aggressive subtype of BC characterised by a lack of ER, PgR and HER2 expression
- gBRCAm, in particular *BRCA1*, is associated with TNBC and should be tested for in all patients
- A neoadjuvant treatment approach is favoured for patients with TNBCs that are cT1c or greater in size, and/or with node-positive disease
- Achieving pCR following neoadjuvant treatment is associated with superior long-term survival outcomes
- The standard NACT backbone includes an anthracycline and a taxane
- The addition of platinum to NACT improves the pCR rate, DFS and OS and can be considered in clinical stage II–III TNBC
- The addition of pembrolizumab to neoadjuvant treatment improves both the pCR rate and EFS and should be discussed with patients with stage II or III disease along with the potential for serious irAEs
- Management options for residual disease include the continuation of pembrolizumab if given in the neoadjuvant setting, capecitabine or olaparib in patients with gBRCAm
- In patients who undergo upfront surgery, adjuvant ChT is indicated for primary tumours >0.5 cm or with positive LNs
- Indications for RT are the same as for other BC subtypes and should be based on the clinical disease stage for patients who were treated with NACT

Further Reading

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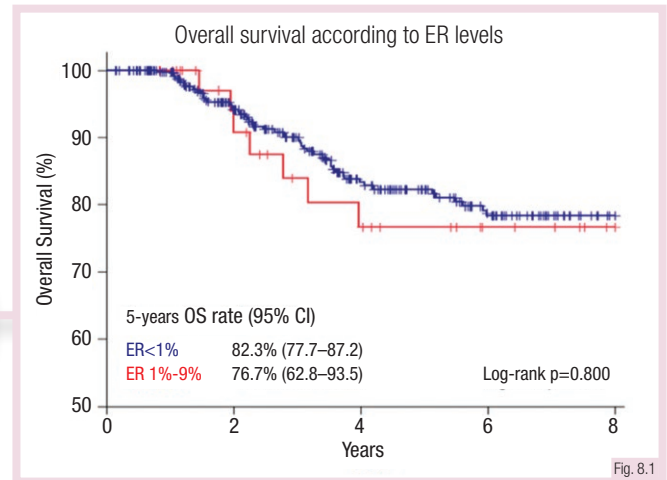
Image sources: **Fig. 7.1.** courtesy of Seow DYB, Tay TKY; **7.2.** Breast Cancer Association Consortium, et al. *N Engl J Med* 2021;384:428-439; **7.3.** Bauer KR, et al. *Cancer* 2007;109:1721-1728; **7.5.** Spring LM, et al. *Clin Cancer Res* 2020;26:2838-2848; **7.7.** Blum JL, et al. *J Clin Oncol* 2017;35:2647-2655; **7.8.** adapted from Mason SR, et al. *Cochrane Database Syst Rev* 2023;9:CD014805; **7.9.** courtesy of P. Schmid. Schmid P, et al. *Ann Oncol* 2023;34:S1254-S1335; **7.11.** Masuda N, et al. *N Engl J Med* 2017;376:2147-2159; **7.12.** Geyer Jr CE, et al. *Ann Oncol* 2022;33:1250-1268; **7.13.** courtesy of Debora de Melo Gagliato, de Melo Gagliato D, et al. *J Clin Oncol* 2013;31,suppl:1022-1022; **7.14.** Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet* 2023;401:1277-1292; **7.15.** Dent R, et al. *Clin Cancer Res* 2007;13:4429-4434. All other images courtesy of the authors.

Risk stratification

Decisions regarding adjuvant therapies are based on estimations of **risk recurrence**. Oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer (BC) is of overall lower risk.

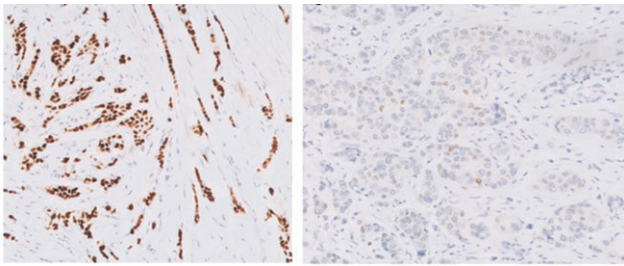
Within this patient group, a higher risk of recurrence is associated with larger primary tumours, high tumour grade, **nodal involvement** and high Ki-67 expression.

Low staining for ER is also associated with **poorer outcomes**.



CI, confidence interval; ER, oestrogen receptor; OS, overall survival.

A case with strong (90%–100%) cell staining for ER (left) vs weak staining (1%–10%) denoting ER-low-positive status (right)



ER, oestrogen receptor.

Fig. 8.2

Tumours with >1% of tumour nuclei positive for ER are defined as **ER-positive**.

ER low-positive classification is defined by an ER expression of 1%–10%. These tumours behave more like ER-negative disease and may be more responsive to chemotherapy (ChT).

ER positivity is a **predictive biomarker** of response to endocrine therapies (ETs).

The **main intrinsic subtypes** of ER-positive, HER2-negative disease, which can be ascertained via genomic testing, are luminal (Lum) A and Lum B. Surrogate estimations can be drawn from clinicopathological features.

Lum B disease is phenotypically more aggressive and more likely to be chemosensitive.

Lum A subtypes may be less chemosensitive, but more likely to be responsive to ET, with a better prognosis.

Defining intrinsic BC subtypes via surrogate clinicopathological features

Intrinsic subtype	Clinicopathological surrogate definition
Luminal A	'Luminal A-like' ER-positive, HER2-negative High PgR Low Ki-67 Low-risk molecular signature (if available)
Luminal B	'Luminal B-like' ER-positive, HER2-negative and either: High Ki-67 or PgR low/negative High-risk molecular signature (if available)

Fig. 8.3

BC, breast cancer; ER, oestrogen receptor; HER2, human epidermal growth factor 2; PgR, progesterone receptor.

REVISION QUESTIONS

1. True or false: the Lum A BC subtype is associated with high sensitivity to chemotherapeutic agents.
2. How is the classification of ER 'low-positive' tumours defined?
3. Name four clinicopathological features of ER-positive BC which are associated with a greater risk of recurrence.

(Neo)adjuvant chemotherapy

Neoadjuvant ChT may be used to potentially **downsize locally advanced disease**, which may be inoperable at diagnosis.

It can be used instead of adjuvant ChT when the treatment decision can be confidently made without **surgical pathology data**.

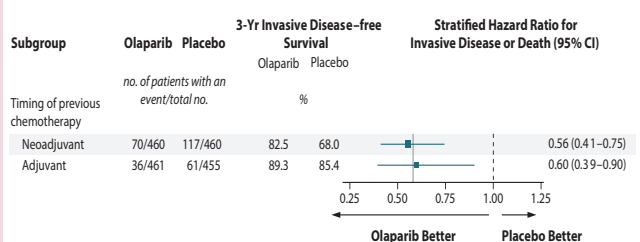
Complete responses to **neoadjuvant ChT** are comparatively less common in ER-positive disease.

EBCTCG meta-analysis of clinical response rates to neoadjuvant ChT according to hormone receptor status		
Biopsy ER and PgR status	% (CR/total)	Rate ratio for clinical CR (95% CI)
ER- and PgR-positive	31.9 (83/260)	0.77 (0.64–0.92)
ER-positive, PgR-negative	26.6 (21/79)	0.71 (0.50–1.02)
ER- and PgR-negative	35.5 (117/330)	1.24 (1.09–1.41)
Unknown	25.4 (325/1278)	0.73 (0.49–1.08)

ChT, chemotherapy; CI, confidence interval; CR, complete response; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; ER, oestrogen receptor; PgR, progesterone receptor.

Fig. 8.4

Efficacy of adjuvant olaparib is independent of the timing of previous ChT, as shown in the OlympiA trial



ChT, chemotherapy; CI, confidence interval; Yr, year.

Unlike triple-negative and HER2-positive tumours, **evidence of post-operative residual disease** does not generally inform adjuvant therapy in *BRCA* wild-type disease.

Neoadjuvant ChT does not affect the efficacy of subsequent targeted adjuvant therapy (poly [ADP-ribose] polymerase [PARP] inhibitors **olaparib** or **abemaciclib**) in high-risk patients.

Among postmenopausal patients with ER-positive, HER2-negative disease, **neoadjuvant ET** can be used to downstage disease, particularly if there are concerns regarding fitness for ChT or in cases of Lum A-like tumours.

In high-risk disease (e.g. node positivity), a sequential **anthracycline → taxane-based** regimen is recommended. Dose-dense regimens are associated with better outcomes.

In lower risk disease (e.g. node negativity, smaller primary tumour size), less intensive or **anthracycline-sparing** regimens may be considered.

In Lum A-like disease with low-risk features, **ChT may be safely omitted** in preference of adjuvant ET.

Superior survival outcomes associated with dose-dense ChT scheduling in patients with high-risk disease

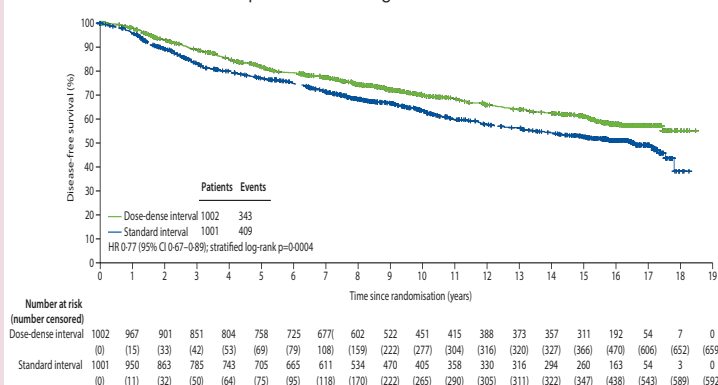


Fig. 8.6

ChT, chemotherapy; CI, confidence interval; HR, hazard ratio.

REVISION QUESTIONS

- Which ChT approach would you adopt in the post-operative management of a premenopausal woman with pT3N2M0 disease?
- In which group of patients can neoadjuvant ChT be replaced with ET?
- True or false: prior exposure to neoadjuvant ChT can reduce the efficacy of adjuvant abemaciclib.

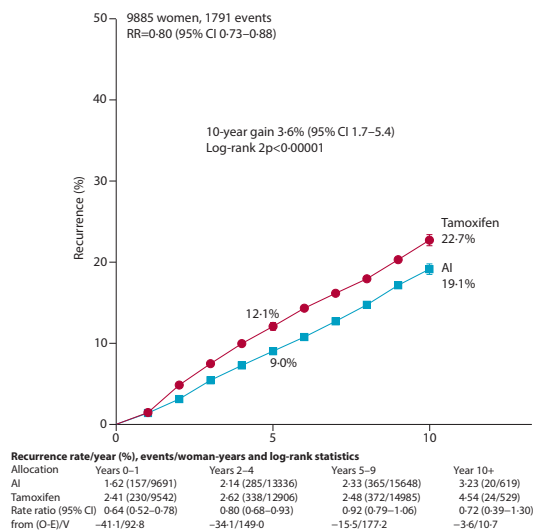
Endocrine therapy

The **current standard** is to offer adjuvant ET for a period of at least 5 years, with potentially poorer outcomes seen with a shorter duration.

Clear benefits are observed with **extension beyond 5 years** (up to 10 years) in patients with high-risk disease (e.g. larger tumour size, nodal involvement).

In postmenopausal women who had already received 5 years of ET, the **ABCSG-16 study** showed no advantage beyond a 2-year extension.

EBCTCG meta-analysis of recurrence rates following five years of TAM vs AI



AI, aromatase inhibitor; CI, confidence interval; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; O-E, observed minus expected; RR, rate ratio; TAM, tamoxifen; V, variance of O-E.

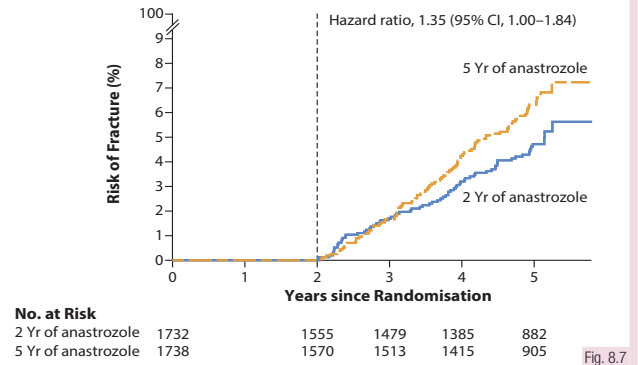
In premenopausal women, the benefit of **ovarian function suppression** (OFS) depends on risk of recurrence (compositive risk score calculation is recommended).

For patients with low-risk disease, **TAM alone** is standard-of-care. For patients with moderate-to-high risk of recurrence, **OFS plus TAM or an AI** is preferred.

Intensification of ET in this patient group can lead to poorer quality of life; therefore careful patient selection according to risk of relapse is paramount.

Extending ET beyond 7 years showed no additional benefit and was associated with an increased rate of fractures

Risk of Bone Fracture



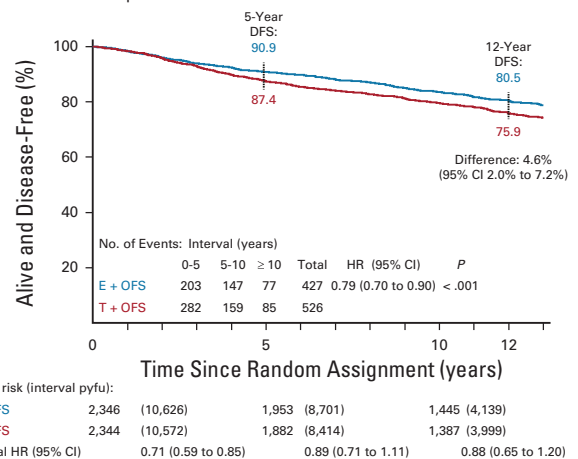
CI, confidence interval; ET, endocrine therapy; Yr, year.

Selection of an ET agent should consider the patient's menopausal status. In **postmenopausal** women, options are either an aromatase inhibitor (AI) or tamoxifen (TAM).

AIs may be given upfront or after a lead-in of TAM over 2-3 years. Treatment decisions should be made on an **individual basis** given the particular side effects of each agent. TAM can cause thrombosis, and, rarely, endometrial cancer. AIs can cause arthralgia and decrease bone mineral density.

Compared with TAM, AIs reduce recurrence rates in about 4% of cases, but their impact on overall survival (OS) is limited.

Improved DFS associated with OFS plus exemestane at 13-year median follow-up of the combined SOFT and TEXT trials



CI, confidence interval; DFS, disease-free survival; E, exemestane; HR, hazard ratio; OFS, ovarian function suppression; pyfu, patient-years of follow-up; T, tamoxifen.

Fig. 8.9

REVISION QUESTIONS

- True or false: in a premenopausal 34-year-old woman with a recent history of pT3N1M0 Lum-like BC, a single-agent AI is an appropriate adjuvant ET.
- What would be the recommended ET in a premenopausal patient with high-risk ER-positive disease?
- What are the side effects specifically associated with AIs and with TAM?

Other adjuvant systemic therapies

In patients at high risk of relapse, significant invasive disease-free survival (iDFS) and distant disease-free survival (DDFS) benefits have been shown by adding the cyclin-dependent kinase 4/6 (CDK4/6) inhibitor **abemaciclib** to standard ET.

Abemaciclib can cause **cytopenias**, **diarrhoea** and **pneumonitis**, and as such patients require increased monitoring in this setting.

Improved iDFS rates have been shown with adjuvant ribociclib plus ET in patients with **lower risk and node-negative** disease in the NATALEE study.

Adjuvant abemaciclib plus ET produced a significantly longer iDFS compared to ET alone in the monarchE study

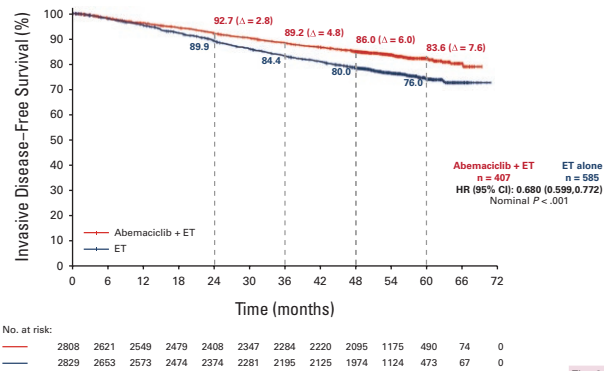


Fig. 8.10

CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; iDFS, invasive disease-free survival.

Adjuvant olaparib improved OS in patients with *BRCA* mutations in the OlympiA study

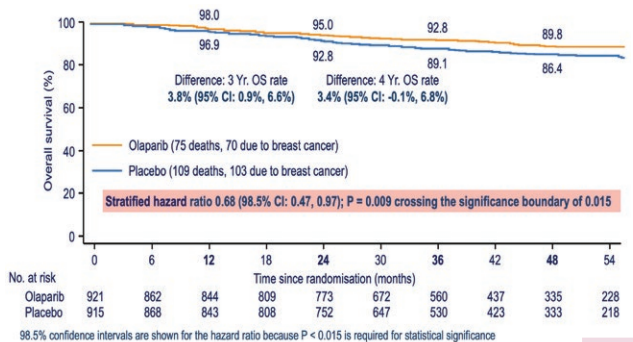


Fig. 8.11

CI, confidence interval; OS, overall survival; Yr, year.

Adjuvant **bisphosphonates** should be discussed with postmenopausal patients (natural or therapy-induced) who are candidates for systemic therapies.

Bisphosphonates confer a **small benefit** in terms of OS, bone recurrence, BC mortality and fracture rates. This is not seen in premenopausal women.

Bisphosphonates are associated with a **small but significant risk** of osteonecrosis of the jaw, eye inflammation, atypical fractures and renal toxicity.

In patients with high-risk disease and *BRCA1* or *BRCA2* pathogenic variants, adjuvant olaparib improves both DDFS and OS.

Olaparib is commonly associated with **gastrointestinal toxicities**, **fatigue** and **cytopenias**. The OlympiA study demonstrated no significant negative effect on quality of life.

Germline *BRCA* sequencing should be considered in patients with high-risk disease to identify those likely to benefit from this adjuvant therapy.

No benefit for bisphosphonates in premenopausal women in terms of several outcomes, including BC-related mortality

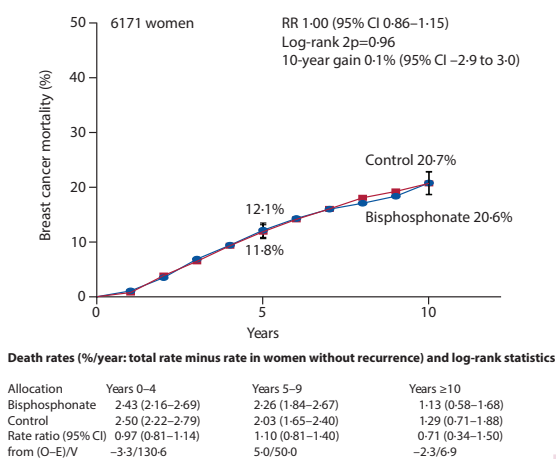


Fig. 8.12

BC, breast cancer; CI, confidence interval; O–E, observed minus expected; RR, rate ratio; V, variance of O–E.

REVISION QUESTIONS

1. Cite some common side effects of abemaciclib.
2. True or false: bisphosphonates are indicated in premenopausal women who are diagnosed with high-risk ER-positive, HER2-negative BC.
3. Should PARP inhibitors be offered to patients with high-risk disease, regardless of *BRCA* status?

Issues for special consideration

The overall fitness of **older patients** for systemic therapies should be assessed. The G8 screening tool can identify those who may benefit from comprehensive geriatric assessment. Fit older patients stand to derive significant benefit from standard treatment.

Older patients may **discontinue** adjuvant therapies due to side effects, which can in turn lead to poorer outcomes.

Fit older patients should be offered **polychemotherapy** if clinically indicated, as single-agent regimens have been associated with inferior outcomes.

A significant proportion of older women discontinued adjuvant ET soon after commencement, with many citing toxicity as the cause

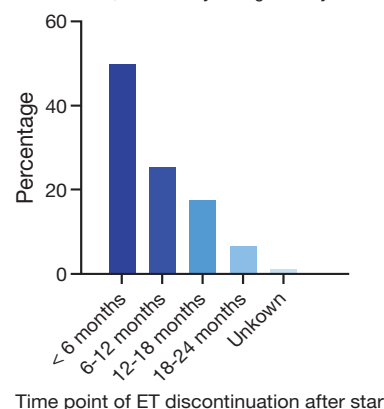
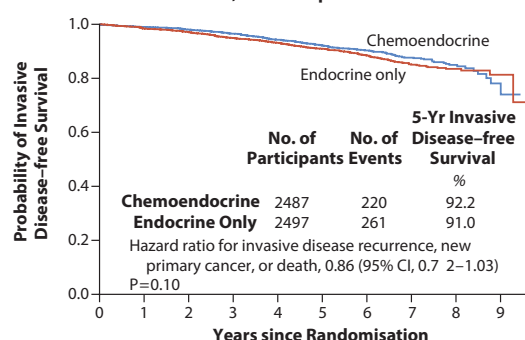


Fig. 8.13

ET, endocrine therapy.

No benefit shown with addition of ChT to ET in terms of iDFS (RxPonder trial)

Invasive Disease-free Survival, All Participants



No. at Risk

	0	1	2	3	4	5	6	7	8	9
Chemoendo-	2487	2279	2123	1940	1691	1477	971	511	175	19
crine group										
Endocrine-	2497	2328	2177	1965	1738	1493	969	502	181	23
only group										

Fig. 8.14

ChT, chemotherapy; CI, confidence interval; ET, endocrine therapy; iDFS, invasive disease-free survival; Yr, year.

In women of childbearing potential, **fertility issues** should be discussed, particularly given the duration of adjuvant therapy in ER-positive disease.

If **pregnancy** is desired following an ER-positive BC diagnosis, adjuvant ET can be temporarily interrupted to allow conception, pregnancy and delivery.

The POSITIVE study (NCT02308085) showed that **temporary interruption of ET** to facilitate pregnancy does not impact short-term disease outcomes, further supporting previous data.

DFS in women with a pregnancy following ER-positive early BC, vs those without a pregnancy

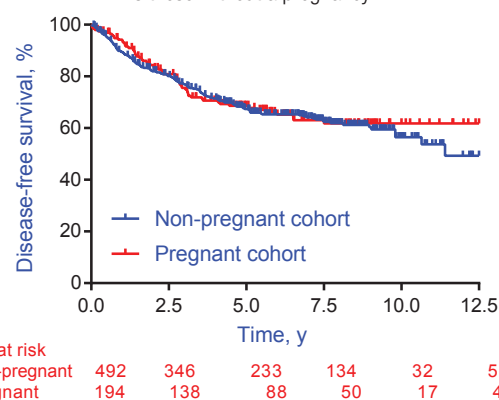


Fig. 8.15

BC, breast cancer; DFS, disease-free survival; ER, oestrogen receptor; y, years.

REVISION QUESTIONS

1. Is it safe to interrupt adjuvant ET for up to two years in order to allow a patient to fall pregnant after a BC diagnosis?
2. Is it best practice to routinely omit polychemotherapy for all older BC patients, in order to avoid toxicities?
3. True or false: gene expression tests should only be used in patients with node-negative disease in order to inform decisions about adjuvant ChT.

Summary: Early ER-positive, HER2-negative breast cancer: systemic therapy

- Risk of disease recurrence can be estimated according to clinicopathological features and/or genomic assays
- Patients at a higher risk of recurrence should be offered more intensive therapies, with de-escalated approaches offered to those at lower risk
- ER-positive disease is generally less chemosensitive than ER-negative disease. However, patients with higher risk features still stand to derive benefit from ChT
- ET is an essential part of adjuvant treatment, with the choice of agent as well as the duration of therapy tailored according to risk of recurrence and patient preference
- TAM is associated with an increased risk of thrombosis and endometrial neoplasia. AIs can cause loss of bone mineral density and arthralgias
- There is evidence supporting the use of adjuvant CDK4/6 inhibitors in addition to ET in high-risk disease
- *BRCA* sequencing should be considered in patients with high-risk disease in order to identify those who may potentially benefit from adjuvant PARP inhibition
- Bone-modifying agents may bestow a small benefit in terms of survival in postmenopausal women, though the associated risk of toxicity must be considered
- In women of childbearing potential, fertility issues should be discussed, particularly given the duration of adjuvant therapy in ER-positive disease
- Pregnancy may be attempted following a diagnosis of Lum-like early BC, but ET must be temporarily suspended to facilitate this. The timing of attempts at conception should be considered at an individual level

Further Reading

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Image sources: **Fig. 8.1.** Dieci MV, et al. *NPJ Breast Cancer* 2021;7:101; **8.2.** adapted from Allison KH, et al. *J Clin Oncol* 2020;38:1346–1366; **8.3.** adapted from Cardoso F, et al; ESMO Guidelines Committee. *Ann Oncol* 2019;30:1194–1220; **8.4.** adapted from Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet Oncol* 2018;19:27–39; **8.5.** adapted from Tutt ANJ, et al; OlympiA Clinical Trial Steering Committee and Investigators. *N Engl J Med* 2021;384:2394–2405; **8.6.** Del Mastro L, et al; Gruppo Italiano Mammella Investigators. *Lancet Oncol* 2022;23:1571–1582; **8.7.** Gnant M, et al; Austrian Breast and Colorectal Cancer Study Group. *N Engl J Med* 2021;385:395–405; **8.8.** Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet* 2015;386:1341–1352; **8.9.** Pagani O, et al; SOFT and TEXT Investigators and the International Breast Cancer Study Group (a division of ETOP IBCSG Partners Foundation). *J Clin Oncol* 2023;41:1376–1382; **8.10.** Rastogi P, et al. *J Clin Oncol* 2024;42:987–993; **8.11.** courtesy of A. Tutt. Tutt ANJ, et al. *Ann Oncol* 2022;33:566–568; **8.12.** Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet* 2015;386:1353–1361; **8.13.** Lemij AA, et al. *Breast Cancer Res Treat* 2022;193:567–577; **8.14.** Kalinsky K, et al. *N Engl J Med* 2021;385:2336–2347; **8.15.** Lambertini M, et al. *J Natl Cancer Inst* 2018;110:426–429.

General considerations

Human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancers (MBCs) constitute ~20% of MBCs and may present as stage IV *de novo* (dnMBC) or recurrent MBC (rMBC).

The prevalence of HER2-positive dnMBC has remained stable since the 1990s. In contrast, the incidence of HER2-positive rMBC has declined in recent years.

For dnMBC, overall survival (OS) has improved significantly for the hormone receptor-positive, HER2-positive subtype and there has been a tendency toward improvement for hormone receptor-negative, HER2-positive tumours.

Distribution of BC subtypes in dnMBC and rMBC

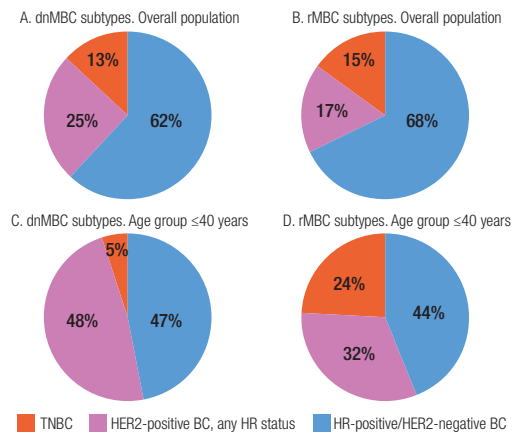


Fig. 9.1

BC, breast cancer; dnMBC, de novo metastatic breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; rMBC, recurrent metastatic breast cancer; TNBC, triple-negative breast cancer.

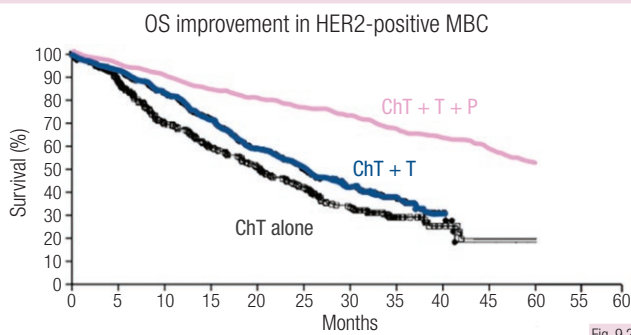


Fig. 9.2

ChT, chemotherapy; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; OS, overall survival; P, pertuzumab; T, trastuzumab.

HER2-positive MBC has an aggressive natural history, with short progression-free survival (PFS) and median OS of ≤2 years without anti-HER2 therapies.

Major improvements related to the introduction of anti-HER2 therapies over the last 2 decades have resulted in prolongation of median OS to >5 years.

Currently, OS in HER2-positive MBC exceeds that of HER2-negative tumours with matching oestrogen receptor (ER) status; the most favourable OS is observed in ER-positive, HER2-positive tumours.

HER2-positive tumours display characteristic patterns of relapse, having a high dissemination rate including haematogenous spread to the liver and brain.

The main risk factors for relapse are: younger age, high disease grade and stage, ER-negative subtype and lower tumour-infiltrating lymphocyte (TIL) score.

Reassessment of ER, progesterone receptor (PgR) and HER2 status for rMBC should always be performed. In the case of discordant HER2 status, anti-HER2 therapy should be considered.

Dissemination pattern in HER2-positive dnMBC and rMBC

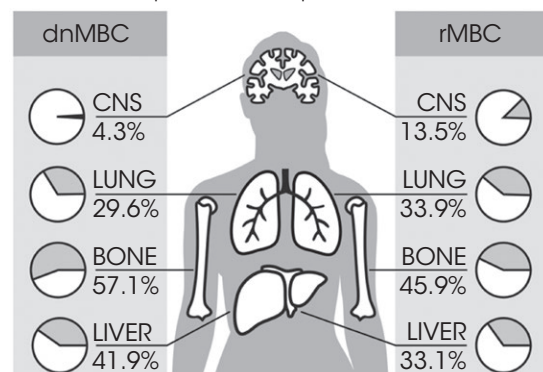


Fig. 9.3

CNS, central nervous system; dnMBC, de novo MBC; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; rMBC, recurrent MBC.

REVISION QUESTIONS

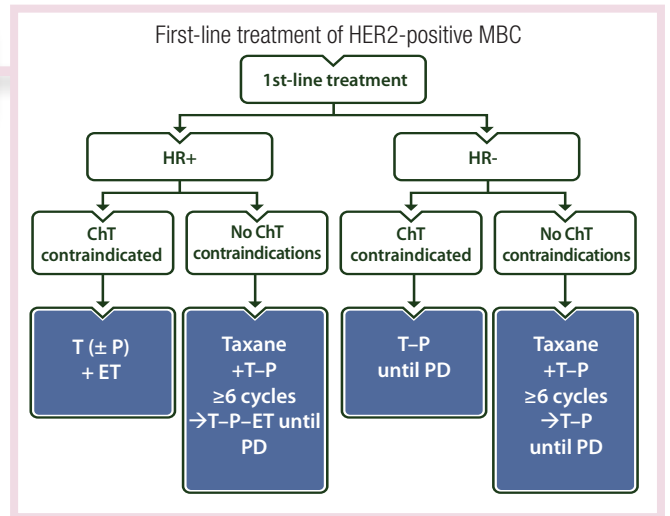
1. What is the frequency of HER2-positive cancers in MBC?
2. Which patients with HER2-positive MBC have the best prognosis?
3. Where does HER2-positive MBC most commonly metastasise?

Principles of treatment

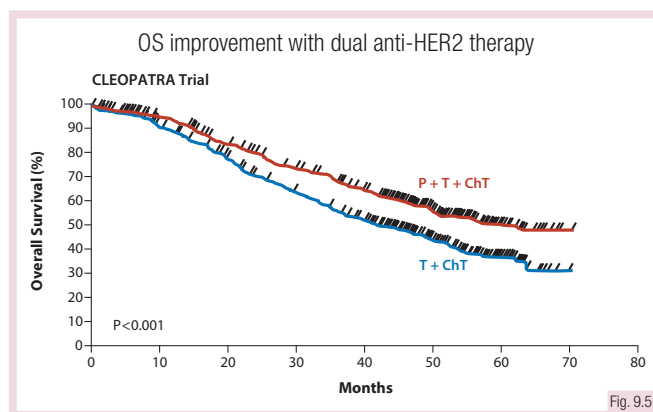
Anti-HER2 therapy should be introduced **at the beginning** of treatment and **continued** throughout the disease course, unless contraindicated.

After achieving disease control with chemotherapy (ChT) plus anti-HER2 agent(s), **maintenance anti-HER2 therapy** should be continued **until progression**.

At progression, **HER2 blockade** should continue with an alternative drug, or trastuzumab rechallenge in combination with **alternative ChT** or **endocrine therapy (ET)**.



ChT, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR-, hormone receptor-negative; HR+, hormone receptor-positive; MBC, metastatic breast cancer; P, pertuzumab; PD, progressive disease; T, trastuzumab. Fig. 9.4



ChT, chemotherapy; HER2, human epidermal growth factor receptor 2; OS, overall survival; P, pertuzumab; T, trastuzumab.

Further developments include **tyrosine kinase inhibitors (TKIs)**: lapatinib, tucatinib, pyrotinib and neratinib, and **antibody–drug conjugates (ADCs)**.

ADCs consist of a **cytotoxic agent** connected via a **linker** to a **monoclonal antibody**, allowing for targeted delivery of the drug to the cancer cells.

Future perspectives include **novel ADCs**, **bispecific antibodies**, **phosphoinositide 3-kinase (PI3K) inhibitors** (in tumours harbouring a *PIK3CA* mutation) and **anticancer vaccines**.

Trastuzumab was approved for MBC by the Food and Drug Administration (FDA) in **1998**, followed by routine HER2 testing, revolutionising the diagnosis and treatment of HER2-positive MBC.

The addition of **pertuzumab** to trastuzumab plus a taxane resulted in an **improved objective response rate, PFS and OS** and became standard in first-line therapy.

Maintenance ET is recommended in ER-positive, HER2-positive tumours after completion of cytotoxic-based therapy, in combination with **dual HER2 blockade**.

Development of anti-HER2 therapies				
Drug class	Drug	FDA-approved in neoadjuvant setting	FDA-approved in adjuvant setting	FDA-approved in metastatic setting
mAbs	Trastuzumab	–	2006	1998
	Pertuzumab	2013	2017	2012
	Emtansine	–	–	2020
	Pertuzumab, trastuzumab and hyaluronidase-zzxf	2020	2020	2020
ADCs	T-DM1	–	2019	2013
	T-DXd	–	–	2019 2022: 2L
TKIs	Lapatinib	–	–	2007
	Neratinib	–	2017	2020
	Pyrotinib	–	–	2018 only in China
	Tucatinib	–	–	2020

2L, second line; ADC, antibody–drug conjugate; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; TKI, tyrosine kinase inhibitor; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan. Fig. 9.6

REVISION QUESTIONS

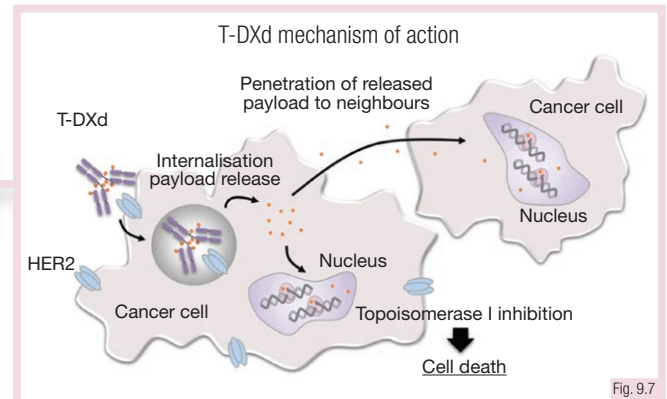
1. How many lines of anti-HER2 therapy should be used?
2. What is the preferred first-line treatment option in HER2-positive MBC?
3. Which TKIs are used in HER2-positive MBC?

Second-line treatment and beyond

Following failure of first-line treatment, **trastuzumab deruxtecan (T-DXd)** leads to remarkable PFS and OS benefits when compared with trastuzumab emtansine (T-DM1).

Efficacy of T-DXd may be attributed to a **high drug-to-antibody ratio (~8)** and to the **'bystander effect'**, enabling the toxic payload to access neighbouring cells.

The most common toxicities of T-DXd are **nausea** and **neutropenia**. **Interstitial lung disease** occurs in ~10% of patients, requiring immediate drug interruption/withdrawal and appropriate treatment.



HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan.

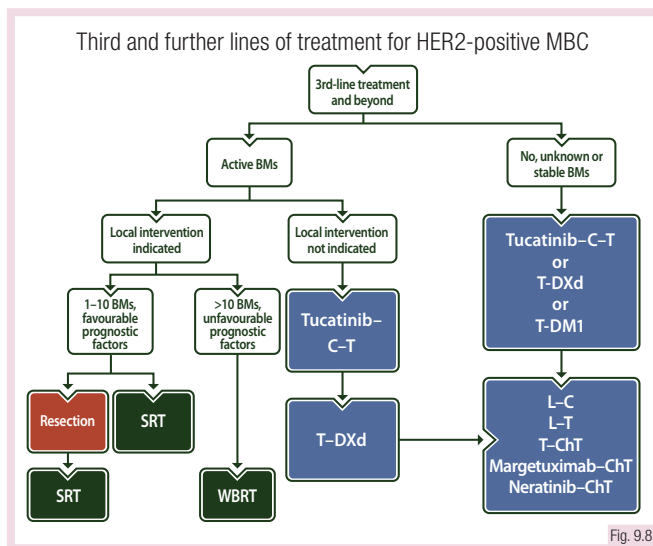


Fig. 9.8

BM, brain metastasis; C, capecitabine; ChT, chemotherapy; HER2, human epidermal growth factor receptor 2; L, lapatinib; MBC, metastatic breast cancer; SRT, stereotactic radiotherapy; T, trastuzumab; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; WBRT, whole-brain radiotherapy.

The **addition of tucatinib** to trastuzumab plus capecitabine beyond second line improved PFS and OS, compared with trastuzumab and capecitabine, including in patients with active **brain metastases**.

In pretreated HER2-positive MBC patients, **margetuximab** plus ChT vs trastuzumab plus ChT resulted in a **slight improvement in PFS**, but no OS benefit, with the possible predictive role of the CD16A-158FF genotype.

Capecitabine plus neratinib, an irreversible pan-HER TKI, led to a PFS benefit and **fewer interventions for central nervous system (CNS) disease**, compared with capecitabine plus lapatinib, at the cost of higher toxicity.

TDM-1, previously standard second-line treatment, has been moved to **further therapy lines**, although its activity after T-DXd is poorly known.

Further therapy options include various combinations of ChT or ET with an anti-HER2 targeted agent: trastuzumab, neratinib or lapatinib.

In the case of contraindications to standard ChT, a combination of **trastuzumab and lapatinib or pertuzumab**, or **metronomic ChT** combined with **anti-HER2 drug(s)**, may be used.

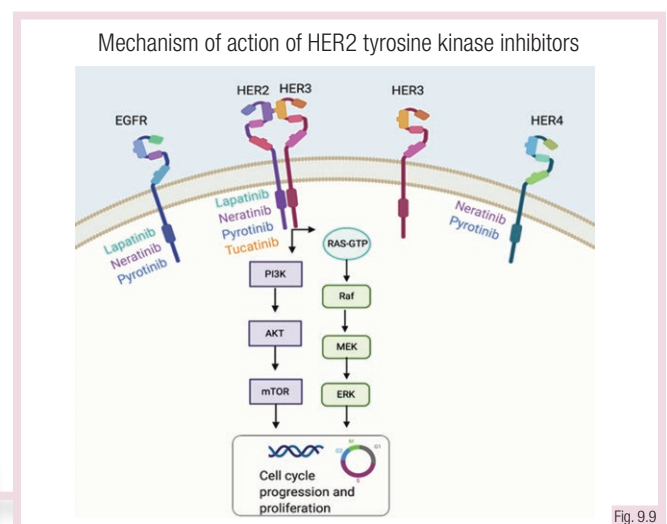


Fig. 9.9

EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; GTP, guanosine triphosphate; HER2/3/4, human epidermal growth factor receptor 2/3/4; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase.

REVISION QUESTIONS

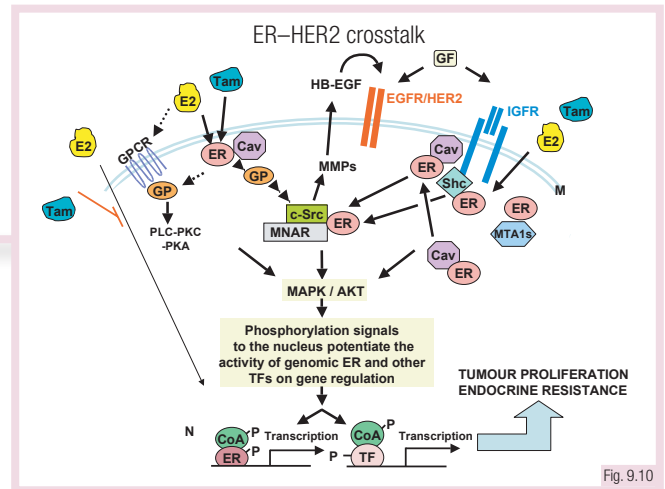
1. What is the current standard second-line therapy in HER2-positive MBC?
2. What are the options when standard ChT is contraindicated?
3. What are the third-line and beyond therapy options in HER2-positive MBC?

Endocrine therapy/brain metastases

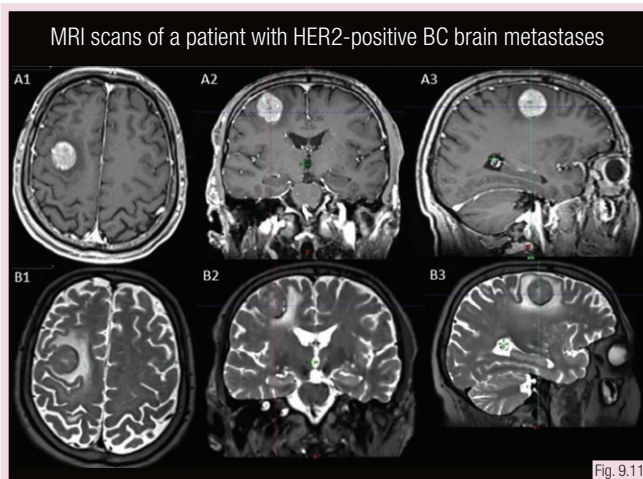
ER-positive, HER2-positive MBC is a distinct subtype (genomically often representing the **luminal HER2-positive subtype**) with **better prognosis**, comprising ~70% of all HER2-positive MBCs.

Despite suggested lower ET sensitivity attributed to **ER-HER2 crosstalk**, the first first-line combination of trastuzumab plus ET exhibits clinically meaningful efficacy and may be considered in **selected patients**.

ET can be administered with **dual HER2 blockade**, resulting in a significant **PFS improvement** with relatively low toxicity, but no proven OS benefit.



AKT, AKT signal transduction pathway; Cav, caveolin-1; CoA, coactivator; c-Src, c-Src-family tyrosine kinases; E2, oestrogen ligand; EGFR, epidermal growth factor receptor; ER, oestrogen receptor; GF, growth factor; GP, G protein; GPCR, GP-coupled receptor; HB-EGF, heparin-binding epidermal growth factor-like growth factor; HER2, human epidermal growth factor receptor 2; IGFR, insulin-like growth factor receptor; M, membrane; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; MNAR, modulator of nongenomic action of ER; MTA1, metastasis-associated gene 1; N, nucleus; P, phosphorylate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; Shc, signalling intermediate molecule; Tam, tamoxifen; TF, transcription factor.



A) T1 and (B) T2 sequence; transverse (1), coronal (2) and sagittal (3) projections. BC, breast cancer; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging.

Brain metastases in patients with HER2-positive tumours occur more often in the **posterior fossa** and are associated with **lower risk of leptomeningeal metastases** and **better prognosis**.

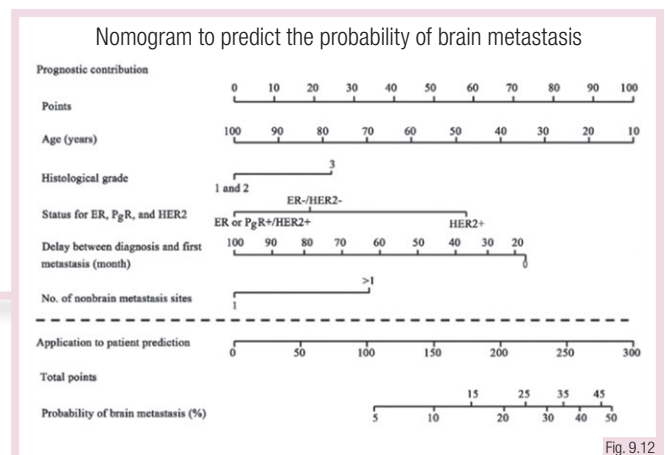
Favourable prognostic factors for patients with **HER2-positive brain metastases** include **ER-positive subtype**, **younger age**, lower number of brain metastases, better performance status and **non-frailty**.

Guidelines recommend **against screening for asymptomatic brain metastases**, both in early and advanced disease, as earlier diagnosis does not improve OS.

Due to improved control of extracranial disease, the incidence of **metastases to the brain** as a sanctuary site can be as high as 40%.

Brain metastases are rare in HER2-positive dnMBC and develop after a **median of 3–4 years** from primary diagnosis, frequently as **isolated intracranial progression**.

Risk factors for the development of brain metastases include **young age**, **higher stage** at diagnosis, **node positivity**, **ER-negative status**, **grade 3** and **inflammatory breast cancer**.



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

REVISION QUESTIONS

1. What determines lower endocrine sensitivity in ER-positive, HER2-positive MBC?
2. How frequent are brain metastases in HER2-positive MBC?
3. What are the favourable prognostic factors in patients with HER2-positive brain metastases?

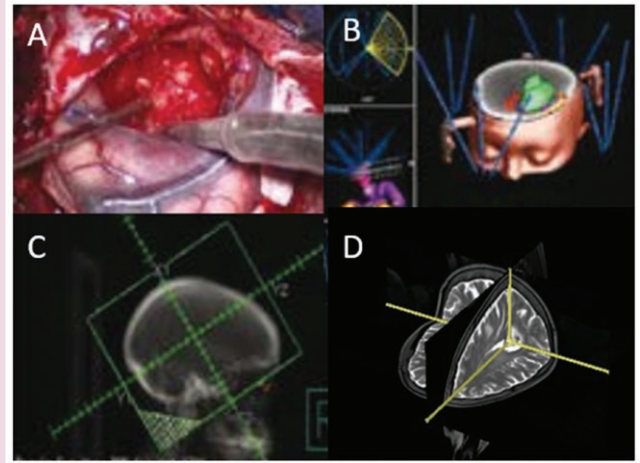
Management of brain metastases/cardiotoxicity of anti-HER2 therapy

Local treatment options for brain metastases include surgery, radiosurgery or whole-brain radiotherapy (WBRT). Systemic therapy alone may also be used.

In view of a relatively long expected OS, WBRT should be avoided whenever possible due to resultant complications, including cognitive dysfunction.

Leptomeningeal disease, associated with a very poor prognosis, more common in lobular carcinomas, occurs in 0.8%–6.6% of HER2-positive MBCs (up to 16% in autopsy studies).

Local treatment options in brain metastases



(A) surgery, (B) SRS, (C) WBRT, (D) brain metastasis positioning. SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

Fig. 9.13

CNS PFS benefit from the addition of tucatinib to trastuzumab plus capecitabine

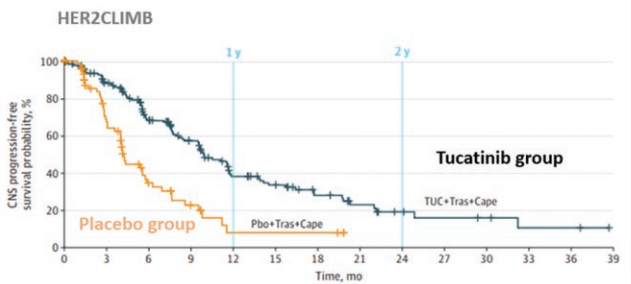


Fig. 9.14

Cape, capecitabine; CNS, central nervous system; mo, months; Pbo, placebo; PFS, progression-free survival; Tras, trastuzumab; TUC, tucatinib.

Isolated intracranial progression, when controllable with local treatments, does not require a change of systemic anti-HER2 therapy.

In the case of stable brain metastases (asymptomatic, not requiring steroid therapy), systemic treatment is preferred, as in the case of extracranial disease.

Systemic treatments with demonstrated activity for active brain metastases (when local intervention is not indicated) include tucatinib plus capecitabine and trastuzumab, T-DXd or capecitabine plus lapatinib.

Trastuzumab may cause cardiotoxicity (usually reversible and not dose-dependent). Assessment of cardiac function is required before and during treatment.

Cardiotoxicity risk factors include prior cardiovascular disease and left ventricular dysfunction, use of anthracyclines, older age, obesity and smoking.

Beta-blockers and angiotensin-converting enzyme inhibitors may protect against trastuzumab-related cardiotoxicity and should be used in case of cardiac dysfunction.

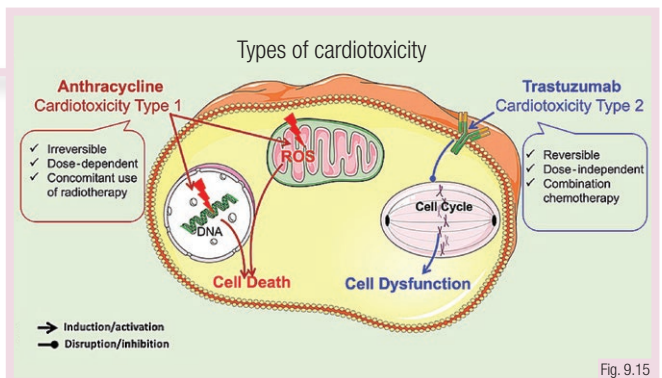


Fig. 9.15

ROS, reactive oxygen species.

REVISION QUESTIONS

1. What are the local treatment options for brain metastases?
2. Is an isolated CNS progression an indication to change systemic therapy?
3. What are the risk factors of trastuzumab cardiotoxicity?

Summary: Metastatic HER2-positive breast cancer: systemic therapy

- HER2-positive MBCs constitute ~20% of MBCs and may present as stage IV *de novo* or recurrent disease
- HER2-positive MBC has an aggressive natural history, but the introduction of anti-HER2 therapies has resulted in significant improvement in treatment outcomes
- Anti-HER2 drugs include monoclonal antibodies, TKIs and ADCs
- Anti-HER2 therapy should be continued throughout the disease course in combination with subsequent treatment lines, unless contraindicated
- The standard first-line combination of taxane, trastuzumab and pertuzumab is usually followed by T-DXd
- Further options involve a regimen including tucatinib, neratinib and lapatinib combined with ChT or ET
- Although combinations of ET plus anti-HER2 therapies have not been shown to improve OS, they can be used in selected cases of ER-positive/HER2-positive MBC
- Risk of brain metastases is increased in HER2-positive cancers and their incidence is rising due to improved control of extracranial disease
- Treatment options for brain metastases include surgery, radiosurgery or WBRT, or systemic therapy alone
- Anti-HER2 treatment-related cardiotoxicity is usually reversible and not dose dependent; regular assessment of cardiac function is required

Further Reading

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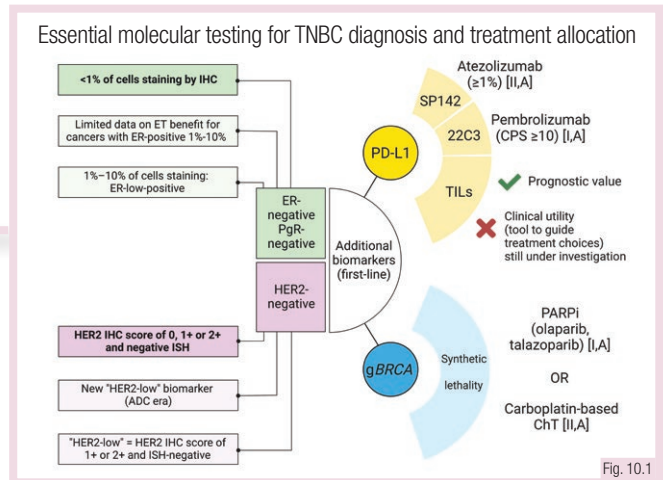
Image sources: **Fig. 9.1.** Conte B, et al. *Clin Breast Cancer* 2022;22:78-87; **9.2.** Slamon DJ, et al. *N Engl J Med* 2001;344:783-792 and Swain SM, et al. *Lancet Oncol* 2020;21:519-530; **9.3.** adapted from Tripathy D, et al. *Oncologist* 2020;25:e214-e222; **9.4, 9.8.** adapted from Gennari A, et al. *Ann Oncol* 2021;32:1475-1495 and ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023; **9.5.** Swain SM, et al. *N Engl J Med* 2015;372:724-734; **9.6.** adapted from Swain SM, et al. *Nat Rev Drug Discov* 2023;22:101-126; **9.7.** Shitara K, et al. *Gastric Cancer* 2021;24:780-789; **9.9.** Schlam I, Swain SM. *Breast Cancer* 2021;7:56; **9.10.** Arpino G, et al. *Endocr Rev* 2008;29:217-233; **9.12.** Minatani N, et al. *J Cancer Ther* 2015;6,727-734; **9.14.** Lin NU, et al. *JAMA Oncol* 2023;9:197-205; **9.15.** Gabani M, et al. *Cureus* 2021;13:e18194. All other figures courtesy of the authors.

10 Metastatic triple-negative breast cancer: systemic therapy

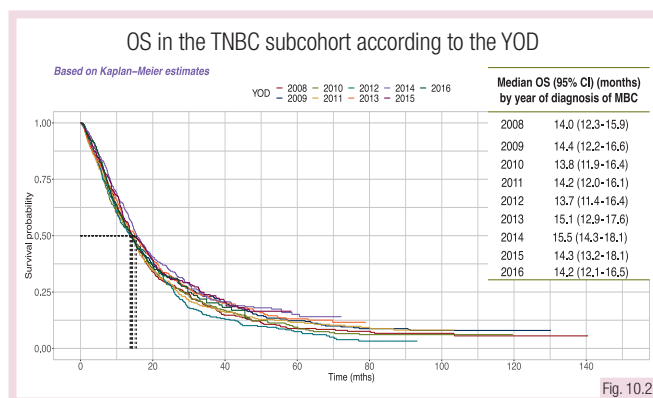
Epidemiology, survival and initial work-up

Triple-negative breast cancer (TNBC) accounts for ~15% of breast cancers (BCs) diagnosed worldwide, which amounts to almost 200 000 cases each year.

TNBC is defined by a <1% expression of oestrogen receptor (ER) and progesterone receptor (PgR) by immunohistochemistry (IHC) and either 0 to 1+ expression of human epidermal growth factor receptor 2 (HER2) by IHC, or IHC 2+ and *in situ* hybridisation (ISH) not amplified.



22C3, PD-L1 IHC 22C3 pharmDx Dako assay; ADC, antibody–drug conjugate; ChT, chemotherapy; CPS, combined positive score; ER, oestrogen receptor; ET, endocrine therapy; gBRCA, germline BRCA; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridisation; PARPi, poly (ADP-ribose) polymerase inhibitor; PD-L1, programmed death-ligand 1; PgR, progesterone receptor; SP142, Ventana PD-L1 assay; TIL, tumour-infiltrating lymphocyte; TNBC, triple-negative breast cancer.



CI, confidence interval; MBC, metastatic breast cancer; mths, months; OS, overall survival; TNBC, triple-negative breast cancer; YOD, year of metastatic diagnosis.

Almost 30% of metastatic TNBCs (mTNBCs) are diagnosed as *de novo* disease, with a high frequency of visceral metastases.

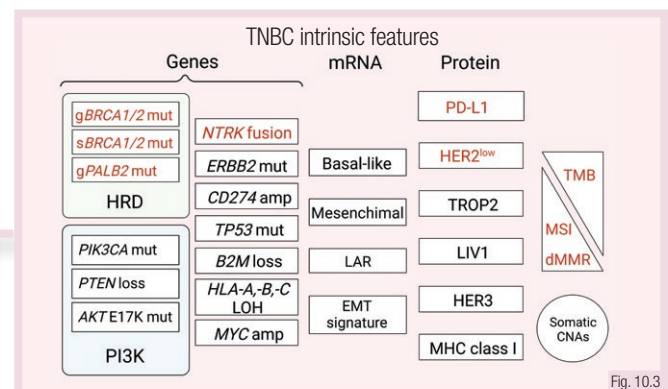
Median overall survival (OS) from onset of metastases is <18 months, without improvement in outcomes in almost a decade.

For most mTNBCs, chemotherapy (ChT) remains the standard treatment. Enrolment in clinical trials is recommended.

In mTNBC, a confirmatory biopsy should be obtained to reassess ER, PgR and HER2, as discordance between primary and metastatic lesions is possible.

Assessment of programmed death-ligand 1 (PD-L1) expression is necessary to identify patients who are eligible for chemoimmunotherapy.

Given the therapeutic implications of poly (ADP-ribose) polymerase inhibitors (PARPis), all patients with mTNBC should undergo genetic evaluation to determine germline *BRCA1/2* carrier status.



Biomarkers in red are used in clinical practice.

amp, amplification; B2M, beta-2-microglobulin; CD, cluster of differentiation; CNA, copy number alteration; dMMR, mismatch repair deficient; EMT, epithelial–mesenchymal transition; g, germline; HER, human epidermal growth factor receptor; HLA, human leukocyte antigen; HRD, homologous recombination deficiency; LAR, luminal androgen receptor; LIV, Zinc transporter LIV-1; LOH, loss of heterozygosity; MHC, major histocompatibility complex; mRNA, messenger RNA; MSI, microsatellite instability; mut, mutated; NTRK, neurotrophic tyrosine receptor kinase; PALB2, partner and localiser of BRCA2; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homologue; s, somatic; TMB, tumour mutational burden; TNBC, triple-negative breast cancer; TROP2, trophoblastic cell surface antigen 2.

REVISION QUESTIONS

1. How is TNBC biologically defined?
2. What is the median OS from onset of metastases in TNBC?
3. Which are the most relevant biomarkers to be assessed for treatment decision-making in the first-line setting?

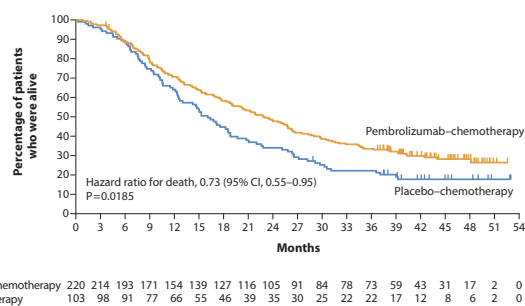
First-line setting: immunotherapy for PD-L1-positive mTNBC

In the **KEYNOTE-355** trial, pembrolizumab plus ChT was associated with a significant progression-free survival (PFS; primary endpoint) and OS benefit (23.0 vs 16.1 months; hazard ratio [HR] 0.73) in patients with a PD-L1 combined positive score (CPS) ≥ 10 tumours.

If CPS ≥ 10 (Dako 22C3), pembrolizumab plus ChT is indicated where the disease-free interval (DFI) is ≥ 6 months (Food and Drug Administration [FDA] approved, European Medicines Agency [EMA] approved).

ChT could include paclitaxel, nab-paclitaxel or carboplatin–gemcitabine.

OS in the CPS ≥ 10 subgroup of KEYNOTE-355 with Kaplan–Meier estimates



CI, confidence interval; CPS, combined positive score; OS, overall survival.

Fig. 10.4

Second interim OS analysis with Kaplan–Meier estimates in the PD-L1 immune cell-positive and PD-L1 immune cell-negative populations (IMpassion130).

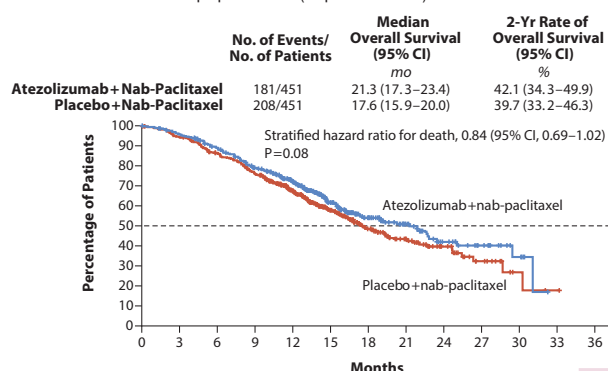


Fig. 10.5

CI, confidence interval; mo, months; OS, overall survival; PD-L1, programmed death-ligand 1.

Unlike the IMpassion130 results, in the PD-L1-positive population of IMpassion131 atezolizumab did not significantly improve PFS or OS compared with placebo.

Possible reasons for the discrepancy include overlapping 95% confidence intervals, suboptimal biomarkers (PD-L1), variations in the premedication and immune effects of ChT and the good performance of the paclitaxel-alone arm.

Based on this data, atezolizumab plus nab-paclitaxel may be considered if PD-L1 expression is $\geq 1\%$ (Ventana SP142) and DFI ≥ 12 months (EMA approved), but it has been withdrawn from the FDA approval process.

In the **IMpassion130** trial, atezolizumab provided a PFS of 7.2 vs 5.5 months (HR 0.80) in the intention-to-treat (ITT) population but no significant benefit in OS (co-primary endpoint).

The trial was hierarchically designed to formally evaluate OS in the PD-L1-positive population only if OS was significantly improved in the ITT population.

Therefore, the OS of 25 vs 18 months favouring the atezolizumab arm in the PD-L1-positive population is limited by the exploratory nature of this analysis.

ICIs plus ChT in the first-line setting in mTNBC (data for PD-L1-positive population)

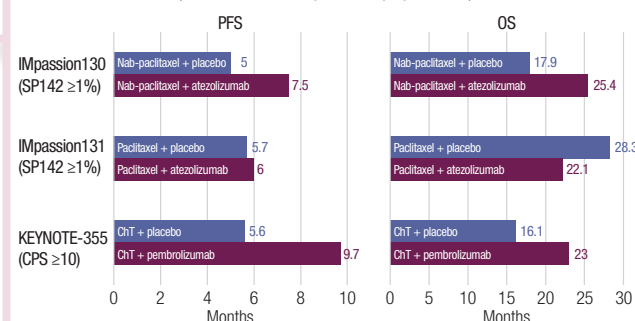


Fig. 10.6

ChT, chemotherapy; CPS, combined positive score; ICI, immune checkpoint inhibitor; mTNBC, metastatic triple-negative breast cancer; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SP142, Ventana PD-L1.

REVISION QUESTIONS

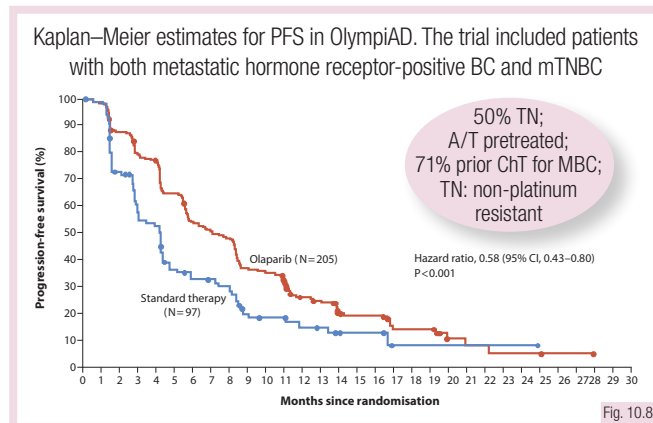
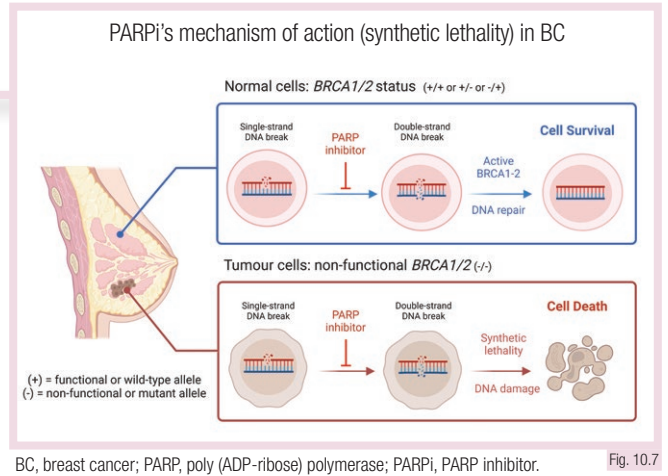
1. Which is the preferred chemoimmunotherapy regimen for the first-line treatment of PD-L1-positive mTNBC?
2. Which assays and cut-offs are commonly used to detect PD-L1 protein expression in mTNBC?
3. What are the main proposed reasons for discrepant results in the IMpassion130 and IMpassion131 trials?

First-line setting: PARP inhibition for germline *BRCA1/2*-mutated mTNBC

Two phase III trials showed the single-agent activity of **olaparib** and **talazoparib** in germline *BRCA1/2* mutation (*gBRCAm*) carriers with mTNBC. In both trials, **PARPis were superior to ChT for PFS**. The trials were not powered to show significant OS benefit.

Thus, in *gBRCAm*, PD-L1-negative mTNBC, a **PARPi is one of the preferred first-line options** (no OS benefit), especially for low-burden metastatic disease.

Neither trial compared PARPis against platinum-based ChT, though each study showed clinical activity of PARPis in the platinum pretreated patients.



A/T, anthracycline and taxane; BC, breast cancer; ChT chemotherapy; CI, confidence interval; MBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; PFS, progression-free survival; TN, triple-negative.

In OlympiAD, among **pretreated *gBRCAm* carriers with mTNBC** (n=102) randomised to olaparib 300 mg twice daily, PFS was improved vs non-platinum-based ChT (HR 0.58).

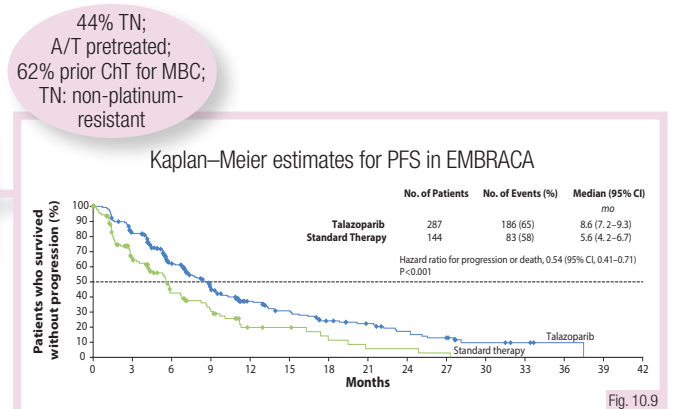
Eligibility criteria included prior anthracycline and taxane (A/T) treatment. However, **no biological rationale justifies withholding PARPis** from patients who have not received a prior A/T regimen.

Indeed, a **post-hoc subset analysis** suggested **improved OS** in patients receiving olaparib who had **not received prior ChT** for metastatic disease.

In the mTNBC subgroup (n=190) of the EMBRACA trial, which enrolled *gBRCAm* carriers, **talazoparib 1 mg once daily improved PFS relative to single-agent ChT** (HR 0.60).

Olaparib also showed activity among patients with pathogenic somatic *BRCA1/2* mutations and germline *PALB2* mutations (TBCRC 048, non-randomised trial).

Sequencing of PARPis with other treatments should take into account prior treatment response, disease burden, PD-L1 status and relative toxicities.



A/T, anthracycline and taxane; ChT, chemotherapy; CI, confidence interval; MBC, metastatic breast cancer; mo, months; PFS, progression-free survival; TN, triple-negative.

REVISION QUESTIONS

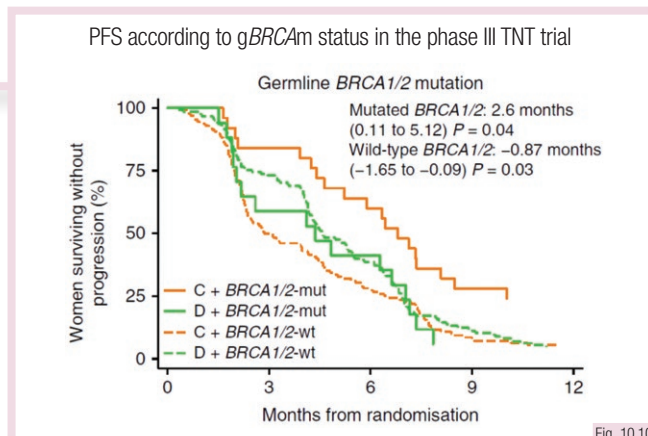
1. Which is one of the preferred first-line treatment options for a patient with *gBRCAm*, PD-L1-negative, mTNBC?
2. What is synthetic lethality?
3. What kind of genetic testing (i.e. somatic vs germline) is needed for prescribing PARPis (level of evidence IA)?

Special settings in mTNBC and later lines of treatment

Platinum-based ChT (e.g. single-agent carboplatin) is associated with a substantial PFS benefit and better tolerance over docetaxel in patients with *gBRCAm* with metastatic BC (MBC, TNT trial).

No studies have directly compared PARPis with a platinum-based regimen. However, **health-related quality of life (HRQoL)** seems to be better with PARPis compared with ChT.

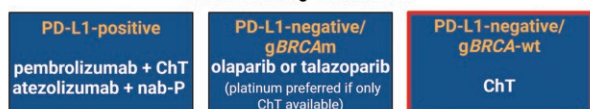
If **PD-L1-negative *gBRCA*-wt** (wild-type), the best options depend on previous treatment, disease presentation, DFI and patient considerations. A **single-agent** taxane or anthracycline is preferred, if not used previously in the (neo)adjuvant setting.



C, carboplatin; D, docetaxel; *gBRCAm*, germline BRCA mutation; mut, mutated; PFS, progression-free survival; wt, wild-type.

Suggested treatment algorithm highlighting ChT options for patients with PD-L1-negative and *gBRCA*-wild-type mTNBC

First-line setting: focus on ChT



General rule: monotherapy in most cases. Combination ChT in selected cases.

No visceral crisis: taxane or anthracycline monotherapy*, with opposite agent used at progression.

Visceral crisis: taxane- or anthracycline-based combination*
-other combinations include carboplatin+gemcitabine, carboplatin+paclitaxel
-If liver visceral crisis (elevated bilirubin), carboplatin monotherapy is one of the best options.

* if not used previously in the (neo)adjuvant setting or DFI ≥ 12 months.

Fig. 10.11

ChT, chemotherapy; DFI, disease-free interval; *gBRCAm*, germline BRCA mutation; mTNBC, metastatic triple-negative breast cancer; nab-P, nab-paclitaxel; PD-L1, programmed death-ligand 1; wt, wild-type.

Later lines: sacituzumab govitecan (SG) is the preferred treatment option, especially after at least two prior lines of ChT, including at least one for MBC.

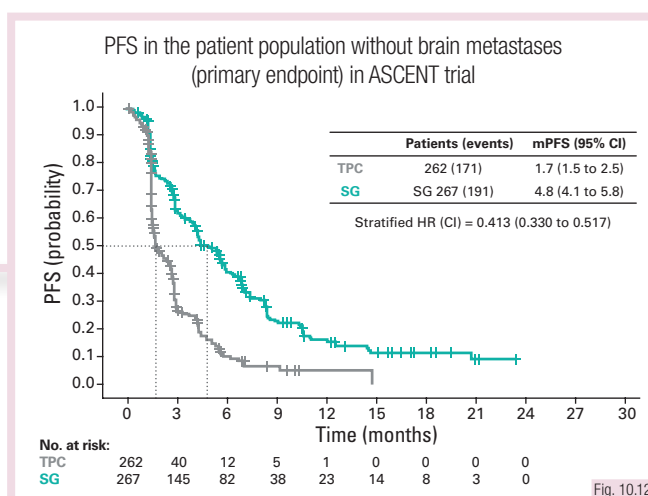
In the **ASCENT trial** (n=529 mTNBC, 2–17 prior treatments), which compared SG with single-agent ChT, PFS was 4.8 vs 1.7 months (HR 0.41) and OS was 11.8 vs 6.9 months (HR 0.51), respectively.

After progression on SG, all single-agent ChT recommendations for HER2-negative disease also apply for mTNBC, such as eribulin, capecitabine and vinorelbine.

If **visceral crisis**, combination therapy may be preferred (i.e. taxane- or anthracycline-based combination, if not used previously in the [neo]adjuvant setting or DFI ≥ 12 months) but mono ChT is also an option; in case of liver visceral crisis, carboplatin monotherapy is one of the best options.

Following the resection of an isolated locoregional recurrence, adjuvant ChT can be considered.

Maintenance therapy in mTNBC is debated as no phase III study has specifically addressed the issue, though immune checkpoint inhibitors (ICIs) may be acceptable.



CI, confidence interval; HR, hazard ratio; mPFS, median PFS; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

REVISION QUESTIONS

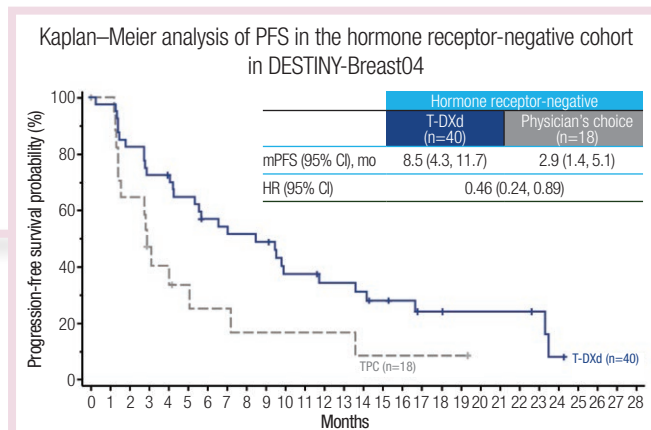
- Which factors should be considered in treatment allocation in case of PD-L1-negative and *gBRCA*-wt mTNBC?
- True or false: sequential monotherapy use of cytotoxic agents is preferred in the vast majority of cases.
- What are the best treatment options for later lines?

Emerging treatment options and investigational agents

Trastuzumab deruxtecan (T-DXd) is an option for HER2-low MBC after prior ChT in the metastatic setting, or if recurrence during adjuvant ChT or within 6 months of its completion.

Although only 58 patients included in the DESTINY-Breast04 trial had hormone receptor-negative disease, PFS was 8.5 months in the T-DXd group and 2.9 months in the physician's choice group (HR 0.46).

In general, treatment for mTNBC should be continued until best response, disease progression or when toxicity requires discontinuation of treatment.



CI, confidence interval; HR, hazard ratio; mo, months; mPFS, median PFS; n, number of patients; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Fig. 10.13

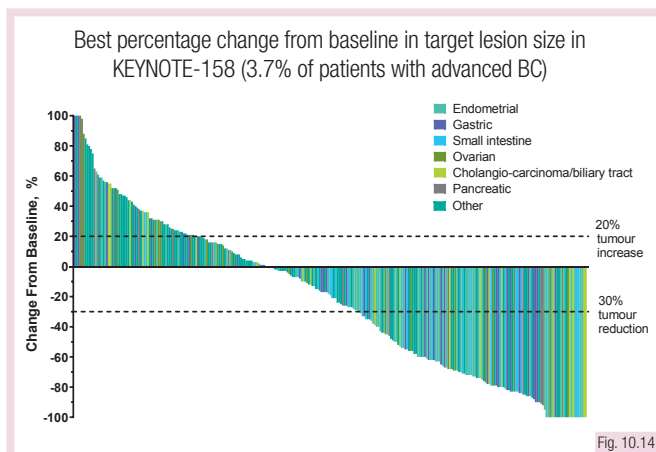


Fig. 10.14

BC, breast cancer.

Investigational approaches include combinations of ICI-antibody–drug conjugates (ADCs), bispecific antibodies, next-generation ADCs and new immune targets.

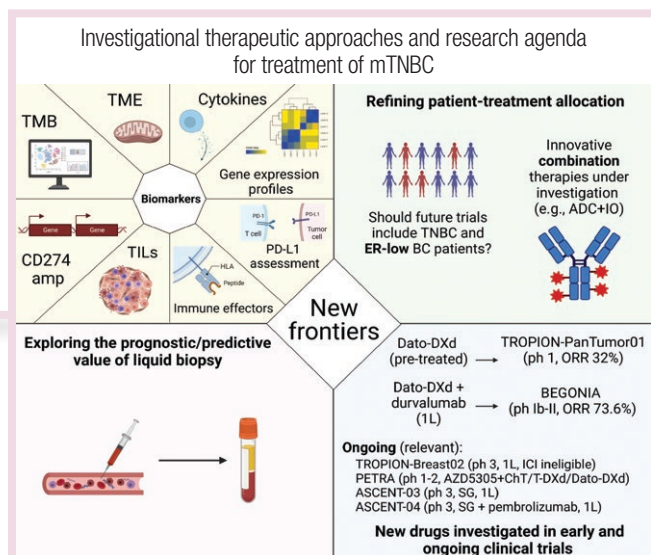
mTNBC with brain metastases has a dismal prognosis. Systemic therapies with improved intracranial activity are urgently needed for these patients.

The prognostic/predictive role of liquid biopsies (e.g. circulating tumour cells, circulating tumour DNA) is promising, although experimental.

No data supports routine use of anti-androgen therapy, inhibitors targeting phosphoinositide 3-kinase (PI3K) or AKT for mTNBC outside clinical trials.

If ChT pretreated ICI-naïve, pembrolizumab is an option in microsatellite instability-high/mismatch repair-deficient/high tumour mutational burden mTNBC.

For patients with tropomyosin receptor kinase (TRK)-positive cancers progressing on other treatments, TRK inhibitors (entrectinib, larotrectinib) are an option.



ADC, antibody–drug conjugate; amp, amplification; BC, breast cancer; CD, cluster of differentiation; ChT, chemotherapy; Dato-DXd, datopotamab deruxtecan; ER, oestrogen receptor; HLA, human leukocyte antigen; ICI, immune checkpoint inhibitor; IO, immunotherapy; L, treatment line; mTNBC, metastatic TNBC; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ph, phase; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TIL, tumour-infiltrating lymphocyte; TMB, tumour mutational burden; TME, tumour microenvironment; TNBC, triple-negative breast cancer.

Fig. 10.15

REVISION QUESTIONS

1. Which are the most clinically relevant tumour agnostic biomarkers in mTNBC?
2. Are there specific systemic treatments for mTNBC with brain metastases?
3. Is there a role for liquid biopsies in mTNBC in current clinical practice?

Summary: Metastatic triple-negative breast cancer: systemic therapy

- TNBC is defined by <1% expression of ER, PgR by IHC and either 0 to 1+ expression of HER2 by IHC, or IHC 2+ and ISH not amplified
- Median OS from onset of metastases is <18 months; there has been no improvement in outcomes in almost a decade
- First-line treatment:
 - If PD-L1-positive, the preferred option is ChT in combination with pembrolizumab
 - If gBRCAm and PD-L1-negative, the preferred options are olaparib, talazoparib or ChT with carboplatin
 - If PD-L1-negative gBRCA-wt, best options depend on previous treatments, disease presentation, DFI and patient considerations
- Later lines:
 - SG is the preferred treatment option, especially in patients who have received two or more prior systemic therapies, including at least one for advanced disease
 - T-DXd is an option for HER2-low patients
 - After progression on SG, single-agent ChT is indicated
- If visceral crisis, combination therapy may be preferred (i.e. taxane or anthracycline-based combination, if not used previously in the (neo)adjuvant setting or DFI ≥12 months) but mono-ChT is also an option; in case of liver visceral crisis, carboplatin monotherapy is one of the best options
- Investigational approaches include ICI–ADC combinations, bispecific antibodies, next-generation ADCs and new immune targets

Further Reading

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Image sources: **Fig. 10.1.** courtesy of the authors (created with BioRender); **10.2.** Grinda T, et al. *ESMO Open* 2021;6:100114; **10.3.** adapted from Bianchini G, et al. *Nat Rev Clin Oncol* 2022;19:91–113 (created with BioRender); **10.4.** Cortés J, et al. *N Engl J Med* 2022;387:217–226; **10.5.** Schmid P, et al. *N Engl J Med* 2018;379:2108–2121; **10.6.** courtesy of Dieci MV, Guarneri V; **10.7.** courtesy of the authors (created with BioRender); **10.8.** Robson M, et al. *N Engl J Med* 2017;377:523–533; **10.9.** adapted from Litton JK, et al. *N Engl J Med* 2018;379:753–763; **10.10.** Tutt A, et al. *Nat Med* 2018;24:628–637; **10.11.** adapted from Gennari A, et al. *Ann Oncol* 2021;32:1475–1495; **10.12.** Bardia A, et al. *J Clin Oncol* 2024;42:1738–1744; **10.13.** Modi S, et al. *N Engl J Med* 2022;387:9–20 (supplementary data); **10.14.** Maio M, et al. *Ann Oncol* 2022;33:929–938; **10.15.** adapted from Tarantino P et al. *NPJ Breast Cancer* 2022;8:23 (created with BioRender).

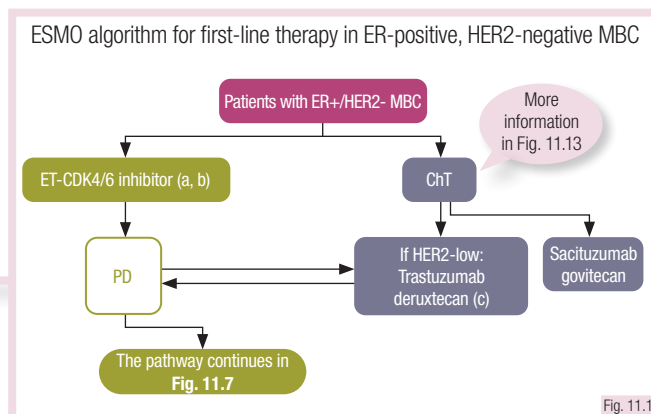
11 Metastatic ER-positive, HER2-negative breast cancer: systemic therapy

Treatment basics

Oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC) is the breast cancer (BC) subtype that has seen the **most substantial improvement in therapy over the last 10 years**.

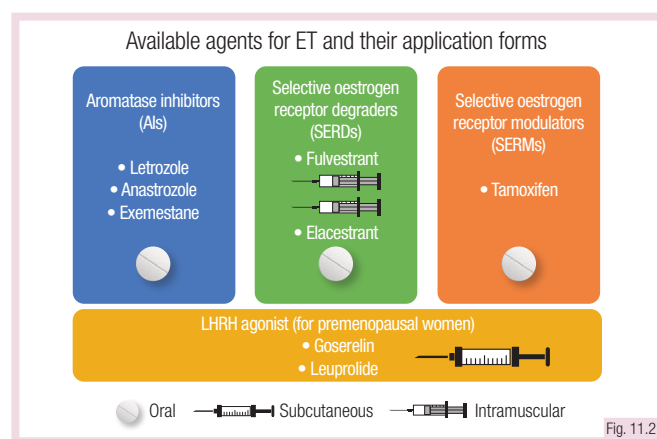
The preferred treatment strategy is **anti-hormonal** with endocrine therapy (ET) in combination with targeted agents ('endocrine-based'), and mostly **orally-administered therapy** from first line onwards for as long as possible.

Chemotherapy (ChT) is reserved for selected cases, mainly after endocrine resistance in later therapy lines or in the situation of imminent organ failure.



(a) OFS if the patient is premenopausal. (b) If relapse <12 months after end of adjuvant AI: fulvestrant-CDK4/6 inhibitor (a); if relapse >12 months after end of adjuvant AI: AI-CDK4/6 inhibitor (a). (c) Trastuzumab deruxtecan can also be given following adjuvant ChT in the setting of fast progression (DESTINY-Breast04/EMA indication).

+, positive; -, negative; AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; ChT, chemotherapy; EMA, European Medicines Agency; ER, oestrogen receptor; ESMO, European Society for Medical Oncology; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; OFS, ovarian function suppression; PD, progressive disease.



ET, endocrine therapy; LHRH, luteinising hormone-releasing hormone.

ET (either as monotherapy or as a backbone of an endocrine-based therapy) consists of an **aromatase inhibitor (AI)**, **tamoxifen** or a **selective ER degrader (SERD)**.

Premenopausal women should additionally receive **ovarian function suppression** either with a luteinising hormone-releasing hormone (LHRH) agonist or by oophorectomy.

After progression under an ET or endocrine-based therapy, the **endocrine backbone should be switched** from second line onwards (e.g. from one AI to another AI, to tamoxifen or to a SERD).

From second line onwards, analysis of germline *BRCA* (*gBRCA*) status and *PIK3CA* status are standard to select appropriate therapy options.

New biomarkers include oestrogen receptor 1 (*ESR1*) mutations, partner and localiser of *BRCA2* (*PALB2*) mutation, further alterations in the *AKT* pathway and the sub-categories of **HER2-negative** and **HER2-low**.

In further therapy lines, **genetic profiling** (tumour/liquid biopsy) might open new therapy options.

Established and emerging targetable biomarkers and required tissue for analysis according to approval status		
ANALYSED IN LIQUID BIOPSY	ANALYSED ON TUMOUR	
- Somatic <i>ESR1</i> mutation - Germline <i>BRCA1/2</i> and <i>PALB2</i> mutation	- HER2 sub-category - Low (IHC 1+ or 2+ and FISH/CISH-negative) - Somatic alterations in the AKT pathway <i>PIK3CA</i> <i>AKT1</i> <i>PTEN</i>	
	IN ADVANCED THERAPY LINE: Tumour profiling (NGS)	

CISH, chromogenic in situ hybridisation; ESR1, oestrogen receptor 1; FISH, fluorescent in situ hybridisation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NGS, next-generation sequencing; PALB2, partner and localiser of *BRCA2*; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homologue.

Fig. 11.3

REVISION QUESTIONS

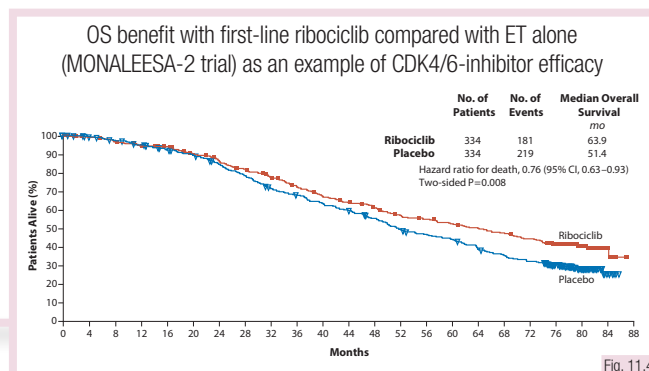
1. What is the basic therapy concept in ER-positive, HER2-negative MBC?
2. Which agents can be used for ET?
3. Which biomarkers should be assessed from second line onwards?

Standard-of-care first-line treatment

Standard first-line treatment is the combination of ET with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i): abemaciclib, palbociclib or ribociclib.

All three agents have shown a significant prolongation of progression-free survival (PFS) in large phase III trials (hazard ratio [HR] ~0.50) compared with ET alone, while maintaining or improving quality of life.

So far, only ribociclib has shown a significant overall survival (OS) benefit (HR ~0.70) in all trials, while abemaciclib improved OS significantly only in later lines (HR 0.76). First-line OS was only numerically improved by abemaciclib.



CI, confidence interval; CDK4/6, cyclin-dependent kinase 4/6; ET, endocrine therapy; OS, overall survival.

One cycle of endocrine-based therapy with a CDK4/6i in combination with ET

	Week 1	Week 2	Week 3	Week 4
Palbociclib 125 mg (100 mg→75 mg)* or ribociclib 600 mg (400 mg→200 mg)*	Daily	Daily	Daily	Pause
Abemaciclib 150 mg (100 mg→50 mg)*	Daily	Daily	Daily	Daily
AI (if MBC is diagnosed at least 12 months after completed adjuvant AI)	Daily	Daily	Daily	Daily
Fulvestrant	Once		**	
LHRH agonist in premenopausal women	Once			

*Dose reduction in case of side effects possible **Additional dose only in the first cycles

Oral Subcutaneous Intramuscular

Fig. 11.5

AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; LHRH, luteinising hormone-releasing hormone; MBC, metastatic breast cancer.

Oral CDK4/6i therapy takes place at a patient's home (which helps them to be independent) but should be accompanied with sufficient patient education and the required control examinations.

The most relevant severe side effects of palbociclib/ribociclib are neutropenia (despite grade 3/4 rates of >60%, febrile neutropenia is very rare [1%]) and fatigue. Ribociclib leads to the highest rates of abnormal liver function among all CDK4/6is and may additionally lead to QT time prolongation.

Patients treated with abemaciclib mainly experience clinically relevant diarrhoea (especially at the beginning of treatment), abnormal liver function, nausea and fatigue, but less haematotoxicity.

CDK4/6is differ in their dosing schemes, side effects and therapy management; detailed information including agent-specific features can be found in the prescribing information.

Palbociclib and ribociclib must be taken once daily for 21 consecutive days followed by 7 days off treatment, while abemaciclib is taken twice daily continuously.

In case of side effects, the medication should be paused and can be reduced according to the prescribing information.

Recommended therapy monitoring for CDK4/6is

	Month 1	Month 2	Month 3 and later
Palbociclib	CBC x 2	CBC x 2	CBC x 1
Ribociclib	CBC x 2 LF test x 2 ECG and electrolytes x 2	CBC x 2 LF test x 2 ECG and electrolytes x 1	Monthly CBC and LF test for 4 months
Abemaciclib	CBC x 2 LF test x 2 Monitor closely for diarrhoea*	CBC x 2 LF test x 2 Monitor closely for diarrhoea*	Monthly CBC and LF test for 2 months Monitor closely for diarrhoea*

All substances

- Additional controls of all parameters might be required as clinically indicated (e.g. in case of side effects, refer to prescribing information for details)
- Every visit: clinical examination, check self-medication including complementary medications for potential interactions, ask for side effects

*Use loperamide at first sign of loose stools.

CBC, complete blood count; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECG, electrocardiogram; LF, liver function.

Fig. 11.6

REVISION QUESTIONS

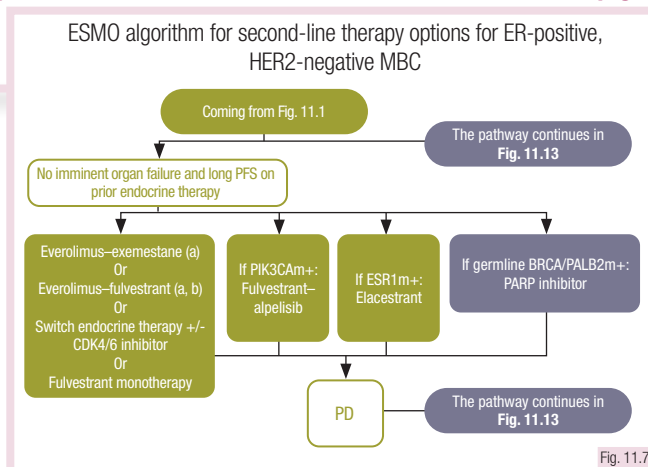
- How can the clinical efficacy of CDK4/6is be described?
- Which schedules should the intake of CDK4/6is follow in clinical practice?
- What are the main side effects of the individual CDK4/6is?

Second-line treatment and beyond – Oral systemic therapies (PARP inhibitors) and biomarker-independent endocrine-based therapy

The optimal therapy sequence from second line onwards is uncertain, especially as there are little data about efficacy after pretreatment with a CDK4/6i and sequencing of available options.

The expression of biomarkers, prior therapies, duration of response, disease burden, patient preference and potential trial options should therefore be considered.

Generally, the continuation of an oral therapy with agents not previously used may help delay the use of intravenous ChT.



(a) OFS if the patient is premenopausal. (b) Preferred if the patient is ESR1 mutation-positive. CDK4/6, cyclin-dependent kinase 4/6; ER, oestrogen receptor; ESMO, European Society for Medical Oncology; ESR1, oestrogen receptor 1; HER2, human epidermal growth factor receptor 2; m, mutation; m+, mutation-positive; MBC, metastatic breast cancer; OFS, ovarian function suppression; PALB2, partner and localiser of BRCA2; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; PFS, progression-free survival; PIK3CA, phosphoinositide 3-kinase catalytic subunit alpha.

Efficacy of PARP inhibitors in gBRCA-mutated MBC

Olaparib (OlympiAD trial)	Talazoparib (EMBRACA trial)
• PFS: +2.8 months (HR 0.58), significant • OS: +2.2 months (HR 0.89), not significant • OS, when used in first-line: +7.9 months (HR 0.55), significant	• PFS: +3 months (HR 0.54), significant • OS: -0.2 months (HR 0.85), not significant

Fig. 11.8

g, germline; HR, hazard ratio; MBC, metastatic breast cancer; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival.

Poly (ADP-ribose) polymerase inhibitors (PARPis; olaparib or talazoparib) lead to a PFS benefit (HR 0.58 with olaparib, 0.54 with talazoparib) compared with mono-ChT in patients with gBRCA1/2 mutations.

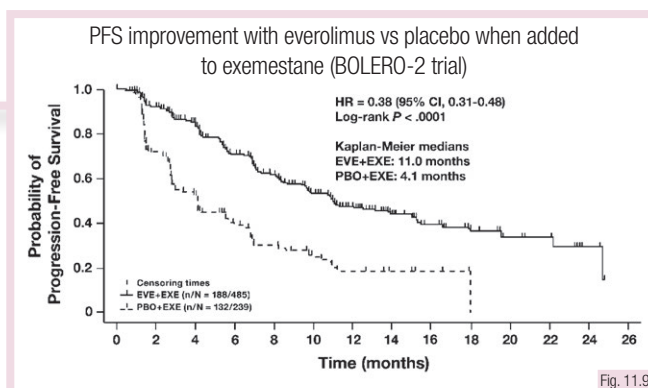
PARPis should be used as early as possible in the therapy sequence, as an exploratory analysis of olaparib has shown OS benefit (HR 0.55) when used in first line but not in later lines.

PARPis provide a better quality of life than ChT. Their main side effects, anaemia, neutropenia, gastrointestinal side effects and fatigue, can be monitored with laboratory controls and managed with dose de-escalation.

The combination of exemestane with the mammalian target of rapamycin (mTOR) inhibitor everolimus is an option that has been shown to prolong PFS (HR 0.38) but not OS, when compared with ET alone.

It does not require a specific biomarker, but in case of known ESR1 mutation, substituting exemestane with fulvestrant should be considered (off-label).

The most clinically relevant side effects of everolimus include stomatitis, anaemia, hyperglycaemia, dyspnoea and fatigue. An active prophylaxis of stomatitis with steroid mouthwashes or a dose reduction may be necessary.



CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.

REVISION QUESTIONS

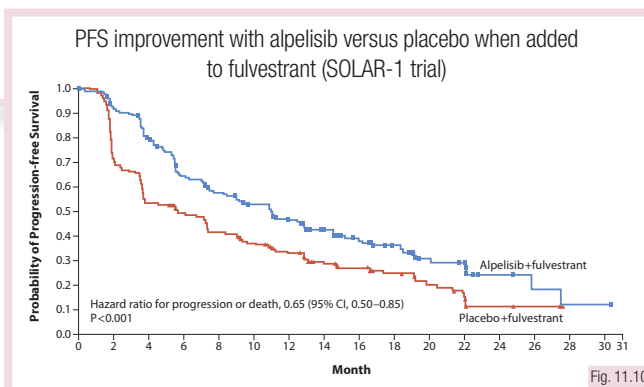
1. Which factors should be considered when choosing second-line treatment?
2. Which targeted therapy can be used for gBRCA1/2 mutation carriers?
3. What are the main side effects of everolimus?

Second-line treatment and beyond – Biomarker-driven endocrine-based therapies

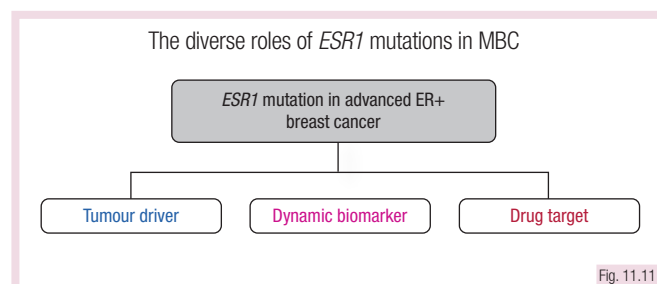
Patients with a *PIK3CA* mutation have a significant PFS benefit (HR 0.65) but no OS benefit with the phosphoinositide 3-kinase (PI3K) inhibitor **alpelisib** in combination with **fulvestrant**, even after pretreatment with a CDK4/6i.

Alpelisib has substantial toxicity (**hyperglycaemia**, **rash**, **gastrointestinal side effects**), which makes patient selection crucial and close patient management and early intervention necessary.

Although alpelisib is approved by the European Medicines Agency (EMA), it is no longer available in some countries and **must be ordered internationally**.



CI, confidence interval; PFS, progression-free survival.



ER+, oestrogen receptor-positive; *ESR1*, oestrogen receptor 1; MBC, metastatic breast cancer.

Tumour *ESR1* mutations are generally acquired from AI treatment as a mechanism of **endocrine resistance**, and therefore in subsequent therapy lines an AI is not the option of choice.

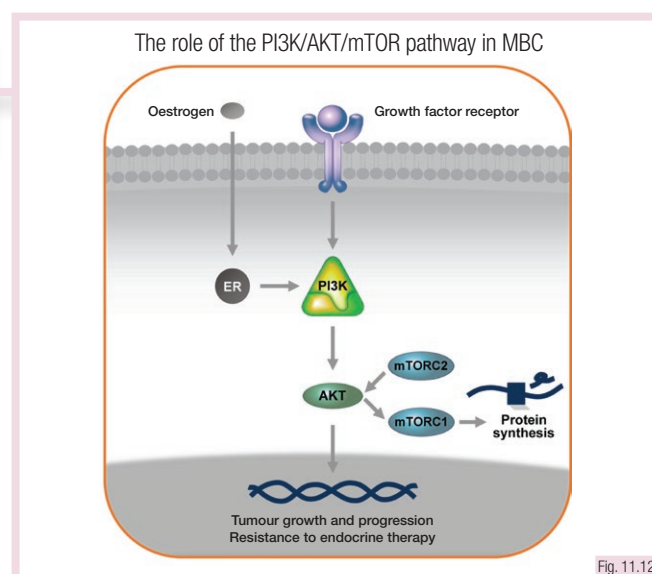
New oral SERDs, such as **elacestrant**, led to a PFS benefit (HR 0.55) compared with other ETs in patients with a tumour *ESR1* mutation (EMERALD trial).

Elacestrant has been **recently approved by the EMA** – the approval requires *ESR1*-mutation testing in a liquid biopsy (circulating tumour DNA).

Recent studies have evaluated **new targets** (especially in the context of pretreatment with a CDK4/6i), deriving from pathways identified as being essential for tumour progression and endocrine resistance.

The AKT inhibitor **capivasertib** led to a PFS improvement (HR 0.60) in combination with fulvestrant, especially, but not only, in tumours carrying AKT pathway alterations (CAPItello-291 trial).

Capivasertib has since received Food and Drug Administration (FDA) and EMA approval for tumours harbouring one or more *PIK3CA*, *AKT1* or *PTEN* (phosphatase and tensin homologue) alterations.



ER, oestrogen receptor; MBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase.

REVISION QUESTIONS

1. Which therapy is possible in the case of a *PIK3CA* tumour mutation?
2. What are the mechanistic and therapeutic roles of *ESR1* in MBC?
3. Which new therapy targets the AKT pathway in MBC?

Third-line treatment and beyond – ChT and new ADCs

Treatment options for patients with endocrine resistance, who have already been treated with targeted agents, or for patients with imminent organ failure, include **ChT** or antibody–drug conjugates (**ADCs**).

ADCs consist of a **monoclonal antibody** (e.g. trastuzumab deruxtecan [T-DXd]; anti-HER2 or sacituzumab govitecan [SG]; anti-trophoblast cell surface antigen 2 [Trop-2]) linked to several **ChT** molecules.

The chosen agent should generally be **continued until disease progression or intolerable toxicity** (except anthracyclines, due to a cumulative maximum dose).

Systemic treatment options in ER-positive, HER2-negative MBC

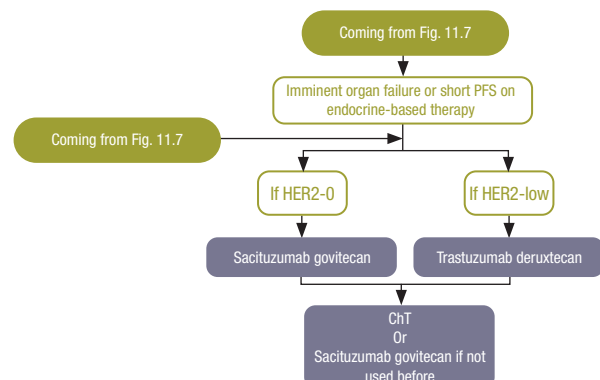


Fig. 11.13

ChT, chemotherapy; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; PFS, progression-free survival.

General and specific toxicities of systemic treatments

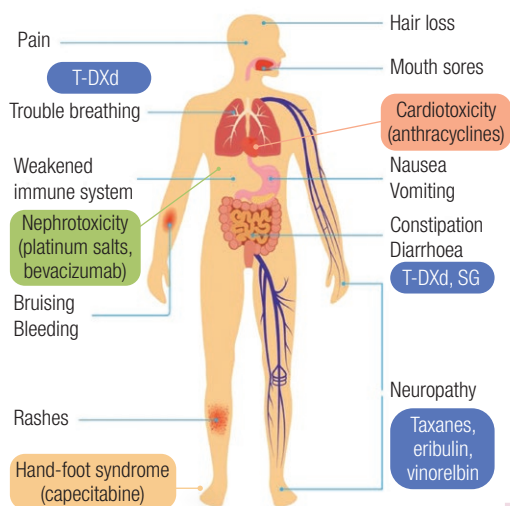


Fig. 11.14

SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan.

The optimal ChT sequence has not been established yet, but **sequential single-agent therapy** is preferred over combination therapies, particularly in the second line and beyond.

Taxanes and anthracyclines (free or liposomal) are highly effective and can be used if patients never received these agents before, or if the time since last use is more than 12 months.

Capecitabine, eribulin, vinorelbine and platinum salts are further treatment options, and for first-line ChT, the combination of bevacizumab and a taxane or capecitabine is approved in some countries.

For patients with HER2-low MBC who have received more than one line of ChT for MBC or with disease relapse <6 months after adjuvant ChT, T-DXd has been shown to **prolong PFS** (HR 0.50) and **OS** (HR 0.64) compared with mono-ChT and is EMA-approved.

SG led to a significant benefit in **PFS** (HR 0.66) and **OS** (HR 0.79) in ER-positive, HER2-negative MBC, and has recently been approved as treatment for the luminal subtype by the FDA and the EMA.

Patients receiving SG must have **had at least two prior lines of ChT for MBC** (or one if disease progressed ≤12 months after [neo]adjuvant therapy) and at least one prior taxane, CDK4/6i and ET (TROPICS-02 trial).

OS for T-DXd compared with ChT of physicians' choice: DESTINY-Breast04

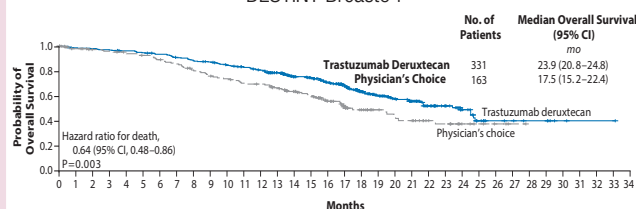


Fig. 11.15

ChT, chemotherapy; CI, confidence interval; mo, months; OS, overall survival; T-DXd, trastuzumab deruxtecan.

REVISION QUESTIONS

1. Which systemic therapy options for third-line therapy and beyond exist for patients with ER-positive, HER2-negative MBC?
2. Which ChT agents are the most effective in BC?
3. What is the role of the new ADCs in ER-positive, HER2-negative MBC?

Summary: Metastatic ER-positive, HER2-negative breast cancer: systemic therapy

- Standard-of-care first-line treatment in ER-positive, HER2-negative MBC consists of a CDK4/6i combined with an endocrine agent (AI or fulvestrant or tamoxifen [except with ribociclib])
- From second line onwards, therapy decisions are biomarker driven; *gBRCA*, *PIK3CA*, *ESR1* mutations and further AKT pathway alterations are considered relevant biomarkers at present
- In *gBRCA1/2* mutation carriers, PARPi monotherapy with olaparib or talazoparib is effective
- The combination of exemestane and everolimus is an effective endocrine-based therapy in the second line which does not require any specific biomarker
- Patients who harbour a tumour *PIK3CA* mutation can be treated with the combination of alpelisib and fulvestrant, and AKT pathway alterations qualify for capivasertib and fulvestrant (FDA- and EMA-approved)
- Tumour *ESR1* mutation is an emerging biomarker which can explain resistance to AIs and the presence of a mutation is required (testing in a liquid biopsy) for the use of elacestrant
- ChT should be reserved for later therapy lines or conditions with imminent organ failure
- ChT should be used as sequential single-agent therapy; anthracyclines and taxanes are the most effective ChT agents in BC (in MBC, depending on previous exposure)
- The new ADCs T-DXd (in HER2-low MBC) and SG show improved survival outcomes in later lines, and both have been recently approved by EMA in this indication
- Choosing the optimal treatment sequence, considering the individual situation, prior therapies and biomarkers, requires high expertise and interdisciplinarity to enable long survival periods for many patients

Further Reading

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Image sources: Fig. 11.1, 11.7, 11.13. adapted from Curigliano G, et al, on behalf of the Clinical Practice Guideline author group. ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023. *Ann Oncol* 2021;32:1475-1495; 11.4. Hortobagyi GN, et al. *N Engl J Med* 2022;386:942-950; 11.8. prepared by authors based on: Robson M, et al. *N Engl J Med* 2017;377:523-533. Litton JK, et al. *Ann Oncol* 2020;31:1526-1535. Robson ME, et al. *Eur J Cancer* 2023;184:39-47; 11.9. Yardley DA, et al. *Adv Ther* 2013;30:870-884; 11.10. André F, et al. *N Engl J Med* 2019;380:1929-1940; 11.11. adapted from Grinshpun A, et al. *Biochim Biophys Acta Rev Cancer* 2023;1878:188830; 11.12. Nunnery SE, Mayer IA. *Drugs* 2020;80:1685-1697; 11.14. adapted from <https://www.medicalnewstoday.com/articles/323485#bruising-and-bleeding>; 11.15. Modi S, et al. *N Engl J Med* 2022;387:9-20. All other figures courtesy of the authors.

More advanced knowledge

Distribution and trends

Breast cancer (BC) is the **second most common malignant tumour**. In 2022, there were almost 2.3 million new cases worldwide (24% of all female cancers), and more than 557 500 in Europe (26% of all female cancers).

The **incidence** of BC has been rising since 2007, and the **number of new cases is set to increase substantially** in the coming years.

This increase may be even greater if considering expected changes in **reproductive factors**, the **obesity epidemic**, **physical inactivity** and increased detection through **screening** in the coming years.

Age-standardised 5-year net survival for women (15–99 years) diagnosed with BC in European countries (2010–2014)

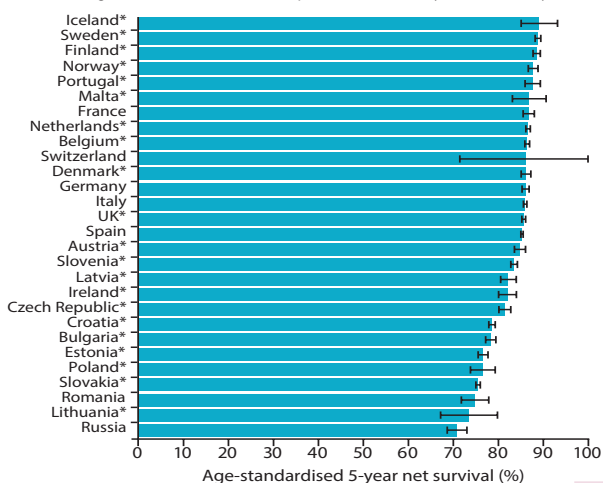


Fig. 12.2

BC, Breast cancer.

Incidence rates are higher in northern and western Europe and considerably lower in eastern Europe, related to differences in screening and prevalence of risk factors and competing risks of death.

Premenopausal mortality rates are slightly higher in **eastern European countries** (3.6/100 000 women/year), while in **women >50 years of age** mortality rates are higher in **western Europe** (62.7/100 000 women/year).

By **reducing modifiable cancer risk factors**, 238 000 BC cases in Europe (28% of all avoidable cancer cases) **could have been avoided** in 2020, and 21 000 BC deaths in 2021.

Estimated number of new female BC cases (in thousands) in Europe (2022–2045)

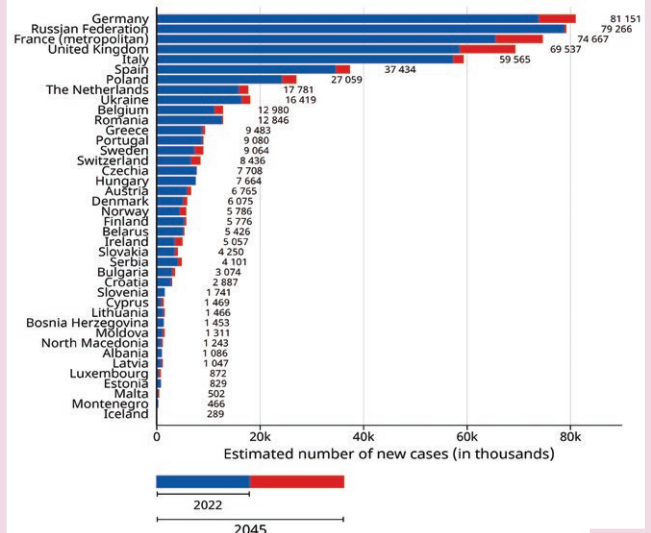


Fig. 12.1

BC, breast cancer.

BC is the **leading cause of cancer death** in women, accounting for 15% of all female cancer deaths worldwide, and >144 000 deaths (16%) in Europe in 2022.

Although **mortality rates have declined** due to better treatment and earlier diagnosis, the ageing of the European population will translate into an absolute **increase in the number of BC deaths** by 2040.

Five-year relative survival rates have improved in Europe, **exceeding 80%** (period 2010–2014), except in some eastern European countries (e.g. Russia and Lithuania).

Estimated age-standardised incidence rates of BC in 2022, females, all ages, Europe

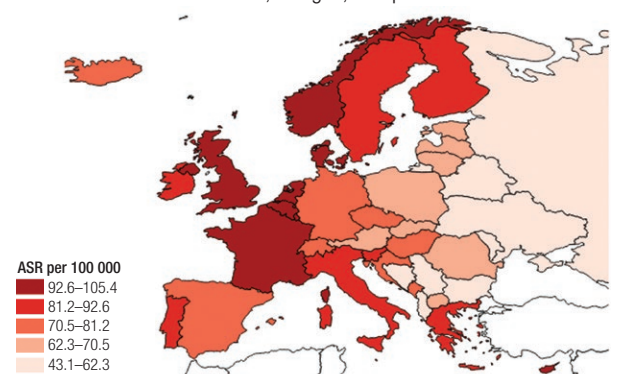


Fig. 12.3

ASR, age-standardised rate; BC, breast cancer.

REVISION QUESTIONS

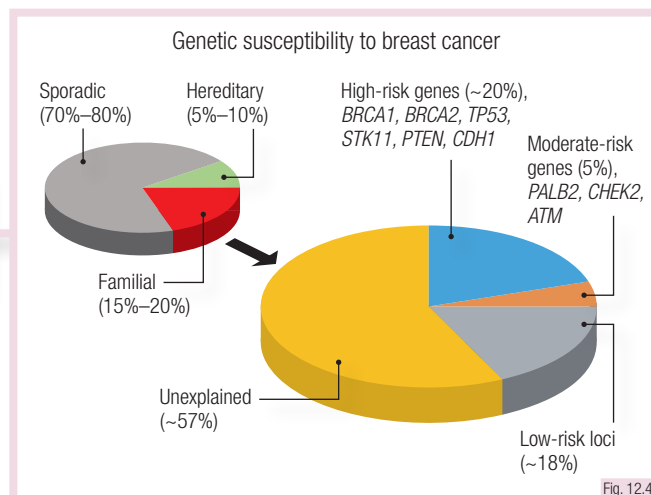
1. Why is BC a public health concern?
2. Is BC a disease of older women?
3. Is there a geographical pattern in BC incidence and mortality?

Main risk factors

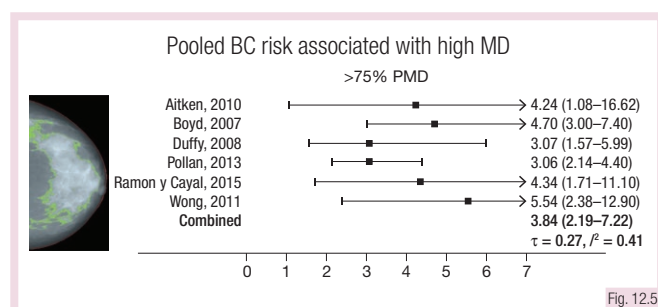
Family history is a **major risk factor** for BC. The risk is greater if the affected relative was diagnosed at a young age and/or is female and increases with the number of affected first-degree relatives.

Although most BC cases are sporadic, **mutations in high-penetrance genes** such as *BRCA1/2* and others explain around 5%–10% of all female BCs, and 15%–20% of all familial BCs.

The cumulative risk of carrying common **low-penetrance genetic variants** also modulates the probability of developing BC. More than 300 low-risk gene loci have been identified so far.



ATM, ataxia telangiectasia mutated; CDH1, cadherin 1; CHEK2, checkpoint kinase 2; PALB2, partner and localiser of BRCA2; PTEN, phosphatase and tensin homologue; STK11, serine/threonine kinase 11; TP53, tumour protein 53.



BC, breast cancer; MD, mammographic density; PMD, percentage of MD.

Women with BC have a higher risk of developing a second primary BC. **Benign breast diseases**, such as atypical hyperplasia or lobular carcinoma *in situ*, also pose **higher BC risk**.

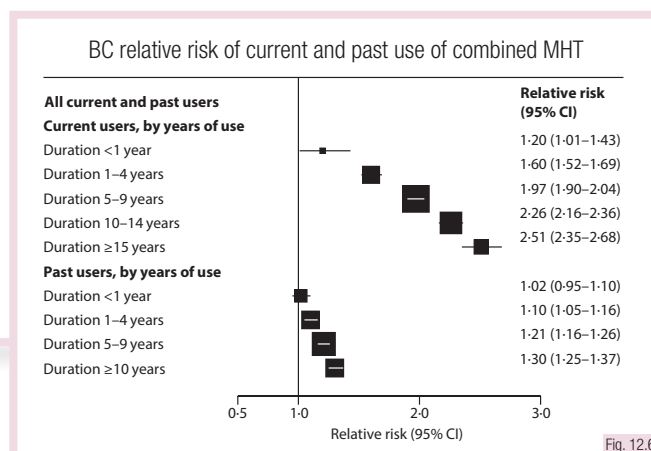
Mammographic density (MD), the ratio of fibroglandular to fatty tissue in the breast, is an intermediate phenotype in BC research and a **strong predictor of BC risk**.

Despite having a hereditary component, **high MD** is related to **young age**, **low body mass index (BMI)** and hormone levels and improves the accuracy of BC risk-prediction models.

Early menarche and/or **late menopause** are associated with an increased BC risk. Premenopausal women have a higher risk than postmenopausal women of the same age.

Multiparity (>3 children), **early pregnancy** (<30 years) and **prolonged breastfeeding** (2% risk reduction for every 5 months) have a **protective effect** against BC.

Long-term use of **combined hormonal therapy** increases BC risk, persisting for more than 10 years. Current and recent use of oral contraceptives also causes a small risk increase.



BC, breast cancer; CI, confidence interval; MHT, menopausal hormone therapy.

REVISION QUESTIONS

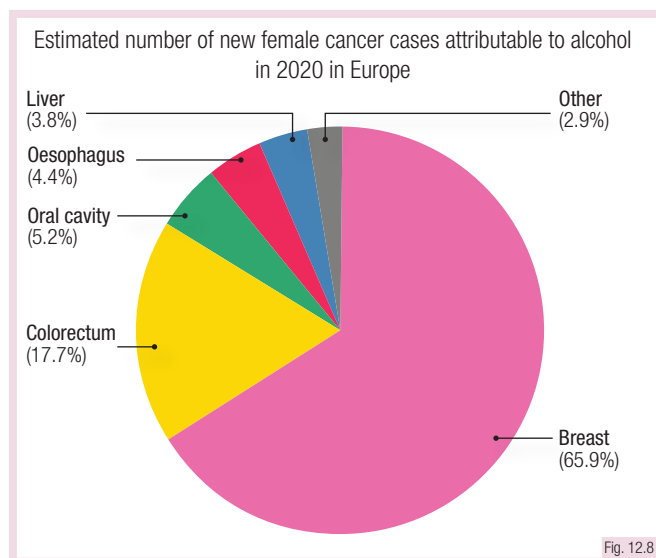
1. What kind of genetic variants play a role in BC?
2. What is MD?
3. Are both endogenous and exogenous hormones related to BC aetiology?

Lifestyle and environmental factors

Obesity, abdominal fatness and adult weight gain are convincing causes of postmenopausal BC. However, body fatness is thought to protect against premenopausal BC.

Developmental factors leading to adult-attained height are a convincing cause of BC. There may also be a relationship between higher birthweight and increased BC risk in premenopausal women.

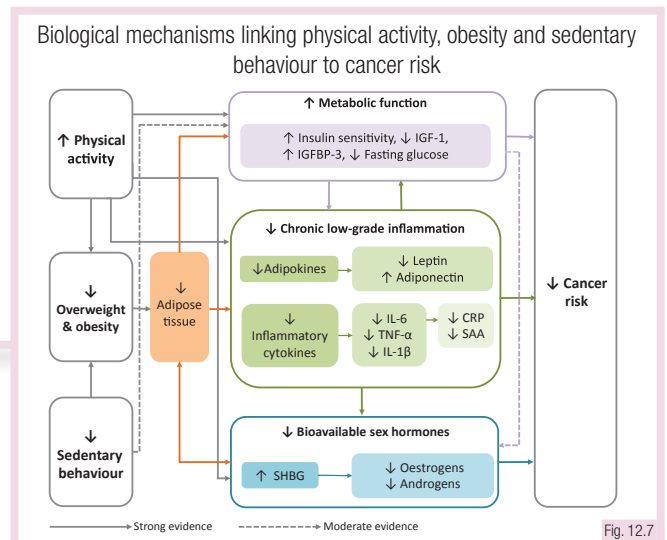
The most physically active women have a 12%–21% lower BC risk than the least active women. Only vigorous intensity physical activities appear to protect against premenopausal BC.



Exposure to ionising radiation, particularly before age 30, is an established carcinogen and increases BC risk even at low doses.

Night-shift work is linked to increased BC risk. The influence of some chemicals (i.e. endocrine disruptors or polycyclic aromatic hydrocarbons) is less conclusive.

Observing the Cancer Prevention Recommendations proposed by the World Cancer Research Fund International and the European Code Against Cancer can help to reduce BC risk.



CRP, C-reactive protein; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; IL-1β, interleukin-1 beta; IL-6, interleukin-6; SAA, serum amyloid A; SHBG, sex hormone-binding globulin; TNF-α, tumour necrosis factor alpha.

Alcohol consumption is a strong BC risk factor with a dose-response relationship. It causes 7% of all new BC cases in Europe, and, due to BC frequency, BC accounts for almost 66% of all alcohol-attributable cancers among women.

The consumption of non-starchy vegetables and foods rich in carotenoids or calcium is thought to decrease BC risk. A 'Mediterranean style' diet has a beneficial effect.

Smoking increases BC risk, particularly among women who smoked for longer periods, with greater intensity, and among those who started smoking before their first full-term pregnancy.



REVISION QUESTIONS

1. What are the biological pathways that link obesity and physical activity with BC risk?
2. Why is time of exposure so important for several BC risk factors?
3. What recommendations related to lifestyle can we give to women who want to reduce their BC risk?

Summary: Epidemiology of breast cancer

- BC is the second most common malignant tumour and the leading cause of cancer death in women, worldwide
- The number of new BC cases and BC deaths in Europe is expected to increase in the near future
- Incidence and mortality rates are higher in western European countries, due to a higher prevalence of unhealthy lifestyles or delays in diagnosis and treatment
- Although most BC cases are sporadic, family history is an important BC risk factor. Some rare high-penetrance gene mutations cause high BC risk, while more common variants confer a small risk
- MD is an intermediate phenotype in BC and a strong predictor of BC risk. It can be influenced by age, BMI and hormonal factors
- Prolonged reproductive period, combined hormonal therapy and oral contraceptives are BC risk factors. Breastfeeding, multiparity and early pregnancy are protective factors
- Body fatness in adulthood is a convincing cause of postmenopausal BC but probably protects against premenopausal BC. Adult-attained height increases BC risk
- Alcohol consumption is a major risk factor for BC. Smoking history, mainly before first full-term pregnancy, is thought to increase BC risk
- Being physically active protects against BC, although evidence for premenopausal women is limited to vigorous physical activity
- Ionising radiation is a strong BC risk factor. Night-shift work seems to increase BC risk. The evidence for other environmental factors is less conclusive

Further Reading

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Image sources: **Fig.12.1, 12.3, 12.8.** International Agency for Research on Cancer (IARC), Lyon, France; 2022; **12.2.** adapted from Allemani C, et al. *Lancet* 2018;391:1023-1075; **12.4.** adapted from Wendt C, Margolin S. *Acta Oncol* 2019;58:135-146; **12.5.** adapted from Bond-Smith D, Stone J. *Cancer Epidemiol Biomarkers Prev* 2019;28:22-31; **12.6.** adapted from Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet* 2019;394:1159-1168; **12.7.** Friedenreich CM, et al. *Mol Oncol* 2021;15:790-800; **12.9.** World Cancer Research Fund/American Institute for Cancer Research, London, UK. Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018. Available at dietandcancerreport.org.

Background and introduction

Approximately 15% of breast cancers (BCs) have a familial background and 5%–10% of BC cases can be linked to a **hereditary cancer** predisposition syndrome.

Hereditary cancers result from a germline **pathogenic variant (PV)** inherited from either parent. The risk of developing BC varies depending on the specific PV.

Familial cancers are characterised by a cluster of cancer cases within a single family, influenced by multiple genetic factors, environmental factors or both.

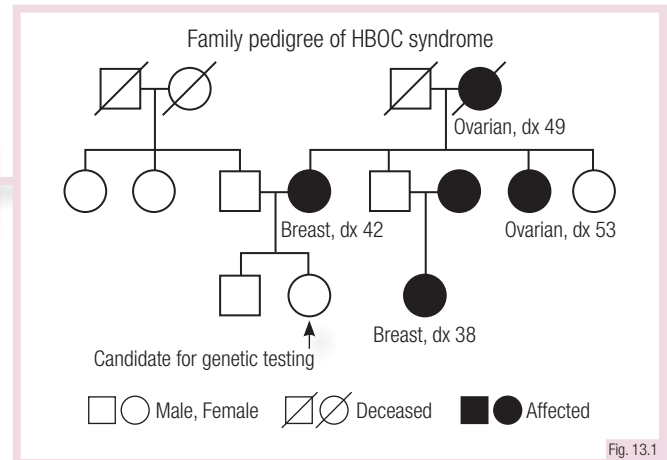


Fig. 13.1

dx, age at diagnosis; HBOC, hereditary breast and ovarian cancer.

Indications for genetic testing

Strong family history of breast, ovarian, pancreatic and/or high-grade/metastatic prostate cancer

Diagnosis of breast cancer before the age of 50

Diagnosis of TNBC before the age of 60

Personal history of ovarian cancer or second breast cancer or male gender

When there are immediate implications for treatment, for example:

- If the patient is eligible for PARPis in the early or advanced setting
- If the patient is <30 years old at diagnosis or personal/family history suggestive of TP53 PV, which is a relative contraindication to radiotherapy

PARPi, poly (ADP-ribose) polymerase inhibitor; PV, pathogenic variant; TNBC, triple-negative breast cancer.

Fig. 13.2

The presence of a **germline PV** has significant implications for therapeutic decisions, risk management for other malignancies and cascade testing for family members.

Genetic counselling and testing should be encouraged whenever there is a suspicion of a hereditary or familial cancer syndrome or immediate clinical implications.

Various models for **pre- and post-test counselling** exist, and should be adapted to comply with local regulations and the resources available.

The use of **multigene assays** is becoming increasingly prevalent. These tests simultaneously analyse a broad set of genes associated with cancer.

If there is a known PV in the family or if the patient has an ethnic background with known prevalent founder mutations, **targeted genetic testing** can be performed.

Germline mutations are found in every cell of the body and are inherited from the parents, whereas **somatic mutations** develop during an individual's lifetime and are limited to specific cells or tissues. Whenever a PV suggestive of a hereditary breast–ovarian cancer (HBOC)-associated syndrome is identified through **tumour genomic testing (somatic mutation)**, germline testing should be conducted to confirm the presence of a hereditary cancer syndrome. Notably, at present, somatic tumour testing does not replace germline testing, and as such the absence of an HBOC-associated PV on somatic testing should not preclude genetic testing.

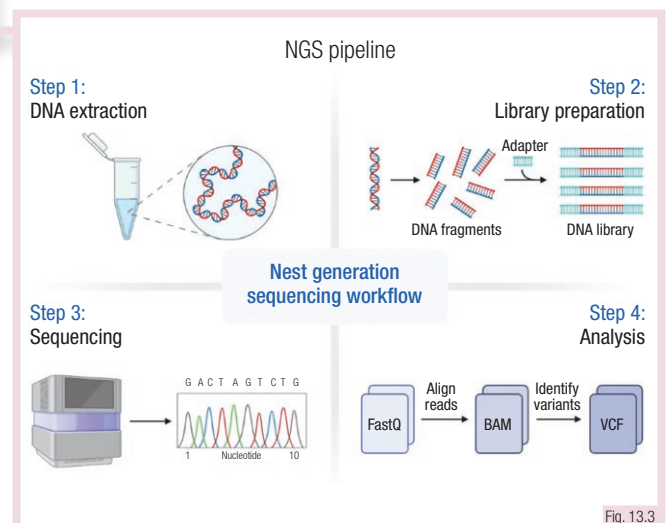


Fig. 13.3

BAM, binary alignment map; NGS, next-generation sequencing; VCF, variant call format.

REVISION QUESTIONS

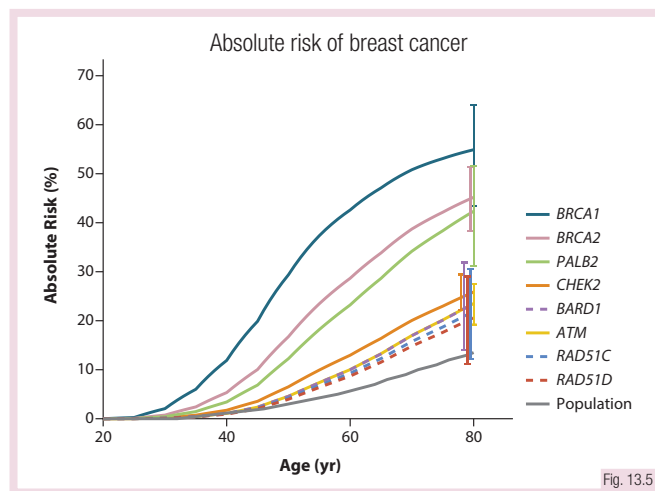
1. What is the difference between hereditary and familial BC?
2. What percentage of BCs is attributed to hereditary cancer syndromes?
3. Who should be referred for genetic counselling and testing?

Genetic counselling and risk management

Genetic testing can yield **positive, indeterminate or negative** results.

Post-test counselling should always be provided and is particularly important, even in the setting of a negative or indeterminate result, especially if there is a significant family cancer history.

In the presence of a positive result, post-test counselling should address **risk management** options for BC and other malignancies and promote **cascade testing**.



ATM, ataxia telangiectasia mutated; CHEK2, checkpoint kinase 2; PALB2, partner and localiser of BRCA2.

Breast **magnetic resonance imaging (MRI)** should be considered the essential component of intensified **screening programmes** and should be performed annually in high-risk individuals.

In the presence of a **BRCA1, BRCA2 or PALB2 PV**, intensified **screening** should start at age 30, or 5 years younger than the age of BC onset in the youngest affected family member.

Risk-reducing mastectomy (RRM) may be considered in unaffected carriers of a high-penetrance PV, depending on their age and individualised risk, and in affected carriers depending on stage of disease.

REVISION QUESTIONS

1. What level of penetrance is defined as 'high risk'?
2. What is the mainstay of screening for BC in individuals with a high-penetrance PV?
3. When should intensified screening commence in individuals with a **BRCA1/2 PV**?

Interpreting results of genetic testing

Result	Action
A positive test Deleterious (pathogenic/likely pathogenic) mutation in a high/moderate-risk gene	Post-test counselling about risk management Cascade family testing
An indeterminate test Variants of unknown significance (VUS) • Deleterious/VUS in a gene of unclear significance • Deleterious variant in a gene unrelated to the specific cancer	Post-test counselling
A negative test No deleterious variant • True negative • False negative/non-informative	Post-test counselling, particularly if there is a significant family history

Fig. 13.4

PVs can be categorised into **moderate-penetrance** (2–4× population risk) genes: ataxia telangiectasia mutated (**ATM**), checkpoint kinase 2 (**CHEK2**) and phosphatase and tensin homologue (**PTEN**), or **high-penetrance** (>4× population risk) genes: **BRCA1, BRCA2**, cadherin 1 (**CDH1**), partner and localiser of **BRCA2 (PALB2)** and **TP53**.

Different genes are associated with different cumulative lifetime disease risks, different age at onset and different **clinical behaviour and phenotypes**, as well as associations with other malignancies.

BRCA1 and BRCA2 PVs significantly **increase the lifetime risk** of ovarian cancer and are also associated with an increased risk for male BC, prostate cancer and pancreatic cancer.

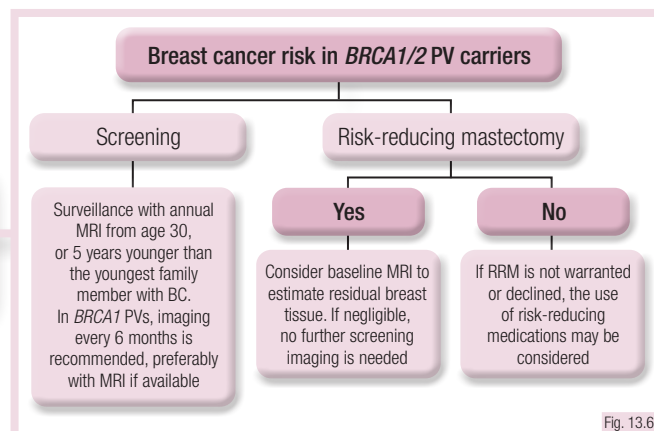


Fig. 13.6

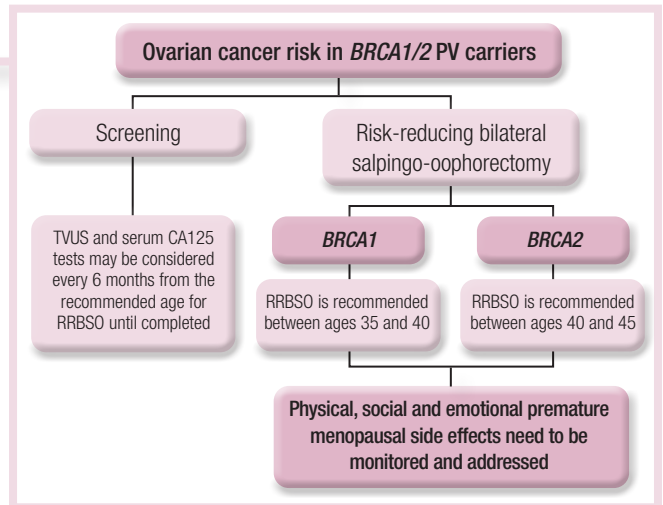
BC, breast cancer; MRI, magnetic resonance imaging; PV, pathogenic variant; RRM, risk-reducing mastectomy.

Risk reduction and therapeutic considerations in hereditary BC

Risk-reducing bilateral salpingo-oophorectomy (RRBSO) is the most effective strategy for ovarian cancer risk reduction in *BRCA1/2* PV carriers.

Clear and absolute **benefits** of RRBSO alongside the **limitations and harms** of screening should be communicated to patients.

Screening and risk reduction strategies for other malignancies need to be **tailored to the predisposing mutation and associated level of cancer risk** (high penetrance vs low penetrance).



CA125, cancer antigen 125; PV, pathogenic variant; RRBSO, risk-reducing bilateral salpingo-oophorectomy; TVUS, transvaginal ultrasound.

Fig. 13.7

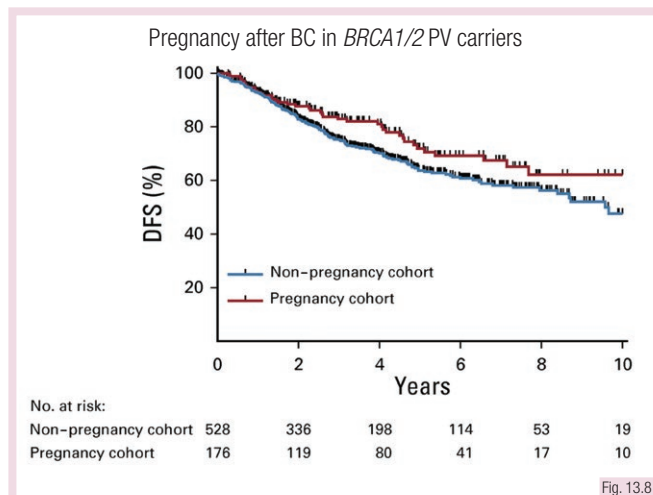


Fig. 13.8

BC, breast cancer; DFS, disease-free survival; PV, pathogenic variant.

Poly (ADP-ribose) polymerase inhibitors (PARPi) exploit deficiencies in the **DNA repair pathway** in *BRCA*-mutated tumours, resulting in cancer cell death.

In individuals with high-risk *BRCA1/2* early BC, **adjuvant olaparib** should be offered, where available.

In the advanced BC setting, for individuals with a *BRCA1/2* PV, PARPi should be offered and may also be considered in the presence of a **germline *PALB2* PV**.

Individuals with HBOC syndrome should be informed about the option of **preimplantation genetic testing**.

The side effects of **premature menopause** need to be addressed in women who have undergone RRBSO, including sexual health, bone health and genitourinary symptoms.

Retrospective studies indicate that **pregnancy after BC** in women with *BRCA1/2* PV is safe and does not appear to worsen maternal prognosis.

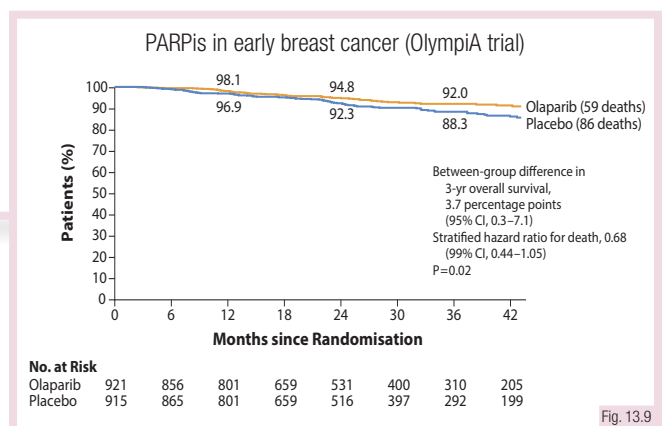


Fig. 13.9

CI, confidence interval; PARPi, poly (ADP-ribose) polymerase inhibitor.

REVISION QUESTIONS

1. What is the optimal strategy for reducing the risk of ovarian cancer in *BRCA1/2* PV carriers?
2. Which reproductive and endocrinological health issues need to be addressed following RRBSO?
3. What treatment is available in the early and advanced settings for *BRCA1/2*-associated BC?

Summary: Genetic counselling and testing

- 5%–10% of BCs are the result of germline PVs in BC predisposition genes
- Genetic testing should be encouraged whenever there is a suspicion of a hereditary cancer syndrome or if the patient is eligible for treatment with a PARPi
- PVs can be categorised as moderate- (2–4× population risk) or high-penetrance (>4× population risk) genes
- High-penetrance genes include *BRCA1*, *BRCA2*, *CDH1*, *PALB2* and *TP53*. Moderate-penetrance genes include *ATM*, *CHEK2* and *PTEN*
- *BRCA1* and *BRCA2* PVs significantly increase lifetime risk of ovarian cancer and are associated with an increased risk of male BC, prostate cancer and pancreatic cancer
- Intensified screening for BC in high-risk individuals should include annual MRI
- RRM may be considered in unaffected and affected carriers of a high-penetrance PV, in certain circumstances
- *BRCA1/2* PV carriers with high-risk early BC should be offered adjuvant olaparib and those with advanced BC should be offered a PARPi

Further Reading

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Image sources: Fig. 13.1. PDQ Cancer Genetics Editorial Board. In: PDQ Cancer Information Summaries. Bethesda (MD): National Cancer Institute (US); 2002; 13.3. courtesy Microbenotes.com; 13.5. Breast Cancer Association Consortium; Dorling L, et al. *N Engl J Med* 2021;384:428-439; 13.6, 13.7. adapted from Cessa C, et al; ESMO Guidelines Committee. *Ann Oncol* 2023;34:33-47; 13.8. Lambertini M, et al. *J Clin Oncol* 2020;38:3012-3023; 13.9. Tutt ANJ, et al. *N Engl J Med* 2021;384:2394-2405. All other figures courtesy of the authors.

Early breast cancer prognostic factors

Tumour, node, metastasis (TNM) parameters reflecting tumour burden remain a strong prognostic factor.

Tumour biology (type, grade, oestrogen receptor [ER], progesterone receptor [PgR], human epidermal growth factor receptor 2 [HER2] status and proliferation by Ki-67) is increasingly relied on, instead of tumour burden alone.

Hormone receptor-positive status is defined by $\geq 10\%$ positive tumour cells (TCs) and ER-low by 1%–9% positive TCs. HER2-positive status is defined by immunohistochemistry (IHC): $>10\%$ TCs with an IHC score of 3+ or $>10\%$ TCs with IHC 2+ and amplification by *in situ* hybridisation (ISH).

Intrinsic subtypes of BC		
Subtypes	Clinicopathological surrogate definition	Therapeutic options
Luminal A	Luminal A-like - ER-positive - HER2-negative - Ki-67-low - PgR-high - Low-risk GES if available	ET CDK4/6*** PARPi if gBRCAm***
Luminal B	Luminal B-like (HER2-negative) - ER-positive - HER2-negative - And either Ki-67-high or PgR-low or High-risk GES if available Luminal B-like (HER2-positive) - ER-positive - HER2-positive - Any Ki-67, any PgR, GES not recommended	ET +/- ChT CDK4/6*** PARPi if gBRCAm***
HER2	HER2-positive (non-luminal) - HER2-positive - ER and PgR absent	Anti-HER2
Basal-like	Triple-negative* - ER and PgR absent** - HER2-negative	ChT Anti-PD-1*** PARPi if gBRCAm***

Ki-67: value $\geq 30\%$ could be considered as clearly high; value $\leq 5\%$ as clearly low.

Absence of universal cut-off value

HER2-negative: IHC zero, 1+ or 2+ non-amplified. PgR high: suggested cut-off value is 20%

*There is ~80% overlap between 'triple negative' and intrinsic basal-like subtype

MBC HER2-negative, ER-low may be considered as triple-negative. *In selected cases

BC, breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ChT, chemotherapy; ER, oestrogen receptor; ET, endocrine therapy; gBRCAm, germline BRCA mutation; GES, gene expression signatures; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MBC, metastatic breast cancer; PARPi, poly (ADP-ribose) polymerase inhibitor; PD-1, programmed cell death protein 1; PgR, progesterone receptor.

Fig. 14.2

Germline *BRCA* mutation (gBRCAm) testing should be offered in case of a strong family history of BC and for patients eligible for adjuvant olaparib therapy.

Response to neoadjuvant therapy (NAT) is measured by residual cancer burden (RCB) and clinical-pathological stage. Pathological complete response (pCR) is favourable for HER2-positive and TNBC.

High-risk groups of patients are defined and assessed at clinical presentation and post-NAT.

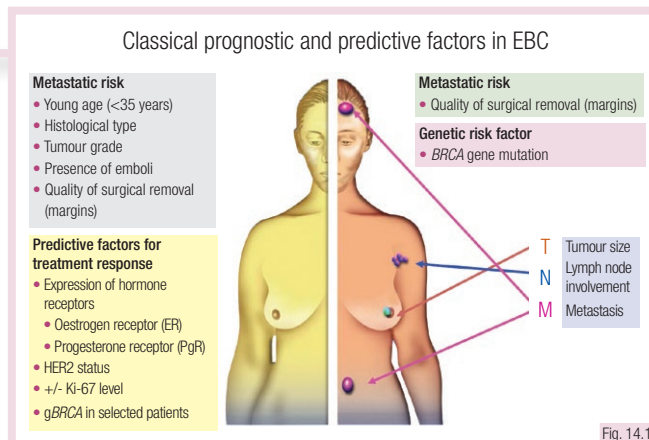


Fig. 14.1

EBC, early breast cancer; gBRCA, germline BRCA; HER2, human epidermal growth factor receptor 2.

Perou's breast cancer (BC) molecular portraits ('intrinsic classification') originally defined four prognostic groups dichotomised by ER and HER2 expression: luminal A, luminal B, HER2-enriched and basal-like.

It is possible to approach intrinsic classification using classical parameters such as hormone receptor and HER2 expression, Ki-67, and gene expression signatures (GES).

Some rare histological subtypes of early BC (EBC) have an excellent prognosis, justifying therapeutic de-escalation, e.g. tubular, cribriform, mucinous ER-positive, HER2-negative BC, adenoid cystic, low-grade metaplastic and secretory triple-negative BC (TNBC).

Histoprognostic criteria in the identification of high-risk patients with EBC	
	High risk
Clinical presentation	Hormone receptor-positive, HER2-negative - pT3 - pN1+ premenopausal - pN2+ postmenopausal - Grade III - High-risk GES if menopausal/luminal B TNBC $\geq pT1c$, pN0 or any pT, pN+ - For histological types with good prognosis $\rightarrow$ N+
Post-neoadjuvant	Hormone receptor-positive, HER2-negative - Poor response (CPS+EG score ≥ 3) TNBC - No pCR HER2-positive - No pCR

Fig. 14.3

CPS + EG, clinical-pathological stage, grade and oestrogen receptor status; EBC, early breast cancer; GES, gene expression signatures; HER2, human epidermal growth factor receptor; pCR, pathological complete response; pN, pathological lymph node involvement; pT, pathological tumour size; TNBC, triple-negative breast cancer.

REVISION QUESTIONS

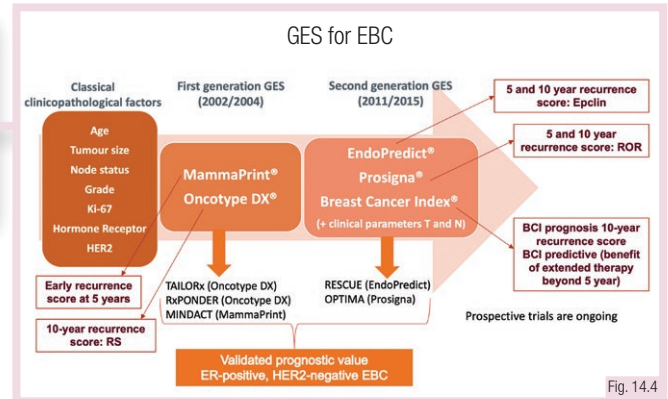
- What are the classical prognostic factors for BC?
- What are the four groups of BC defined in the intrinsic classification?
- What are the histoprognostic criteria used for the identification of high-risk patients with EBC?

Gene expression signatures – rebiopsy

GES give additional prognostic information to guide adjuvant therapy de-escalation/precision in **luminal EBC** and to tailor endocrine therapy (ET) type and duration. GES are not indicated in the case of luminal BC with ≥ 4 positive lymph nodes (LNs), for HER2-positive EBC or TNBC.

First-generation GES are centrally performed and have been clinically validated in large prospective trials.

Second-generation GES use combined parameters (biological and clinical) and can be executed locally on dedicated instruments, though Breast Cancer Index (BCI[®]) is centrally performed. These have been validated retrospectively, mainly for BC patients >50 years.



BCI, Breast Cancer Index[®]; EBC, early breast cancer; ER, oestrogen receptor; GES, gene expression signatures; HER2, human epidermal growth receptor factor 2; N, node status; ROR, risk of recurrence; RS, recurrence score; T, tumour size.

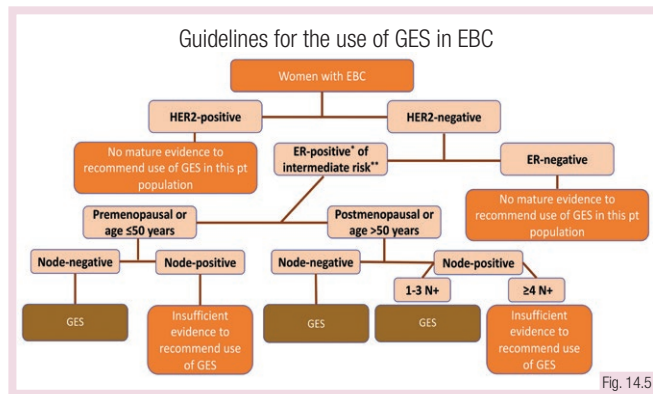


Fig. 14.5

*Ki-67 may also be evaluated after a short course of preoperative ET to indicate endocrine responsiveness (Ki-67 $\leq 10\%$)

**With uncertainty about indications for adjuvant ChT

ChT, chemotherapy; EBC, early breast cancer; ER, oestrogen receptor; ET, endocrine therapy; GES, gene expression signatures; HER2, human epidermal growth receptor factor 2; pt, patient.

At first diagnosis of metastatic BC (MBC), a biopsy should be carried out to confirm histology and re-assess tumour biology (ER, PgR, HER2). Biomarker assessment on bone biopsy is only possible in the case of slow decalcification without acid buffer.

A change in biomarker expression has been observed in ~20% for ER, up to 33% for PgR (more frequently loss of expression than gain) and in 8% of HER2-positive cases (equally often gain or loss).

ET or anti-HER2 therapy should be considered when ER/PgR or HER2 status is positive in at least one biopsy, regardless of timing. In case of an ER-low phenotype and HER2-negative status (HER2 zero, 1+ or 2+ non-amplified), the case may be considered as TNBC/HER2-zero or HER2-low.

Women with EBC aged >50 years, without LN involvement (N0) or with 1–3 positive LNs, may safely avoid chemotherapy (ChT) in the case of low-risk GES or a luminal A profile by Prosigna[®].

Women with EBC aged ≤ 50 years, without LN involvement (N0), may safely avoid ChT in the case of low-risk GES. N1 patients benefit from ChT regardless of GES results.

The Clinical Treatment Score at 5 Years (CTS5) estimates the risk of recurrence after 5 years of ET. BCI[®], if available, may be offered to N0–N1 patients aged >50 years, who have received 5 years of ET, to guide decisions about extended ET.

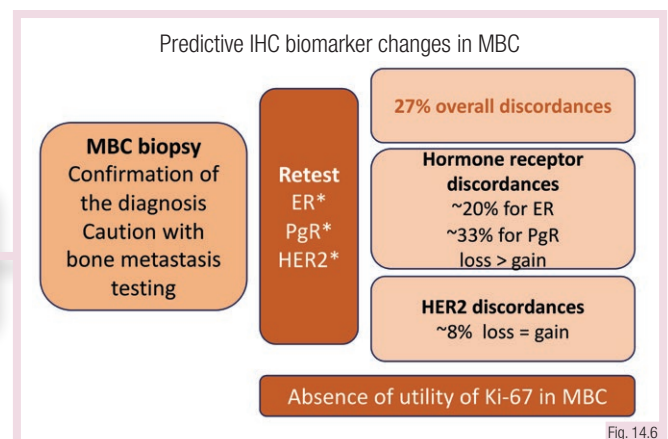


Fig. 14.6

*ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) I-A

ER, oestrogen receptor; ESMO, European Society for Medical Oncology; HER2, human epidermal growth receptor factor 2; IHC, immunohistochemistry; MBC, metastatic breast cancer; PgR, progesterone receptor.

REVISION QUESTIONS

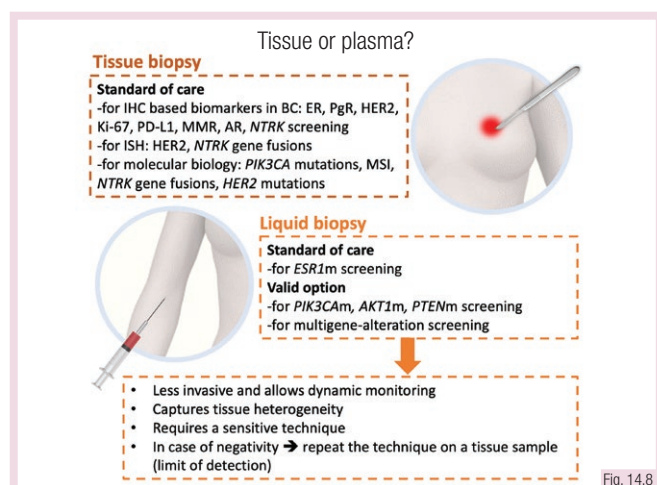
1. What are the characteristics of first- and second-generation GES?
2. What are the indications of GES for women aged <50 years and >50 years with EBC?
3. Is a biopsy required at metastatic relapse of BC?

Other predictive factors for MBC: ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

HER2-low status corresponds to BC with a 1+ or 2+ non-amplified HER2 status. The positivity of at least one sample during the evolution of BC is required for eligibility to trastuzumab deruxtecan (T-DXd).

Anti-programmed death-ligand 1 (PD-L1) treatment in metastatic TNBC (mTNBC) is subject to specific tests, e.g. antibody 22C3 (Dako), a **combined positive score** ≥ 10 for pembrolizumab and antibody SP142 (Ventana) **immune cells** $\geq 1\%$ for atezolizumab.

Screening for neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions can be performed by IHC but molecular confirmation is mandatory. Testing for **microsatellite instability** (MSI) by IHC and molecular tests is an option for checkpoint inhibitors. **Androgen receptor** (AR) status by IHC is an option for mTNBC but cut-off is not validated.

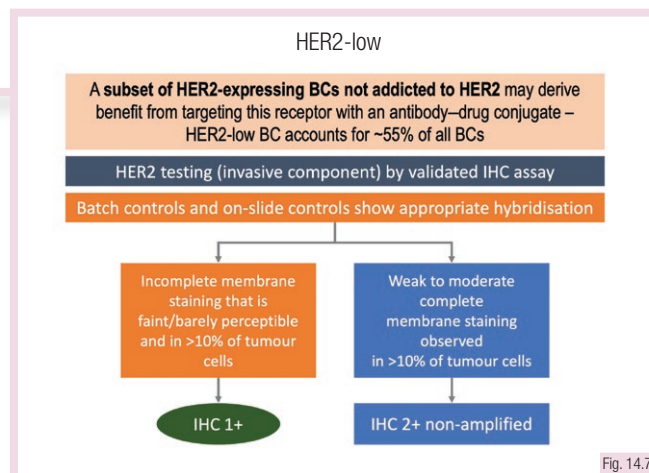


AR, androgen receptor; BC, breast cancer; ER, oestrogen receptor; *ESR1*, oestrogen receptor 1; HER2, human epidermal growth receptor factor 2; IHC, immunohistochemistry; ISH, in situ hybridisation; m, mutation; MMR, mismatch repair; MSI, microsatellite instability; *NTRK*, neurotrophic tyrosine receptor kinase; PgR, progesterone receptor; *PTEN*, phosphatase and tensin homologue; PD-L1, programmed death-ligand 1.

Biomarkers for ER-positive, HER2-negative MBC: *gBRCA*m, HER2-low status, *PIK3CA*m, *AKT1*m, *PTEN*m, *ESR1*m. *gPALB2*m is optional. If drugs are available: testing for *NTRK* fusions, MSI status may be considered. If clinical trials are available: *ERBB2/HER2*m, *gPALB2*.

Biomarkers for mTNBC: *gBRCA*m, PD-L1, HER2-low status, *gPALB2*m optional. If drugs are available: *NTRK* fusions, MSI status. If clinical trials are available: *ERBB2/HER2*m, AR status (IHC).

Biomarkers for HER2-positive MBC: none except HER2 status 3+ or 2+ amplified, MSI and *NTRK* fusions.

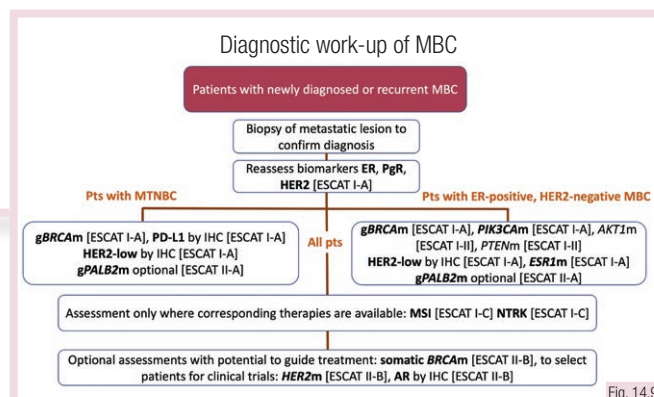


BC, breast cancer; HER2, human epidermal growth receptor factor 2; IHC, immunohistochemistry.

Activating or non-activating *PIK3CA*-*AKT*-*PTEN* mutations occur in 30%–40% of ER-positive, HER2-negative MBCs. Molecular testing is performed on EBC or MBC tissue samples or by liquid biopsies (LBs). In case of negative LB, the *PIK3CA*, *AKT*, *PTEN* status must be evaluated on a BC biopsy sample for eligibility to *PIK3CA* or *AKT1* inhibitors.

*gBRCA*m is present in 2%–5% of BCs. These patients are candidates for treatment with a poly (ADP-ribose) polymerase (PARP) inhibitor. *PALB2* germline testing is optional for PARP inhibition.

ESR1 (oestrogen receptor 1) mutations (20%–40% of ER-positive BCs) are mostly induced by aromatase inhibitor (AI) therapy and confer resistance to AIs. Testing by LB may be performed after the first line of treatment.



AR, androgen receptor; BC, breast cancer; ER, oestrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; *ESR1*, oestrogen receptor 1; g, germline; HER2, human epidermal growth receptor factor 2; IHC, immunohistochemistry; m, mutation; MBC, metastatic breast cancer; MSI, microsatellite instability; mTNBC, metastatic triple-negative breast cancer; *NTRK*, neurotrophic tyrosine receptor kinase; *PALB2*, partner and localiser of *BRCA2*; PD-L1, programmed death-ligand 1; PgR, progesterone receptor; *PTEN*, phosphatase and tensin homologue; pts, patients; TNBC, triple-negative breast cancer.

REVISION QUESTIONS

1. What are the ESCAT biomarkers to assess in MBC by IHC?
2. What are the ESCAT biomarkers to assess in MBC by molecular biology (on tissue or plasma)?
3. What are the biomarkers of interest in MBC by tumour subtypes?

Summary: Prognostic and predictive factors

- The most important prognostic factors in EBC are expression of ER/PgR, HER2 and proliferation markers, number of involved regional LNs, tumour histology and size, grade and presence of peritumoural vascular or lymphatic invasion
- In EBC, ER/PgR, HER2 and gBRCAm are the only validated predictive factors, allowing for selection of patients for ET, anti-HER2 treatment and PARP inhibitors, respectively
- Intrinsic molecular classification reflects the biological properties of tumours. Four distinct classes are recognised: luminal A, luminal B, HER2-enriched and basal-like
- Women with EBC aged >50 years without LN involvement (N0) or with 1–3 positive LNs may safely avoid ChT in the case of low-risk GES or a luminal A subtype
- In ER-positive HER2-negative EBC, MammaPrint® and Oncotype DX® have value to estimate prognosis, as do Prosigna® and EndoPredict®. BCI® has value for prediction of extended ET
- GES are not recommended for HER2-positive and triple-negative EBC, or for ER-positive, HER2-negative EBC with ≥4 positive LNs
- At first diagnosis of MBC, a biopsy is recommended to confirm histology and reassess tumour biology (ER, PgR, HER2)
- Proven biomarkers (tissue or LB) for ER-positive, HER2-negative MBC:
 - gBRCAm, HER2-low status (IHC)
 - PIK3CAm, AKT1m, PTENm, ESR1m (LB)
- Proven biomarkers for mTNBC: gBRCA, PD-L1 (IHC), HER2-low status (IHC)
- Proven biomarkers for HER2-positive MBC: none

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Image sources: Fig. 14.1. adapted from Harbeck N, et al. *Nat Rev Dis Primers* 2019;5:66; 14.2. adapted from Cardoso F, et al. *Ann Oncol* 2019;30:1194–1220; 14.3. adapted from Référentiel Francilien de Pathologie Mammaire (Sénorif) 2021–2023, Gustave Roussy; 14.4. adapted from Varnier R, et al. *Cancers (Basel)* 2021;13:4840; 14.5. Andre F, et al. *J Clin Oncol* 2022;40:1816–1837; 14.6. adapted from Gennari A, et al. *Ann Oncol* 2021;32:1475–1495; 14.7. adapted from Wolff AC, et al. *J Clin Oncol* 2018;36:2105–2122; 14.8. adapted from Gennari A, et al. *Ann Oncol* 2021; 32:1475–1495; Pascual J, et al. *Ann Oncol* 2022;33:750–768; 14.9. adapted from Gennari A, et al. *Ann Oncol* 2021; 32:1475–1495; Mosele MF, et al. *Ann Oncol* 2024;35:588–606.

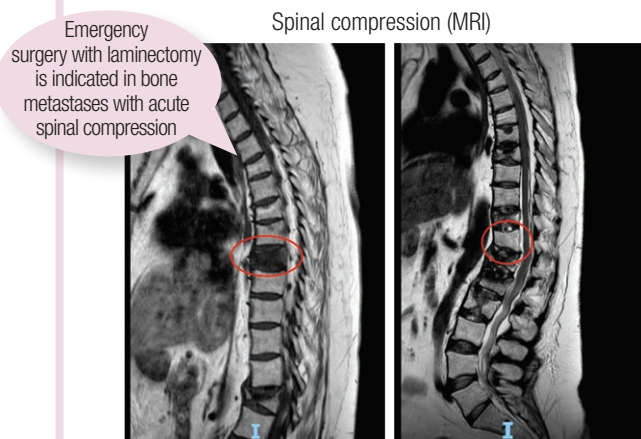
15 Organ-specific problems in metastatic breast cancer

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 subtype, develop bone metastases which are predominantly mixed: osteolytic and osteoblastic.

Nearly half of patients with MBC who are untreated for bone metastases suffer from **skeletal-related events (SREs)** and/or **hypercalcaemia**, leading to significant morbidity and mortality.

Standard detection procedures are bone scintigraphy and X-ray or a whole body computed tomography (CT) scan. However, ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET)-CT has a higher sensitivity and specificity for detection of bone metastases. Magnetic resonance imaging (MRI) is recommended to assess spinal metastases.



MRI, magnetic resonance imaging.

Fig. 15.2

Therapy with BMAs should **start at diagnosis of bone metastases** and continue, even in disease progression, until **performance status (PS)** deterioration. **Calcium and vitamin D supplements** may be useful.

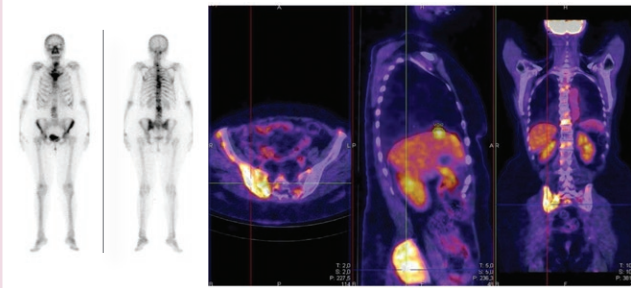
The **optimal duration of BMA therapy** has not been established, but it is reasonable to discontinue therapy after 2 years for patients in remission. BMAs are also recommended in osteoblastic lesions.

BMAs are generally well tolerated; **renal toxicity** (for zoledronate) and **osteonecrosis of the jaw** are uncommon but potentially serious conditions. Before BMA initiation, patients should have a **dental evaluation** and complete any required dental treatment. If a procedure is necessary during treatment, the BMA must be stopped 6 weeks before and restart 6 weeks after.

REVISION QUESTIONS

1. How frequent are bone metastases in patients with MBC?
2. What are the treatment options for bone metastases in patients with MBC?
3. In patients with MBC, when should treatment with BMAs be stopped?

^{18}F -FDG-PET-CT and bone scintigraphy in patients with bone metastases



^{18}F -FDG, ^{18}F -fluorodeoxyglucose; CT, computed tomography; PET, positron emission tomography.

Fig. 15.1

A **multidisciplinary approach** is essential to manage patients with bone metastases and prevent SREs.

In case of moderate/severe painful metastases and in case of risk of pathological fracture, **radiotherapy (RT)** can be used. **Orthopaedic surgery** may be necessary to stabilise or prevent fractures.

Bone-modifying agents (BMAs), bisphosphonates or denosumab, should be used in combination with systemic therapy to **decrease the rate of SREs**. BMAs delay SREs, relieve symptoms and improve quality of life.

Recommended BMAs

Drug name	Method of administration	Recommended dose
Zoledronate	Intravenous	4 mg over no less than 15 minutes every 3–4 weeks*. ^o
Denosumab	Subcutaneous	120 mg/4 weeks **. ^o

* There is evidence that a 12-week schedule is equally effective after 3–6 months of therapy in stable disease (FAST Trial).

** Denosumab is more effective than zoledronate in delaying first and subsequent SREs. A 12 weeks schedule is possible after 6–12 months.

^o Consider a larger interval of administration after 2 years of BMAs to reduce the risk of ONJ.

BMA, bone-modifying agent; ONJ, osteonecrosis of the jaw; SRE, skeletal-related event.

Fig. 15.3

Central nervous system metastases

Breast cancer (BC) is one of the leading causes of brain and leptomeningeal metastases. Central nervous system (CNS) metastases are more frequent in human epidermal growth factor receptor 2 (HER2)-positive and triple-negative BC, compared with hormone receptor-positive subtypes (25% vs 10%). Screening for brain metastases (BMs) in asymptomatic patients is not recommended.

The incidence of CNS metastases is rising, most likely due to advances in diagnostics and systemic treatment, with patients with MBC living long enough to develop CNS metastases.

The recommended diagnostic test is MRI, which is markedly more sensitive than CT.

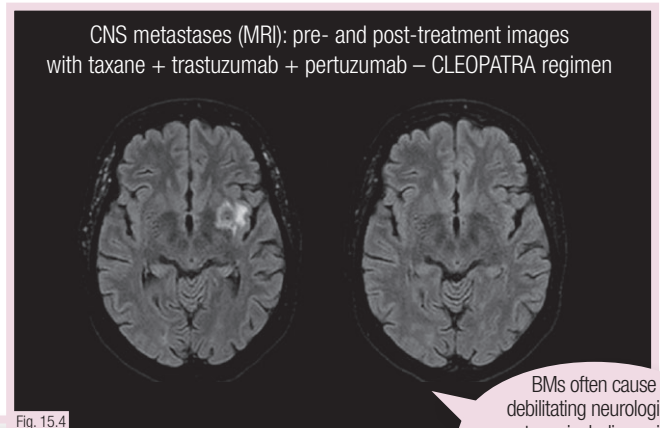


Fig. 15.4

BM, brain metastasis; CNS, central nervous system; MRI, magnetic resonance imaging.

BMs often cause debilitating neurological symptoms including seizures, headaches, confusion, cognitive impairment and paralysis

Survival analysis in patients with brain metastases according to BC subtypes

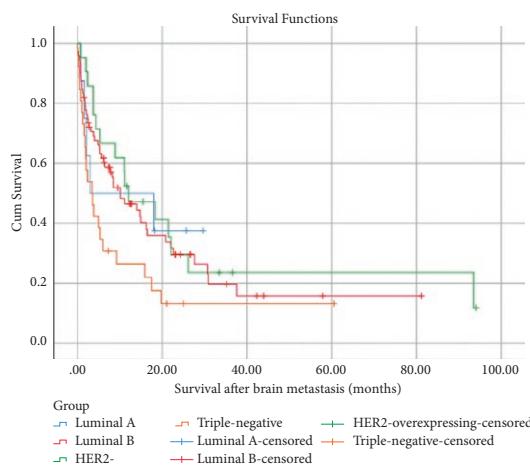


Fig. 15.5

BC, breast cancer; Cum, cumulative; HER2, human epidermal growth factor receptor 2.

Leptomeningeal metastases occur in ~5% of patients with MBC, mostly in heavily pretreated disease. Possible signs include increased intracranial pressure, cranial or spinal nerve injury and cognitive dysfunction.

Treatment is often limited to symptom control. In patients with good PS and controlled extracranial disease, craniospinal RT can be considered.

Other options include stereotactic body RT (SBRT) in focal leptomeningeal disease (LMD) and intrathecal drugs (chemotherapy [ChT] or trastuzumab in HER2-positive patients), although intrathecal strategies may not be more effective than systemic. Data from a small number of trials on the efficacy of systemic therapy for LMD, such as tucatinib and T-DXd, are emerging.

The median survival of patients with CNS metastases is increasing, especially in patients with HER2-positive disease.

Corticosteroids can provide rapid symptom relief. In HER2-positive patients with MBC with progression in the CNS only, systemic therapy should not be changed, if local control can be achieved with local treatments. Surgical resection or stereotactic RT is recommended, when technically and clinically feasible.

In HER2-positive patients, there are proven regimens for active BMs, such as tucatinib in combination with capecitabine–trastuzumab or trastuzumab deruxtecan (T-DXd) in stable BMs. Trastuzumab emtansine (T-DM1) also has activity in BMs.

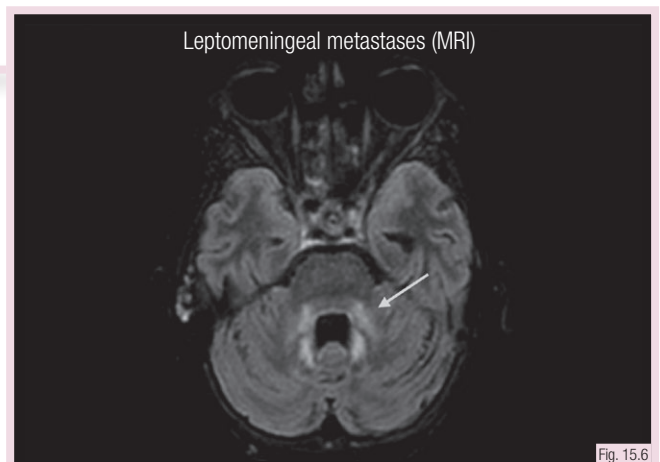


Fig. 15.6

MRI, magnetic resonance imaging.

REVISION QUESTIONS

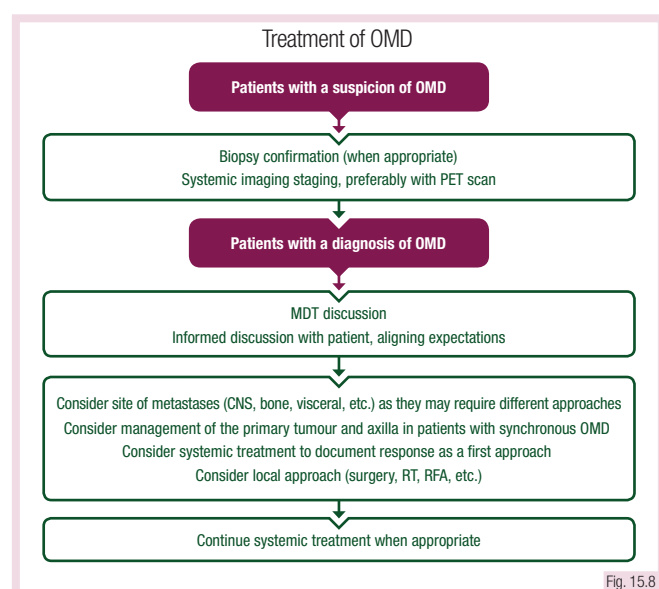
1. Is screening for BMs recommended in asymptomatic patients?
2. What are treatment options for active BMs in HER2-positive patients?
3. When can craniospinal RT be considered?

Oligometastatic disease

Oligometastatic disease (OMD) describes patients with a low-volume tumour burden. There is no standard definition, but the most accepted one includes ≤ 5 metastatic lesions, not necessarily in the same organ.

Patients with OMD represent $\leq 10\%$ of all cases of MBC. ^{18}F -FDG PET-CT is the most sensitive diagnostic tool in this situation.

Treatment strategies should be discussed by a multidisciplinary team and can include surgery, local ablative therapy or RT in addition to systemic treatment.

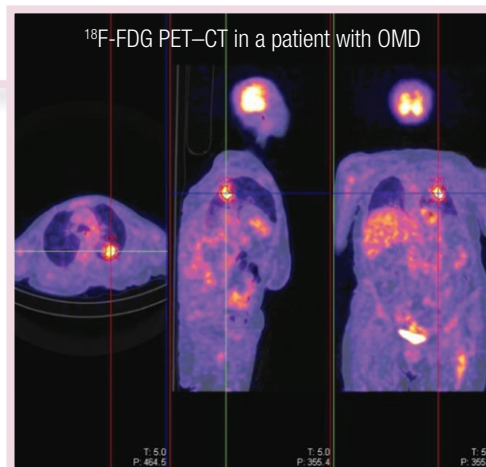


CNS, central nervous system; MDT, multidisciplinary team; OMD, oligometastatic disease; PET, positron emission tomography; RFA, radiofrequency ablation; RT, radiotherapy.

Approximately 5%–15% of all patients with MBC develop liver metastases without extrahepatic disease. Available evidence shows a high survival rate in patients treated with local surgical or ablative therapy in addition to systemic therapy.

Since there are no data to support the effect of local therapy on survival, it should only be proposed in selected cases of good PS, limited liver involvement and after the 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).

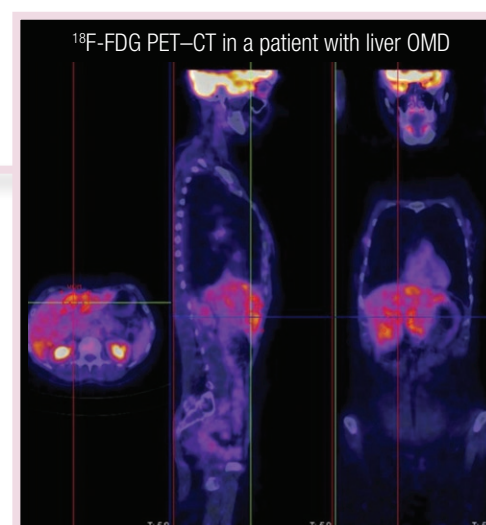


^{18}F -FDG, ^{18}F -fluorodeoxyglucose; CT, computed tomography; OMD, oligometastatic disease; PET, positron emission tomography. Fig. 15.7

Although MBC remains an incurable disease, surgical resection in combination with systemic therapy is a potentially curative treatment in patients with OMD and sometimes they can reach the status of long-term survivors.

SBRT to oligometastatic lesions in addition to systemic therapy has the potential to improve both progression-free and overall survival.

There are no definitive criteria to select patients who might benefit from multimodal therapy; long disease-free survival, low disease burden, oestrogen receptor (ER) or HER2 positivity, completeness of resection and good PS should be considered.



^{18}F -FDG, ^{18}F -fluorodeoxyglucose; CT, computed tomography; OMD, oligometastatic disease; PET, positron emission tomography. Fig. 15.9

REVISION QUESTIONS

1. How frequent is OMD in MBC and which is the most sensitive diagnostic exam?
2. What are the criteria to propose local therapy in OMD patients?
3. What is a recommended treatment approach in patients with oligometastatic BC?

Summary: Organ-specific problems in metastatic breast cancer

- Bone is the most common site of metastases in patients with MBC, and bone metastases 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 SREs 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 one of the most common causes 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 patients with MBC with CNS metastases are increasing
- In case of extracranial disease control, craniospinal RT can be considered. Surgical resection or SBRT is recommended for limited numbers of CNS lesions. There is also evidence for systemic therapy with CNS activity, such as T-DXd or tucatinib in combination with capecitabine–trastuzumab in HER2-positive patients
- Leptomeningeal involvement is a rare condition, developing mostly in heavily pretreated patients in a late phase of MBC. Craniospinal RT may be appropriate in selected patients with controlled extracranial disease and good PS in addition to systemic therapy
- In some MBC patients with OMD, long-term survival can be achieved by multimodal therapy
- MBC patients with a long disease-free interval, a low number of metastases at the involved site, ER positivity, good PS and demonstrated benefit from systemic therapy may benefit from radical local treatment of oligometastatic sites in addition to systemic therapy

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Epidemiology and clinical features

Male breast cancer (BC) accounts for <1% of all BC diagnoses worldwide. The lifetime risk of BC is ~1:1000 for men and ~1:8 for women.

The mean age at diagnosis is 67 years, which is older than the average age at diagnosis for women (62 years), according to the Surveillance, Epidemiology, and End Results (SEER) database.

The incidence of male BC increases linearly and steadily with age with a single peak at around 75 years. This is in contrast with BC in women, where incidence has one peak of early-onset disease and a second peak with a later age at onset.

Risk factors for male BC		
Genetics	Endocrine	Other
Klinefelter syndrome	Klinefelter syndrome	Radiation
<i>BRCA2</i> (to a lesser extent <i>BRCA1</i>)	Testicular abnormalities (undescended testis, congenital inguinal hernia, orchidectomy, mumps orchitis)	Race (black males)
Family history	Exogenous oestrogen or testosterone use	History of bone fractures
PTEN (Cowden syndrome)	Liver disease	Lack of exercise
Androgen receptor	Obesity	Occupational exposures (electromagnetic fields, high temperatures)
p53	Patients treated for prostate cancer	
<i>CHEK2</i>	Hyperprolactinaemia	
<i>PALB2</i>		
<i>CYP17</i>		

Known risk factors

Suggestive but not conclusive risk factors

Fig. 16.2

BC, breast cancer; CHEK2, checkpoint kinase 2; PALB2, partner and localiser of BRCA2; PTEN, phosphatase and tensin homologue.

Evaluation of disease extension and stage classification should follow female BC guidelines. Breast magnetic resonance imaging (MRI) can be used if mammogram and ultrasound is inconclusive.

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

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

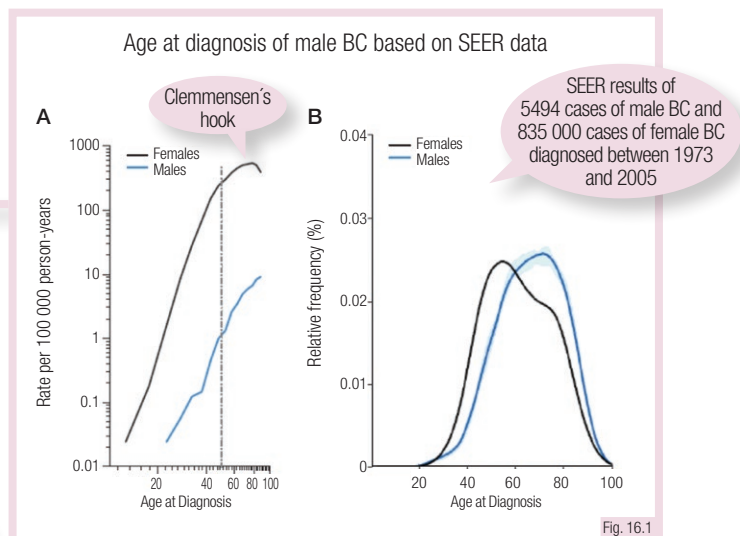


Fig. 16.1

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

There is a family history of breast or ovarian cancer in 15%–20% of male BC patients (relative risk of 2.5). The diagnosis of BC in men is an indication for genetic testing.

BRCA2, and to a lesser extent *BRCA1*, mutations contribute to 4%–40% of hereditary BCs in men, as opposed to 5%–10% in female BC. However, men carrying *BRCA1/2* mutations have a lower cumulative risk of BC compared with women (1.2% and 6.8% at age 70, respectively).

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

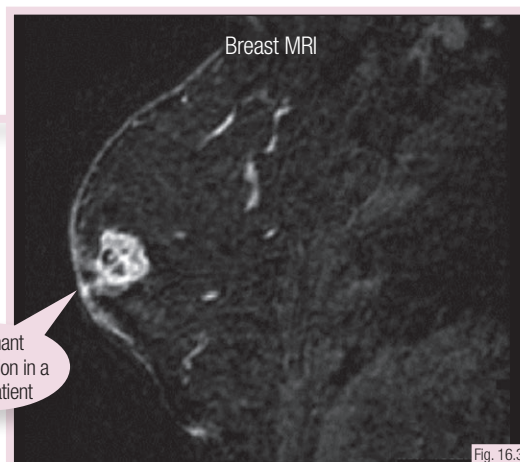


Fig. 16.3

MRI, magnetic resonance imaging.

REVISION QUESTIONS

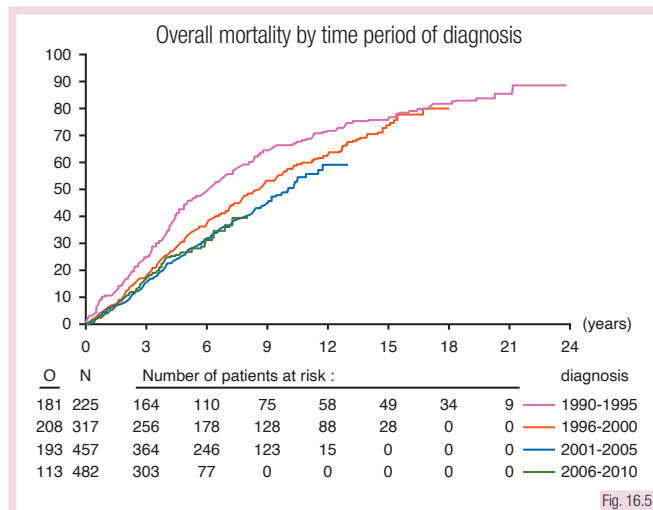
1. What is the mean age at diagnosis of BC in men?
2. What are the known risk factors for BC in men?
3. What are the differential characteristics between male and female BC?

Histopathology, prognosis and local treatment

Histology is most frequently (80%–95%) that of an **invasive carcinoma of no special type**, with **ER-positive** (99%), progesterone receptor (**PgR**)-positive (96%), androgen receptor (**AR**)-positive (97%) and **Ki-67 low** (61.1%).

A diagnosis of human epidermal growth factor receptor 2 (**HER2**)-positive or triple-negative BC (TNBC) in a male patient demands thorough confirmation in view of its rarity (8.7% and <1%, respectively) – data from the **International Male BC Programme (IMBCP) joint analysis**.

Luminal tumours show **distinct features**: M1 resembles the luminal subtype of female BC, while M2 exists only in male patients, is associated with an upregulated immune response and ER signalling and has a better prognosis than M1.

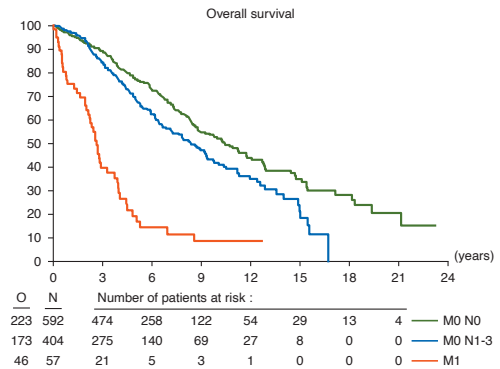


Standard **local treatment** for localised disease includes **surgery** and **radiotherapy** (RT).

Mastectomy is usually performed due to the lack of breast tissue in men and central location of most tumours. However, **breast-conserving surgery** is safe and should be considered whenever technically feasible (better aesthetical outcomes can be obtained with oncoplastic techniques). **Sentinel LN** (SLN) biopsy should be performed in clinically node-negative disease as it is feasible and safe in men and associated with less morbidity.

RT should follow the indications accepted for female BC with particular caution to **cardiovascular toxicity**.

OS Kaplan–Meier curves for all patients, by stage at diagnosis



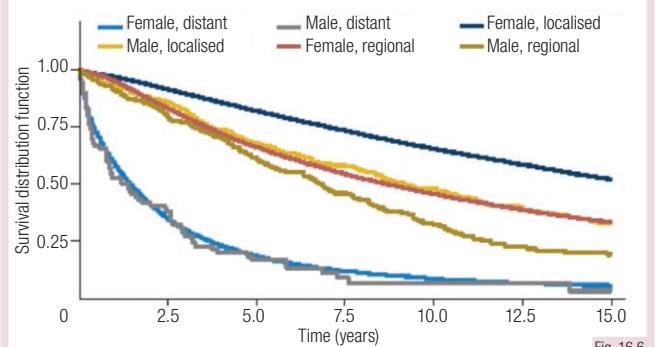
OS, overall survival.

The most important **prognostic factors** for male BC are stage and **lymph node (LN) status** at diagnosis. The IMBCP joint analysis also confirmed that **ER** and **PgR status** are prognostic and associated with better outcomes. Conversely, grade, Ki-67 and immunohistochemistry-surrogate subtypes were not associated with outcomes.

Mortality rates improved between 1990 and 2010. 5-year overall survival has been estimated as: stage I, 75%–100%; stage II, 50%–80%; stage III, 30%–60%; and stage IV, 9%–16%.

Studies show that **survival rates are worse for men compared with women** and the IMBCP also revealed a lower quality of cancer care in male patients.

OS rates by sex and stage in an international population-based study: 459 846 women and 2655 men in Denmark, Finland, Geneva, Norway, Singapore and Sweden



OS, overall survival.

REVISION QUESTIONS

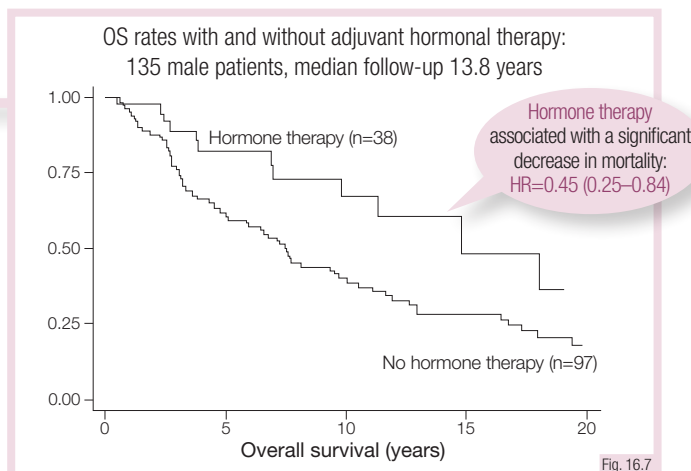
1. What are the main histopathological characteristics of male BC?
2. What are the most important prognostic factors for male BC?
3. What is the standard local treatment for early BC in male patients?

Systemic treatment and follow-up

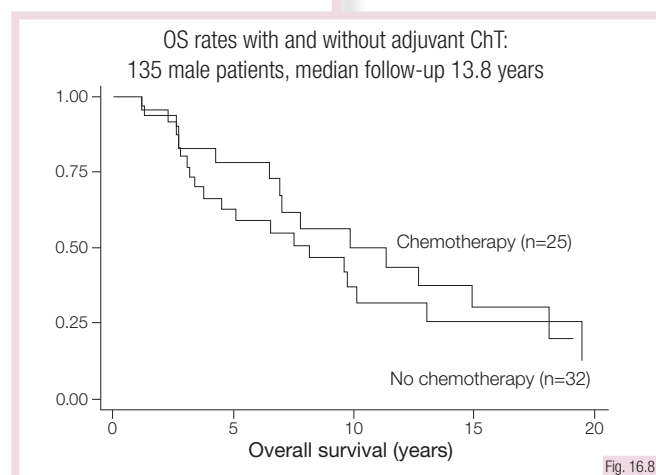
Tamoxifen is recommended for adjuvant endocrine therapy (ET, 5–10 years) in ER-positive disease; if contraindicated, consider aromatase inhibitors (AIs) but only in combination with luteinising hormone-releasing hormone (LHRH) agonists.

There is little data on **neoadjuvant anti-HER2 agents** in HER2-positive male BC, but their use is highly recommended given the therapeutic effect of these agents in women.

Adjuvant chemotherapy (ChT) should be considered for men with intermediate- or high-risk disease. Genomic test results should be interpreted with caution.



HR, hazard ratio; OS, overall survival.



ChT, chemotherapy; OS, overall survival.

Standard first-line treatment in ER-positive/HER2-negative **advanced disease** is a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor combined with ET, as for female patients.

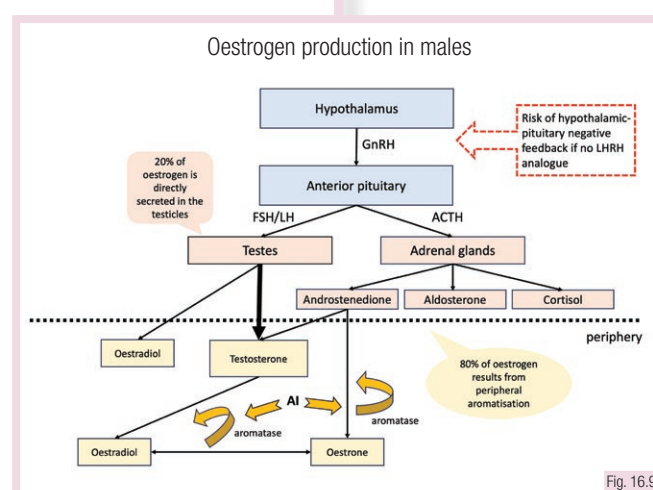
Tamoxifen in male BC is the preferred agent (response rates $\geq 80\%$). In case of progression, **AIs + an LHRH agonist** (or surgical orchidectomy) or **fulvestrant** should be considered. AIs alone may be used but the response should be monitored closely.

ChT is considered when ET-based options have been exhausted, there is no response, the disease is ER-negative and/or there is a visceral crisis. **Supportive and palliative care** measures are essential.

All **targeted agents** available for female BC (such as anti-HER2 agents, everolimus, PIK3CA inhibitors, poly [ADP-ribose] polymerase inhibitors [PARPis] and antibody–drug conjugates [ADCs]) should also be available for male patients and used according to the same guidelines.

In 2020 the Food and Drug Administration (FDA) released guidance to promote drug development in this setting. It provides clear recommendations for the **inclusion of men in clinical trials of BC drugs**.

The American Society of Clinical Oncology guidelines recommend **annual ipsilateral mammogram** in the case of male BC treated with lumpectomy, and **annual contralateral mammogram** only if there is a history of BC with a genetic predisposition mutation.



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

REVISION QUESTIONS

1. Which systemic treatment is indicated in a male patient with pT1N1M0, ER-positive, Ki-67 10%, HER2-negative BC?
2. What is the preferred first-line treatment for a male patient with ER-positive metastatic BC with mild symptoms?
3. When is ChT recommended in the metastatic setting?

Summary: Breast cancer in men

- Epidemiology: <1% of all BCs; incidence occurs at an older age compared with women, with disease frequently presenting at more advanced stages
- Histology: majority is invasive carcinoma of no special type, ER-positive and HER2-negative
- Mortality has improved over time; the reported worse survival compared to women may be related to more advanced disease at diagnosis and comorbid illnesses
- The most important prognostic factors are LN status, tumour size and ER status
- Surgery: mastectomy or breast-conserving surgery if feasible, and SLN biopsy or axillary dissection as per female BC guidelines
- RT should follow female BC guidelines
- Tamoxifen is the mainstay treatment in the adjuvant and metastatic settings since ER-positive disease is highly predominant. Als combined with an LHRH agonist are a treatment option if contraindication or progression on tamoxifen. In the metastatic setting, the standard first-line therapy is ET combined with a CDK4/6 inhibitor
- ChT is beneficial in the adjuvant setting in high-risk disease and should be used in the metastatic setting when endocrine-based options are exhausted or ineffective, in the very rare cases of ER-negative disease and/or when in visceral crisis
- All targeted agents available for female BC (such as anti-HER2 agents, everolimus, PIK3CA inhibitors, PARPis and ADCs) should also be available for male patients and used according to the same guidelines
- Efforts should be made to include men in clinical trials, assess the efficacy of new agents and combat the stigma associated with this disease

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Epidemiology

Breast cancer (BC) is the **most frequently diagnosed malignancy in women ≤ 40 years of age** and the leading cause of cancer-related deaths in young women.

Lack of **screening programmes** in this age range and the higher risk of **unfavourable biological features** may lead to diagnosis at later stages and a worse prognosis.

Increased **awareness and attention** is needed by healthcare providers on the potential diagnosis of BC in young women.

Trends in cancer incidence rates by site in young women in the US

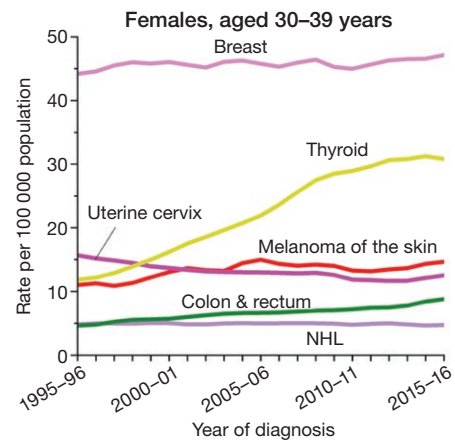


Fig. 17.1

Rates are age-adjusted to the 2000 US standard population and are 2-year moving averages. NHL, non-Hodgkin lymphoma.

BC subtypes according to age determined by gene expression profiling

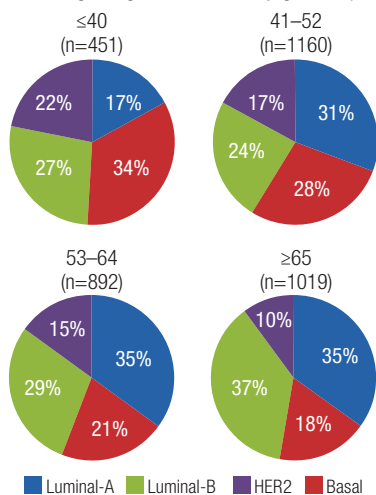


Fig. 17.2

BC, breast cancer; HER2, human epidermal growth factor receptor 2.

Women diagnosed at a young age are more likely to carry germline **pathogenic variants** in **hereditary BC** predisposition genes, particularly *BRCA1* and *BRCA2*.

Young age is a criterion for referring patients to **genetic counselling** and has subsequent potential implications on prevention and screening, local and systemic treatments as well as reproductive and survivorship issues.

While carrying a pathogenic variant in *BRCA* genes impacts the care of young BC patients, it does **not** seem to affect their prognosis.

In young women, the **most aggressive BC subtypes** (i.e. triple-negative, human epithelial growth factor receptor 2 [HER2]-positive and luminal B-like) are **more frequently diagnosed** than in older patients.

Young women with BC face a variety of **age-related concerns at diagnosis**, including sexual dysfunction, fertility, body image, financial, psychosocial and social issues.

The management of BC in young women is challenging, requiring **additional attention and expertise** from healthcare providers dealing with these patients.

OS by *BRCA* mutation status in patients with BC

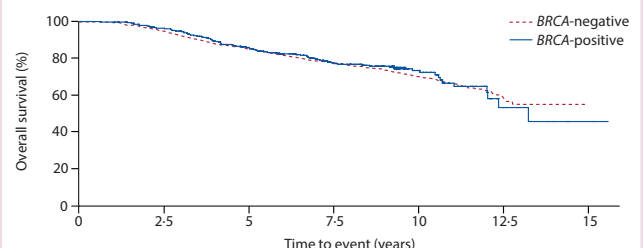


Fig. 17.3

BC, breast cancer; OS, overall survival.

REVISION QUESTIONS

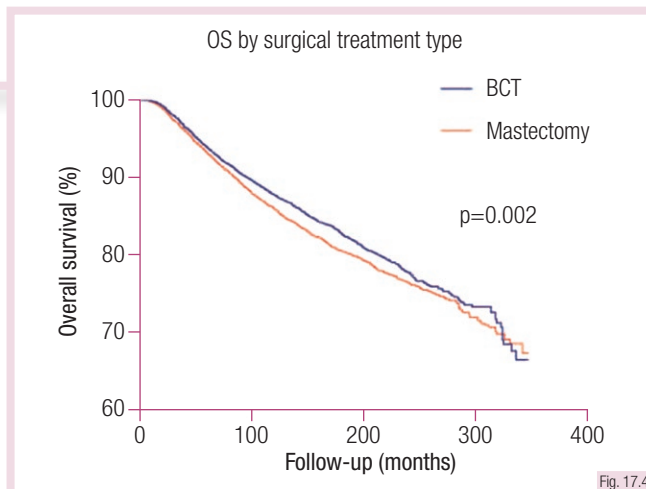
1. What is the most frequently diagnosed cancer in young women?
2. Is BC biology influenced by young age at diagnosis?
3. Should genetic counselling be considered in young patients?

Treatment

Surgical treatment in young women with BC has the same indications as for older patients. Despite the higher rate of locoregional recurrence in young patients, mastectomy is not associated with improved survival.

After breast-conserving surgery, **adjuvant radiotherapy (RT)** is **essential**. Caution should be paid in cases of patients harbouring pathogenic variants in *TP53*, for whom mastectomy (to avoid RT) is considered the preferred option.

Immediate **breast reconstruction** after skin-sparing and nipple-sparing mastectomy improves cosmetic results and does not seem to **impact on risk of local recurrences**.

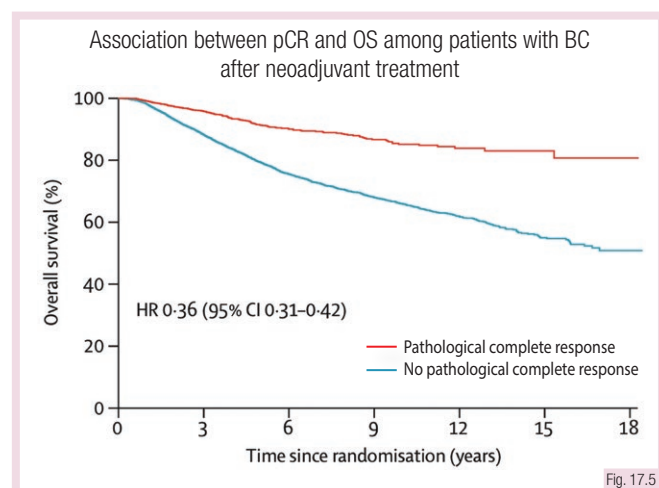


BCT, breast-conserving therapy; OS, overall survival.

Systemic treatment, both in the early and metastatic settings, should follow BC guidelines and be tailored to clinicopathological features and the patient's characteristics; **young age per se must not be considered a reason** to administer more aggressive therapies.

For patients with **triple-negative** or **HER2-positive stage II and III BC** tumours >1 cm and/or node-positive, **neoadjuvant therapy** should be considered the preferred approach.

In patients receiving preoperative treatment, adjuvant therapies are mainly based on the degree of response, given the **prognostic value of pathological complete response (pCR)** and the increasing number of therapeutic strategies after surgery.

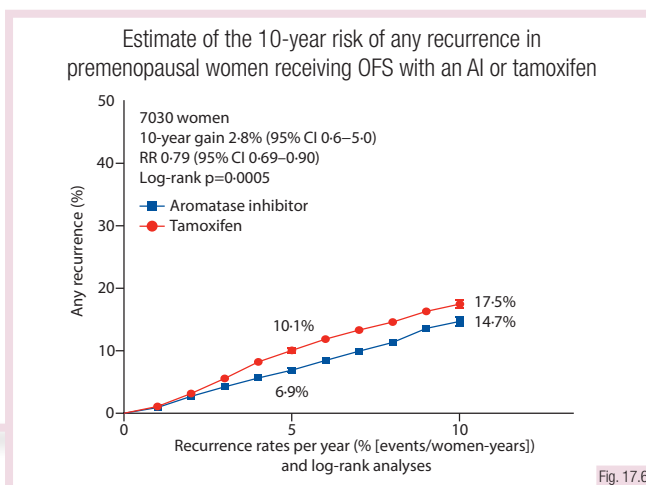


BC, breast cancer; CI, confidence interval; HR, hazard ratio; OS, overall survival; pCR, pathological complete response.

For luminal-like BCs, important efforts have been made to better stratify the prognosis of patients and to **escalate** or **de-escalate** adjuvant **therapies** according to their risk of recurrence.

In premenopausal women with node-negative BC, **genomic tests** can guide chemotherapy (ChT) choices, while in young patients with node-positive disease their role remains controversial.

Adjuvant **endocrine therapy (ET)** options for premenopausal patients with BC are tamoxifen alone, ovarian function suppression (OFS) plus tamoxifen, or OFS plus aromatase inhibitors. **Risk of recurrence and patient preferences** are key to treatment decision-making.



AI, aromatase inhibitor; CI, confidence interval; OFS, ovarian function suppression; RR, rate ratio.

REVISION QUESTIONS

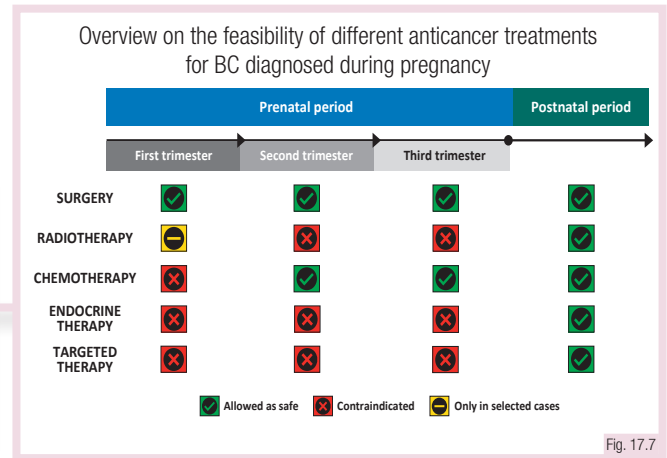
1. Does surgical approach differ between young and old patients?
2. What is the role of pCR in adjuvant treatment decision-making for patients with BC?
3. How does young age at diagnosis influence the choices of adjuvant treatments?

Pregnancy and fertility issues in young patients during and after BC

Around 1 in every 3000 pregnancies may be complicated by a BC diagnosis. Treatment planning by a multidisciplinary team is key to balancing the potential benefits for the mother and the risks to the foetus.

The best treatment should be chosen according to the **biological characteristics** of the disease and the **trimester of pregnancy**. Termination of pregnancy does not improve prognosis.

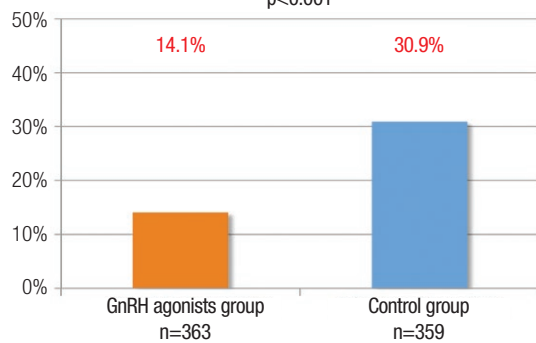
When initiated after the first trimester, **ChT can be safely administered**. Targeted agents, immunotherapy and ET are contraindicated for the duration of the whole pregnancy.



BC, breast cancer.

Premature ovarian insufficiency rates among BC patients who received (neo)adjuvant ChT with or without concurrent use of GnRH agonists

OR 0.38 (95% CI 0.26–0.57)
p<0.001



BC, breast cancer; ChT, chemotherapy; CI, confidence interval; GnRH, gonadotropin-releasing hormone; OR, odds ratio.

All young patients with BC who are candidates for gonadotoxic therapies should receive appropriate **oncofertility counselling at diagnosis**, regardless of **age and stage of disease**.

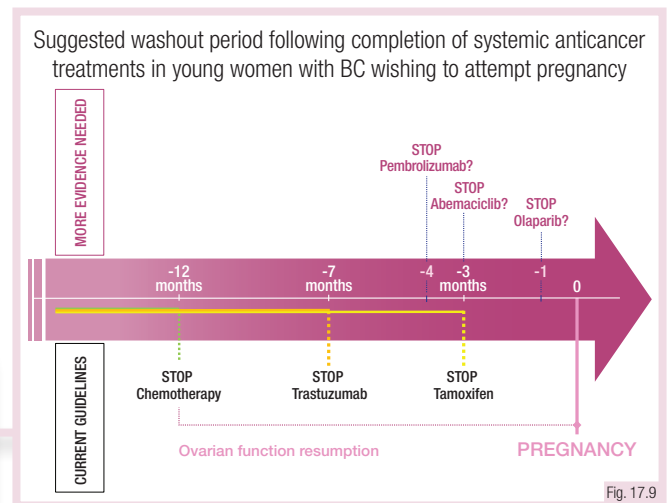
Most ChT regimens have important mid- and long-term side effects, including the risk of **premature ovarian insufficiency and infertility** in young women.

In all patients wishing to preserve ovarian function, concomitant administration of gonadotropin-releasing hormone (GnRH) agonists **during ChT** decreases the risk of premature ovarian failure, but it is not a guarantee for retaining ovarian function and therefore other methods (see below) should be sought.

Cryopreservation of oocytes/embryos before starting ChT is the standard fertility preservation technique in young patients with BC.

When oocyte/embryo cryopreservation cannot be recommended, **cryopreservation of ovarian tissue** is an alternative strategy in selected patients.

Pregnancy after proper treatment and follow-up is safe for both the mother and the child. Special considerations, including the possibility to temporarily interrupt adjuvant ET, should be discussed when planning a pregnancy in patients with luminal-like BC.



BC, breast cancer.

REVISION QUESTIONS

1. What are the main issues to consider when planning anticancer treatment in patients diagnosed with BC during pregnancy?
2. What are the indications for oncofertility counselling in young patients with BC?
3. How should patients be counselled about pregnancy after treatments for BC?

Summary: Breast cancer in young women

- BC is the most frequent malignancy in women ≤ 40 years of age and represents the leading cause of cancer-related deaths in this population
- Compared with older women, young women are characterised by a higher risk of developing more aggressive BC subtypes
- Young women diagnosed with BC have a higher probability of carrying germline pathogenic variants in BC predisposition genes. Genetic counselling is always indicated in these patients
- Surgical and RT approaches for young women with BC should follow the same recommendations as for older patients
- Systemic treatments should be tailored to clinicopathological features and patient characteristics; young age *per se* must not be considered a reason to administer more aggressive therapies
- For young patients with luminal-like node-negative BC, genomic tests can help in better selecting the patients requiring adjuvant ChT
- Risk of BC recurrence and patient preference are key when choosing adjuvant ETs
- Treatment of BC during pregnancy should follow similar considerations as outside pregnancy but take into account the trimester of pregnancy at diagnosis
- Oncofertility counselling at diagnosis is mandatory for all young patients who are candidates for ChT. Oocyte/embryo cryopreservation is the first recommended technique to be discussed for fertility preservation
- Pregnancy after proper treatment and follow-up for BC is safe for both the mother and the child. In luminal-like BC, special considerations including the possibility to temporarily interrupt adjuvant ET should be discussed

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General principles

Breast cancer (BC) incidence increases with age, and in high-income countries, ~50% of cases occur in women aged ≥ 65 years.

In Northern and Western Europe, the crude BC incidence and mortality rates among women aged ≥ 65 years are 295 and 135 per 100 000 women, respectively.

Although BC is a frequent cause of death in older women diagnosed with this disease, competing risks of mortality should also be considered.

BC mortality in relation to all-cause mortality in 14 048 BC patients with median follow-up of 4.7 years

Age group (years)	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

BC, breast cancer.

Fig. 18.1

39% of patients with BC aged ≥ 80 years who died during follow-up died because of BC

Towards a new precision-oncology paradigm for older adults with BC

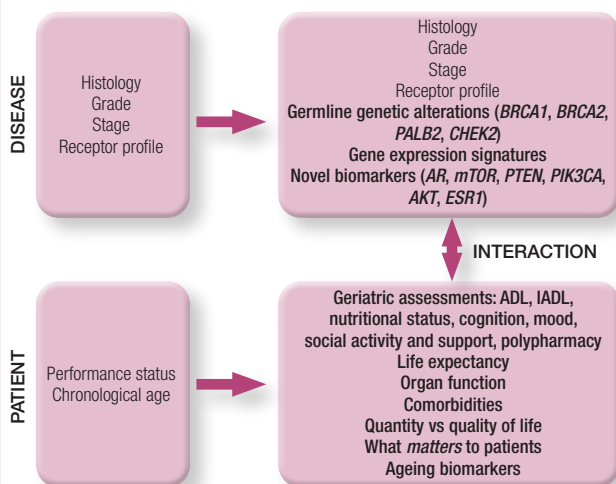


Fig. 18.2

ADL, activities of daily living; AR, androgen receptor; BC, breast cancer; CHEK2, checkpoint kinase 2; ESR1, oestrogen receptor 1; IADL, instrumental activities of daily living; mTOR, mammalian target of rapamycin; PALB2, partner and localiser of BRCA2; PTEN, phosphatase and tensin homologue.

The likelihood of germline mutations at older age is lower and therefore not commonly tested.

BC generally has a more indolent biology in older adults, with a higher prevalence of low-grade hormone receptor-positive tumours.

Nevertheless, all subtypes can occur in all age groups, and tumour biology should dictate treatment choice.

Systematic BC screening benefit decreases with age and may cause overtreatment. Screening is unlikely to be beneficial after the age of 75 years.

Older adults with BC are less likely to be treated according to the established standard of care and are more prone to receiving under- or overtreatment, compared with their younger counterparts.

Evaluation of general health status, measured by geriatric assessment, estimates life expectancy, predicts treatment toxicities and leads to geriatric/non-oncological interventions.

Differences in BC biology according to age

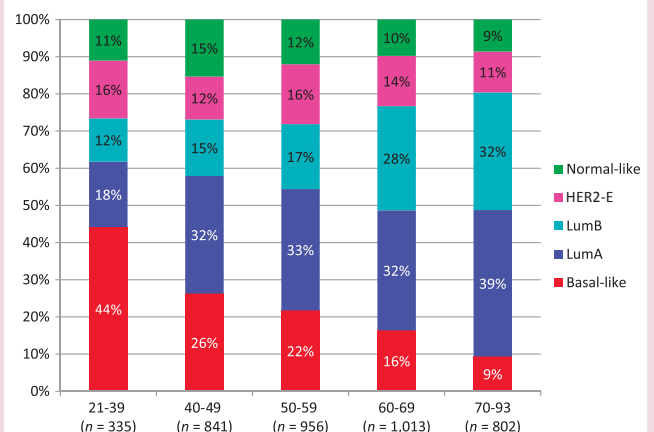


Fig. 18.3

BC, breast cancer; HER2-E, human epidermal growth factor receptor 2, enriched; LumA/B, luminal A/B.

REVISION QUESTIONS

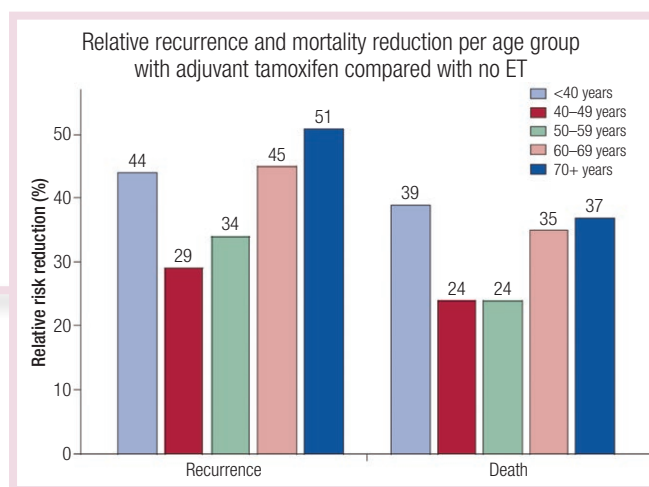
1. Does the benefit of BC screening increase with age?
2. What are the benefits of geriatric assessment in older adults with BC?
3. How are breast tumours different in older vs younger women?

Locoregional and endocrine therapy

In older adults with hormone receptor-positive BC, **primary endocrine therapy** (ET) instead of surgery is associated with an increased risk of local relapse, while mortality is not affected within the first 4–5 years of follow-up. Surgery followed by de-escalated adjuvant treatments is feasible in most older individuals.

The efficacy of **adjuvant ET** is independent of age and the choice of endocrine agent should be informed by relapse risk and toxicity profile.

Limited data are available on **adjuvant abemaciclib** in older adults. However, this cyclin-dependent kinase 4/6 (CDK4/6) inhibitor may be considered in fit, older adults with a high risk of BC recurrence.



ET, endocrine therapy.

Fig. 18.4

Study	n	Inclusion criteria	F.U. (y)	Local relapse	Overall survival (10y)
CALGB 9343	636	≥70y T ≤2 cm, N- ER+	12.6	Local/regional recurrence RT: 2% No RT: 10%	RT: 67% 13/166 died from BC No RT: 66% 8/168 died from BC
PRIME II	1326	≥65y T ≤3 cm, N- ER+	9.1	Ipsilateral BC recurrence RT: 1% No RT: 9.5%	RT: 80.8% 15/113 died from BC No RT: 80.7% 16/118 died from BC

BC, breast cancer; BCS, breast-conserving surgery; ER+, oestrogen receptor-positive; F.U., follow-up; N-, node-negative; RT, radiotherapy; T, tumour; y, years.

Fig. 18.5

Whole-breast radiotherapy (RT) is the standard of care in older adults after breast-conserving surgery (BCS), but can be omitted in those with low-risk disease and/or short life expectancy.

Partial breast irradiation is an alternative in selected cases (grade 1-2 pN0, hormone receptor-positive, human epidermal growth factor receptor 2 [HER2]-negative tumours ≤30 mm with radial margins ≥1 mm).

Hypofractionated regimens offer similar locoregional control and safety as standard schedules, while requiring fewer visits, and are recommended in older adults.

Adjuvant **bisphosphonates** may be considered also in older adults who have **higher prevalence of osteopenia and osteoporosis**.

The **pharmacology** of systemic agents may change as a person ages and can have an impact on toxicity and efficacy.

Upfront dose reductions and schedule modifications are controversial but should be considered based on the **pharmacology** and toxicity of individual agents.

Parameter changes	Clinical implications	Systemic agents
Decreased absorption	Oral chemotherapy may be less effective in older adults	Capecitabine
Reduced distribution volume	Serum concentrations and toxicity of several cytotoxic agents might increase	Taxanes
Reduced hepatic metabolism	Serum concentrations of cytotoxic agents may change	Taxanes, cyclophosphamide, anthracyclines
Reduced renal excretion	Dosing should be adapted to avoid increased serum concentrations	Carboplatin, methotrexate

Fig. 18.6

REVISION QUESTIONS

- Does primary surgery lead to higher survival compared with primary ET in older adults with hormone receptor-positive BC?
- Should all older adults with BC treated with BCS receive adjuvant RT?
- Does age have a clinically relevant impact on the pharmacokinetics of anticancer drugs?

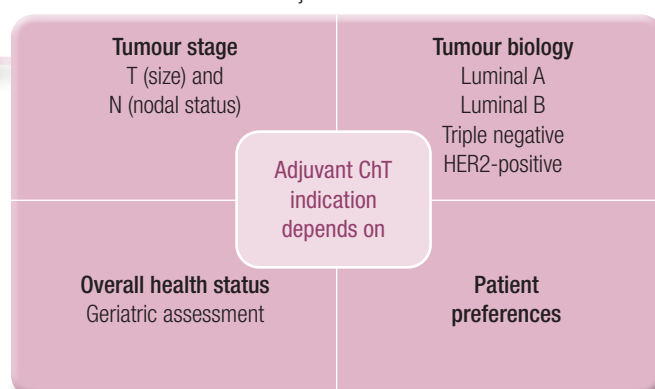
Chemotherapy and targeted therapy

The use of **adjuvant chemotherapy (ChT)** should not be guided by age alone, but also by geriatric assessment, tumour stage and biology, general health status and patient's preferences.

ChT may be considered for selected fit, older adults with high-risk luminal **node-positive tumours** and triple-negative or HER2-positive tumours.

The **Age Gap Decision tool** (<https://agegap.shef.ac.uk/>) may be used to guide discussions with patients about adjuvant ChT.

Considerations for adjuvant ChT recommendations



ChT, chemotherapy; HER2, human epidermal growth factor receptor 2.

Fig. 18.7

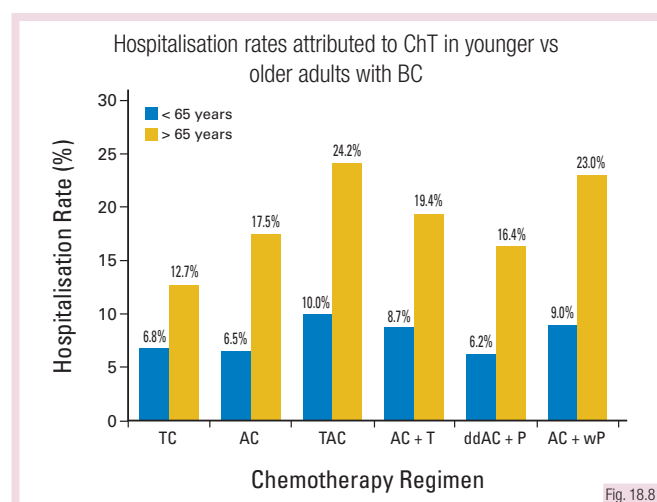


Fig. 18.8

AC, doxorubicin and cyclophosphamide; BC, breast cancer; ChT, chemotherapy; ddAC, dose-dense AC; P, paclitaxel; T, docetaxel; TAC, docetaxel, doxorubicin, cyclophosphamide; TC, docetaxel and cyclophosphamide; wP, weekly paclitaxel.

Neoadjuvant systemic therapy (ChT or ET) may be considered in carefully selected, fit, older adults as it is in younger patients.

For older adults with hormone receptor-positive metastatic BC (MBC), **ET is preferred** with a CDK4/6 inhibitor added in the first or second line. For those requiring ChT, single-agent regimens should be considered.

For HER2-positive MBC, similarly to younger patients, trastuzumab ± pertuzumab can be chosen, preferably in combination with weekly paclitaxel or another ChT partner, or with ET in luminal disease. **Age-specific data on novel anti-HER2 agents are still limited.**

Standard adjuvant ChT regimens in older adults include taxanes (**docetaxel/cyclophosphamide** or weekly paclitaxel), and/or anthracyclines for some.

Adjuvant trastuzumab is safe and effective in older adults. Shorter courses or omission of ChT may be considered in case of low-risk tumours and/or general health problems. Adjuvant anti-HER2 therapy (≤1 year duration) with a taxane (or without ChT in frail persons) may be favoured.

Older persons are more prone to ChT side effects. The Cancer and Aging Research Group-Breast Cancer (CARG-BC) **ChT toxicity prediction tool** can be used to predict these risks and inform discussions with patients (https://www.cancercalc.com/carg_bc.php).

Practical tools to inform decision-making for older adults with BC

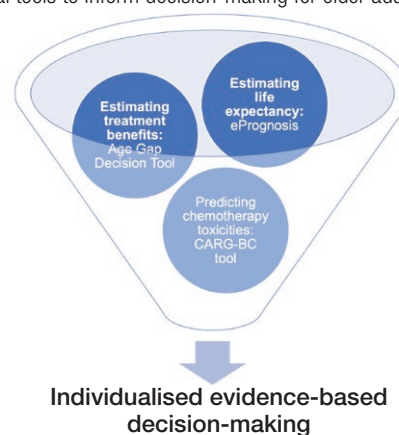


Fig. 18.9

BC, breast cancer; CARG-BC, Cancer and Aging Research Group-Breast Cancer.

REVISION QUESTIONS

1. What tools are available to predict the benefits and complications of ChT in older adults with BC?
2. Which ChT regimens are preferentially used in older adults with early BC?
3. Which treatments can be considered in older adults with HER2-positive MBC?

Summary: Breast cancer in the older population

- Approximately 50% of BC cases in high-income countries are diagnosed in adults ≥ 65 years, and a significant proportion of older patients with BC ultimately die from non-cancer related causes
- BC has a more indolent biology and behaviour in older adults; however, the entire range of BC subtypes is also observed in this age group
- Geriatric assessments allow an accurate evaluation of functional age to direct oncological and non-oncological personalised interventions to optimise BC management
- Primary ET may be considered instead of surgery in older adults with hormone receptor-positive BC with limited life expectancy
- Adjuvant ET improves BC mortality outcomes regardless of age. Abemaciclib may be considered for fit, older patients at high risk of recurrence
- The benefit of adjuvant RT after BCS depends on life expectancy and risk of BC relapse
- Adjuvant ChT is feasible, but older adults are more prone to experience complications. ChT regimens evaluated in older adults should be favoured
- Neoadjuvant and post-neoadjuvant systemic therapy approaches may be considered in carefully selected, fit, older adults similarly to their younger counterparts
- Upfront surgery followed by subsequent de-escalated adjuvant treatment may often be feasible
- Adjuvant trastuzumab is safe and effective in older adults but shorter courses of trastuzumab or omission of ChT may be considered in older adults with low-risk tumours and/or severe comorbidities/general health problems
- For older adults with MBC, ET $\pm$ CDK4/6 inhibitors is safe and well tolerated. The safety and efficacy of additional targeted agents is less clear
- For those with MBC: if ChT is required, single-agent regimens should be considered; if anti-HER2 therapy is required, the same considerations as for younger individuals should apply; however, age-specific data on novel anti-HER2 agents are limited

Further Reading

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Local recurrence of breast cancer: definition, staging and primary therapy

Local recurrence (LR) of breast cancer (BC) is defined as the **reappearance** of cancer on the ipsilateral chest wall or within residual breast tissue after mastectomy or breast-conserving therapy (BCT).

Regional recurrence (RR) describes tumour involving regional lymph nodes (LNs). Following previous locoregional therapy patients may have aberrant lymphatic drainage, and RR may occur in non-typical locations such as contralateral axillary LNs.

At the time of **locoregional recurrence (LRR)**, restaging should rule out metastatic disease. Recurrence should be confirmed **histologically**, including receptor status.

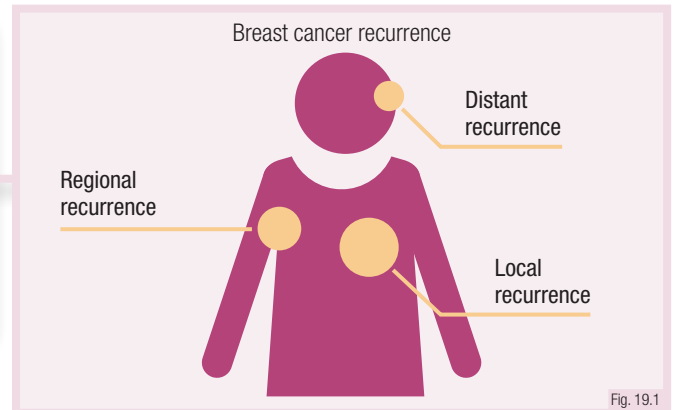


Fig. 19.1

Local treatment may provide palliation even in the presence of metastases



Fig. 19.2

Patients not eligible for second BCT should be treated with mastectomy. If reconstruction is desired, **prior** use of radiotherapy (RT) as well as a new indication for postoperative RT should be considered.

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

For patients who did not undergo postmastectomy RT before, **comprehensive chest wall and regional nodal RT** is the standard treatment. Treatment limited to the chest wall, or to involved LNs only, **increases the risk** for subsequent recurrences in those patients.

Factors associated with poor overall survival at the time of LRR include: age ≤ 45 years, large primary tumours, multiple macroscopically involved LNs, extracapsular invasion, axilla level 3/4 (supra/infracavicular) failures, combined local and nodal LRR and interval < 48 months to first LRR.

Patients with **isolated LR** should be treated with **curative intent**. Historically, salvage mastectomy was the standard treatment after BCT. However, a second BCT can be considered in selected low-risk patients (based on tumour- and patient-related factors) where side effects from previous RT are limited and a good cosmetic outcome is anticipated.

Locoregional treatment of LRR can be added in case of metastatic disease for **palliation and/or to prolong progression-free survival**.

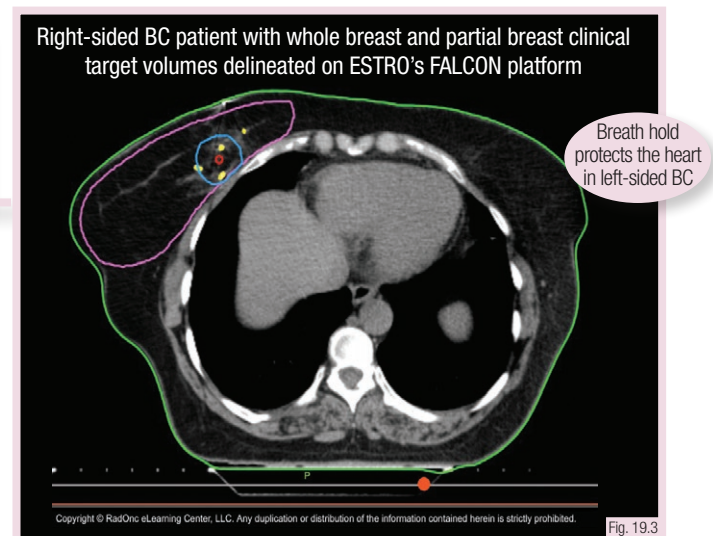


Fig. 19.3

Green: body contour. Pink: breast. Yellow: clips. Red: primary tumour bed. Light blue: CTV partial breast. BC, breast cancer; CTV, clinical target volumes; ESTRO, European Society for Radiotherapy and Oncology.

REVISION QUESTIONS

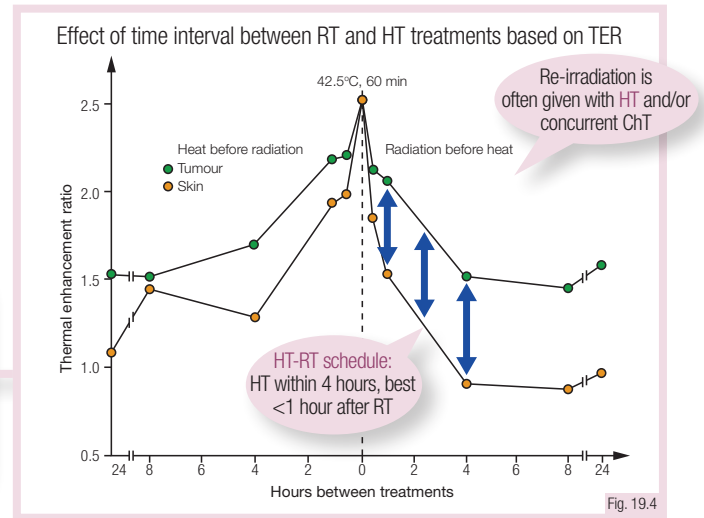
1. Is histological confirmation needed in cases of suspected LRR?
2. Is it relevant to determine receptor status on this material?
3. Can local treatment be offered to patients with disseminated disease?

Local recurrence of breast cancer after mastectomy

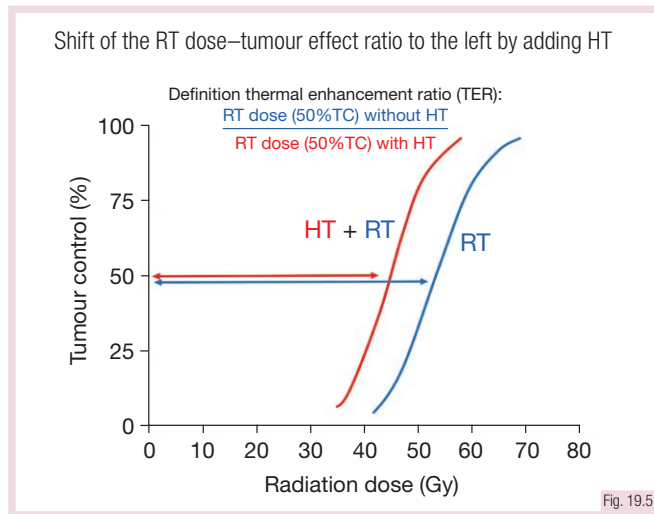
Optimal treatment to the chest wall, after previous postmastectomy RT, often includes **re-irradiation of the chest wall**.

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

Effective re-irradiation requires a dose of 50 Gy-equivalent for controlling microscopic disease. A schedule of 40 Gy in 15 fractions over 3 weeks is often preferred to reduce adverse effects from the accumulated radiation dose. Re-irradiation combined with **hyperthermia (HT)** may also be considered.



ChT, chemotherapy; HT, hyperthermia; RT, radiotherapy; TER, thermal enhancement ratio.



HT, hyperthermia; RT, radiotherapy; TC, tumour control.

HT is given once or twice a week for 60 minutes at a median temperature of 41–43°C, preferably shortly before or after RT. **Radiosensitisation** by HT is quantified using the thermal enhancement ratio (TER).

Longer fractionation RT schedules are often used in combination with HT to **increase the radiosensitisation** period. The aim is good palliation for lesions >5 cm, and curative intent for lesions ≤5 cm and for microscopic disease.

A meta-analysis of phase II/III studies showed better complete response (CR) rates for BC patients treated with RT + HT than for patients receiving RT alone.

After re-irradiation to a total dose of 36 Gy in 12 fractions and HT treatment twice a week to 42°C, the patient achieved a **durable CR**.

The amount of **residual breast tissue** left after surgery has a major impact for defining **target volumes**, as recommended by the European Society for Radiotherapy and Oncology (ESTRO) guidelines.

Durable complete response after 36 Gy re-irradiation combined with hyperthermia



Fig. 19.6

REVISION QUESTIONS

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

Local recurrence of breast cancer after breast-conserving therapy

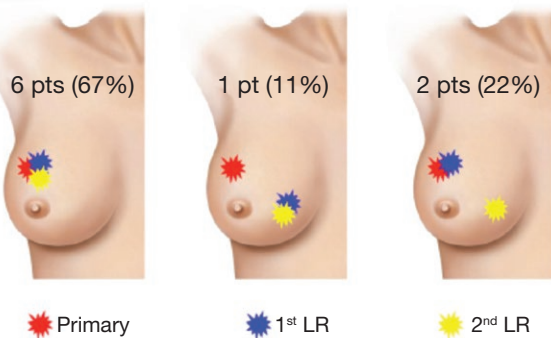
Based on a meta-analysis of 17 randomised trials, patients aged >40 years at the time of first BCT, consisting of surgery and RT, have a 10-year LRR rate of <3%.

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

Mastectomy is the standard of care for most patients with LR following BCT. Patients treated with breast-conserving surgery alone for a LR, without RT, have ~35% risk of a subsequent LRR.

Likelihood of achieving durable tumour control depends on tumour size, and is best for microscopic disease

Sites of primary tumour and first and second LRs



LR, local recurrence; pts, patients.

Fig. 19.8

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

Partial breast RT using other techniques, such as external beam RT, is a valid option based on results of the NRG Oncology/Radiation Therapy Oncology Group (RTOG) 1014 study.

Currently, a global collaboration led by the Groupe Européen de Curiethérapie (GEC)-ESTRO is developing guidelines for selection and treatment of patients for second BCT.

Adding RT prolongs PFS in BCS

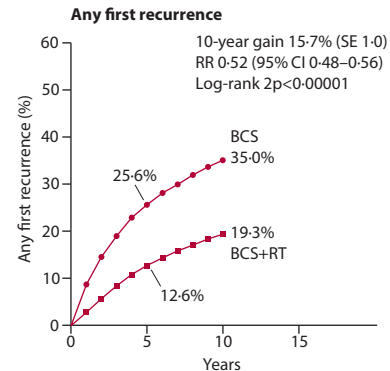


Fig. 19.7

BCS, breast-conserving surgery; CI, confidence interval; PFS, progression-free survival; RR, rate ratio; RT, radiotherapy; SE, standard error.

In selected patients who request breast conservation, salvage BCT can be considered even in the case of earlier RT. Careful patient selection is needed and postoperative partial breast irradiation is required.

Tumour size (<2 cm), location, disease-free interval, genetics (*BRCA*), absence of previous RT-related toxicity, favourable tumour subtype and patient preference should be evaluated.

Rule of thumb for second BCT: i) patients who are eligible for partial breast RT (low-risk features), ii) disease-free interval of >36 months, iii) second BCT will maintain good cosmesis, iv) no RT toxicity, v) re-irradiation (re-RT) can be performed with expected minimal toxicity.

Interstitial brachytherapy after salvage BCS



Fig. 19.9

BCS, breast-conserving surgery.

REVISION QUESTIONS

1. What is the standard treatment of LR after BCT?
2. What are the rates of LRR after BCT for a LR with and without RT?
3. Can salvage BCT be offered to all patients with LR after BCT?

Summary: Locally recurrent disease

- At the time of LRR after mastectomy or BCT, all patients must undergo disease restaging prior to local treatment, to rule out metastatic disease
- Local treatment may provide palliation even in the presence of disseminated disease
- Any suspected LRR should be confirmed histologically, including the assessment of standard prognostic and predictive factors
- Patients with isolated LRR represent a heterogeneous group. Salvage treatment depends on the primary locoregional treatment, previous systemic treatment, site of recurrence, extent of disease and the patient's comorbidities and wishes
- Management is based on a multidisciplinary assessment. It generally requires combined modality therapy, which should be tailored to patient-, tumour- and treatment-related factors, taking into account the available expertise and infrastructure which may require referral to specialised centres
- Patients undergoing mastectomy should be evaluated for indications for postmastectomy RT, independent of immediate or delayed breast reconstruction planning
- Second BCT consisting of lumpectomy with re-irradiation can be offered for selected patients based on low-risk features and absence of limiting side effects after previous RT
- For LR of BC in previously irradiated areas, HT added to re-irradiation is the treatment of choice. When possible, this should be preceded by volume-reducing systemic therapy or surgery
- Chances for durable tumour control depend on the size of the tumour: microscopic > small > extensive
- Maximal effort should be applied to limit the potential long-term toxicity

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Image sources: Fig. 19.1. melbournebreastcancersurgery.com.au; 19.3. courtesy of RadOnc eLearning Center: EduCase, used with permission; 19.4. adapted from Overgaard J. *Int J Radiat Oncol Biol Phys* 1980;6:1507-1517; 19.7. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet* 2011;378:1707-1716; 19.8. Hannoun-Levi JM, et al. *Radiother Oncol* 2013;108:226-231. All other figures courtesy of the authors.

Breast cancer survivorship overview

Current 5-year survival for early breast cancer (BC) is >80%. At the end of 2020, 7.8 million women were alive having been diagnosed with BC in the previous 5 years.

The increasing number of cancer survivors and the recognition of their complex healthcare needs has led to the creation of the field of cancer survivorship care.

Up to 50% of survivors of BC live with at least one distressing long-term physical symptom, 30% face emotional distress and 20% struggle to rejoin the workplace.

Proportion of patients reporting a severe dysfunction or symptom after diagnosis

Selected dimensions of health-related quality of life	Diagnosis*	2 years afterwards*
Emotional function (EORTC QLQ-C30)	36.3	28.3
Cognitive function (EORTC QLQ-C30)	29.9	38.4
Social function (EORTC QLQ-C30)	16.0	24.9
Fatigue (EORTC QLQ-C30)	23.1	33.6
Pain (EORTC QLQ-C30)	26.5	51.0
Dyspnoea (EORTC QLQ-C30)	27.2	45.2
Insomnia (EORTC QLQ-C30)	36.1	37.4
Financial difficulties (EORTC QLQ-C30)	13.4	14.6
Sexual enjoyment (EORTC QLQ-BR23)	29.5	38.4
Body image (EORTC QLQ-BR23)	15.2	32.7
Breast symptoms (EORTC QLQ-BR23)	13.6	23.0
Arm symptoms (EORTC QLQ-BR23)	19.7	37.4
Upset by hair loss (EORTC QLQ-BR23)	59.2	72.2

*% of patients reporting poor health-related quality of life in each domain.

EORTC, European Organisation for Research and Treatment of Cancer; QLQ-BR23, Quality of Life Questionnaire, Breast Cancer Module; QLQ-C30, Core Quality of Life Questionnaire.

Fig. 20.1

Cancer survivorship care quality framework

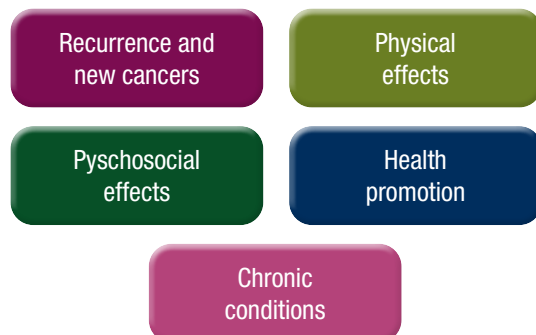


Fig. 20.2

The care plan for BC survivors should address (i) physical and (ii) psychosocial effects of cancer, (iii) concomitant chronic diseases, (iv) surveillance for recurrences and new cancers, and (v) cancer prevention and health promotion.

Importantly, there are substantial gaps between the recommendations in survivorship care guidelines and what is delivered in clinical practice, with a high proportion of patients living with unmet survivorship needs.

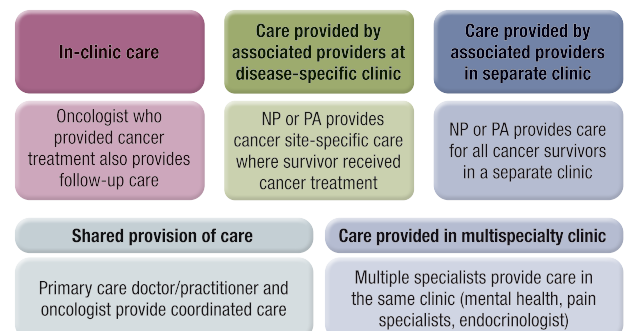
These needs should be addressed with personalised care as BC survivors are a heterogeneous group and identification of those most at risk of complications should be encouraged.

Several care models have been developed that structure the delivery of survivorship care by primary-care providers, oncologists, nurses and multidisciplinary teams.

Each survivorship care model has advantages and care-delivery challenges.

The choice of model(s) should be based on local resources and their accessibility and also influenced by the patient. Minimal standards for accreditation of survivorship models should be created and implemented.

Models of survivorship care



NP, nurse practitioner; PA, physician assistant.

Fig. 20.3

REVISION QUESTIONS

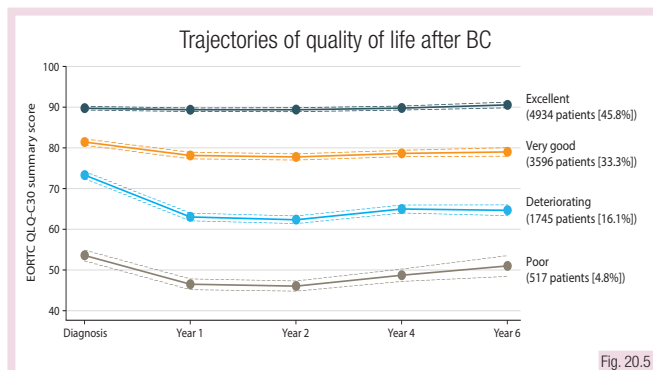
1. What are the core survivorship care domains that form the cancer survivorship care quality framework?
2. What common challenges do BC survivors face?
3. What are some examples of models of survivorship care?

Breast cancer follow-up

Individualised clinical follow-up care should be provided to all BC survivors. Survivorship care plans (SCPs) can facilitate communication on survivorship issues, although there is no evidence that SCPs alone impact outcomes. Comprehensive needs-assessment tools exist.

Detailed cancer-related history and examination should be done every 3–6 months for the first 3 years after primary therapy, then every 6–12 months for the next 2 years (total of 5 years). Afterwards, breast imaging is guided according to national screening programmes.

Follow-up during the first 5 years includes breast imaging with annual mammography. Magnetic resonance imaging (MRI) of the breast is recommended only in persons at high risk of recurrence.



BC, breast cancer; EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, Core Quality of Life Questionnaire.

A healthy lifestyle should be recommended including counselling to maintain a healthy weight, eat a balanced diet (high in vegetables, fruits, wholegrains and legumes, and low in saturated fats) and limit alcohol consumption.

Patients should maintain physical activity with the goal of 150 minutes of moderate or 75 minutes of vigorous aerobic exercise per week and strength exercises at least 2 days per week.

Survivors should avoid smoking and those who smoke should be referred to cessation counselling.

REVISION QUESTIONS

1. What is the frequency of follow-up visits that should be anticipated?
2. What exams are needed during follow-up care?
3. What health-related behaviours should be encouraged?

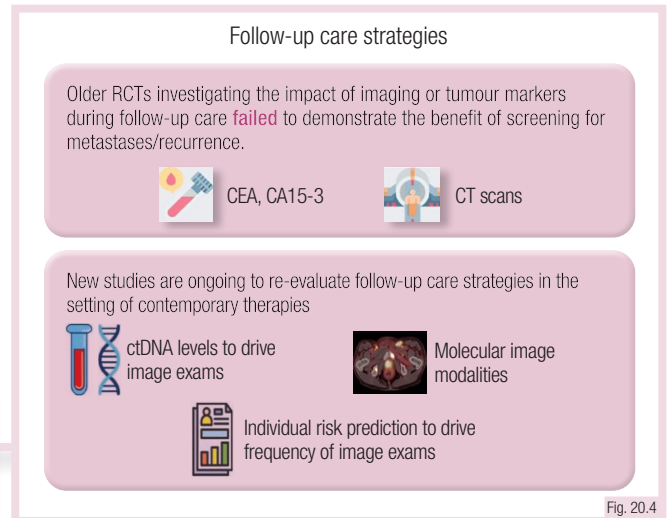


Fig. 20.4

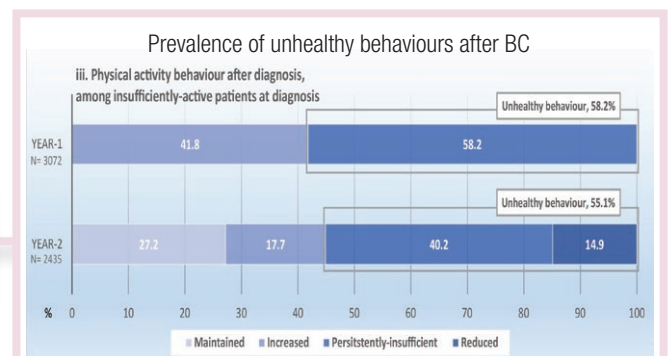
CA15-3, cancer antigen 15-3; CEA, carcino-embryonic antigen; CT, computed tomography; ctDNA, circulating tumour DNA; RCT, randomised controlled trial.

Survivorship care should include screening for other cancers as per national screening programmes. Post-menopausal survivors should have a baseline bone density scan, repeated every 2 years if an aromatase inhibitor is prescribed – frequency adapted according to results.

Cardiovascular monitoring should be performed during use of adjuvant anti-HER2 (human epidermal growth factor receptor 2) therapy or as clinically indicated.

Education on cardiac risk factors and symptoms of alert should be provided.

A patient's family history of cancer and the need for genetic counselling should be assessed, as well as social (financial, return to work) and sexual needs (fertility, pregnancy, contraception). Different quality of life trajectories after BC exist.



BC, breast cancer; N, number of patients.

Fig. 20.6

Mitigation of treatment-related side effects

Common symptoms and dysfunctions present in survivors include: **body image and sexual concerns, arm morbidity, lymphoedema, neuropathy, fatigue, insomnia, hot flushes, vaginal dryness, musculoskeletal symptoms, weight gain, cognitive impairment, emotional distress and infertility.**

Symptoms can be managed using both **pharmacological and non-pharmacological approaches.**

Treatment should be **individualised.** In the case of non-pharmacological treatment, this can be in-person, digital, self-delivered or guided.

Workflow to assess symptoms and treatment-related side effects in breast cancer survivors

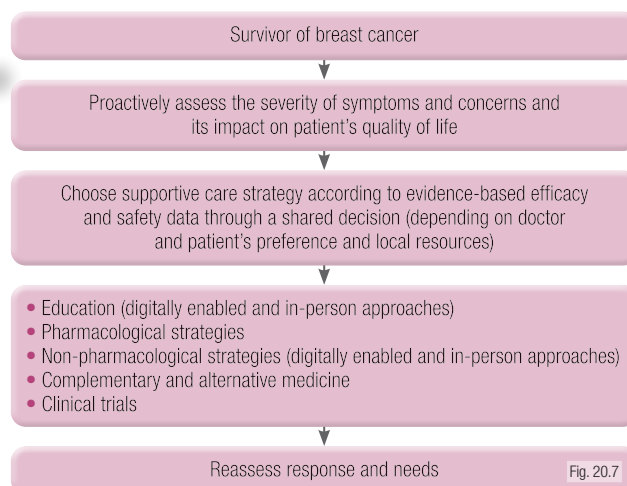


Fig. 20.7

Efficacy of selected non-pharmacological strategies in core symptoms/concerns experienced by survivors of BC

Selected non-pharmacological strategies	Fatigue	Arthralgia & muscle pain	Hot flushes	Insomnia	Emotional distress	Sexual dysfunction	Weight gain	Cognitive impairment
Physical activity*	•••	•••	•••	•••	••	•	•••	•
Cognitive behavioural therapy*	•••	–	•••	•••	•••	•••	•••	••
Cognitive training*	–	–	–	–	–	–	–	•••
Hypnosis	•• (during radiotherapy)	–	••	–	–	–	–	–
Mindfulness*	••	•	••	•••	•••	–	•	•
Acupuncture	••	•••	•••	–	–	–	–	–
Yoga*	••	•	•	•••	•	–	–	–

••• Compelling evidence (data from RCTs); •• intermediate evidence; • preliminary evidence (pilot cohort studies or underpowered RCTs).
*Care delivery of these interventions can be facilitated by digital health.
BC, breast cancer; RCT, randomised controlled trial.

Fig. 20.8

Non-adherence to endocrine therapy (ET) is associated with impaired clinical outcomes. Although reasons for non-adherence are multifactorial, ET side effects such as menopause-related symptoms and musculoskeletal symptoms can be contributing factors.

Often-neglected or **taboo symptoms** should be proactively assessed and evidence-based supportive care services proposed.

Pharmacological and non-pharmacological strategies exist to help patients cope with ET-related symptoms. **Non-pharmacological interventions are advantageous as they have fewer or no side effects and act on multiple symptoms.**

Pain should be addressed including assessment of the type of pain and contributing factors. For neuropathic pain, numbness and tingling, duloxetine can be offered.

Regarding **lymphoedema**, treatment can include weight loss counselling and referral to a physical or occupational therapist or lymphoedema specialist, including lymphovascular anastomose operations.

Survivorship is an evolving field; new therapies will come with new challenges. There are still major domains of research and care action to be explored.

ESMO Expert Consensus Statements on Cancer Survivorship: key priorities

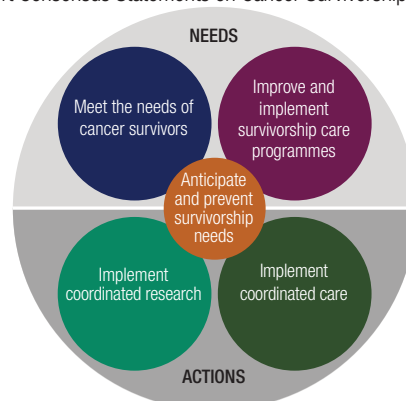


Fig. 20.9

ESMO, European Society for Medical Oncology.

REVISION QUESTIONS

1. What major symptoms should be proactively assessed in BC survivors?
2. What alternatives can patients with severe hot flushes be offered?
3. What alternatives can patients with lymphoedema be offered?

Summary: Survivorship and follow-up care

- BC survivors face a number of physical and psychosocial challenges after diagnosis of cancer, through treatment and beyond, which require coordinated multidisciplinary care
- Areas that should be addressed in BC survivorship include the physical and psychosocial effects of cancer, chronic diseases, surveillance for recurrences and new cancers, and cancer prevention and health promotion
- Several care models exist for BC survivors (nurse led, oncologist led, primary-care led)
- Follow-up during the first 5 years includes breast imaging with annual mammography. Bone health evaluation should be performed for patients using aromatase inhibitors
- A healthy lifestyle should be recommended including physical activity (150 minutes/week), maintaining a healthy weight, eating a balanced diet and cessation of smoking
- Common everyday challenges BC survivors may face include sexual and body image concerns, cognitive dysfunction, emotional distress, insomnia, persistent fatigue, neuropathic pain, hot flushes and vulvovaginal and musculoskeletal symptoms
- Pharmacological and non-pharmacological approaches exist to help patients cope with these burdensome symptoms
- Digital tools may facilitate a needs assessment and the delivery of non-pharmacological supportive care approaches

Further Reading

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Appendix 1: WHO Classification of Tumours of the Breast, 5th Edition (2019)

Epithelial tumours of the breast

- Benign epithelial proliferations and precursors
 - Usual ductal hyperplasia
 - Columnar cell lesions, including flat epithelial atypia
 - Atypical ductal hyperplasia
- Adenosis and benign sclerosing lesions
 - Sclerosing adenosis
 - Apocrine adenosis and adenoma
 - Microglandular adenosis
 - Radial scar / complex sclerosing lesion
- Adenomas
 - Tubular adenoma
 - Lactating adenoma
 - Ductal adenoma
- Epithelial-myoepithelial tumours
 - Pleomorphic adenoma
 - Adenomyoepithelioma
 - Malignant adenomyoepithelioma
- Papillary neoplasms
 - Intraductal papilloma
 - Papillary ductal carcinoma *in situ*
 - Encapsulated papillary carcinoma
 - Solid papillary carcinoma (*in situ* and invasive)
 - Invasive papillary carcinoma
- Non-invasive lobular neoplasia
 - Atypical lobular hyperplasia
 - Lobular carcinoma *in situ*
- Ductal carcinoma *in situ*
- Invasive breast carcinoma
 - Invasive breast carcinoma of no special type
 - Microinvasive carcinoma
 - Invasive lobular carcinoma
 - Tubular carcinoma
 - Cribriform carcinoma
 - Mucinous carcinoma
 - Mucinous cystadenocarcinoma
 - Invasive micropapillary carcinoma
 - Carcinoma with apocrine differentiation
 - Metaplastic carcinoma
- Rare and salivary gland-type tumours
 - Acinic cell carcinoma
 - Adenoid cystic carcinoma
 - Secretory carcinoma
 - Mucoepidermoid carcinoma
 - Polymorphous adenocarcinoma
 - Tall cell carcinoma with reversed polarity
- Neuroendocrine neoplasms
 - Neuroendocrine tumour
 - Neuroendocrine carcinoma

Fibroepithelial tumours and hamartomas of the breast

- Hamartoma
- Fibroadenoma
- Phyllodes tumour

Tumours of the nipple

- Epithelial tumours
 - Syringomatous tumour
 - Nipple adenoma
 - Paget disease of the breast

Mesenchymal tumours of the breast

- Vascular tumours
 - Haemangioma
 - Angiomatosis
 - Atypical vascular lesions
 - Postradiation angiosarcoma of the breast
 - Primary angiosarcoma of the breast
- Fibroblastic and myofibroblastic tumours
 - Nodular fasciitis
 - Myofibroblastoma
 - Desmoid fibromatosis
 - Inflammatory myofibroblastic tumour
- Peripheral nerve sheath tumours
 - Schwannoma
 - Neurofibroma
 - Granular cell tumour
- Smooth muscle tumours
 - Leiomyoma
 - Leiomyosarcoma
- Adipocytic tumours
 - Lipoma
 - Angiolipoma
 - Liposarcoma
- Other mesenchymal tumours and tumour-like conditions
 - Pseudoangiomatous stromal hyperplasia

Haematolymphoid tumours of the breast

- Lymphoma
 - Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
 - Follicular lymphoma
 - Diffuse large B-cell lymphoma
 - Burkitt lymphoma
 - Breast implant-associated anaplastic large cell lymphoma

Tumours of the male breast

- Epithelial tumours
 - Gynaecomastia
 - Carcinoma *in situ*
 - Invasive carcinoma

Metastases to the breast

Genetic tumour syndromes of the breast

- BRCA1/2*-associated hereditary breast and ovarian cancer syndrome
- Cowden syndrome
- Ataxia-telangiectasia
- Li-Fraumeni syndrome, *TP53*-associated
- Li-Fraumeni syndrome, *CHEK2*-associated
- CDH1*-associated breast cancer
- PALB2*-associated cancers
- Peutz-Jeghers syndrome
- Neurofibromatosis type 1

Abbreviations: CDH1, cadherin 1; CHEK2, checkpoint kinase 2; PALB2, partner and localiser of BRCA2; TP53, tumour protein 53; WHO, World Health Organization.

Appendix 2: UICC 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 <i>in situ</i>
Tis (DCIS)	Ductal carcinoma <i>in situ</i>
Tis (LCIS)	Lobular carcinoma <i>in situ</i> ^a
Tis (Paget)	Paget disease of the nipple not associated with invasive carcinoma and/or carcinoma <i>in situ</i> (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorised 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 4b
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 localised 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 <i>absence</i> 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 <i>absence</i> 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

- 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.

Abbreviations: AJCC, American Joint Committee on Cancer; H and E, haematoxylin and eosin; TNM, tumour, node, metastasis; UICC, Union for International Cancer Control.

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BREAST CANCER

SECOND EDITION

ESSENTIALS *for* CLINICIANS

edited by

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The second edition of *Breast Cancer: Essentials for Clinicians*, offers a comprehensive overview for early-career oncologists. Divided into two sections, the book combines fundamental with advanced knowledge, ensuring clinicians are informed of the latest advancements in the diagnosis, treatment and support of patients with breast cancer.

Section A covers essential topics including epidemiology, clinical presentation, staging, pathology and the latest treatment modalities in systemic therapy, radiotherapy and surgery. This foundation provides a robust framework for clinical decision-making.

Section B explores some of the more nuanced aspects of breast cancer care, addressing genetic testing and prognostic and predictive factors, including targeted therapies tailored to breast cancer subtypes and/or specific biomarkers. Chapters on breast cancer in men, older patients and young women, address the specificities of these unique patient populations, while a chapter on survivorship focuses on the management of early and late toxicities during and after treatment.

