ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

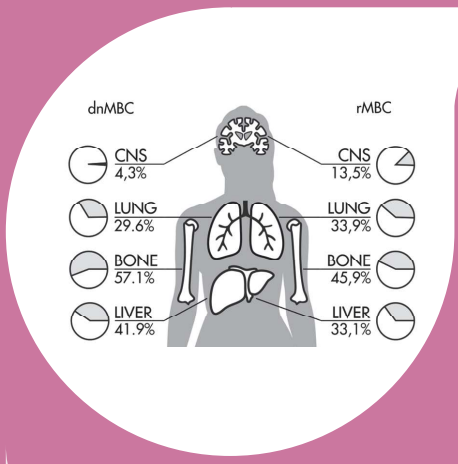
www.esmo.org

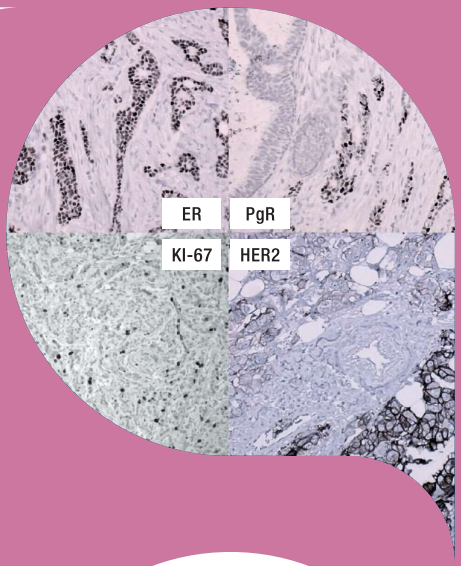
edited by
Fatima Cardoso
Vivianne Tjan-Heijnen
Ivana Božović-Spasojević
Marta Vaz Batista

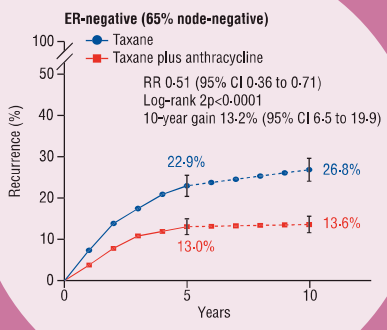
BREAST CANCER

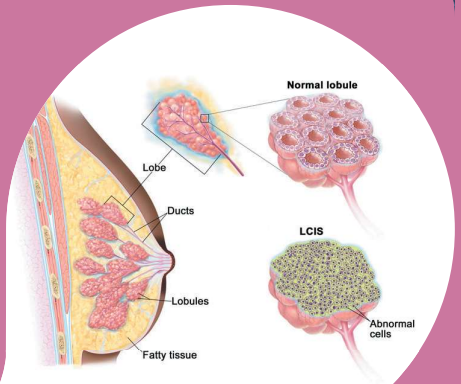
SECOND EDITION

ESSENTIALS *for* CLINICIANS









ESMO Press

Breast Cancer
Essentials for Clinicians

Second edition

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Breast Cancer
Essentials for Clinicians

Second edition

Edited by

Fatima Cardoso

Breast Unit, Champalimaud Clinical Centre/Champalimaud Foundation, Lisbon, Portugal

Vivianne Tjan-Heijnen

Department of Medical Oncology, Maastricht University Medical Center (MUMC+) Comprehensive Cancer Center, Maastricht, Netherlands

Ivana Božović-Spasojević

Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

Marta Vaz Batista

Hospital Professor Doutor Fernando Fonseca EPE, Amadora, Portugal

ESMO Press

Second edition published in 2024 by ESMO Press.

First edition published in 2017 by ESMO Press.

A CIP record for this book is available from the British Library.

ISBN: 978-88-944465-9-3

For orders, corporate sales, foreign rights, and reprint permissions, please contact:

ESMO Head Office

Licensing and Publications Sales

Via Ginevra 4

6900 Lugano

Switzerland

Tel: +41 (0)91 973 19 00

Email: publication_support@esmo.org

www.esmo.org

Contents

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
Institute for Oncology and Radiology of Serbia, Belgrade, Serbia
On behalf of all editors

Editors

Fatima Cardoso, MD, PhD

Breast Unit, Champalimaud Clinical Centre/Champalimaud Foundation, Lisbon, Portugal

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.

Vivianne Tjan-Heijnen, MD, PhD

Department of Medical Oncology, Maastricht University Medical Center (MUMC+) Comprehensive Cancer Center, Maastricht, Netherlands

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.

Ivana Božović-Spasojević, MD, PhD

Daily Chemotherapy Hospital, Institute for Oncology and Radiology, Belgrade, Serbia

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.

Marta Vaz Batista, MD

Hospital Professor Doutor Fernando Fonseca, Amadora, Portugal

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.

Contributors

G. Antonarelli
Division of New Drugs and Early Drug Development for Innovative Therapies, European Institute of Oncology, IRCCS, Milan; Department of Oncology and Hematology-Oncology (DIPO), University of Milan, Milan, Italy

L. Arecco
Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genoa; Department of Medical Oncology, U.O.C. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

N.M.L. Battisti
Department of Medicine, Breast Unit, The Royal Marsden NHS Foundation Trust, Sutton, UK

L. Biganzoli
Department of Oncology, Hospital of Prato, Azienda USL Toscana Centro, Prato, Italy

F. Cardoso
Breast Unit, Champalimaud Clinical Centre/Champalimaud Foundation, Lisbon, Portugal

M.-J. Cardoso
Breast Unit, Champalimaud Clinical Centre/Champalimaud Foundation, Lisbon, Portugal

J.J. Chan
Division of Medical Oncology, National Cancer Centre Singapore, Singapore

N. Cichowska-Cwalińska
Department of Oncology and Radiotherapy, Medical University of Gdańsk; Early Phase Clinical Trials Centre, Medical University of Gdańsk, Gdańsk, Poland

C. Corti
Division of New Drugs and Early Drug Development for Innovative Therapies, European Institute of Oncology, IRCCS, Milan; Department of Oncology and Hematology-Oncology (DIPO), University of Milan, Milan, Italy

H. Crezee
Department of Radiation Oncology, Amsterdam University Medical Centers/University of Amsterdam, Cancer Center Amsterdam, Treatment and Quality of Life, Cancer Biology and Immunology, Amsterdam, Netherlands

G. Curigliano
Division of New Drugs and Early Drug Development for Innovative Therapies, European Institute of Oncology, IRCCS, Milan; Department of Oncology and Hematology-Oncology (DIPO), University of Milan, Milan, Italy

M. de Henau
Department of Plastic, Reconstructive and Hand Surgery, Maastricht University Medical Center (MUMC+), Maastricht; GROW, School for Oncology and Reproduction, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, Netherlands

R.A. Dent
Division of Medical Oncology, National Cancer Centre Singapore, Singapore

M.A. Franzoi
Breast Cancer Survivorship Research Program – Unit INSERM 981, Gustave Roussy; Division of Interdisciplinary Patients Care Pathways (DIOPP), Gustave Roussy, Villejuif, France

A. Gennari
Medical Oncology, University of Eastern Piedmont, Novara, Italy

N. Harbeck
Breast Center, Gynecologic Cancer Center, Department of Obstetrics and Gynecology, CCC Munich and BZKF, LMU University Hospital, LMU Munich, Munich, Germany

A. Hester
Breast Center, Department of Obstetrics and Gynecology, CCC Munich and BZKF, LMU University Hospital, LMU Munich, Munich, Germany

G. Jerusalem
Medical Oncology Department, Centre Hospitalier Universitaire (CHU) de Liège and Liège University, Liège, Belgium

H. Joensuu
Comprehensive Cancer Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

O. Kaidar-Person
Breast Radiation Unit, Sheba Tel Hashomer, Ramat Gan; School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

M. La Commare
Medical Oncology, Istituto Oncologico Veneto IRCCS, Padova, Italy

M. Lambertini
Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genoa; Department of Medical Oncology, U.O.C. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

V. Lope
Cancer and Environmental Epidemiology Unit, National Center of Epidemiology, Instituto de Salud Carlos III (ISCIII), Madrid; Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), ISCIII, Madrid, Spain

M.G. Mastropasqua
Department of Precision and Regenerative Medicine and Ionian Area, University of Bari Aldo Moro, School of Medicine, Bari, Italy

A. McCartney
School of Clinical Sciences, Monash University, Melbourne; Department of Medical Oncology, Monash Health, Melbourne, VIC, Australia

I. Meattini
Department of Experimental and Clinical Biomedical Sciences ‘M. Serio’, University of Florence, Florence, Italy

T. Meretoja
Comprehensive Cancer Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

M.L.H. Milo
Department of Oncology, Aalborg University Hospital, Aalborg, Denmark

B.V. Offersen
Department of Experimental Clinical Oncology, Department of Oncology, Danish Centre for Particle Therapy, Aarhus University Hospital Clinical Medicine, Aarhus University, Aarhus, Denmark

S. Paluch-Shimon
Sharett Institute of Oncology, Hadassah University Hospital & Faculty of Medicine Hebrew University, Ein Kerem, Jerusalem, Israel

F. Penault-Llorca
Département de Pathologie et de Pathologie Moléculaire, Centre Jean Perrin, Clermont-Ferrand, France

M. Pollán
Cancer and Environmental Epidemiology Unit, National Center of Epidemiology, Instituto de Salud Carlos III (ISCIII), Madrid; Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), ISCIII, Madrid, Spain

P. Poortmans
Department of Radiation Oncology, Iridium Network, Wilrijk-Antwerp; Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

C. Pottier
Medical Oncology Department, Centre Hospitalier Universitaire (CHU) de Liège, Liège, Belgium

E. Senkus
Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland

M.L. Smidt
GROW, School for Oncology and Reproduction, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht; Department of Surgery, Maastricht University Medical Center (MUMC+), Maastricht, Netherlands

B. Sousa
Breast Unit, Champalimaud Clinical Centre/Champalimaud Foundation, Lisbon, Portugal

J.Z.C. Tan
Division of Medical Oncology, National Cancer Centre Singapore, Singapore

T.J. Tan
Division of Medical Oncology, National Cancer Centre Singapore, Singapore

C. Valenza
Division of New Drugs and Early Drug Development for Innovative Therapies, European Institute of Oncology, IRCCS, Milan; Department of Oncology and Hematology-Oncology (DIPO), University of Milan, Milan, Italy

J.A.F. van Rooij
Department of Plastic, Reconstructive and Hand Surgery, Maastricht University Medical Center (MUMC+), Maastricht; GROW, School for Oncology and Reproduction, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, Netherlands

I. Vaz-Luis
Breast Cancer Survivorship Research Program – Unit INSERM 981, Gustave Roussy; Division of Interdisciplinary Patients Care Pathways (DIOPP), Gustave Roussy, Villejuif, France

G. Viale
Department of Pathology and Laboratory Medicine, European Institute of Oncology IRCCS, Milan, Italy

M.T.F.D. Vrancken Peeters
Department of Surgery, Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam; Department of Surgery, Amsterdam University Medical Center, Amsterdam, Netherlands

H. Wildiers
University Hospitals Leuven, Department of General Medical Oncology, Leuven, Belgium

R. Wuerstlein
Breast Center, Gynecologic Cancer Center, Department of Obstetrics and Gynecology, CCC Munich and BZKF, LMU University Hospital, LMU Munich, Munich, Germany

Y.B. Wygoda
Sharett Institute of Oncology, Hadassah University Hospital & Faculty of Medicine Hebrew University, Ein Kerem, Jerusalem, Israel

Abbreviations

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

The editors would like to thank the authors for their hard work and dedication to the task of updating this book and express their gratitude to the members of the ESMO Educational Publications Working Group and Educational Committee for their support in this initiative, as well as the ESMO Breast Cancer Faculty. The editors also wish to thank Claire Bramley, Aude Galli, Matthew Hillier and Nicki Peters from ESMO, for their support in the preparation of this publication.

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

What every oncologist should know

1 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

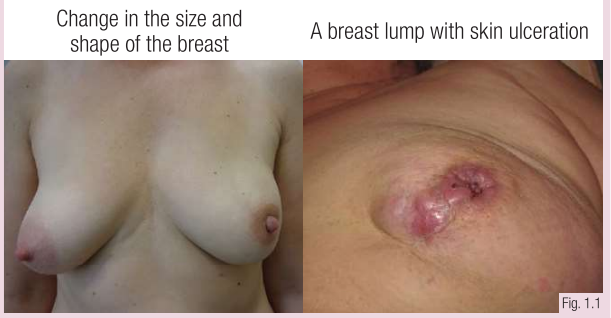


Fig. 1.1

Inflammatory cancer in the left breast

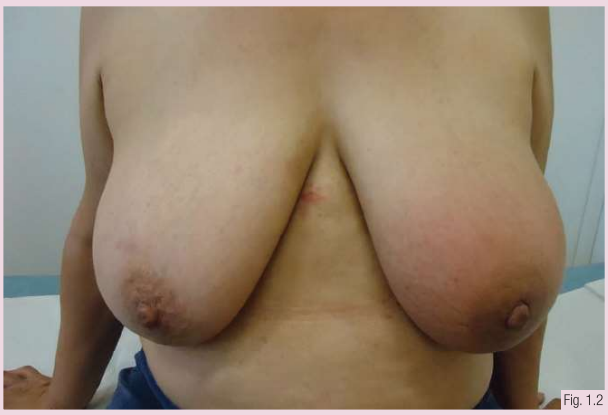


Fig. 1.2

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

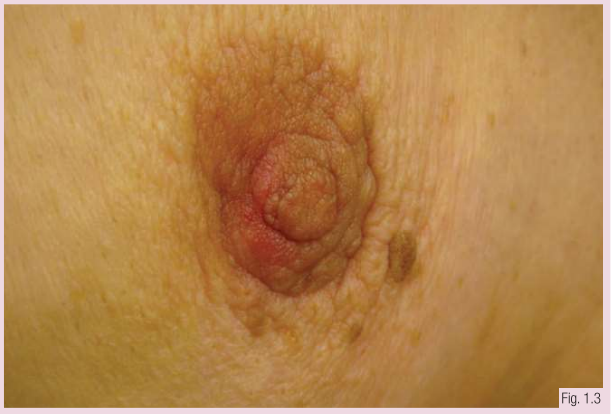


Fig. 1.3

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.

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

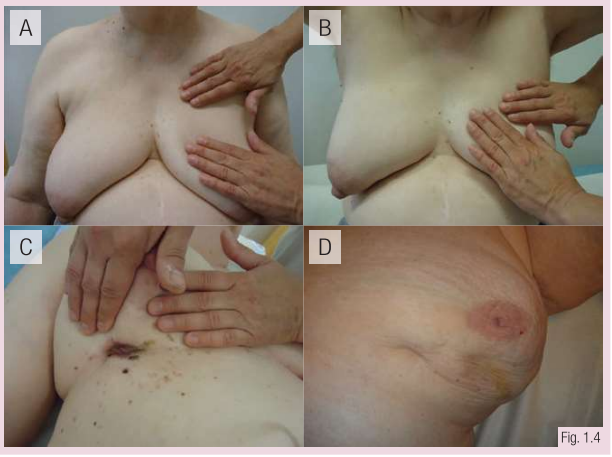


Fig. 1.4

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

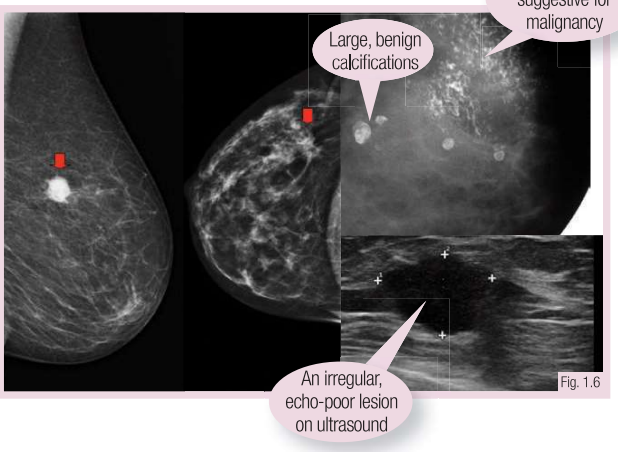


Fig. 1.6

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?

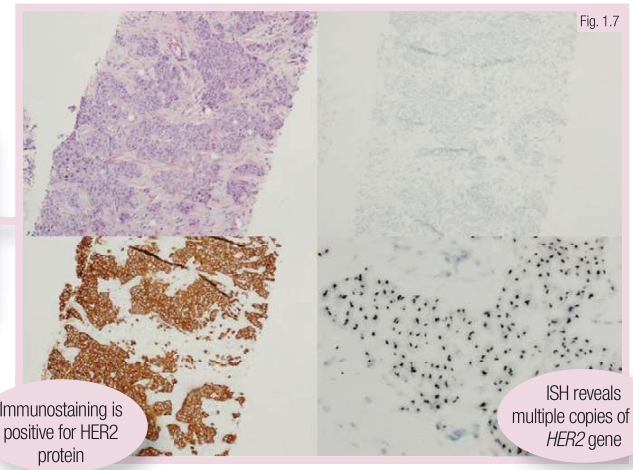
Percutaneous needle biopsy and axillary staging

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.

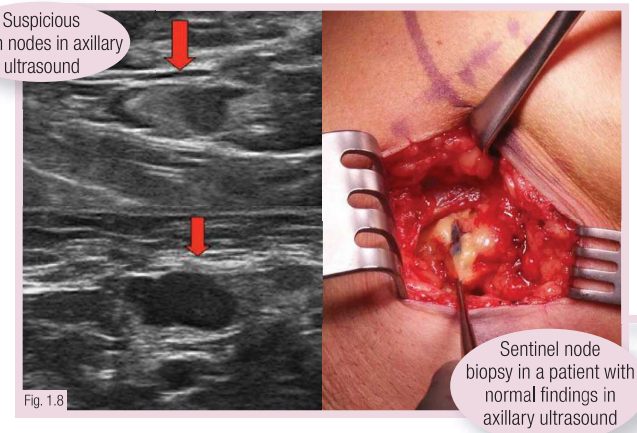
The diagnostic accuracy of fine needle aspiration cytology (FNAC) is lower than that of CNB and depends on the skill of the investigator. FNAC may be used to detect LN metastases and is also useful in the diagnosis and treatment of breast cysts.

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.

Axillary ultrasound and sentinel lymph node biopsy



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.

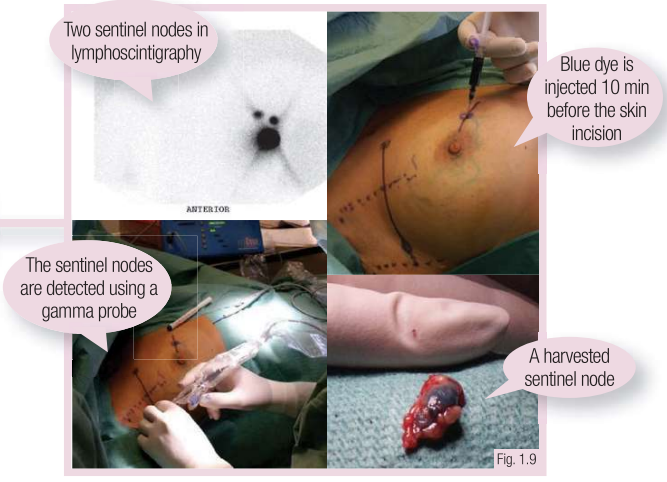
A sentinel lymph node biopsy (SLNB) is carried out when metastases are not detected at axillary US.

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.

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

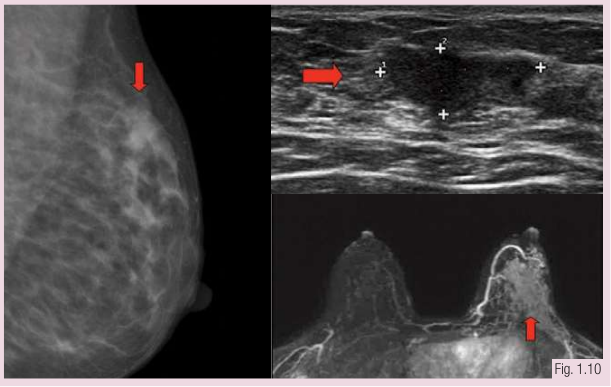


Fig. 1.10

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

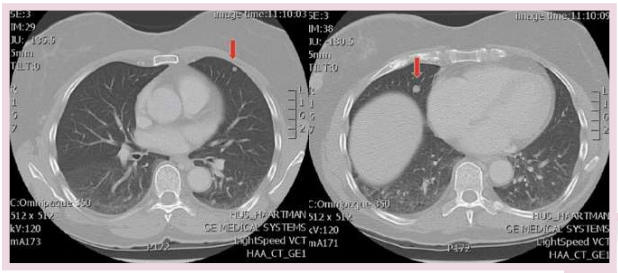


Fig. 1.11

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

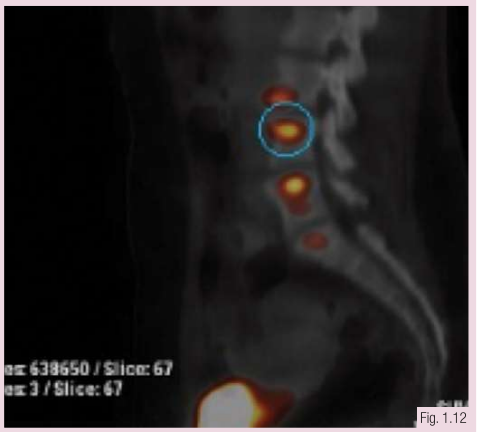


Fig. 1.12

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

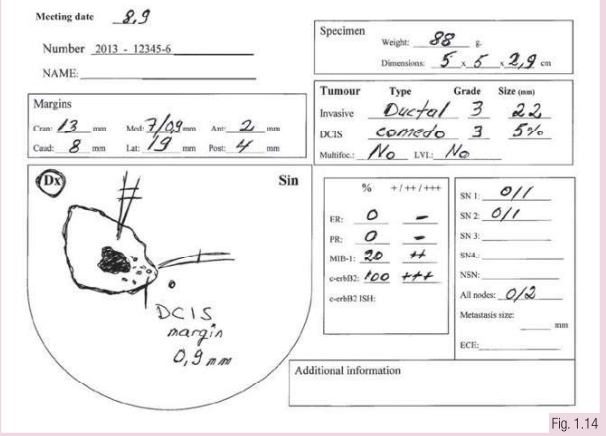


Fig. 1.14

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

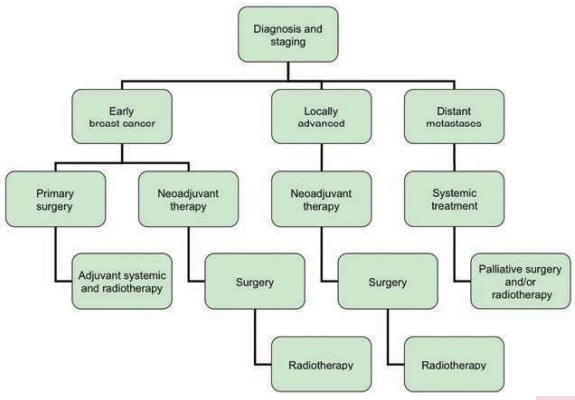


Fig. 1.15

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.

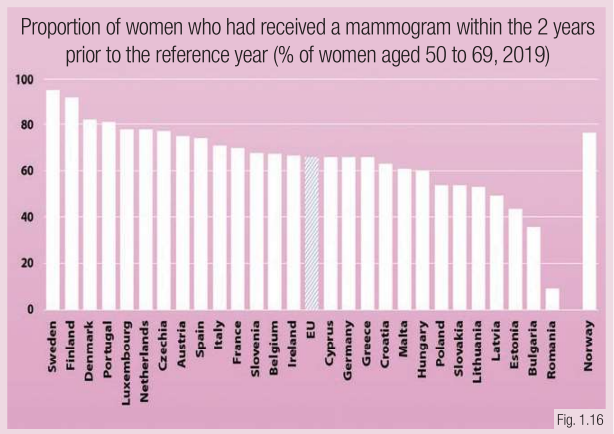


Fig. 1.16

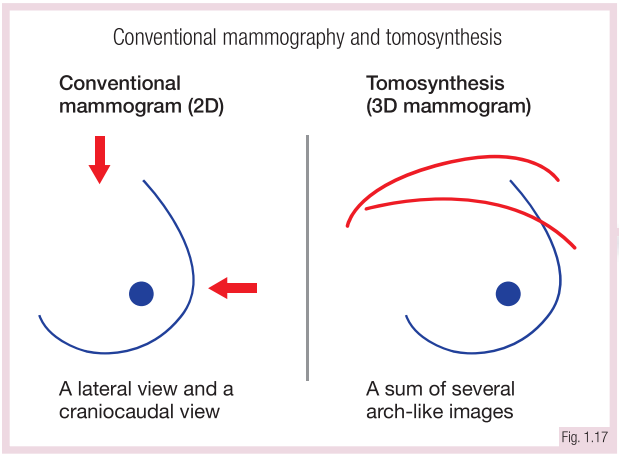


Fig. 1.17

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.

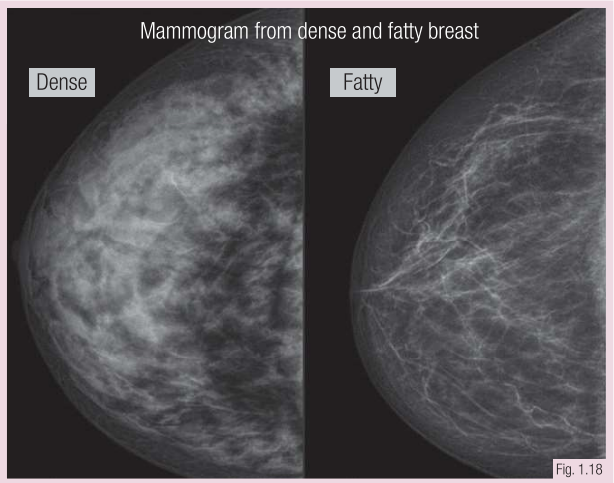


Fig. 1.18

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.

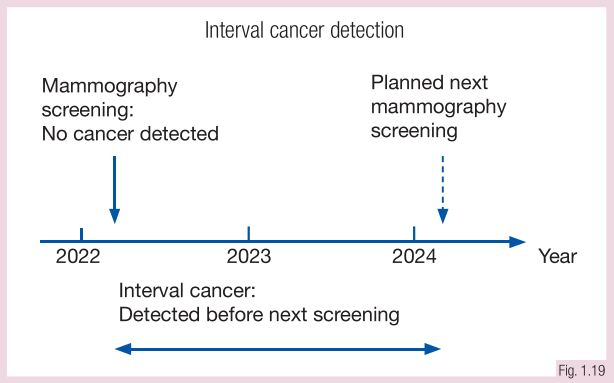


Fig. 1.19

US-guided breast biopsy

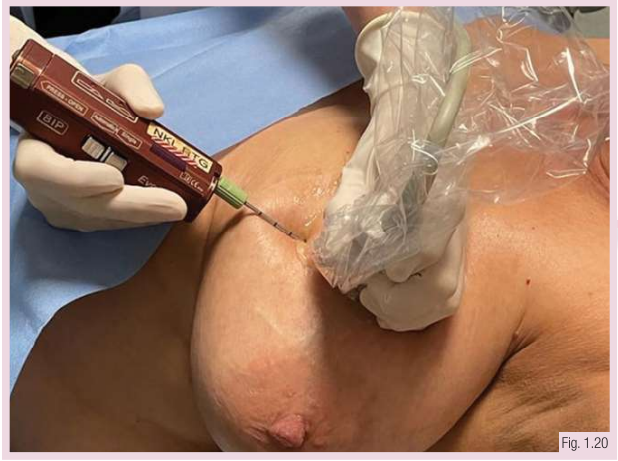


Fig. 1.20

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.

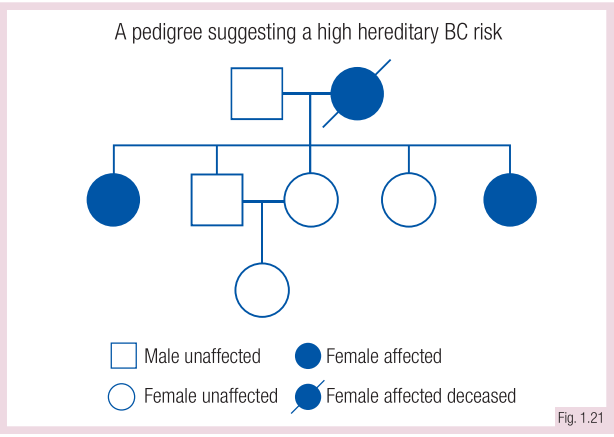


Fig. 1.21

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

Bakker MF, de Lange SV, Pijnappel RM, et al. Supplemental MRI screening for women with extremely dense breast tissue. N Engl J Med 2019; 381:2091–2102.

Biganzoli L, Marotti L, Hart CD, et al. Quality indicators in breast cancer care: an update from the EUSOMA working group. Eur J Cancer 2017; 86:59–81.

Flemban AF. Overdiagnosis due to screening mammography for breast cancer among women aged 40 years and over: a systematic review and meta-analysis. J Pers Med 2023; 13:523.

Giorgi Rossi P, Lebeau A, Canelo-Aybar C, et al; ECIBC Contributor Group. Recommendations from the European Commission Initiative on Breast Cancer for multigene testing to guide the use of adjuvant chemotherapy in patients with early breast cancer, hormone receptor positive, HER-2 negative. Br J Cancer 2021; 124:1503–1512.

European Guidelines on Breast Cancer Screening and Diagnosis. https://healthcare-quality.jrc.ec.europa.eu/ecibc/european-breast-cancer-guidelines (date last accessed, 10 October 2024).

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

Krop I, Ismaila N, Andre F, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline focused update. J Clin Oncol 2017; 35:2838–2847.

Loibl S, André F, Bachelot T, et al; ESMO Guidelines Committee. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2024; 35:159–182.

Sessa C, Balmaña J, Bober SL, et al; ESMO Guidelines Committee. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. Ann Oncol 2023; 34:33–47.

Wang M, He X, Chang Y, et al. A sensitivity and specificity comparison of fine needle aspiration cytology and core needle biopsy in evaluation of suspicious breast lesions: a systematic review and meta-analysis. Breast 2017; 31:157–166.

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.