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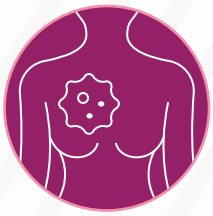
An Overview of Breast Cancer

Understanding breast cancer classification, screening techniques, treatment principles, and new research directions



Classification of breast cancer (BC)

Morphological classification (mainly diagnostic and prognostic)[1]

- Tumour type: Currently there are 18 different tumour types
- Tumour grade: 3 grades are identified, depending on the degree of differentiation
- Tumour stage: Determined based on tumour invasiveness, lymph node status, infiltration of other tissues, and lesions at distant sites

Molecular classification (mainly predictive but can provide diagnostic and prognostic values)[1]

Single gene classifier
- Oestrogen receptor *(ER)*, human epidermal growth factor receptor 2 *(HER2)*, and *PDL-1* inform treatment decision
- Progesterone receptor (*PR*), *Ki67* serve as prognostic markers
- *BRCA1*, *BRCA2*, and *PALB2* are considered as familial predisposition genes

Multiple gene classifier
- Multiple genes are assessed simultaneously to evaluate risk in specific BC classes, particularly the luminal class

Global gene expression and genomic classification
- Enriched in intrinsic molecular subtypes such as luminal, *HER2*, and basal
- Classification based on mutational signatures
- Integrated classification based on a combination of transcriptomic and genomic classification

Variables determining therapy classification

- Patients either received systemic therapy-naive (those who have not received systemic therapy) or treated (those who have undergone systemic therapy previously)
- Patients either neoadjuvant therapy-treated or adjuvant-treated
- Types of therapy such as hormonal, cytotoxic, targeted, or immunotherapy
- Line of therapy (first-line vs. second- or third-line therapy)

BC biomarkers

Molecular biomarkers[2]

Employed to characterise heterogeneity and define molecular subtypes for improved cancer management and prognosis
- Cell proliferation marker: *Ki67*
- Receptor status: Oestrogen/oestradiol receptor *(ER), PR, and HER2*

Genetic biomarkers

- Facilitate effective characterisation of mutations that could increase the likelihood of detecting aggressive BC
- Involve gene variants identified in genetic sequencing and gene expression profiling/signatures (GEP/S)

GEP/S[2]

- Multigene expression analysis of the tumour biopsy samples
- Serves as a valuable tool for BC prognosis and management
- Elucidates tumour variations, even between tumours that have the same genetic predispositions, immunohistochemical (IHC) markers, or anatomical staging

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BC screening[2,3]

- BC screening encompasses screening tests to identify BC or abnormalities at an early stage, before appearance of symptoms

- Early diagnosis of BC:
  - Requires improved accessibility to diagnostic care services
  - Enables accurate identification using appropriate diagnostic tools
  - Facilitates timely access to cancer treatment

BC screening recommendations[4]

For women with average BC risk

Mammography is the most recommended screening method
- Ensures early detection of smaller cancer lesions, leading to less invasive treatment and minimal BC-related mortality
- Screening frequencies vary across different age groups

For women with high BC risk (as determined based on family history, genetics [*BRCA1/2* and other mutations], and radiation exposure)

Screening tests
- Magnetic resonance imaging (MRI) screening recommended in addition to annual mammography
- Additional screening methods, such as ultrasound or digital breast tomosynthesis (DBT) recommended for dense breasts
- Guidelines are continuously evolving to provide more personalised screening strategies tailored to individual risks and benefits

- **An advanced mammography technique called DBT, utilises low-dose X-ray device to visualise breast tissue in three dimensions**
- **Clinical guidelines recommend DBT for BC screening considering its risks**
- **Radiation exposure and cost of examination are factors affecting the application of DBT**

Established methods of BC screening and diagnosis[4]

Technique	Features	Sensitivity	Specificity
Breast physical examination	Entails inspection and palpation of the breast and surrounding areas	–	–
Clinical breast examination	Performed by a physician	40% to 69%	88% to 99%
Breast self-examination	Performed by the patient herself	12% to 41%	–
Conventional mammography	Can identify abnormal areas but cannot prove that it is cancer	86.9%	88.9%
Full-field digital mammography	Uses digital detectors for image conversion	70% to 88.8%	75.2% to 92%
Digital breast tomosynthesis	Advanced mammography technology, involves 3D reconstruction of breast tissue Increases detection rates and decreases recall rates	~ 90%	–
Ultrasonography	Detects fluid-filled cysts and solid tumors Primary imaging modality	100%	89.1%
MRI	Non-invasive with no radiation	58%; 93%-100% in conjunction with mammography	–
Positron emission tomography/ computed tomography (PET/CT)	Combination of functional and anatomical imaging Useful for staging and monitoring	61% to 85%	76% to 80%

Awareness of BC and its early symptoms can enable an individual to seek expert's clinical opinion on time, leading to improved treatment outcomes[4]

Problems with current screening and diagnostic tools[4]

- Inadequate access to BC diagnostic tools can cause delays in diagnosis
- False positive screening may lead to overdiagnosis and subsequent overtreatment
- Screening procedures can cause pain, discomfort, and stress
- Lack of medical facilities in rural settings can affect early diagnosis

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Principles of cancer therapy[5]

For nonmetastatic BC, the main goals of therapy are:

- To eradicate tumour from the breast tissue and regional lymph nodes
- To prevent metastatic recurrence

Local therapy for nonmetastatic BC[5]

Surgical treatment is considered only if clear margins can be achieved, and it involves:
- Total mastectomy
- An excision plus radiation procedure

Radiation therapy in BC is used as treatment for:
- Whole breast or a portion of the breast (after lumpectomy)
- The chest wall (after mastectomy)
- The regional lymph nodes

Contraindications to surgery include:
- Presence of diffuse microcalcifications on breast imaging
- Positive pathologic margins after lumpectomy
- Disease that cannot be addressed by excision of a single breast tissue region, except in highly selected patients
- Collagen vascular diseases such as scleroderma
- Prior radiotherapy to the involved breast

Post-lumpectomy whole-breast radiation is a standard component of therapy for breast conservation

Systemic therapy for BC[5]

Systemic therapy for nonmetastatic disease can be administered based on subtype:
- Preoperative (neoadjuvant)
- Postoperative (adjuvant)
- Both neoadjuvant and adjuvant

BC subtype guides the administration of standard systemic therapy, in both metastatic and nonmetastatic BC
- Endocrine therapy (ET) for hormone receptor (HR)+ tumours → tamoxifen or aromatase inhibitors
- Chemotherapy for triple-negative BC
- Targeted Therapy: HER2-positive breast cancer, trastuzumab (herceptin) or pertuzumab (perjeta)

Typical systemic therapies for nonmetastatic disease (agents, route, and duration)[5]

HR+ and ERBB2–	ERBB2+	Triple-negative
ET (all patients): • Tamoxifen, letrozole, anastrozole, or exemestane • Oral therapy • 5–10 years Chemotherapy (some patients): • Adriamycin/ cyclophosphamide (AC) • Adriamycin/cyclophosphamide/ paclitaxel (AC-T) • Docetaxel/cyclophosphamide (TC) • Intravenous therapy • 12–20 weeks	Chemotherapy plus ERBB2-targeted therapy (all patients): • Paclitaxel/trastuzumab (TH) • Adriamycin/cyclophosphamide/ paclitaxel/trastuzumab ± pertuzumab (AC-TH±P) • Docetaxel/carboplatin/trastuzumab ± pertuzumab (TCH±P) • Intravenous therapy • 12–20 weeks of chemotherapy • 1 year of ERBB2-targeted therapy ET (if also HR+): • Tamoxifen, letrozole, anastrozole, or exemestane • Oral therapy • 5–10 years	Chemotherapy (all patients): • AC • AC-T • TC • Intravenous therapy • 12–20 weeks

Standard approach to therapy of metastatic BC[5]

Therapy Type	HR+ and ERBB2– Serial endocrine therapy-based regimens until disease is endocrine resistant, then transition to single-agent chemotherapy	ERBB2+ (HR+ or HR–) ERBB2-targeted agent combined with chemotherapy, or combined with endocrine therapy if HR+	Triple-negative Single-agent chemotherapy
Initial line(s) of therapy	Aromatase inhibitor plus CDK4/6 inhibitors Median progression-free survival = 24.8 months Overall response rate = 53%–59% In some patients, CDK4/6 inhibitor may be reserved for second line	Taxane + trastuzumab + pertuzumab Median progression-free survival = 18.5 months Overall response rate = 80% Selected patients with HR+/ERBB2+ disease can receive endocrine therapy plus ERBB2-targeted therapy Ado-trastuzumab emtansine Median progression-free survival = 9.6 months Overall response rate = 47% ERBB2-targeted agent plus chemotherapy or endocrine therapy if HR+	Single-agent chemotherapy Taxane Median progression-free survival = 4.5 months Overall response rate = 36% Platinum Median progression-free survival = 3.1 months Overall response rate = 31% Anthracycline
Later lines of therapy	Hormonal and/or targeted therapy or surgical menopause Fulvestrant ± everolimus Exemestane + everolimus Tamoxifen Abemaciclib (if ≥1 line prior hormonal therapy and ≥1 line prior chemotherapy) Olaparib or talazoparib (if germline *BRCA1/2* mutation) If resistant to multiple lines of hormonal therapy, transition to single-agent chemotherapy	ERBB2-targeted agent plus chemotherapy or endocrine therapy if HR+ Trastuzumab + chemotherapy Trastuzumab + endocrine therapy Lapatinib + capecitabine	Single-agent chemotherapy Capecitabine Eribulin Vinorelbine Gemcitabine Olaparib or talazoparib (if germline *BRCA1/2* mutation)

Guidelines for improving the standard of diagnosis and treatment for BC patients both in early and metastatic BC

- The St Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023[6]
- ESMO expert consensus statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer[7]
- HER2 Testing in Breast Cancer: ASCO-College of American Pathologists Guideline Update[8]
- Designing clinical trials based on modern imaging and metastasis-directed treatments in patients with oligometastatic breast cancer: a consensus recommendation from the EORTC Imaging and Breast Cancer Groups[9]
- Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up[10]
- ESMO Expert Consensus Statements on the management of breast cancer during pregnancy (PrBC)[11]

Recent key trials in BC research[12]

- **Mammography Screening with Artificial Intelligence trial (MASAI):** High level of evidence on Artificial Intelligence for the early detection of BC
- **KEYNOTE-756:** Phase III: Neoadjuvant pembrolizumab (pembro) or placebo (pbo) + chemotherapy (chemo) for early-stage high-risk ER+/HER2 early BC
  Followed by adjuvant pembro or pbo + ET
- **NATALEE trial:** Ribociclib and ET as adjuvant treatment in HR+/HER2 early BC
  Primary endpoint of invasive disease-free survival achieved 3.3% absolute reduction
- **TROPION-Breast01:** Phase III trial, datopotamab deruxtecan significantly extended progression-free survival vs. chemotherapy in patients with HR+, HER2-low or negative BC13
- **TROPiCS-02:** 34% reduction in risk of progression or death (hazard ratio 0.66, $p < 0.001$)
  Treatment with sacituzumab govitecan for advanced HR+/HER2– BC
- **LUMINA trial:** Effects of omitting radiotherapy after breast conserving surgery in luminal A BC
- **KATHERINE trial:** Trastuzumab emtansine for residual invasive HER2+ BC14
- **MonarchE trial:** Abemaciclib plus ET for HR+, HER2–, node-positive, high-risk early BC
  Sustained benefit in distant relapse-free survival (dRFS)
  4-year dRFS: 5.9% absolute improvement (88.4% vs. 82.5%, hazard ratio 0.659, $p < 0.001$)

Key messages

- Increased access to diagnostic care services is crucial for early detection of BC
- Molecular and genetic analysis is essential for determining the appropriate systemic therapy based on BC subtype
- Early and accurate identification of BC greatly improves treatment outcomes
- Tailoring treatment strategies based on subtype, improves patient prognosis and survival rates
- Understanding the principles of cancer therapy, including surgical and radiation option, is crucial for effectively managing BC

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