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Key Insights on Early and Metastatic Breast Cancers

An overview of early and advanced breast cancers with special focus on staging, molecular subtypes, risk factors and risk stratification, risk of developing breast cancer, and therapeutic options

Overview of breast cancer (BC)[1,2]

BC is a disease where the cells of the breast tissue grow uncontrollably and form tumours
Leading cause of cancer-related death for women worldwide

Early BC (EBC)[2]
Cancer contained within the breast tissue or limited to the axillary lymph nodes

Metastatic BC (MBC)
Cancer that has spread to distant organs of the body

30% of patients with EBC may develop distant metastases months or years after receiving initial treatment[3]

Epidemiology[1]

Tumour stage	Cases by stage at diagnosis (%)	5-year relative survival (%)
Localised	63	99.6
Regional	28	86.7
Distant	6	31.9

Early detection improves chances of survival five years after diagnosis

Tumour grade, size, and lymph node involvement[4]

Tumour stage
Size of the cancer and spread

Tumour grade
Degree of abnormality in cells when observed under the microscope

Tumour (T), lymph node (N), and metastasis (M) staging system or TNM system:
Stage 1: tumour is <2 cm across
Stage 2: tumour is >2 cm but <5 cm across
Stage 3: tumour is >5 cm
Stage 4: tumour of any size growing into the chest wall or skin

N1: cancer in 1–3 axillary lymph nodes
N2: cancer has spread to >4 but <10 axillary lymph nodes
N3: cancer has spread to >10 axillary lymph nodes, collarbone lymph nodes, with at least one area of cancer spread of >2 mm
M: cancer has spread to distant organs

Stage and grade, among other factors, of BC at the time of diagnosis determine the appropriate treatment regimen and length of survival

Accurate case and staging information collected and maintained by cancer registries are important for the assessment of survival curves and other epidemiological variables[5]

BC is a heterogeneous, phenotypically diverse group comprising biological subtypes that have distinct prognosis, progression, and response to therapy

Histological subtypes[6]

Invasive breast carcinoma of no special type
- 70–75%
- Special morphological characteristics and various histological patterns

Invasive lobular carcinoma
- 5–15%
- Discohesive tumour cells
- Estrogen receptor positive (ER^+), human epidermal receptor 2 negative ($HER2^-$), aberrant E-cadherin

Invasive mucinous carcinoma
- 2%
- Low/middle-grade tumour
- Extracellular mucin pool
- ER^+, positive for progesterone receptor (PR^+), $HER2^-$
- Rare special entities: <1%

Intrinsic or molecular subtypes[6]

Immunohistochemistry

Luminal A
- ~40%
- Best prognosis
- ER^+ and/or PR^+, $HER2^-$
- Low Ki-67

Luminal B
- ~20%
- ER^+ and/or PR^+, $HER2^{+/-}$
- Ki-67 >20%

Molecular classification

HER2 enriched
- ~10–15%
- ER^-, PR^-, $HER2^+$

Triple-negative
- ~15–20%
- Worst prognosis
- ER^-, PR^-, $HER2^-$

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Risk of developing BC[7]

As per the National Institute for Health and Care Excellence guidelines

General population risk
- Lifetime risk of developing BC: 11%
- BCs develop beyond the age of 50

Moderate-risk
- Lifetime risk of developing BC: 17–30%
- 3–8% chance of developing BC between the ages of 40 and 50

High-risk
- Lifetime risk of developing BC: >30%
- >8% chance of developing BC between the ages of 40 and 50

Significantly higher chance of developing BC at a younger age than those in the general population

Accurate risk stratification in BC will enable tailoring of screening programmes to identify and target at-risk populations, reducing BC-specific mortality[8]

Genetic risk factors of BC[9,10,11]

15% of BC are associated with a genetic predisposition and 50% of these cases are associated with BReast CAncer gene 1/2 (*BRCA1/2*)

High penetrance genes
- *BRCA1*
- *BRCA2*
- Epithelial cadherin or E-Cadherin gene (*CDH1*)
- Phosphatase and tensin homolog gene (*PTEN*)
- *STK11*
- *TP53*

Moderate penetrance genes
- Checkpoint kinase 2 (*CHEK2*)
- Partner and localiser of BRCA2 (*PALB2*)
- RADiation-sensitive protein 51 Paralog C (*RAD51C*)
- *ATM*
- *BRIP1*

Low penetrance genes
- *MDM4*, 19p13.1, and *TERT-CLPTM1L* rs10069690 are loci exclusive to triple-negative BC and BRCA1-associated BC
- *FGFR2, LSP1, MAP3K1, TGF-β1, TOX3, RECQL, MUTYH, MSH6, NF1*, and *NBN*

BC risk assessment tools and models[12,13,14]

Gail/BC risk assessment tool (BCRAT) model
Estimates the risk of developing BC over 5 years and over a lifetime, based on non-genetic risk factors

Claus model
Considers only the family history of BC to estimate risk

BRCAPro model
- BRCAPro, a Bayesian computer program or statistical model, calculates an individual's chances of being a carrier of *BRCA1*/*BRCA2* pathogenic germline variants (PGVs)
- Considers personal and family history of BC and ovarian cancer to identify the presence of *BRCA1*/*BRCA2* PGVs

Breast cancer surveillance consortium (BCSC) model
BCSC risk calculator estimating a woman's 5- and 10-year risk of developing invasive BC based on:
- Age, race/ethnicity, family history of BC, prior biopsy, and breast density

Tyrer-Cuzick/international breast cancer intervention study (IBIS) model
Estimates the individual risk of BC over time and the probability of *BRCA1*/*BRCA2* PGVs

Breast and ovarian analysis of disease incidence and carrier estimation algorithm (BOADICEA)/CanRisk model
Estimates the probability of *BRCA1*/*BRCA2* PGVs and BC incidence based on family history and genotypes for PGVs

PENN II model, myriad model, lambda model, and couch model are some of the other BC risk assessment models

Screening the overall population for BC[15]

Personalised RISk-based MAmma screening study (PRISMA)

Participants
Asymptomatic women aged 50–75 years

PRISMA identified the need for:
- Risk-tailored communication of risk assessment results
- Standardised risk assessments within national policies

Karolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA) study

Participants: 70,000 women

Developed CAD2Y, a new model for individualised short-term risk prediction that integrates mammographic features with clinical factors

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European Society for Medical Oncology (ESMO) guidelines on the treatment of EBC[16,17]

Local anticancer treatment

Surgery

- Breast-conserving surgery (BCS) followed by radiation therapy (RT)
- For large tumours, neoadjuvant chemotherapy (NAC) is used to shrink tumour prior to BCS
- Axillary lymph node (ALN) involvement is managed by ALN dissection

RT

- For low-risk patients, partial breast irradiation is effective with low toxicity
- For high-risk patients (younger age, a higher burden of disease in the breast and axilla, and biological characteristics) post-mastectomy RT is recommended

Systemic anticancer treatment

Chemotherapy

Reduces risk of recurrence by 30% in EBC

- NAC for high-risk patients
  - Converts inoperable tumour to resectable
  - Eliminates micrometastatic lesions
  - Decreased mastectomy rates

Ki-67 is a predictive marker for response to NAC and NA endocrine therapy

- Adjuvant chemotherapy (AC)

Hormone or endocrine therapy (ET)

- **Adjuvant ET for ER$^+$ and/or PR$^+$ (tamoxifen) BC for 5–10 years**
  - Reduces the recurrence risk by 50% in the first 4 years

ER/PR positivity is a predictive biomarker for ET

In postmenopausal patients, aromatase inhibitor monotherapy or tamoxifen for 5–7 years is recommended

Targeted therapy

- Anti-HER2 targeted therapy, trastuzumab +/-pertuzumab (1 year) with non-anthracyclin-based AC or NAC in TDM1 HER2+ patients without a complete response to neoadjuvant prescription

HER2 positivity is a predictive biomarker for anti-HER2 therapy

- Immune checkpoint inhibitors (ICIs)
- CDK4/6 inhibitors

ESMO guidelines on treatment of MBC[16,18]

Biomarker assessment

- ER, PR, and HER2
- Germline *BRCA1/2* mutation (*gBRCAm*) status
- Programmed death-ligand 1 (PD-L1) status
- Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)
- Estrogen receptor alpha gene (ESR1)

Luminal BC (ER$^+$ PR$^+$ HER2$^-$ MBC)

First-line treatment

- CDK4/6 inhibitors combined with ET
- Chemotherapy for patients with visceral crises

Second-line treatment

- Previously untried ET agents in combination with targeted therapies, such as PI3K, mTOR, or poly (ADP-ribose) polymerase (PARP) inhibitors
- Chemotherapy

HER2-positive BC

First-line treatment

- For ER$^-$ PR$^-$ HER2$^+$
  - Trastuzumab and pertuzumab with chemotherapy (if not contraindicated)
- For ER$^+$ PR$^+$ HER2$^+$
  - Add ET to trastuzumab with chemotherapy (if not contraindicated)
  - ET as maintenance

Second-line treatment

- Patients without brain metastasis
  - Anti-HER2 therapy and chemotherapy

Third-line therapy

- Sacituzumab govitecan monotherapy
- Chemotherapy

Triple negative BC (TNBC)[18]

First-line systemic treatment

- For PD-L1-positive
  - Chemotherapy with ICIs
  - Pembrolizumab
  - Atezolizumab
- For *gBRCAm* mTNBC
  - Carboplatin
- For PD-L1-negative and *gBRCA*-wild-type mTNBC
  - Chemotherapy
  - Anthracyclines or taxanes as monotherapy or combination
  - Nab-paclitaxel–carboplatin
  - Sacituzumab govitecan-hziy

Brain metastasis is more common in HER2+ patients and TDXd and tucatinib are available for the treatment of such patients

In patients with MBC, clinical decision-making for personalised treatment is based on biomarker expression[18]

ESMO-MCBS v1.1 score: 3; ESCAT score: I-C

- Larotrectinib

Unresectable or metastatic microsatellite instability-high/mismatch repair deficient tumours

- Pembrolizumab

ESMO-MCBS v1.1 score: 3; ESCAT score: I-C

- Entrectinib

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Importance of a multidisciplinary team[18]

Optimal metastatic disease management requires an interdisciplinary approach

Oncology and/or BC nurses
Proactively screen for and manage treatment-emergent toxicities

Multimodality treatment specialists
Administer local image-guided ablative therapy, radiotherapy, and systemic therapies

Subspecialists
Monitor skeletal-related changes in patients with bone metastasis

Neurologists, surgeons, oncologists RT, nurses, psychologist, pathologist, radiologist, nutrition, geneticists, orthopaedics and other subspecialists
Manage the central nervous system and other situations

Palliative care should be introduced early and offered both in an inpatient and an outpatient setting[18]

Optimal symptom control
Proactive symptom management and patient education help to alleviate side effects and improve quality of life

Psychological, social, and spiritual support

Patient-reported outcomes to capture the patient experience and perceived impact of treatment and toxicity on health status

Care management for: • Pain • Dyspnoea • Cachexia • Fatigue • Depression and anxiety

Good communication between and joint decision-making by the patient and healthcare professionals are essential to ensure mutual understanding of treatment expectations and goals[18]

Key messages

- **Early and accurate diagnosis of BC is key to improving treatment outcomes**
- **Risk stratification or identification of an individual's risk of BC enables the adoption of treatment programmes to target at-risk populations**
- **Accurate clinical staging, biomarker status, and specific molecular alterations are critical for prognosis, therapeutic decision-making, and implementation of personalised treatment choices**

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