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- **Portuguese Consensus on Breast Cancer Management 2025: Updated Recommendations from the Portuguese Society of Senology**

SOCIEDADE PORTUGUESA DE ONCOLOGIA

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Consensus

Portuguese Consensus on Breast Cancer Management 2025: Updated Recommendations from the Portuguese Society of Senology

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Abstract

Breast cancer remains the most frequently diagnosed malignancy and a leading cause of cancer-related mortality among women in Portugal. Ensuring optimal patient outcomes and promoting standardized clinical management nationwide require the continuous integration of emerging scientific evidence into clinical practice. In May 2025, the Portuguese Society of Senology (Sociedade Portuguesa de Senologia) convened a multidisciplinary expert panel to update the 2022 X National Consensus on Breast Cancer in light of the latest scientific evidence.

The consensus was developed through a structured, collaborative process involving nine dedicated working groups. These groups comprised multidisciplinary experts representing key specialties involved in breast cancer management, including surgery, radiology, pathology, medical oncology, radiation oncology, and medical genetics, as well as experts in digital technologies and related technical disciplines. Each working group reviewed the relevant scientific literature, answered specific clinical questions, and developed preliminary recommendations. These were subsequently discussed in a plenary session. All authors approved the final document, assessed the levels of evidence, and unanimously agreed on the proposed recommendations.

The complete recommendations of the XI National Consensus on Breast Cancer [ISBN 978-989-33-9573-8] are available on the Portuguese Society of Senology website (www.spsenologia.pt). This article summarizes these recommendations, with the aim of supporting clinicians in evidence-based decision-making and promoting equitable, standardized, and high-quality care across all healthcare institutions nationwide.

Keywords: *Breast Neoplasms/diagnosis; Breast Neoplasms/diagnostic imaging; Breast Neoplasms/drug therapy; Breast Neoplasms/pathology; Breast Neoplasms/radiotherapy; Consensus Statement; Portugal; Precision Medicine.*

Introduction

According to GLOBOCAN, an estimated 2.3 million new cases of breast cancer were diagnosed in 2022, comprising 11.6% of all cancer cases, and around 670 000 women died of the disease globally, making it the fourth leading cause of cancer mortality worldwide.[1] Breast cancer is the most commonly diagnosed cancer (23.8%) and the leading cause of cancer death (15.4%) in women,[1] notwithstanding the progresses that have been made in screening in recent years. According to the same source, breast cancer is the second most diagnosed cancer in Portugal (12.9% of all new cancer cases), the fourth leading cause of cancer death (6.5%), and also the most diagnosed cancer in women (28.2%).[2]

Optimal breast cancer management requires a strategy implemented by a multidisciplinary team including oncologists, radiologists, pathologists, surgeons, dietitians/nutritionists, social workers, mental health professionals, and palliative care and rehabilitation specialists, among others, that can provide comprehensive patient support from early screening and diagnosis through treatment, survivorship, and rehabilitation.

The Portuguese Society of Senology (SPS, Sociedade Portuguesa de Senologia) issues periodic recommendations on the multidisciplinary clinical management of breast cancer, encompassing screening, diagnosis, treatment, and follow-up. This article summarizes the XI National Consensus on Breast Cancer [ISBN 978-989-33-9573-8]. Its aim is to support clinicians in evidence-based decision-making while also considering patients' individual values, preferences, and circumstances.

Methods

The XI National Consensus on Breast Cancer was developed by a multidisciplinary panel comprising experts with recognized expertise in breast cancer management (including medical oncologists, breast surgeons, radiologists, radiation oncologists, pathologists, gynecologists, geneticists, and plastic surgeons), as well as experts in other relevant fields (including researchers specializing in artificial intelligence and technical disciplines such as engineering). The panel comprised experts from nine areas: radiology, precision medicine, axillary lymph node management, management of precursor lesions, treatment of luminal breast cancer, treatment of triple-negative and human epidermal growth factor receptor 2 (HER2)-positive breast cancer, hereditary breast cancer, radiotherapy, and artificial intelligence. For each area, the experts identified and critically reviewed relevant evidence published since the X National Consensus (2022) and developed new or updated recommendations accordingly. The strength of each recommendation was graded according to levels of evidence and grades of recommendation adapted from the Infectious Diseases Society of America-United States Public Health Service grading system (**Table 1**).[3] In May 2025, the working group met in person in central Portugal to discuss the preliminary work and finalize the consensus document.

Results

1. DETECTION AND DIAGNOSIS

• Can breast ultrasound be performed as a stand-alone examination in women over 40 years of age?

Breast ultrasound (US) is the first-line imaging modality in young women (<40 years) presenting with breast symptoms, as well as in pregnant or breastfeeding women. It is also an important complementary modality for the characterization of masses or asymmetries identified on mammography, targeted assessment of magnetic resonance imaging (MRI) findings ("second-look US"), axillary evaluation, and image-guided biopsy procedures.

Recommendations

- The use of US alone in asymptomatic women aged >40 years for breast cancer screening ("screening US") is not recommended. Instead, US should be performed as a complementary modality to mammography — preferably digital breast tomosynthesis (DBT) with synthesized two-dimensional (2D) images — when indicated for breast cancer detection.[4]
- Breast US may be considered as a supplemental screening tool in women with dense breasts (Breast Imaging Reporting and Data System [BI-RADS] categories C and D). It increases breast cancer detection rates,[5,6] but also increases the detection of benign findings, many of which require additional assessment and, in some cases, biopsy confirmation.[7]

Table 1. Levels of Evidence and Grades of Recommendation used in the XI National Consensus on Breast Cancer.

Levels of evidence	
I	Evidence from at least one large randomized controlled trial of good methodological quality (low potential for bias), or meta-analyses of well-conducted randomized trials without significant heterogeneity,
II	Evidence from small randomized trials or large randomized trials with suspected bias (lower methodological quality), or meta-analyses of such trials or of trials with demonstrated heterogeneity.
III	Evidence from prospective cohort studies.
IV	Evidence from retrospective cohort studies or case–control studies.
V	Evidence from studies without a control group, case reports, or expert opinion.
Grades of recommendation	
A	Strong evidence for efficacy with substantial clinical benefit; strongly recommended.
B	Strong or moderate evidence for efficacy, but with limited clinical benefit; generally recommended.
C	Insufficient evidence for efficacy, or benefit does not outweigh risks or disadvantages (e.g., adverse events, costs); optional.
D	Moderate evidence against efficacy or for adverse outcomes; generally not recommended.
E	Strong evidence against efficacy or for adverse outcomes; never recommended.

• What is the role of mammography beyond population-based screening?

Beyond population-based screening, mammography is recommended in women aged >40 years [II; B].[8–10] Whenever available, mammography should be replaced by DBT with synthesized 2D images, given its additional benefits in increasing breast cancer detection rates[11] and reducing false-positive findings. These imaging modalities should ideally be complemented by breast US, which further contributes to increased cancer detection rates, including when performed in addition to tomosynthesis.[12]

Recommendations

- From the age of 40 years onwards, breast US has a complementary role[13] and should be performed after mammography, with findings integrated into a single combined imaging report.
- When integration of mammographic and US findings is not feasible, the radiologist performing the US should have prior access to the mammographic images to ensure appropriate interpretation and imaging correlation.

• Is the new Directorate-General of Health (DGS) guideline applicable to all clinical situations or only to population-based screening?

The new guideline issued by the Directorate-General of Health (DGS, Direção-Geral da Saúde published in www.dgs.pt/normas-orientacoes-e-informacoes) in December 2024 recommends the use of DBT as the primary test in organized, population-based breast cancer screening programs [Conditional recommendation; very low level of evidence].[14] This recommendation applies to asymptomatic women aged 45 to 74 years without a personal history of breast cancer and without known genetic risk.

All women outside this age range – namely women over 40 years of age who are not included in the population-based screening program – should have access to digital mammography or breast tomosynthesis combined with breast US, or, in selected cases, breast MRI. The same applies to women over 74 years of age, for whom surveillance should be individualized according to clinical status and life expectancy.

Recommendations

- In women younger than 40 years, breast US is recommended as the first-line imaging modality and may be complemented by mammography or DBT when clinically or sonographically indicated.
- Breast US is not recommended for breast cancer screening and should not be used as a stand-alone examination in women over 40 years of age, except in specific situations, such as pregnancy, recent breast trauma, mastitis or breast abscess, or when mammography has been performed within the previous 12 months.

• What is the role of contrast-enhanced mammography (CEM)?

Although digital mammography remains the most widely used imaging modality for breast cancer screening and diagnosis, its sensitivity is significantly reduced in women with dense breast tissue.

Contrast-enhanced mammography (CEM), also referred to as dual-energy mammography or contrast-enhanced spectral mammography, enables an integrated assessment of anatomical and functional data. However, it is a relatively recent technique, with a limited number of large-scale population-based studies, and its clinical indications are not yet fully established. In addition, it has several relevant limitations, including contraindications or precautions related to iodinated contrast media in patients with a history of hypersensitivity reactions or renal impairment; the presence of artifacts in women with breast implants; reduced coverage of lesions adjacent to the inframammary fold, the pectoral muscle, or the nipple-areolar complex; increased background parenchymal enhancement (which, in MRI, may be mitigated through multiparametric assessment); and reduced sensitivity for certain histological subtypes, such as lobular and mucinous carcinomas. On the other hand, CEM is generally more accessible than MRI, with higher patient acceptance, lower cost, and consistent diagnostic performance across published studies.[15–18]

Recommendations

- CEM may be used as a first-line imaging modality for the assessment of suspicious lesions or findings detected on breast screening[19–21] and as an alternative to MRI in the preoperative setting, particularly when MRI is unavailable or poorly tolerated, provided that it is complemented by axillary US.
- CEM may be used as an alternative to MRI for screening women at intermediate risk (15%–20%) or women with dense breasts when MRI is unavailable, contraindicated, or not feasible due to access limitations or patient preference [III; B].

• Management of lesions of uncertain malignant potential (B3)

B3 lesions, or lesions of uncertain malignant potential, constitute a broad and heterogeneous group of breast abnormalities, which may present with or without atypia.

Recommendations

- Vacuum-assisted excision is the preferred approach for selected B3 lesions, such as radial scar/complex sclerosing lesion, flat epithelial atypia, classic lobular carcinoma in situ (LCIS), and intraductal papilloma without atypia, provided that radiopathological concordance is established.[22–24]
- When vacuum-assisted biopsy (VAB) is performed with excisional intent, the use of larger-gauge (G) needles (preferably 7G) is recommended, with retrieval of at least 12 tissue cores, corresponding to a total tissue weight of approximately 4 g.[23,24]
- Surgical excisional biopsy is the preferred approach in cases of phyllodes tumor and atypical ductal hyperplasia. However, vacuum-assisted excision may be considered in selected

cases, such as benign phyllodes tumors or lesions with atypical ductal hyperplasia amenable to complete excision.[22–24]

Less common B3 lesions, such as adenomyoepithelioma, granular cell tumor, and microglandular adenosis, as well as other lesions with challenging histological classification, generally benefit from surgical excisional biopsy.[23]

Each case of a B3 lesion should be discussed within a multidisciplinary board to confirm radiopathological correlation and to assess lesion extent, individual patient risk factors, and local resource availability, in order to define the most appropriate therapeutic approach and follow-up strategy.[24]

Recommendations

- After excision of a B3 lesion with atypia, annual surveillance with digital mammography or DBT is recommended for at least 5 years after diagnosis to allow for early detection of carcinoma.[23,24]
- Breast MRI surveillance may be considered in women with a personal history of atypical ductal hyperplasia or LCIS and intermediate risk (15%–20%) of developing breast cancer.[25]
- In women with contraindications to breast MRI, CEM is a valid alternative.[26,27]

Evidence regarding the long-term follow-up of B3 lesions treated exclusively with vacuum-assisted excision, without subsequent surgical excision, remains inconclusive.

Breast imaging and management after breast cancer diagnosis

• How should locoregional and distant staging of breast cancer be performed?

Staging should be performed according to the 8th edition of the TNM classification system of the American Joint Committee on Cancer (AJCC).[28,29]

· Locoregional staging

Conventional mammography, performed in mediolateral oblique and craniocaudal views (either digital 2D mammography or digital breast tomosynthesis), constitutes the baseline imaging modality for locoregional staging of breast cancer. However, its sensitivity is limited, and it has inherent limitations in the assessment of structures relevant to locoregional staging, such as axillary lymph nodes and internal mammary chain lymph nodes.[30]

Breast and axillary US and, when appropriate, chest wall US may be combined – ideally with CEM – to complete initial locoregional staging.[30] US is also the most frequently used modality for preoperative lesion localization, due to greater patient comfort and the ability to provide real-time imaging.[31]

Recommendations

- Bilateral mammography and breast and axillary US are the recommended modalities for locoregional staging [I; A].[29]
- Breast MRI is recommended for assessing disease extent,30 including the involvement of adjacent structures and regional lymph nodes [I; A].[29,30,32]

DBT provides higher sensitivity than conventional 2D mammography for lesion detection, particularly in women with dense breasts, and allows improved morphological characterization of architectural distortions and microcalcifications, contributing to more accurate diagnostic assessment. It may be used as an initial imaging modality, either complementing or replacing conventional mammography, depending on resource availability and clinical context [II; B].[29]

CEM may be an alternative for breast cancer staging in cases where MRI is unavailable or contraindicated [II; B].[29,30,32] However, it has limitations related to its two-dimensional nature and inability to temporally characterize heterogeneous enhancement patterns.[32]

Recommendations

- The main clinical indications for breast MRI are [I; A][29]:
  - · Assessment of disease extent, with detection of multifocal, multicentric, and bilateral lesions, particularly in younger women (<50 years), aggressive tumor subtypes (HER2-positive and triple-negative), ductal carcinoma in situ (DCIS), invasive lobular carcinoma, and dense breast patterns.
  - · Evaluation of response to neoadjuvant chemotherapy.
  - · Investigation of occult breast cancer.
  - · Screening of women with confirmed genetic risk.
  - · Assessment of Paget disease of the breast.
  - · Discordance between conventional imaging findings (mammography/US) and clinical examination.
  - · Evaluation of women with breast implants.

Additional suspicious foci detected on breast MRI should undergo histological characterization whenever they have an impact on surgical strategy and/or staging. Although breast MRI is not currently recommended for routine use in all patients, its use is justified in the aforementioned clinical settings, as it may provide clinically relevant information for therapeutic decision-making.[33]

· Distant staging

Routine systemic staging is not recommended in asymptomatic patients with early-stage, low-risk disease (stages I–II).[29,33]

Recommendations

- Distant staging is recommended in patients with [III; A][29]:
  - · Locally advanced disease (e.g., positive axillary lymph nodes or cT3–T4 tumors).
  - · Aggressive biological subtypes (HER2-positive or triple-negative breast cancer [TNBC]).
  - · Abnormal clinical or laboratory findings.

- The following examinations are indicated:
  - Chest computed tomography (CT).
  - Abdominopelvic CT (or abdominal MRI in cases of indeterminate liver lesions).
  - Whole-body bone scintigraphy.
- Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) may be preferred in high-risk settings, such as locally advanced disease, triple-negative or HER2-positive tumors, or when conventional imaging modalities yield inconclusive results [II; B].[29]
- Brain MRI should be reserved for patients presenting with neurological symptoms suggestive of secondary central nervous system (CNS) involvement.[25,33]

The usefulness of PET/CT for staging invasive lobular carcinoma remains unclear, and there are no definitive recommendations for its routine use in this subgroup.[34]

• Do newer preoperative localization techniques offer advantages over pre-existing techniques?

New non-wire, non-ionizing (NWNI) preoperative localization techniques—such as radiofrequency identification tags and ferromagnetic seeds—offer several advantages in terms of logistical flexibility and safety, with the potential for improved cosmetic outcomes and higher rates of negative surgical margins. In addition, they avoid risks associated with the use of radioactivity and reduce complications inherent to wire-guided localization techniques.[35,36] These techniques represent a relevant advance in breast-conserving surgery (BCS) for the treatment of non-palpable breast lesions.[35,36]

• Do CEM and MRI have comparable sensitivity and specificity in assessing response to neoadjuvant therapy?

The available evidence indicates that, although MRI generally demonstrates superior overall performance, breast MRI and CEM have similar sensitivity and specificity in the assessment of response to neoadjuvant treatment.

Recommendations

- CEM may be a valid alternative to MRI when MRI is contraindicated, poorly tolerated, unavailable, or inaccessible [II; B].[37–39]

Can minimally invasive local therapies be considered equivalent to lumpectomy? In which patient subgroups?

Based on current evidence, minimally invasive local therapies—such as radiofrequency ablation, cryoablation, or vacuum-assisted excision—cannot be considered equivalent to lumpectomy for the treatment of breast cancer.[40–42]

Recommendations

- Minimally invasive local therapies may be considered an option for local disease control in patients who are not suitable candidates for surgery due to clinical contraindications [II; B]

Results from ongoing studies, such as MINIVAB[42] and the SMALL Trial,[43] as well as available long-term follow-up data from the ICE3 Trial,[44] are awaited to further clarify this issue and provide more robust evidence.

• What imaging modalities and follow-up intervals are recommended for women with a personal history of breast cancer?

Recommendations

- Follow-up after BCS
  - Annual mammography is the recommended imaging modality [II; A].[10,29,45–49]
  - The decision to discontinue surveillance should be individualized, taking into account patient age, comorbidities, preferences, and the risk of subsequent breast cancer. The International Society of Geriatric Oncology (SIOG) suggests discontinuing surveillance mammography in patients with a life expectancy of less than five years.[46]
  - Annual breast MRI is recommended in patients with a personal history of breast cancer who have dense breasts, were diagnosed before the age of 50 years, or have additional risk factors.[47]
  - MRI is also indicated in women at high risk (>20%–25%), including carriers of pathogenic variants in breast cancer susceptibility genes, first-degree relatives of mutation carriers who have not undergone genetic testing, or women with a history of chest irradiation at a young age.
- Follow-up after mastectomy
  - Clinical surveillance is recommended after mastectomy when the breast parenchyma has been completely excised. US may be performed for the evaluation of suspicious clinical findings.[33]
  - Breast MRI may be used to confirm or exclude the presence of significant residual breast parenchyma when this is clinically suspected and may be useful for the evaluation of selected patients with breast reconstruction.[33]

2. MOLECULAR CHARACTERIZATION OF BREAST CANCER (PRECISION MEDICINE)

• What are the standard biomarkers, and how should the initial stratification be performed?

Recommendations

- The initial evaluation of invasive breast carcinoma should include immunohistochemical assessment of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression in the primary tumor, with confirmation by in situ hybridization (ISH) in cases with an equivocal HER2 immu-

nohistochemistry (IHC) result (2+), as this analysis allows classification into the main clinically relevant breast cancer subtypes (luminal, HER2-positive, and triple-negative) and guides systemic treatment selection and the overall multidisciplinary management strategy [I, A].

- In addition to these essential biomarkers, specific tests and biomarkers should be considered according to the tumor subtype (luminal, HER2-positive, or triple-negative).

Luminal (ER/PR-positive, HER2-negative) breast cancer

Recommendations

- In patients with localized (non-metastatic) disease, particularly those with clinicopathological features associated with an intermediate risk of recurrence, a multigene expression assay performed on primary tumor tissue (e.g., Oncotype DX®, MammaPrint®, or Prosigna®) may be used, according to the specific clinical setting and assay indication, to assess recurrence risk and inform decisions regarding the potential benefit of adding chemotherapy to adjuvant endocrine therapy (ET) [I, A].[50]
- In metastatic setting, testing for activating phosphatidylinositol 3-kinase catalytic subunit alpha (PIK3CA) mutations should be performed to assess eligibility for treatment with phosphatidylinositol 3-kinase (PI3K) inhibitors (e.g., alpelisib or inavolisib) in combination with ET [I, A].[51] This assessment should be performed at the time of first disease progression or at the initiation of the relevant treatment line, preferably using a metastatic lesion sample, when available.
- In patients whose disease progresses during ET with an aromatase inhibitor (AI), testing for estrogen receptor 1 (ESR1) mutations should be performed, as these alterations are associated with resistance to this class of agents [I, B]. The results may inform the selection of subsequent ET and support the use of fulvestrant or an oral selective estrogen receptor degrader (SERD), such as elacestrant, rather than an alternative AI [II, B].
- In patients with metastatic disease, germline breast cancer susceptibility gene (BRCA)1/2 testing should be performed at the time of diagnosis of advanced disease (if not previously performed), to assess eligibility for treatment with poly(ADP-ribose) polymerase (PARP) inhibitors [I, A].[50]
- In patients with heavily pretreated advanced disease or limited therapeutic options, broader genomic profiling using next-generation sequencing (NGS) may be considered to identify rare but potentially actionable alterations, such as *AKT1*, *PTEN*, or *FGFR1* mutations, *NTRK* gene fusions, or high tumor mutational burden (TMB), which may predict benefit from targeted therapies or immunotherapy [V, B].

HER2-positive breast cancer

HER2 amplification and/or overexpression is the key predictive biomarker in this breast cancer subtype and determines the use of anti-HER2 therapies across all disease stages.

Recommendations

- In patients with early-stage HER2-positive breast cancer, only the initial HER2 assessment is required, as anti-HER2 targeted therapy is indicated irrespective of additional molecular biomarkers [I, A].
- In the metastatic setting, HER2 status should be reassessed in a biopsy specimen from a metastatic lesion whenever feasible to confirm the persistence of HER2 expression/amplification [II, B]. If a previously HER2-positive tumor converts to HER2-negative at metastization, treatment should be guided by the updated HER2 status, and HER2-targeted therapy should generally not be continued [III, B]
- Routine testing for *PIK3CA* mutations is not standard practice, as no approved therapy specifically targeting this alteration is currently available in HER2-positive breast cancer [II, B].
- In patients experiencing disease progression after multiple lines of HER2-targeted therapy, comprehensive genomic profiling using NGS may be considered to identify resistance-associated alterations (e.g., *ERBB2* mutations, which may confer sensitivity to specific HER2-targeted tyrosine kinase inhibitors [TKIs]) or other potentially actionable alterations in alternative signaling pathways that could support enrolment in biomarker-driven clinical trials or the use of emerging targeted therapies [III, C].

Triple-negative (ER/PR-negative, HER2-negative) breast cancer

Recommendations

- All patients with early-stage TNBC should undergo germline *BRCA1/2* (*gBRCA1/2*) testing regardless of age [I; A].
- Patients with *gBRCA1/2*-mutated, high-risk, early-stage disease may be eligible for adjuvant treatment with olaparib, based on the results of the OlympiA trial [I; A].[52]

Assessment of stromal tumor-infiltrating lymphocytes (TILs) may provide prognostic information in early-stage disease, with higher TIL density associated with more favourable outcome [II; B].[53]

However, TIL assessment does not currently influence the indication for adjuvant chemotherapy, which remains standard of care in this subtype.

Recommendations

- In metastatic setting, programmed death-ligand 1 (PD-L1) expression should be assessed in tumor tissue, either from the primary tumor or a metastatic lesion, whichever is available [I; A].
- Patients with PD-L1-positive tumors (combined positive score [CPS] ≥10) should receive pembrolizumab in combination with chemotherapy as first-line treatment for metastatic disease [I; A].[50]

The SP142 immune-cell algorithm is not interchangeable with 22C3 CPS for selecting pembrolizumab in metastatic TNBC. The KEYNOTE-355 CPS >ou= (usar só um simbolo, com os 2 significados) 10 indication is linked to validated 22C3 scoring PD-L1 expression should be determined by IHC using a validated assay (SP142 or 22C3). Depending on the assay used, PD-L1 expression may be reported as percentage of PD-L1-positive immune cells or as a CPS.

Recommendations

- All patients with metastatic breast cancer may be considered for gBRCA1/2 testing to determine eligibility for PARP inhibitor therapy [I; A].[50]
- If a somatic *BRCA1/2* mutation is identified through tissue- or plasma-based NGS, germline testing should be performed to determine whether the alteration is of germline origin, as only gBRCA mutations are currently an approved indication for treatment with PARP inhibitors [I; A].[51]
- In addition to PD-L1 and BRCA testing, the following molecular tests may be considered in selected metastatic TNBC cases:
  - Microsatellite instability (MSI) and TMB – High MSI (MSI-H) and high TMB (≥10 mutations/Mb) may confer eligibility for pembrolizumab treatment regardless of tumor subtype (tumor-agnostic approval) [II; B].
  - Oncogenic gene fusions (e.g., *NTRK1*, *NTRK2*, or *NTRK3* fusions) – May confer eligibility for targeted therapies such as larotrectinib or entrectinib [II; B].

Tumors with low HER2 expression (HER2-low and HER2-ultralow)

Although HER2-low and HER2-ultralow tumors do not constitute distinct molecular subtypes of breast cancer, their identification is clinically relevant in light of current therapeutic indications, particularly for trastuzumab deruxtecan (T-DXd).

Recommendations

- The latest recommendations from the College of American Pathologists (CAP) for biomarker testing in breast cancer should be followed,[54] with particular attention to the technical requirements for reliably detecting low levels of HER2 expression [V, A].

• Which sample should be used (primary tumor versus metastatic lesion)?

Recommendations

- Whenever possible, treatment decisions should be based on the analysis of the most recent and clinically relevant tumor specimen — typically obtained from a biopsy of a metastatic lesion or recurrent disease —, as the biological profile of breast cancer may evolve over time and under therapeutic pressure [II; A].
- Whenever feasible, rebiopsy of a metastatic lesion should be performed to confirm tumor subtype (ER, PR, HER2) and assess additional biomarkers, particularly in cases of clinicopathological discordance or a long interval since the initial diagnosis [II; B].
- Ideally, a biopsy of metastatic tissue should be obtained before treatment decisions are made [V; B]. Liquid biopsy may be used as a complementary tool to identify subclonal alterations or molecular abnormalities that may not be adequately captured in tissue samples.

When metastatic tissue cannot be obtained due to lesion location, procedural risk, or time constraints, molecular characterization should rely on information from the primary tumor and/or liquid biopsy.

Recommendations

- Acquired *ESR1* and *HER2* mutations may emerge during treatment as a result of therapeutic selective pressure, being therefore more frequently detected in advanced disease. Accordingly, testing for these acquired mutations in the primary tumor tissue is not recommended [I; A].
- Somatic *PIK3CA* and *BRCA1/2* mutations are generally early events in tumor evolution and are frequently maintained during disease progression. Therefore, molecular analysis of the primary tumour may be sufficient to assess these alterations when metastatic tissue is unavailable [II; A].
- The timing of molecular testing should be aligned with clinical decision-making:
  - *PIK3CA* testing should be available when planning second-line ET following cyclin-dependent kinase 4/6 (CDK4/6) inhibitor treatment, or first-line treatment in metastatic setting for patients experiencing early relapse while receiving adjuvant AI therapy.
  - PD-L1 testing should be performed before initiation of first-line treatment for metastatic TNBC.
  - The results of germline testing should be available before standard treatment options have been exhausted to avoid missing the opportunity to administer biomarker-directed targeted therapies [V; B].

• Which molecular tests should be used?

In breast cancer, targeted NGS is the most commonly used sequencing method and typically includes genes of clinical relevance, such as *PIK3CA*, *TP53*, *ESR1*, *BRCA1/2*, *AKT1*, *PTEN*, and *ERBB2*, among others. The European Society for Medical Oncology (ESMO) guidelines recommend multigene NGS testing in metastatic breast cancer when the identification of actionable alterations may guide the use of approved targeted therapies (e.g., *PIK3CA* mutations) or facilitate enrolment in molecularly matched clinical trials.[55]

Recommendations

- NGS is the preferred method for simultaneous assessment of multiple clinically relevant genomic alterations that may inform treatment selection [II; A].
- The fixed "50-100 gene" panel recommendation may not be universally applicable. Focus instead on validated detection of all clinically variant types, including relevant copy number changes and fusions. [V; B] .

Droplet digital polymerase chain reaction (ddPCR) may be used to monitor the dynamics of clinically relevant mutations, such as *ESR1* and *PIK3CA*, during the course of treatment and to confirm previously identified or suspected mutations, offering higher analytical sensitivity than conventional sequencing methods.

Recommendations

- ddPCR is particularly useful for the detection and monitoring of specific mutations in circulating tumor DNA (ctDNA), due to its ability to identify variants present at very low variant allele frequencies (as low as 0.01%–0.1%) [III; B].

Sanger sequencing may be used to confirm selected variants identified by NGS, complement germline NGS panels by covering regions that are inadequately sequenced, and verify pathogenic germline variants before clinical validation and reporting. Currently, its role is primarily supportive, serving as a method for variant confirmation and validation or as an alternative in resource-limited settings where NGS is not available.

• How to choose between liquid biopsy and tumor tissue biopsy?

Recommendations

- Tumor tissue biopsy remains the gold standard for cancer diagnosis, tumor characterization, and histopathological confirmation of molecular alterations [I; A].
- ctDNA analysis through liquid biopsy may be useful as an initial molecular screening tool and for dynamic disease monitoring (e.g., detection of mutations in plasma) [I; A].

When a clinically relevant alteration is identified in liquid biopsy, the result may directly inform treatment decisions. However, a negative ctDNA result does not exclude the presence of the alteration because of the possibility of limited ctDNA shedding. Therefore, if the clinical question remains relevant, tissue biopsy should be performed whenever feasible to confirm the absence of the alteration.[51] This complementary approach helps ensure that treatment decisions are guided by the most comprehensive and reliable molecular information available while optimizing patient care.

• What are the recommendations for germline and somatic genetic testing?

Germline (hereditary) indications genetic testing (see section 3: HEREDITARY BREAST CANCER)

Recommendations

- *gBRCA1/2* testing should be performed early in the course of advanced disease in all patients with HER2-negative metastatic breast cancer who may be candidates for treatment with PARP inhibitors, regardless of age or family history [I; A].[50]
- Germline testing should preferably be performed using NGS-based multigene panels including, at least, *BRCA1* and *BRCA2*, as well as other clinically relevant cancer predisposition genes, such as *ATM*, *BARD1*, *BRIP1*, *CDH1*, *CHEK2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *STK11*, *NF1*, and *TP53* [I; B].

In the Portuguese setting, testing methods should include testing for the BRCA2 founder alteration *c.156_157insAlu*[50], as well as large genomic rearrangements (deletions or duplications).

Clinicians and Pathologists are encouraged to request information about this before sending samples for germinal testing.

Only pathogenic or likely pathogenic variants should be considered clinically actionable for PARP Inhibitors treatment decisions; variants of uncertain significance (VUS) should not guide treatment.[50]

Somatic (tumor) genomic testing

Recommendations

- The following somatic tests should be considered in metastatic breast cancer according to tumor subtype and clinical context:
  - *PIK3CA* mutations in HR-positive/HER2-negative tumors, to identify patients who may benefit from PI3K inhibitors [I; A].
  - Somatic *BRCA1/2* variants when germline testing is negative [III; C]. Although current regulatory approvals are restricted to *gBRCA1/2* mutations, a small subset of patients with isolated somatic BRCA2 mutations may benefit from PARP inhibitors (case-by-case decision or in the context of clinical trials).

Somatic *BRCA1/2* variants identified through tumor testing should prompt confirmatory germline testing, as approximately 50% of BRCA pathogenic or likely pathogenic detected in tumor tissue correspond to inherited germline variants (particularly *BRCA2*), which benefit from PARP inhibitors [I; A].[51]

- PD-L1 expression by IHC in TNBC– Although not a genomic biomarker, PD-L1 assessment is an essential component of molecular profiling and is required to determine eligibility for immunotherapy [I; A].
- MSI – Although rare in breast cancer, MSI can be assessed by NGS or PCR-based microsatellite testing. The presence of MSI-H status predicts benefit from immune checkpoint inhibitors [II; B].
- Other potentially actionable alterations, depending on the testing panel used:

- Neurotrophic receptor tyrosine kinase (*NTRK*) gene fusions – Detectable by fusion-capable NGS assays or by pan-TRK IHC as a screening method; TRK inhibitors are approved for patients harboring these alterations [II; B].
- High TMB – When available through NGS, TMB assessment may identify patients eligible for tumor-agnostic immunotherapy with pembrolizumab [II; B].
- Less common alterations in clinically relevant genes:

  AKT1 mutations (~3% of luminal breast cancers): evidence from clinical trials supports the benefit of AKT pathway inhibition, including capivasertib-based treatment strategies [I; C].

  FGFR1 amplification (~10% of luminal breast cancers): no approved targeted therapies are currently available, although several agents are under clinical investigation.

  ERBB2 (HER2) mutations (approximately 1%–3% of luminal breast cancers): emerging evidence suggests potential benefit from HER2-targeted therapies, including neratinib and trastuzumab deruxtecan (T-DXd), although these indications remain off-label [I; C].

- In accordance with international guidelines (ESMO and National Comprehensive Cancer Network [NCCN]), testing should, at a minimum, include biomarkers linked to approved targeted therapies. In HR-positive/HER2-negative disease, these include alterations in the *PIK3CA/AKT/PTEN* pathway and *gBRCA1/2* status, whereas in TNBC, PD-L1 assessment is mandatory to guide treatment selection [I; A].[25,57]

3. HEREDITARY BREAST CANCER

• When should hereditary breast cancer be suspected and which genetic alterations should be tested?

Recommendations

Germline genetic testing should be performed in the following cases:

- Women diagnosed with unilateral breast cancer at ≤50 years of age.
- Men diagnosed with breast cancer at any age.
- Women with breast cancer at any age who meet one of the following criteria:
  - TNBC diagnosed at any age.
  - Bilateral breast cancer.
  - Two primary breast cancers (with a high likelihood of representing distinct primary tumors, e.g., different histological subtypes).
  - Breast cancer and epithelial (non-mucinous) ovarian, fallopian tube, or primary peritoneal cancer, diagnosed synchronously or metachronously, at any age.
  - Lobular breast cancer and a personal or family history (first- or second-degree relative) of diffuse gastric cancer.
  - Breast cancer at any age with a first-degree relative (parent, sibling, or child) diagnosed with:
    - Breast cancer at ≤50 years of age.
    - Ovarian, fallopian tube, or primary peritoneal cancer.
    - Pancreatic cancer.
    - High-risk or metastatic prostate cancer.
  - Breast cancer and a family history of breast and/or prostate cancer (any degree of relationship) in at least two relatives on the same side of the family, diagnosed at any age.
- Patients with the following therapeutic indications:
  - Advanced HER2-negative breast cancer eligible for treatment with PARP inhibitors.
  - Breast cancer with high risk of relapse eligible for adjuvant treatment with PARP inhibitors.
- Individuals of Ashkenazi Jewish ancestry with breast cancer.

• Which genetic testing strategy should be used?

Recommendations

- A NGS multigene panel with copy number variant (CNV) analysis should be performed (ideally in the family index case), preferably using a peripheral blood sample. The panel should include the following genes: *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CDH1*, *CHEK2*, *PALB2*, *PTEN*, *STK11*, *TP53*, *RAD51C*, and *RAD51D* [III, A]. [58,59]
- In addition, testing for the Portuguese founder mutation *BRCA2 c.156_157insAlu* should be performed, as this variant may not be detected by all currently available NGS methodologies.

Identified variants should be classified according to the recommendations of the American College of Medical Genetics and Genomics (ACMG). [56] Only pathogenic or likely pathogenic variants should be considered clinically actionable; variants of uncertain significance (VUS) should not guide clinical management.

• Who should request genetic testing?

Recommendations

- Genetic testing should be requested by the treating physician or, depending on the organization of each center, by a clinical geneticist or another physician, preferably at the time of diagnosis or as soon as possible thereafter.
- Predictive testing, particularly in unaffected relatives, should be requested within the context of a Medical Genetics consultation.
- If testing has not been requested by a clinical geneticist, referral to a Medical Genetics consultation should be performed whenever a hereditary cancer predisposition variant is identified (through the identification of a pathogenic variant [PV] or likely pathogenic variant [LPV] in a hereditary cancer predisposition gene) or whenever a variant of uncertain significance (VUS) is identified.
- Referral to a Medical Genetics consultation should also be considered in families with an atypical cancer history or a diagnosis of rare tumors.

• How should patients with a strong suspicion of hereditary cancer be managed when genetic testing does not identify a pathogenic variant?

In families with a strong history suggestive of a hereditary cancer predisposition syndrome — particularly those with multiple affected generations, early-onset disease, and/or rare tumor types — surveillance of unaffected relatives should be considered according to the most likely hereditary cancer syndrome and the malignancies identified within the family.

Repeat genetic testing should also be considered, particularly if additional cases of cancer arise within the family or if previous testing was limited, reflecting the dynamic nature of hereditary cancer risk assessment.

Recommendations

- Genetic testing using an NGS multigene panel should be considered in patients who meet established criteria for genetic testing or who have clinical features consistent with a specific hereditary cancer syndrome and who previously underwent negative or inconclusive genetic testing without the use of NGS-based multigene panel testing [II; A].
- Periodic re-evaluation of VUS should be performed to update variant interpretation in light of emerging evidence. VUS findings should not be used to guide clinical management decisions [V; A].

• How should PV/LPV carriers be managed?

The development of a surveillance and risk management plan should be based on a comprehensive, individualized assessment that considers not only the identified gene and PV/LPV, but also other genetic and non-genetic individual risk factors (e.g., age and reproductive history).[60] CanRisk is a validated online tool that can assist in this assessment by estimating an individual's breast cancer risk and likelihood of carrying pathogenic variants associated with hereditary breast cancer.[61,62]

Recommendations *(asymptomatic carriers)*

BRCA1, BRCA2, or PALB2 PVs/LPVs (hereditary breast and ovarian cancer syndrome)

- Clinical breast examination every 6-12 months is recommended, starting between 25 and 30 years of age, or 5 years before the age at diagnosis of the youngest affected family member, for carriers of PVs in other high-penetrance genes. [63,64]
- Breast imaging surveillance should be initiated between 25 and 30 years of age (or 5 years before the age at diagnosis of the youngest affected relative) with annual breast MRI.
- From 30 years of age, annual mammography should be added to annual breast MRI.
- The upper age limit for continuing MRI surveillance should be individualized,[62] taking into account the patient's overall health status, life expectancy, breast density, and comorbidities.[61]
- In carriers of *BRCA1* PVs, alternating breast MRI and mammography every 6 months may be considered because of the more rapid growth rate of these tumours.[61]

TP53 PVs/LPVs (Li-Fraumeni syndrome)

- Clinical breast examination every 6-12 months is recommended, starting at 18 years of age.[62,65]
- Annual whole-body MRI and annual breast MRI are recommended from 18 years of age.[62,65]
- Individualized risk management should consider not only the genotype but also the individual and family phenotype.

PTEN PVs/LPVs (Cowden syndrome)

- Clinical breast examination every 6-12 months is recommended, starting at 25 years of age, or 5-10 years before the age at diagnosis of the youngest affected family member.[61,62]
- Annual breast MRI is recommended from 30 years of age, with the addition of annual mammography from 40 years of age.[61,64]

CDH1 PVs/LPVs (hereditary diffuse gastric cancer)

- Annual mammography and annual breast MRI are recommended from 30-35 years of age (or 5 years before the age at diagnosis of the youngest affected family member).[61–63]
- Risk-reducing breast surgery may be considered following multidisciplinary discussion.[63]

STK11 PVs/LPVs (Peutz–Jeghers syndrome)

- Annual mammography and annual breast MRI are recommended from 30 years of age (or 5 years before the age at diagnosis of the youngest affected family member).[61,62]

Carriers of PVs/LPVs in moderate-penetrance genes (ATM, BARD1, CHEK2, NF1, RAD51C, RAD51D)

- Annual mammography is recommended from 40 years of age.
- The decision to include breast MRI should be individualized according to the patient's risk profile.
- Individual risk should be estimated using validated risk prediction models, such as CanRisk.[61]

Male carriers of PVs/LPVs

- In men carrying *BRCA2* PVs/LPVs, annual clinical breast examination is recommended from 35 years of age, and annual mammography from 50 years of age, or 10 years before the age at diagnosis of the youngest male family member with breast cancer, whichever occurs first [V; C].[61,66]

Transgender individuals carrying PVs/LPVs

- For transgender men carrying *BRCA1* or *BRCA2* PVs/LPVs who retain breast tissue (i.e., who have not undergone bilateral mastectomy or who have residual breast tissue), annual breast imaging with MRI or mammography is recommended from 25-30 years of age.[67]
- For transgender women carrying *BRCA1* or *BRCA2* PVs/LPVs, the same surveillance protocol recommended for cisgender men should be followed.[67]

Patients with active cancer

For patients with an active diagnosis of breast cancer, decisions regarding breast imaging (breast US, mammography, and breast MRI) and potential risk-reducing surgery (ipsilateral mastectomy, contralateral mastectomy, and bilateral salpingo-oophorectomy [BSO]) should be individualized, taking into account the patient's prognosis, age, family history, and preferences.

Cancer survivors

The surveillance and risk management plan for cancer survivors should take into account the risk of second primary breast cancers in the index breast, the risk of contralateral breast cancer, the risk of malignancies in other organs associated with the identified PV (e.g., ovary, pancreas, and stomach), and the type of primary surgery performed, including whether BCS was performed and whether contralateral risk-reducing mastectomy was undertaken.

• Which carriers of PVs/LPVs should be considered for risk-reducing mastectomy?

Asymptomatic carriers

Bilateral risk-reducing mastectomy (BRRM) is the most effective strategy for breast cancer prevention in carriers of *BRCA1* and *BRCA2* PVs/LPVs, reducing breast cancer risk by approximately 90%.[68,69]

In symptomatic carriers, the choice of mastectomy technique — total mastectomy, skin-sparing mastectomy, or nipple-sparing mastectomy (NSM) — depends on tumor-related factors, including tumor size, location, and its relationship to the skin and/or nipple. In asymptomatic carriers, NSM with immediate breast reconstruction is generally the preferred approach, as it effectively reduces breast cancer risk while providing superior cosmetic outcomes.[70,71]

To date, there is no robust evidence regarding the impact of BRRM on outcomes in carriers of PVs/LPVs in other high-penetrance genes. However, given their substantially increased cancer risk, this strategy may be individually considered in these patients.

For carriers of PVs/LPVs in moderate-penetrance genes, there is no evidence that BRRM improves survival. Therefore, the decision should be based not only on the presence of the genetic variant but also on the patient's family history and individual risk factors.[61,62,72,73]

Recommendations

- BRRM should be considered in the following patients:
  - Women carrying *BRCA1* PVs/LPVs.
  - Women carrying *BRCA2* PVs/LPVs, for whom the survival benefit of BRRM has not been demonstrated, the decision should be individualized according to individual risk profile, family history, and patient preferences [IV; C].
  - Women carrying PVs/LPVs in *TP53*, *PTEN*, *STK11*, *CDH1*, and *PALB2*, taking into account individual risk profile and family history [IV; C].
- BRRM is generally not recommended for women carrying PVs/LPVs in moderate-penetrance genes (*ATM*, *BARD1*, *CHEK2*, *NF1*, *RAD51C*, and *RAD51D*), but it may be considered based on the individual's risk profile and family history [IV; C].
- Psychological support should be offered to all carriers to provide counseling and support throughout the decision-making process [IV; B].
- atients who are candidates for BRRM should undergo breast MRI within 6 months before surgery [V; C].

Symptomatic carriers

Breast cancer diagnosis and PV/LPV status

For women with unilateral sporadic early-stage breast cancer, breast-conserving treatment (when feasible) is the preferred option, as it is associated with higher breast cancer-specific survival and overall survival (OS) rates compared with mastectomy.[74]

For women with unilateral breast cancer who carry a PV/LPV in the *BRCA1* or *BRCA2* genes, the choice of breast-conserving treatment remains controversial. The decision regarding locoregional management should consider the risk of ipsilateral breast tumor recurrence and new primary breast cancer in the index breast, the risk of contralateral breast cancer, and factors modifying these risks.[75,76]

In women with breast cancer who carry a PV/LPV in moderate-penetrance genes, there is insufficient evidence to systematically recommend bilateral mastectomy/risk-reducing mastectomy. However, this approach may be considered on an individual basis, taking into account the patient's individual risk and family history.[77,78]

Carriers of *BRCA1* or *BRCA2* PVs/LPVs are not candidates for partial breast irradiation (PBI) techniques following BCS.

Carriers of *ATM* PVs/LPVs should receive radiotherapy whenever clinically indicated.[77]

Recommendations

- Every effort should be made to ensure that the results of genetic testing are available before locoregional treatment decisions are made, whenever clinically feasible.
- BRRM is recommended for women with stage I–III breast cancer carrying a PV/LPV in the *TP53* gene [IV; C].
- For young women (<40 years) with stage I–III TNBC and a PV/LPV in the *BRCA1* gene, a more radical approach should be considered (total mastectomy combined with contralateral risk-reducing mastectomy) [IV; C].
- Breast-conserving treatment may be considered for women aged >40 years with stage I–III breast cancer who carry a PV/LPV in high-penetrance genes (excluding *TP53*). The decision should be individualized according to age, gene involved, specific variant, factors modifying the risk of ipsilateral recurrence and contralateral breast cancer, prognosis of the index tumor, family history, and the ability to maintain intensive and appropriate imaging surveillance [IV; C].
- For women with stage I–III breast cancer who carry a PV/LPV in moderate-penetrance genes, locoregional treatment decisions should not be based solely on the presence of the variant. In these cases, breast-conserving treatment should remain the preferred option when clinically indicated [IV; C].
- Skin-sparing and nipple-sparing mastectomy are safe surgical approaches for women with stage I–III breast cancer and PVs/LPVs in high- or moderate-penetrance genes who are eligible for mastectomy [IV; C].

Diagnosis of PV/LPV after breast cancer treatment

Recommendations

- The same principles described in the previous section apply: the risk of ipsilateral recurrence in women previously treated with BCS and the risk of contralateral breast cancer should be considered [IV; C].

Diagnosis of PV/LPV after ovarian cancer treatment

Recommendations

- For women diagnosed with ovarian cancer who carry a PV/LPV in the *BRCA1* or *BRCA2* genes, BRRM should only be considered in those who remain in remission 5 years after diagnosis, given the high risk of ovarian cancer recurrence [IV; C].

Diagnosis of PV/LPV after treatment of other cancers

Recommendations

- In women with other malignancies associated with hereditary cancer predisposition syndromes (e.g., pancreatic or gastric cancer) carrying PVs/LPVs in high-penetrance genes, the recommendation for BRRM should take into account the stage and prognosis of the index malignancy [V; C].

• Up to what age should risk-reducing mastectomy be considered?

Evidence supporting BRRM after the age of 55 years is limited. The decision should consider the carrier's overall health status, life expectancy (ideally ≥10 years), and the presence of comorbidities.[61,79]

Recommendations

- BRRM may be considered in high-risk asymptomatic carriers of PVs/LPVs, with the greatest benefit generally observed when performed between 30 and 55 years of age [IV; C].

• Is surveillance recommended after risk-reducing mastectomy?

Recommendations

- Annual clinical evaluation and regular breast self-awareness are recommended [V; C].
- Routine imaging surveillance is not recommended.
- Breast MRI may be considered in selected cases, particularly when residual fibroglandular tissue (RFT) is suspected, to assess its extent. If the amount of RFT is considered clinically significant (based on the radiologist's subjective assessment), targeted surveillance with US or MRI may be considered [V; C].

• Which patients should be considered for risk-reducing bilateral salpingo-oophorectomy?

Recommendations

- Women with pathogenic/likely pathogenic variants (PV/LPV) associated with an increased risk of ovarian cancer should undergo risk-reducing surgery after completion of childbearing and taking into account family history.61
- BSO should be considered [II; B]:

  In women aged 35–40 years who carry a PV/LPV in the *BRCA1* gene.

  In women aged 40–45 years who carry a PV/LPV in the *BRCA2* gene.

  In women aged 45–50 years who carry a PV/LPV in the *BRIP1*, *RAD51C*, *RAD51D*, or *PALB2* genes.[61,62]
- Risk-reducing salpingectomy with delayed oophorectomy should not be considered outside the context of clinical trials, as the safety of this strategy has not yet been established.[80]
- In women without a personal history of breast cancer who undergo BSO before the age of 45 years, menopausal hormone therapy (MHT) may be initiated for up to 4 years without increasing breast cancer risk [II; A].*81,82*
- After the age of 45 years, initiation of MHT should be individualized, taking into account the severity of menopausal symptoms, previous risk-reducing mastectomy, and the presence of risk factors for osteoporosis [IV; C].
- In women with an intact uterus, a progestogen should be added at the time of BSO. Micronized progesterone may be preferred, as available evidence suggests a lower breast cancer risk compared with some synthetic progestogens [I; A].[83,84]

Levonorgestrel and dydrogesterone are associated with a lower risk of breast cancer compared with other progestogens [I; A].[83,85,86]

- In women who have undergone hysterectomy, estrogen-only therapy should be administered at the time of BSO, as it is not associated with an increased risk of breast cancer [I; A].[85]
- The use of combined hormonal contraceptives is not contraindicated in carriers of PVs/LPVs. However, the decision should be individualized, considering factors such as the woman's age, previous risk-reducing breast surgery, anticipated duration of contraceptive use, and impact on the menstrual cycle [I; A].[61,87]

• What are the reproductive options for carriers of PVs/LPVs?

Fertility preservation in carriers of PVs/LPVs should be discussed not only at the time of diagnosis but also throughout the treatment journey.

Oocyte cryopreservation is the preferred fertility preservation technique for women with breast cancer and a high risk of treatment-related ovarian failure.[61]

Women carrying PVs/LPVs in the *BRCA1* and *BRCA2* genes — particularly *BRCA1* — have lower serum anti-Müllerian hormone levels and a possible reduction in ovarian reserve. Therefore, they should receive fertility counseling, particularly if they are considering delaying pregnancy.[5]

Recommendations

- Within the context of the National Health Service (NHS), women diagnosed with early-stage breast cancer who have an indication for chemotherapy (neoadjuvant or adjuvant) and/or ET should be referred for an oncofertility consultation, provided they meet the following criteria: age <40 years, incomplete reproductive plans, favorable prognosis, and adequate ovarian reserve (assessed by anti-Müllerian hormone levels and/or antral follicle count) [II; A].
- Reproductive counselling for these women should include discussion of prenatal diagnostic techniques and medically assisted reproduction options, given the high probability of transmission of the PV/LPV to offspring [III; A].[61]

4. MANAGEMENT OF PRECURSOR LESIONS

Precursor lesions comprise a heterogeneous group of breast lesions classified as lesions of uncertain malignant potential. This group includes lesions with varying degrees of risk of progression to malignancy, as well as lesions whose morphological heterogeneity precludes a definitive diagnosis on core needle biopsy (CNB) specimens. These recommendations apply exclusively to carcinoma in situ.

• What is new in the imaging diagnosis of ductal carcinoma in situ?

Recommendations

- Digital mammography remains the gold standard for the diagnosis of DCIS, primarily due to its high sensitivity for the

detection of microcalcifications, which are often the sole radiological manifestation of the disease [I; A].[88,89]

- DBT, also known as three-dimensional (3D) mammography, is recommended as an advanced imaging modality because of its ability to reduce tissue overlap and improve the detection of non-palpable lesions, including DCIS, compared with conventional 2D digital mammography [I; A].[90–92]

US is used as a complementary imaging modality to mammography, being particularly useful for the characterization of breast masses and for guiding biopsy procedures. It also plays an important role in axillary assessment, particularly in patients with suspicious axillary findings or features associated with an increased risk of occult invasion, such as high-grade DCIS, comedo necrosis, or extensive disease.

Recommendations

- In cases of suspected nodal involvement, axillary assessment with US-guided CNB is recommended [I (as a complement to mammography)/II (for axillary evaluation); A/B].[93–97]
- Contrast-enhanced breast MRI is the recommended supplemental screening modality for women with extremely dense breasts and for those at high risk of breast cancer [I; A].[98–101] Breast MRI may also provide findings suggestive of metastatic nodal involvement during axillary evaluation.[102–104]
- CEM may be considered as an alternative to breast MRI for the evaluation of microcalcifications not associated with a mass [II–III; B].[105]
- Post-treatment surveillance should consist of annual mammographic follow-up, particularly during the first five years after breast-conserving therapy.
- Breast MRI should be considered in women with dense breasts or a family history of breast cancer [II; B].[106,107]

• Can vacuum-assisted biopsy be considered a therapeutic, in addition to a diagnostic, option for ductal carcinoma in situ?

Recommendations

- Vacuum-assisted biopsy (VAB) is the preferred technique for the histological diagnosis of microcalcifications and small suspicious breast lesions, providing greater diagnostic accuracy than CNB in specific settings and enabling the retrieval of a larger volume of tissue [I; A–B].[108–110]

VAB has been investigated as a minimally invasive approach for the treatment of DCIS. However, its use as a definitive therapeutic strategy is not currently endorsed by international guidelines. Feasibility studies have suggested potential therapeutic applicability in selected cases, but robust evidence from large-scale prospective studies with long-term follow-up remains lacking.

Recommendations

- Surgical excision remains the standard treatment for DCIS and for non-classic LCIS [III; C].[111,112]

• Should immunohistochemical characterization be performed in ductal carcinoma in situ?

Current evidence does not support the routine use of immunohistochemical molecular profiling of DCIS to assess the risk of progression to invasive carcinoma or to guide surgical management, adjuvant treatment decisions, or follow-up strategies.[113–115]

For these purposes, risk stratification should instead be based on established histopathological features, including lesion size, margin distance, nuclear grade, architectural pattern, presence of necrosis, presence of microcalcifications, and ER expression.

• Which patients with a preoperative diagnosis of ductal carcinoma in situ should undergo synchronous sentinel lymph node biopsy?

Recommendations

- Sentinel lymph node biopsy (SLNB) is not recommended in patients with DCIS undergoing breast-conserving treatment [I, A].[116,117]
- SLNB may be considered in patients with DCIS when there is radiological or histopathological suspicion of invasive carcinoma [IV, C].[118,119]
- SLNB should be performed in patients with DCIS undergoing mastectomy [I, A].[118,119]

• What margin justifies re-excision after breast-conserving surgery for carcinoma in situ?

Recommendations

- A 2-mm negative margin is adequate for carcinoma in situ treated with BCS followed by whole-breast irradiation (WBI) [I, A].[120]
- Routine surgical re-excision for margins <2 mm is not recommended in patients who will undergo adjuvant radiotherapy [I; B].[121,122]

Surgical re-excision to obtain wider margins may be considered in selected cases, such as patients with multiple margins <2 mm or those who decline adjuvant radiotherapy.[123,124]

The decision to perform re-excision should be made within the context of a multidisciplinary discussion, taking into account the risks associated with additional surgery and the patient's absolute risk of local recurrence.

• What are the recommended radiotherapy regimens and the criteria for omitting radiotherapy?

Hypofractionated adjuvant radiotherapy regimens may be used as an alternative to longer conventional fractionation schedules. In patients at intermediate or high risk of recurrence, or in the presence of close surgical margins, a tumor bed boost significantly reduces the risk of local recurrence.[125]

PBI is an alternative to WBI in selected patients, particularly those with low- or intermediate-grade tumors measuring ≤2.5 cm and surgical margins ≥3 mm.[29,126,127]

Recommendations

- Omission of adjuvant radiotherapy may be considered in selected patients with screen-detected DCIS, low- or intermediate-grade disease, tumor size ≤2.5 cm, surgical margins ≥3 mm, estrogen receptor-positive disease, and who are receiving adjuvant endocrine therapy [II, B].[25,29,128]
- This decision should be made within the context of a multidisciplinary team discussion and through shared decision-making with the patient, taking into account the patient's age, comorbidities, preferences, and the potential adverse effects of radiotherapy.

• Which patients with ductal carcinoma in situ should receive endocrine therapy, and which agent and dose should be used?

Recommendations

- Adjuvant ET for 5 years should be considered in patients with estrogen receptor-positive DCIS after BCS and radiotherapy [I, A].[129]
- The decision to initiate ET should be made within the context of a multidisciplinary team discussion and through shared decision-making with the patient, taking into account the expected benefits and potential risks of treatment.

In low-risk patients (i.e., those older than 50 years with low- or intermediate-grade, hormone receptor-positive DCIS), omission of ET may be considered.[130,131]

Recommendations

- In premenopausal women, tamoxifen 20 mg/day is the preferred ET option [I, A].
- A reduced dose of tamoxifen (5-10 mg/day for 3 years) may be considered in patients who experience significant toxicity or are at increased risk of adverse effects [I, A].
- In postmenopausal women, either tamoxifen or anastrozole may be considered. Anastrozole is the preferred option for women younger than 60 years [I, A].[25,29,132,133]

5. AXILLARY MANAGEMENT

• In which patients undergoing primary surgery can pathological axillary staging be omitted?

Recommendations

- SLNB may be omitted in post-menopausal women >50 years of age with unifocal, early-stage invasive breast cancer presenting with favorable biological features (hormone receptor [HR]-positive, HER2-negative, grade 1–2), clinical tumor size ≤2 cm (cT1), clinically node-negative axilla (cN0), and negative preoperative axillary imaging (iN0) who are candidates for primary BCS followed by adjuvant radiotherapy [I; A].[116,117,134]
- Preoperative axillary imaging assessment is mandatory [I; A].
- Patients with a negative axillary US examination, or with a single indeterminate/suspicious axillary lymph node shown to be negative on US-guided fine-needle aspiration or core needle biopsy, may be considered eligible for omission of SLNB.[116,117,134]

Axillary assessment may also be performed using MRI, which has demonstrated diagnostic performance comparable to that of axillary US in this setting.[116,117,134]

In axillary assessment, well-defined morphological criteria should be applied, preferably using classification systems that stratify the degree of suspicion for nodal metastasis (e.g., the Bedi and Amonkar classifications), in order to standardize imaging evaluation and reduce the risk of false-negative findings.[135–138]

Among sampling techniques, US-guided CNB has demonstrated higher diagnostic sensitivity than fine-needle aspiration cytology (88.2% *vs* 72.5%), while both methods exhibit high specificity and a positive predictive value close to 100%. In cases of discordance between imaging findings and cytological results, or when cytological samples are inadequate or non-diagnostic, a CNB is recommended. The use of vacuum-assisted axillary biopsy is not recommended.[97,134,139]

Assessment of primary breast tumor size and evaluation of disease focality may be performed by mammography and US or by breast MRI.[140,141]

Breast MRI provides higher sensitivity for the detection of multifocal, multicentric, and bilateral disease and is highly accurate for assessing tumor extent and estimating tumor size.

Recommendations

- Breast MRI is recommended for patients with dense breasts and for those with invasive lobular carcinoma. Alternatively, CEM may be considered.[140–142]
- If the final surgical pathology examination reveals a tumor classified as >pT2 or histological grade 3, SLNB should be considered [I; A].

• What are the implications of omitting pathological axillary staging for adjuvant treatment decision-making?

Recommendations

- Adjuvant radiotherapy may be omitted in women aged ≥70 years with tumors ≤2 cm, clinically and radiologically node-negative (N0), HR-positive/HER2-negative, who are candidates for adjuvant endocrine therapy, as available evidence indicates that it does not have a significant impact on overall or disease-free survival [I; B].[143]
- PBI is recommended only in patients with pathologically node-negative axillary lymph nodes.[25,29,144,145] Patients who are candidates for PBI should undergo axillary staging with SLNB [I; A].[146–148]
- In patients who are candidates for omission of SLNB, the decision to administer adjuvant chemotherapy remains unchanged, as it is based primarily on tumor biology and genomic risk rather than axillary nodal status [I; B].[29,149]
- Recommendations regarding the use of genomic testing should not be modified by the omission of SLNB [I; A].
- The decision to use adjuvant CDK4/6 inhibitors is not significantly affected in patients eligible for omission of SLNB [I; B].

Omission of SLNB may result in potential undertreatment of a small subgroup of eligible patients with occult node-positive disease.

• In which patients with low-volume cN1 disease undergoing primary surgery can axillary lymph node dissection be omitted?

Recommendations

- In patients with invasive breast cancer, clinically node-positive (cN+) disease, and an indication for primary surgery, level I/II axillary lymph node dissection (ALND) remains the standard approach [I; A].
- In patients with low-volume cN1 disease (defined as the absence of palpable adenopathy and imaging evidence of ≤2 suspicious lymph nodes that have been histologically confirmed and clipped) who are candidates for primary surgery (postmenopausal women with HR-positive/HER2-negative tumors) and are expected to receive adjuvant radiotherapy, selective axillary dissection may be considered [III; C].
- Patients with pathological stage pN2–3 disease who undergo primary selective axillary dissection should undergo ALND [I; A].

• How should axillary tumor burden be radiologically assessed?

Recommendations

- Given their complementary roles, axillary US [I; A] and breast MRI [I; B] are the preferred imaging modalities for the assessment of axillary tumor burden.
- The key imaging predictors of axillary tumor burden that should be routinely reported on axillary US include lymph node location, number, and morphological characteristics.[150]
- Morphological assessment should be performed using well-defined criteria, such as those described in the Bedi and Amonkar classification systems.[135,136]

• In which patients with cN1 disease who achieve ypN0 status after primary systemic therapy can adjuvant regional nodal irradiation be omitted?

Recommendations

- Regional nodal irradiation may be omitted in selected patients with breast cancer who initially present with cT1–2N1 disease (≤3 involved lymph nodes) and are older than 50 years.
- Patients with minimal residual nodal disease classified as ypN0(i+) should generally be considered equivalent to ypN0, in accordance with the recommendations of the ESMO and the NCCN. Therefore, ypN0(i+) status does not, by itself, constitute a mandatory indication for regional nodal irradiation [I; C].[151–154]

• In which patients with residual disease after primary systemic therapy can axillary lymph node dissection be omitted?

Recommendations

- Axillary lymph node dissection (ALND) may be omitted in patients with ypN0(i+) disease [II; B].[152]
- The currently available evidence does not support the omission of ALND in patients with ypN1(mi)[155,156] or ypN1a disease.[157–159]

6. RADIOTHERAPY

• What are the indications for the use of hypofractionated radiotherapy?

Recommendations

- **Breast**
  - Moderate hypofractionation is recommended as the standard approach regardless of age, disease stage, tumor biological subtype, surgical margin status, use of a tumor bed boost, breast size, use of oncoplastic techniques, or systemic therapy [I; A].[160–166]
  - Ultrahypofractionation (26 Gy in 5 fractions) may be recommended as a standard-of-care option [I; A].[163,164,166]
  - Conventional fractionation may be considered in selected cases [I; C].[160,161,164,165]
- **Chest wall (without reconstruction)**
  - Moderate hypofractionation is recommended as the standard approach [I; A].[161,162,164,167]
  - Ultrahypofractionation (26 Gy in 5 fractions) may be recommended as a standard-of-care option [I; A].[163,164,166]
  - Conventional fractionation may be considered in selected cases [I; C].[164,168–170]
- **Chest wall (with immediate reconstruction)**
  - Moderate hypofractionation is recommended as the standard approach [I; A].[162,164,167,169]
  - Conventional fractionation may be considered [I; C].[164,169,170]
- **Regional nodal irradiation**
  - Moderate hypofractionation is recommended as the standard approach [I; B].[161,162,164,167]
  - Conventional fractionation may be considered in selected cases [I; C].[164,168,170,171]
  - Ultrahypofractionation (26 Gy in 5 fractions) may become a recommended approach in the near future, pending publication of the survival analysis of the nodal subgroup from the FAST-Forward trial.[163,164,166]

• Which radiotherapy techniques should be used?

Recommendations

- Deep inspiration breath hold (DIBH) [I; A] [172]
  - DIBH should be prioritized according to anatomical location, particularly for:
    - Left-sided breast irradiation [V; A]
    - Internal mammary node irradiation [V; A]
  - DIBH may also be used in the setting of ultrahypofractionation.
- Intensity-modulated radiotherapy techniques [III; B] [173]
  - The use of intensity-modulated radiotherapy techniques is recommended, ranging from three-dimensional field-in-field (3D-FiF) techniques to more advanced approaches, such as volumetric modulated arc therapy (VMAT) and hybrid techniques [IV; B].
- Treatment accuracy [III, B][173]
  - In the setting of ultrahypofractionation, image-guided radiotherapy (IGRT), potentially combined with surface-guided radiotherapy (SGRT), is recommended to ensure accurate patient positioning and treatment delivery. Positional uncertainties should be minimized using appropriate verification and correction strategies, with a level of accuracy comparable to that required for stereotactic body radiotherapy (SBRT) [V; B].

• What are the indications and recommended techniques for partial breast irradiation?

Recommendations

- Patients meeting the eligibility criteria outlined below (**Table 2**) may be considered for PBI [I; B] [144,164]
- The presence of an extensive intraductal component (EIC) should be considered a criterion for exclusion from PBI [IV; C].[174]
- Recommended PBI techniques include external beam radiotherapy (EBRT) and brachytherapy.[144,164]
  - External beam radiotherapy (EBRT)
    - Dose and fractionation schedules should follow current ESTRO[175] and ASTRO[144] recommendations.
    - The recommendations outlined in the section "Which radiotherapy techniques should be used?" apply.
  - Brachytherapy
    - Dose and fractionation schedules should follow current ESTRO[175] and ASTRO[144] recommendations.

• What are the indications for tumor bed boost irradiation?

Recommendations

- Omission of tumor bed boost may be considered in patients with an estimated risk of local recurrence of <3% at 5 years and <6% at 10 years [IV; B].[176]
- A tumor bed boost is recommended in patients with at least one of the following characteristics [IV; B]:[161,176]
  - age <50 years
  - positive surgical margins
  - grade 3 tumors
  - triple-negative breast cancer
- Other factors associated with an increased risk of local recurrence may also be considered when deciding whether to administer a tumor bed boost, including[177–179]:
  - lymphovascular invasion (LVI)
  - extensive intraductal component (EIC)
  - larger pathological tumor size (particularly >3 cm)
  - response to neoadjuvant systemic therapy, particularly the presence of residual invasive disease

Tumor bed delineation and surgical reporting after BCS [IV; B][180,181]

- Target volume delineation should not rely exclusively on

Table 2. Eligibility criteria (ESTRO and ASTRO) considered for PBI.

Criterion	ESTRO[164]	ASTRO[144]
Age	≥50 years	≥40 years (40-49 years: moderate evidence)
Histology	Luminal-like subtypes	IDC-NOS or other favourable subtypes
ILC	No	No (conditional)
DCIS	Screen-detected; low-intermediate grade; ≤2.5 cm; margin ≥3 mm	Screen-detected; low-intermediate grade; ≤2 cm; margin ≥2 mm
Grade	Grade 1–2	Grade 1–2
Tumor size	pT1-2 (≤30 mm)	pT1 (≤20 mm)
Margins	>2 mm	Negative
Multicentricity	Unicentric	Unicentric
Multifocality	Unifocal	Unifocal
LVI	No	No (conditional)
ER/PR status	ER-positive	ER-positive
pN status	pN0 (including isolated tumor cells)	pN0 (i-, i+)
Primary chemotherapy	No	NA
BRCA status	–	Negative

ASTRO, American Society for Radiation Oncology; DCIS, ductal carcinoma in situ; ER, estrogen receptor; IDC-NOS, invasive ductal carcinoma, not otherwise specified; ILC, invasive lobular carcinoma; ESTRO, European Society for Radiotherapy and Oncology; LVI, lymphovascular invasion; NA, not applicable; PR, progesterone receptor

the surgical scar or the postoperative seroma.

- As a standard approach, the tumor bed should be marked with titanium clips, ideally five: four corresponding to the radial margins and one to the posterior margin. Clips should be placed within the breast parenchyma rather than in adipose tissue. The use of dedicated clips for tumor bed marking, distinguishable in size from vascular clips, should be considered.
- Depending on local availability and expertise, alternative marking methods may be considered, including gold markers, three-dimensional bioabsorbable markers, or liquid markers.
- In oncoplastic procedures, the surgical report should explicitly describe the final three-dimensional location of the original tumor bed, including the final anatomical location of the four radial margins.
  - Clip placement at a specific margin may be omitted when the corresponding parenchymal resection margin is determined by the surgical technique rather than by tumour location and is remote from the tumour bed. Alternatively, the projection of that margin onto the chest wall may be marked.
  - In oncoplastic procedures involving volume displacement, particularly Clough level II techniques, the use of a liquid marker may be preferred when available.
  - In oncoplastic procedures involving partial volume replacement with local or locoregional dermoadipose flaps, when resection creates a tissue defect extending into the donor site, additional clips should be placed on the chest wall to delineate the estimated boundaries of the surgical cavity or the anatomical boundaries of the breast.

• What are the indications for reirradiation?

Recommendations [173]

- Local recurrence

a) After BCS [III; B]

- Whenever feasible, complete excision of the recurrent lesion should be performed.
- Although mastectomy remains the standard treatment, repeat BCS may be considered in selected patients who meet the following criteria:
  - Unifocal recurrence, confirmed by breast imaging (mammography, breast US, and MRI).
  - Recurrent tumor size <2-3 cm.
  - Absence of skin involvement.
  - Age >50 years.
  - Recurrence-free interval >48 months.
  - Patient preference.
  - Technical feasibility of repeat BCS with an acceptable cosmetic outcome.
- Patients should be informed of the increased risk of subsequent local recurrence associated with repeat BCS.
- Repeat BCS should be followed by reirradiation. Partial breast reirradiation, particularly using brachytherapy, is the approach for which the greatest clinical experience is available.

b) After mastectomy [IV; B]

- Whenever feasible, complete excision of the recurrent lesion should be performed.
- If technically feasible, reirradiation of the site of recurrence should be considered, even when negative surgical margins have been achieved.
- Irradiation of the regional nodal basins should be considered in patients whose regional nodes have not been previously irradiated.
- In patients with chest wall recurrence after previous radiotherapy, hyperthermia may be considered in combination with reirradiation, although no OS benefit has been demonstrated.

- Regional nodal recurrence [IV; B]
  - Whenever technically feasible, surgical treatment should be preferred.
  - Reirradiation of previously irradiated regional nodal basins may be considered on a case-by-case basis in patients with adverse prognostic factors associated with a high risk of further regional nodal recurrence, following discussion with the patient of the potential benefits and risks.
    - Irradiation of previously unirradiated regional nodal basins should be considered.
  - Alternatively, stereotactic body radiotherapy (SBRT) to the involved lymph node may be considered on a case-by-case basis.

• In which patients may radiotherapy be omitted?

Recommendations

- Omission of adjuvant radiotherapy (RT) after BCS may be considered in selected patients aged >70 years with ER-positive, HER2-negative tumors at low clinical and/or genomic risk who are receiving endocrine therapy, particularly in the presence of significant comorbidities and/or a life expectancy <10 years.[182,183]
- Even in this favorable-prognosis subgroup, omission of RT is associated with an increased risk of local recurrence. Therefore, the decision to omit RT should be made through shared decision-making with the patient, following discussion of the potential benefits and risks [I; C].[182,183]

• What are the recommendations for the concurrent use of radiotherapy and systemic therapy?

Recommendations[184]

- Radiotherapy and cyclin-dependent kinases 4/6 (CDK4/6) inhibitors
  - Concurrent administration of CDK4/6 inhibitors and adjuvant locoregional radiotherapy (RT) is not recommended, except in an investigational setting (clinical trial or prospective cohort registry) [V; A]. An interval of 14-21 days should be observed after completion of locoregional RT before resuming treatment with a CDK4/6 inhibitor.
  - Concurrent administration of CDK4/6 inhibitors and whole-brain radiotherapy (WBRT) or intracranial stereotactic radiosurgery (SRS) is not recommended, except in an investigational setting (clinical trial or prospective cohort registry) [IV; A].

- Concurrent administration of CDK4/6 inhibitors and extracranial palliative or ablative RT, including stereotactic body radiotherapy (SBRT), may be considered [IV; B].

- Radiotherapy and phosphoinositide 3-kinase (PI3K) inhibitors
  - Concurrent administration of PI3K inhibitors and RT is not recommended [V; D]. An interval of 2-4 weeks should be observed after completion of RT before resuming treatment with a PI3K inhibitor.

- Radiotherapy and mechanistic target of rapamycin (mTOR) inhibitors
  - Concurrent administration of mTOR inhibitors and RT is not recommended [V; C]. An interval of 2-4 weeks should be observed after completion of RT before resuming treatment with an mTOR inhibitor.

- Radiotherapy and anti-HER2-targeted agents (excluding antibody-drug conjugates)
  - Trastuzumab or pertuzumab may be administered concurrently with adjuvant locoregional RT [I; A].
  - Trastuzumab or pertuzumab may be administered concurrently with WBRT or intracranial SRS [IV; B].
  - Lapatinib may be administered concurrently with WBRT or intracranial SRS [II; B].
  - Newer HER2-targeted TKIs, including neratinib and tucatinib, should not be administered concurrently with RT, except in an investigational setting (clinical trial or prospective cohort registry) [V; C]. An interval of 7 days should be observed after focal brain RT and 21 days after WBRT before resuming treatment.

- Radiotherapy and antibody-drug conjugates
  - Concurrent administration of trastuzumab emtansine (T-DM1) and adjuvant locoregional RT may be considered [II; B].
  - Concurrent administration of T-DM1 and WBRT or intracranial SRS is not recommended [IV; D].
  - Concurrent administration of newer ADCs, including T-DXd, and RT is not recommended, except in an investigational setting (clinical trial or prospective cohort registry) [V; C].

- Radiotherapy and PARP inhibitors
  - Concurrent administration of PARP inhibitors and RT in the adjuvant or metastatic setting is not recommended, except in an investigational setting (clinical trial or prospective cohort registry) [II; A]. An interval of 14 days should be observed after completion of locoregional RT before initiating treatment with a PARP inhibitor.
  - Concurrent administration of PARP inhibitors and RT in advanced breast cancer is not recommended, except in the context of a clinical trial [II; D].

- Radiotherapy and immunotherapy
  - Concurrent administration of immunotherapy and adjuvant locoregional RT may be considered [II; B].
  - Concurrent administration of immunotherapy and RT, including ultrahypofractionated stereotactic regimens, may be considered [II; B]

For the purposes of these recommendations, RT was considered concurrent with systemic therapy when administered within a period corresponding to fewer than five half-lives of the systemic agent.[185]

7. TREATMENT OF LUMINAL BREAST CANCER

• For which patients with early luminal breast cancer is ovarian function suppression recommended?

Recommendations

- The addition of ovarian function suppression to ET for 5 years is recommended in premenopausal women with high-risk luminal breast cancer, particularly those aged <35 years, with axillary lymph node involvement, and/or with grade 3 tumors [I, A].[25,186,187]

Table 3. Drug half-lives and concomitant administration with radiotherapy[185]

Drug	Mean half-life	5 half-lives
Olaparib	15 hours	75 hours (≈ 3 days)
Lapatinib	24 hours	120 hours (≈ 5 days)
Abemaciclib	24.8 hours	124 hours (≈ 5 days)
Palbociclib	28.8 hours	144 hours (≈ 6 days)
Everolimus	30 hours	150 hours (≈ 6 days)
Ribociclib	29.7 – 54.7 hours	148.5 – 273.5 hours (≈ 6 - 11 days)
Talazoparib	90 hours	450 hours (≈ 19 days)
Trastuzumab-emtansine	96 hours	480 hours (≈ 20 days)
Trastuzumab-deruxtecan	168 hours	840 hours (≈ 35 days)
Trastuzumab	456 hours	2280 hours (≈ 95 days)
Bevacizumab	480 hours	2400 hours (≈ 100 days)
Pembrolizumab	552 hours	2760 hours (≈ 115 days)
Atezolizumab	648 hours	3240 hours (≈ 135 days)

• Which patients should be considered for extended ET beyond 5 years?

Recommendations

- Extension of ET beyond 5 years should be considered in the following cases [I, A][188–192]:
  - Patients with axillary lymph node involvement (N+).
  - Patients with high-risk node-negative (N0) disease with the following characteristics: young age, T3-T4 tumors, grade 3 tumors, or a genomic signature indicative of high risk.

These recommendations do not apply to patients with low ER expression, limited life expectancy due to significant comorbidities, or intolerance to endocrine therapy.

Whenever feasible, sequential treatment with tamoxifen and aromatase inhibitors may be considered to optimize efficacy while minimizing treatment-related adverse effects.

• Is temporary interruption of endocrine therapy safe in patients wishing to conceive?

Recommendations

- Pregnancy after a diagnosis of hormone receptor-positive breast cancer is not associated with an increased risk of cancer [I, A].[193,194]
- Temporary interruption of ET for up to 2 years to allow pregnancy may be considered, as it has not been associated with an increased risk of recurrence in women with stage I–III hormone receptor-positive breast cancer [I, B].[193,194]

• In patients with luminal breast cancer and germline BRCA1/2 mutations, should a CDK4/6 inhibitor or a PARP inhibitor be added to endocrine therapy?

Recommendations

- One year of adjuvant olaparib is the preferred treatment for patients with germline *BRCA1/2* mutations and high-risk disease, defined as ≥4 positive axillary lymph nodes or an inadequate response to (neo)adjuvant chemotherapy (CPS+EG score ≥3, where CPS includes clinical and pathological stage and EG includes ER status and histological grade) [I, A].[29,195]

Currently, there are no robust clinical data to support the sequencing of CDK4/6 inhibitors after completion of adjuvant olaparib.

• What is the indication for perioperative endocrine sensitivity testing?

Recommendations

- Following a 4-week course of preoperative endocrine therapy, assessment of endocrine sensitivity based on the change in Ki-67 (≤10%) may be used to estimate the potential benefit of adjuvant chemotherapy in patients with 0-3 positive lymph nodes [II, B].[29,196–199]
- This approach should be applied to a patient population with more restrictive criteria than those of the ADAPT trial: pre- or postmenopausal women with T1c-T2, N0-1 disease (maximum of one positive lymph node), histological grade 2 or 3 tumors, and a baseline Ki-67 >15% (or <40% in grade 3 tumors).

• Which patients should undergo genomic testing to assess the potential benefit of adjuvant chemotherapy?

Recommendations

- Genomic testing should be considered in patients with an intermediate clinical risk in whom clinicopathological features, including age, tumor size, tumor grade, Ki-67 proliferation index, and nodal involvement, do not provide sufficient information to determine the indication for adjuvant chemotherapy.

The Oncotype DX genomic assay is the most extensively validated genomic test for estimating the potential benefit of adjuvant chemotherapy. The assay generates a Recurrence Score (RS) ranging from 0 to 100, with RS 0-10 considered low risk, RS 11-25 intermediate risk, and RS ≥26 high risk of recurrence. When interpreted together with clinical and pathological features, the RS helps estimate recurrence risk and the potential absolute benefit of chemotherapy.[200]

• Which patients with HR-positive/HER2-negative N0 breast cancer should receive adjuvant chemotherapy?

Recommendations

- In addition to endocrine therapy, adjuvant chemotherapy should be considered in the following patients with HR-positive/HER2-negative, N0 breast cancer:

a) Patients who have undergone Oncotype DX genomic testing

- Premenopausal and postmenopausal patients with high genomic risk (RS ≥26) [I, A].
- Premenopausal patients aged ≤50 years [I, A]:
  - with a RS of 21–25, irrespective of clinical risk; or
  - with a RS of 16–20 and high clinical risk (defined as: tumor size ≥3 cm for grade 1 tumors, ≥2 cm for grade 2 tumors, and ≥1 cm for grade 3 tumors; ER or PR expression <75% and/or Ki-67 ≥15%)

b) Patients who have not undergone Oncotype DX genomic testing

- Premenopausal and postmenopausal patients with high clinical risk (defined above) [I, A].

• Which patients with HR-positive/HER2-negative, N1 breast cancer should receive adjuvant chemotherapy?

Recommendations

- Premenopausal patients with HR-positive/HER2-negative, node-positive (N1) breast cancer should receive adjuvant chemotherapy [I, A].[29,201]

Assessment of anti-Müllerian hormone (AMH) may be considered to optimize the selection of premenopausal patients for adjuvant chemotherapy. An AMH concentration ≥10 pg/mL has been associated with a greater likelihood of deriving benefit from chemotherapy.[202]

Recommendations

- In postmenopausal patients with HR-positive/HER2-negative, N1 breast cancer, the indication for adjuvant chemotherapy should be individualized according to menopausal status, biological/genomic risk, and clinicopathological risk [I, A].[29,203]

• Which patients with HR-positive/HER2-negative breast cancer should receive anthracycline-based chemotherapy?

The use of anthracyclines should be individualized according to the patient's clinical and genomic risk, with the aim of minimizing potential toxicities (e.g., cardiovascular toxicity) without compromising therapeutic efficacy.

Recommendations

- Anthracycline-based chemotherapy is recommended for the following patients with HR-positive/HER2-negative breast cancer:
  - Patients with tumors ≥T3 [I, B].
  - Patients with ≥2-3 positive axillary lymph nodes (N2/N3 disease) [I, A].
  - Postmenopausal women with T2N0 tumors and either an Oncotype DX Recurrence Score (RS) ≥31 or a MammaPrint High 2 result [I, B].
- In premenopausal women with node-negative disease (N0) and in premenopausal or postmenopausal women with N1 disease, anthracycline-based chemotherapy may be considered at lower RS thresholds [II, B].

• What is the recommended number of cycles of the taxane/cyclophosphamide regimen?

Recommendations

- In patients who are not eligible for anthracyclines or in whom omission of anthracyclines is considered appropriate, six cycles of the taxane/cyclophosphamide regimen are recommended [I, B].

• What are the indications for adjuvant CDK4/6 inhibitor therapy in HR-positive/HER2-negative breast cancer?

The addition of a CDK4/6 inhibitor to adjuvant ET is an effective strategy to reduce the risk of recurrence in patients with high-risk disease. Therefore, an individualized assessment of the patient's risk of recurrence is essential to determine whether a CDK4/6 inhibitor should be added to ET and to guide the selection of the most appropriate CDK4/6 inhibitor.[192,204–206]

Recommendations

- Patients with stage II high-risk breast cancer (N1/Nmic disease with histological grade 3 and/or tumor size ≥5 cm) or stage III disease should receive 2 years of abemaciclib in combination with ET [I, A].[206,207]
- Patients with stage II node-positive (N+, excluding Nmic) or stage III breast cancer should receive 3 years of ribociclib in combination with ET consisting of an aromatase inhibitor, with or without goserelin [I, A].[206,208]
- Patients with stage II node-negative (N0) breast cancer with grade 3 tumors, or grade 2 tumors with Ki-67 ≥20% and/or a high-risk genomic signature, should receive 3 years of ribociclib in combination with ET consisting of an aromatase inhibitor, with or without goserelin [I, B].[206,208]

In patients who meet the eligibility criteria for adjuvant treatment with more than one CDK4/6 inhibitor, abemaciclib may be considered the preferred option based on the available published evidence and shorter treatment duration. However, the choice of CDK4/6 inhibitor should also take into account the toxicity profile of each agent, as well as the patient's comorbidities and preferences.

• What is the recommended first-line treatment for patients with metastatic HR-positive/HER2-negative breast cancer?

Recommendations

- The combination of ET and a CDK4/6 inhibitor is the current standard first-line treatment for patients with metastatic luminal (HR-positive/HER2-negative disease) breast cancer [I, A].209–216
- The exception to the above recommendation comprises patients presenting with visceral crisis, for whom chemotherapy remains the recommended first-line treatment option [III, C].
- In patients with primary or secondary endocrine resistance, the choice of ET partner should take into account the disease-free interval and prior endocrine treatment exposure [I, A].
- The combination of ET with abemaciclib id the preferred first-line option for patients with primary endocrine resistance [I, C].[212,217]
- The combination of an AI with goserelin and ribociclib is the preferred first-line treatment for premenopausal patients [I, A].[216]
- Palbociclib is an appropriate therapeutic option for patients

with multiple comorbidities, polypharmacy, and greater clinical frailty [V, C].[210,213]

- The use of ET as monotherapy in first-line setting should be reserved for selected clinical cases [II; C]:
  - frail patients or patients with significant comorbidities who are not candidates for the addition of a CDK4/6 inhibitor;
  - selected patients with oligometastatic disease undergoing ablative locoregional treatment;
  - patients with a low metastatic tumor burden;
  - patients with a prolonged disease-free interval after adjuvant treatment;
  - patient preference.

• What is the recommended second-line treatment for patients with metastatic HR-positive/HER2-negative breast cancer?

The selection of second-line treatment after progression on ET combined with a CDK4/6 inhibitor should take into consideration tumor biology (level of ER expression: 1%–9% *vs* ≥10%), reassessment of HER2 status, presence of actionable genomic alterations, duration of response to previous treatment (primary *versus* secondary endocrine resistance), tolerability to prior therapy, and presence of rapidly progressive visceral disease.[209,218]

In patients with high ER expression, durable response to previous treatment (secondary endocrine resistance), and indolent disease behavior, a subsequent line of ET is generally indicated.

Recommendations

- Elacestrant is recommended for postmenopausal women and men with luminal breast cancer harboring ESR1 mutations after disease progression on at least one line of ET combined with a CDK4/6 inhibitor [I, C; ESMO-Magnitude of Clinical Benefit Scale (MCBS) v1.1 score: 3].[219,220]
- The combination of fulvestrant and everolimus is recommended for women and men with luminal breast cancer after disease progression on at least one line of ET and may be considered in patients with ESR1 mutations when elacestrant is unavailable [I, B].[219–221]
- The combination of capivasertib and fulvestrant is recommended for premenopausal or postmenopausal women and men with luminal breast cancer harboring one or more *PIK-3CA*, *AKT1*, and/or *PTEN* alterations after disease progression on at least one line of ET combined with a CDK4/6 inhibitor or relapse during or within 12 months after completion of adjuvant ET [I, B; ESMO-MCBS v1.1 score: 3].[222,223]
- PARP inhibitors (olaparib, talazoparib) are recommended for patients with germline *BRCA1/2* mutations after progression on ET [I, A].[224,225]
- The combination of everolimus and fulvestrant may be considered, particularly in the presence of *ESR1* mutations [II, B].[227–229]
- Continued CDK4/6 inhibition with a switch to another agent within the same class may be considered in selected clinical scenarios, although the magnitude of benefit is modest [II, C].[230,231]
- Continuation of the same CDK4/6 inhibitor after disease progression has not demonstrated clinically meaningful benefit and is not recommended [II, C].[232]

The combination of palbociclib, fulvestrant, and avelumab has shown promising results in a phase II study; however, validation in phase III trials is required before it can be considered for a formal clinical recommendation [II, C].[233]

• What are the indications for the use of ADCs in metastatic HR-positive/HER2-negative breast cancer?

Antibody-drug conjugates (ADCs) are an important therapeutic option for patients with metastatic HR-positive/HER2-negative breast cancer, particularly after progression on endocrine-based therapies.

Recommendations

- T-DXd should be considered for patients with metastatic HR-positive/HER2-low breast cancer after ET and at least one prior line of chemotherapy, according to the DESTINY-Breast04 trial [I, A].[234,235,236]
- T-DXd has also demonstrated clinical benefit in patients with HR-positive/HER2-ultralow metastatic breast cancer in the DESTINY-Breast06 trial.[237] However, in Portugal, its current indication remains restricted to HER2-low tumors and does not yet include the HER2-ultralow population [I, A].
- T-DXd may be considered as an alternative to chemotherapy in selected patients with early progression (<6 months) after ET plus CDK4/6 inhibitor treatment, particularly those with high tumor burden or clinically significant symptoms [I, A].[238]
- Sacituzumab govitecan should be considered for patients with metastatic HR-positive/HER2-negative breast cancer previously treated with ET, CDK4/6 inhibitors, and ≥2 prior lines of chemotherapy, according to the TROPiCS-02 trial [I, A].[239,240]
- Datopotamab deruxtecan (Dato-DXd) demonstrated a progression-free survival benefit in the TROPION-Breast01 trial but is not currently available in Portugal [I, A].[241–243]
- In patients with stable brain metastases, available data suggest clinical activity with T-DXd and sacituzumab govitecan; however, evidence remains exploratory [II, C].[244–247]
- Reassessment of HER2 status is recommended in patients previously classified as HER2-negative (IHC 0), as HER2 expression may be reclassified as HER2-low, potentially enabling treatment with T-DXd [III, C].[248]

Whenever feasible and clinically accessible, biopsy of metastatic lesions is recommended for reassessment of HER2 status and other relevant biological markers.[209]

• What is the recommended treatment sequence for patients with metastatic HR-positive/HER2-negative breast cancer?

Currently, no prospective randomized clinical trials have directly compared T-DXd with sacituzumab govitecan; therefore, the optimal sequencing strategy cannot be definitively established. Considering the patient populations enrolled and the results of the respective clinical trials, T-DXd may be considered at earlier treatment stages compared with sacituzumab govitecan, particularly in patients with extensive visceral disease. Nevertheless, factors such as the safety profile of each treatment and patient preferences should play a central role in therapeutic decision-making.

Recommendations

- T-DXd is recommended in patients with HR-positive/HER2-low breast cancer with endocrine-refractory disease who have received 1-2 prior lines of chemotherapy, based on the significant OS and progression-free survival (PFS) benefit demonstrated in the DESTINY-Breast04 trial [I, A; ESMO-MCBS v1.1 score: 4].[236,249]
- T-DXd is recommended in patients with HR-positive/HER2-ultralow breast cancer after progression on ET, based on the significant PFS benefit demonstrated in the DESTINY-Breast06 trial [I, A; ESMO-MCBS v1.1 score: 3].[237]
- Sacituzumab govitecan is recommended in patients with metastatic HR-positive/HER2-negative breast cancer after multiple prior lines of treatment including CDK4/6 inhibitors and chemotherapy, based on the OS and PFS benefit demonstrated in the TROPiCS-02 trial [I, B; ESMO-MCBS v1.1 score: 4].[239,240]

There are currently no prospective randomized clinical trials supporting the use of a second ADC after progression on a prior ADC. Therefore, treatment selection should be guided by regulatory approval criteria and/or the eligibility criteria of the clinical trials supporting each indication.

Recommendations

- The sequencing of ADCs should be guided by their respective regulatory approval criteria and/or the eligibility criteria of the clinical trials supporting their approval [V, A].

• Which biomarkers should be assessed in metastatic HR-positive/HER2-negative breast cancer?

Several therapeutic options are currently available for drugs targeting specific molecular alterations identified through predictive biomarker testing.

Recommendations

- When multiple biomarkers are available, priority should be given to those supported by the strongest scientific evidence for the patient's specific clinical circumstances, taking into account previous treatment history (e.g., drugs previously used with subsequent disease progression, or progression during treatment with a specific drug class in the adjuvant setting) [I, A].
- When biomarkers are associated with multiple therapeutic options supported by comparable levels of evidence, an individualized assessment of the risk-benefit profile should be performed through shared decision-making between the oncologist and the patient.
- In the absence of direct comparative data, the ESMO-MCBS may be a useful tool to support therapeutic decision-making [III, B].
- In selected cases, repeat biopsy for biomarker assessment may be considered if relevant biomarkers have not been previously assessed, provided that the patient's clinical condition allows sufficient time to complete the diagnostic process (including biopsy scheduling, biomarker analysis, and authorization for the use of the corresponding therapy if a biomarker-positive result is identified) [III, B].
- *PIK3CA* pathway alterations should be assessed in patients with endocrine-resistant disease to guide the use of targeted therapies (alpelisib, inavolisib) [I, A].[250]
- *ESR1* mutations should be assessed after progression on AI therapy to guide the use of SERDs (elacestrant; camizestrant under investigation) [II, B].[251,252]
- HER2-low/ultralow status should be assessed in metastatic setting after ≥1 prior lines of chemotherapy to identify patients who may be candidates for T-DXd [I, A].[253,254]
- Germline *BRCA1/2* pathogenic variants should be assessed in all patients with HER2-negative metastatic breast cancer, irrespective of age, family history, or tumor subtype [I, A].[255,256]
- *NTRK* gene fusions should be assessed in patients with refractory disease who have no available therapeutic options [II, C].[257,258]
- MSI/mismatch repair (MMR) status should be assessed in patients with refractory disease, as it may support the use of immunotherapy (pembrolizumab; off-label in Europe) [II, C].[259]
- Assessment of germline *PALB2* variants may be considered as part of broader germline testing panels, given emerging evidence of sensitivity to PARP inhibitors [II, C].[260]
- CDK4/6 inhibitors, the mTOR inhibitor everolimus, and the anti-TROP2 ADCs sacituzumab govitecan and datopotamab deruxtecan can be used without the need for predictive biomarker selection [I, A].

8. TREATMENT OF TRIPLE-NEGATIVE AND HER2-POSITIVE BREAST CANCER

• How should risk stratification be performed and what is the role of molecular classification in TNBC?

Histological classification is the cornerstone of risk stratification and prognostic assessment in TNBC.

In addition to histological characterization, the following parameters with potential implications for risk stratification should be reported, whenever applicable:

– TILs – Have prognostic value in early-stage TNBC and should be reported as a percentage.

– Residual cancer burden – Provides independent prognostic information and should be reported after neoadjuvant chemotherapy,
– PD-L1 expression – Has predictive value in metastatic setting and should be assessed using the CPS.
– Germline alterations in *BRCA* genes (*BRCA1/2*) and other DNA repair genes – Relevant for therapeutic decision-making and assessment of hereditary cancer risk.
– HER2-low phenotype (IHC 1+ or IHC 2+/ISH-negative) – Predictive biomarker in metastatic setting.

The expression of the luminal androgen receptor and molecular classification of TNBC currently lack sufficient evidence to support routine clinical implementation, and their use should be restricted to the clinical trial setting.

Molecular classification of TNBC is not routinely incorporated into clinical risk stratification and should not be used to guide therapeutic decisions outside clinical trials.

• In TNBC, from what tumor size should adjuvant chemotherapy be recommended?

In TNBC, the decision between neoadjuvant therapy and upfront surgery followed by adjuvant treatment should be based on clinical stage, patient comorbidities, the potential for surgical downstaging, and the prognostic and therapeutic implications of achieving a pathological complete response (pCR).

Recommendations

- Adjuvant chemotherapy should be considered in patients with TNBC with tumors ≥5 mm (T1b) [II, B].

• What are the indications for neoadjuvant therapy in TNBC and HER2-positive breast cancer?

Recommendations

- Neoadjuvant therapy is indicated for most patients with TNBC and HER2-positive breast cancer with clinical stage II-III disease (tumors >2 cm or with clinically or radiologically detected nodal involvement), given its ability to reduce tumor burden, increase the likelihood of BCS, provide relevant prognostic information through pCR assessment, and enable subsequent treatment adaptation according to response [I, A].
- Upfront surgery followed by adjuvant chemotherapy is recommended for patients with TNBC cT1cN0 disease. Neoadjuvant therapy without immunotherapy may be considered when tumor downstaging is required or when assessment of treatment response may influence subsequent therapeutic decisions [II, B].
- Upfront surgery followed by adjuvant treatment with paclitaxel and trastuzumab is recommended in patients with HER2-positive pT1cN0 tumors [II, A]. Neoadjuvant therapy may be considered when downstaging is required, in selected patients with high biological or clinical risk, or when response assessment may influence subsequent therapeutic decisions [II, B].
- Upfront surgery may be considered for small tumors (T1a/T1b) without axillary lymph node involvement (N0), particularly when surgery is technically feasible with satisfactory cosmetic outcomes and when subsequent systemic treatment decisions are not dependent on pathological response [III, C].

• What is the role of immunotherapy in the neoadjuvant and adjuvant treatment of TNBC?

The KEYNOTE-522 trial demonstrated that the addition of pembrolizumab to neoadjuvant chemotherapy (anthracyclines, taxanes, and platinum-based chemotherapy) significantly increased the pCR rate (64.8% *vs* 51.2%), improved event-free survival at 36 months (84.5% *vs* 76.8%), and prolonged OS at 60 months (86.6% *vs* 81.7%; HR 0.66; *p*=0.0015) in patients with TNBC.[261–263]

Recommendations

- Pembrolizumab in combination with neoadjuvant chemotherapy, followed by adjuvant pembrolizumab monotherapy to complete a total treatment duration of 1 year, is recommended for patients with clinical stage II-III TNBC (tumors >2 cm or with clinically or radiologically detected lymph node involvement) [I, A].
- Adjuvant treatment of TNBC after neoadjuvant chemotherapy and pembrolizumab should be adapted according to the pathological response obtained, as follows:
  - pCR: Continue pembrolizumab until completion of 1 year of total treatment, irrespective of the response achieved. There is no robust evidence supporting discontinuation of adjuvant pembrolizumab after pCR [I, A].
  - Residual disease:
  · Without germline *BRCA1/2* mutations: Continue adjuvant pembrolizumab until completion of 1 year of total treatment [I, A]. Adjuvant capecitabine (6-8 cycles) may be added [II, B].
  · With germline *BRCA1/2* mutations: Continue adjuvant pembrolizumab until completion of 1 year of total treatment. Adjuvant olaparib should be considered [I, A].

Concomitant administration of olaparib and capecitabine is not recommended. In the absence of evidence supporting the optimal sequencing strategy, olaparib may be administered during or after completion of pembrolizumab [III, C].

• What are the indications for neoadjuvant therapy, and how should adjuvant treatment be adapted according to response in HER2-positive breast cancer?

As in TNBC, in HER2-positive breast cancer, the decision between neoadjuvant therapy and upfront surgery followed by adjuvant treatment should be based on clinical stage, patient comorbidities, the potential for surgical downstaging, and the prognostic and therapeutic implications of achieving a pCR.

In HER2-positive disease, the NeoSphere[264,265] and TRYPHAENA[266,267] trials demonstrated the efficacy of neoadjuvant dual HER2 blockade with trastuzumab and pertuzumab combined with chemotherapy (anthracyclines and/or taxanes), achiev-

ing high pCR rates (up to approximately 66%) with a manageable cardiac safety profile.

This approach is recommended for patients with locally advanced and/or clinically node-positive disease.

Recommendations

- Adjuvant treatment of HER2-positive tumors after neoadjuvant chemotherapy and dual HER2 blockade should be adapted according to the pathological response obtained, as follows:
  - pCR: Continue adjuvant anti-HER2 therapy with trastuzumab (with or without pertuzumab) until completion of 1 year of total treatment, according to baseline risk and treatment tolerability [I; A].
  - Residual invasive disease: Administer T-DM1 for 14 cycles, based on the results of the KATHERINE trial,[268] which demonstrated a clear benefit of replacing trastuzumab with T-DM1, with a 50% reduction in the risk of invasive recurrence (invasive disease-free survival [iDFS]: 88.3% *vs* 77.0%) [I; A].

• Which patients with HER2-positive breast cancer should receive anthracycline-based chemotherapy regimens in the neoadjuvant and/or adjuvant setting?

The TRAIN-2 trial demonstrated that anthracycline-free regimens (e.g., TCHP – docetaxel, carboplatin, trastuzumab, and pertuzumab) provide similar efficacy to anthracycline-containing regimens, with lower hematological and cardiac toxicity.[269,270]

Therefore, the use of anthracyclines is not mandatory in the treatment of low- to intermediate-risk HER2-positive tumors and is generally reserved for selected patients with more extensive disease, aggressive tumor biology, or specific clinical characteristics.

Recommendations

- Anthracycline-based regimens may be considered in selected patients with high clinical and biological risk features (including lymph node involvement, high tumor burden, or aggressive biological characteristics), when the potential benefit is considered to outweigh the associated risks [II, B].
- Anthracycline-free regimens (e.g., TCHP) should generally be preferred in patients with low- to intermediate-risk disease, given their comparable efficacy and more favorable toxicity profile, particularly regarding cardiovascular safety [I, A].

• What are the preferred treatment strategies for patients with low-risk HER2-positive early breast cancer (T1a/bN0)?

Treatment decisions should be based on clinical stage, response to neoadjuvant therapy, molecular subtype, germline mutation status, and the patient's individual risk profile.

In low-risk disease (T1a/bN0), the therapeutic approach varies according to tumor size. In T1a disease (≤5 mm), omission of systemic therapy may be considered, with treatment decisions individualized according to the patient's clinical and biological characteristics.

In T1b disease (6-10 mm), the APT trial demonstrated excellent outcomes with weekly paclitaxel for 12 weeks combined with trastuzumab for 1 year (3-year iDFS of 98.7%) (Ref. 11).[271] This regimen is currently considered a standard de-escalated adjuvant approach for patients with small, node-negative HER2-positive breast cancer.

Recommendations

- Omission of chemotherapy may be considered for patients with T1aN0 tumors, given the favorable prognosis of this subgroup [II–III, C].
- Adjuvant chemotherapy with weekly paclitaxel combined with trastuzumab should be considered for patients with T1bN0 tumors [II, A].

• Should central nervous system staging be performed in asymptomatic patients with metastatic TNBC or HER2-positive breast cancer, and how should CNS imaging surveillance be conducted?

Currently, there is no evidence from randomized clinical trials supporting routine CNS imaging for staging or surveillance in patients with metastatic breast cancer without signs or symptoms suggestive of brain metastases.

Contrast-enhanced brain MRI is the most sensitive imaging modality for detecting small brain lesions, edema, and leptomeningeal metastases. Brain CT should be reserved for patients with contraindications to MRI or urgent clinical scenarios.[272–274]

Recommendations

- CNS imaging is not recommended for patients without signs or symptoms suggestive of brain metastases, either at metastatic diagnosis or during routine disease surveillance.
- Brain imaging is recommended for patients with neurological symptoms suggestive of CNS involvement, preferably with contrast-enhanced brain MRI [II; B].[218]
- Follow-up of patients with known brain metastases should preferably be performed with contrast-enhanced brain MRI every 3 months during the first 2 years and every 6 months thereafter [II; A].[275]

• What is the preferred first-line treatment for patients with previously untreated metastatic HER2-positive breast cancer?

a) Patients eligible for chemotherapy and anti-HER2 therapy

Recommendations

- The preferred first-line treatment option for patients with previously untreated HER2-positive metastatic breast cancer

is a taxane combined with dual HER2 blockade (trastuzumab plus pertuzumab), irrespective of HR status (HR-positive/negative) [I; A].
- Vinorelbine combined with dual HER2 blockade may be an alternative regimen for patients with contraindications to taxane therapy [III; C].
- Maintenance ET combined with dual HER2 blockade is recommended for patients with HER2-positive/HR-positive tumors [I; A]. The addition of palbociclib may be considered in selected patients.
- Maintenance therapy with dual HER2 blockade alone (trastuzumab plus pertuzumab) is recommended for patients with HER2-positive/HR-negative tumors after discontinuation of chemotherapy [I; A].

b) Patients not eligible for chemotherapy

Recommendations

- Except in specific circumstances, omission of chemotherapy is not recommended as a first-line treatment strategy for patients with advanced HER2-positive breast cancer [I, A].
- First line ET combined with anti-HER2 therapy should only be considered for patients with HR-positive tumors when limitations are precluding the use of the standard regimen of chemotherapy plus trastuzumab and pertuzumab. Dual HER2 blockade with trastuzumab and pertuzumab is the preferred anti-HER2 strategy in this setting ref32 [II, B].
- For patients unable to receive chemotherapy, dual HER2 blockade combined with ET may be used in HR-positive tumors [II; B], whereas dual HER2 blockade without ET may be considered in selected patients with HR-negative tumors [III; C].

• What is the preferred first-line treatment for patients with metastatic HER2-positive breast cancer relapsing after (neo)adjuvant therapy?

The selection of first-line treatment for patients who relapse after (neo)adjuvant therapy should be based on prior therapies received, time to relapse, performance status, overall clinical condition, comorbidities, and the availability of therapeutic options.

a) Patients relapsing ≥12 months after (neo) adjuvant treatment

Recommendations

- First-line treatment with a taxane in combination with dual HER2 blockade (trastuzumab plus pertuzumab) is recommended for patients who relapse ≥12 months after (neo)adjuvant treatment, based on the results of the CLEOPATRA trial [I; A].[276–278]

b) Patients relapsing ≤6 months after (neo)adjuvant treatment

Recommendations

- First-line treatment with T-DXd is recommended for patients who relapse ≤6 months after (neo)adjuvant treatment, based on the results of the DESTINY-Breast03 trial [I; A].[279–281]

c) Patients relapsing 6-12 months after (neo) adjuvant treatment

Recommendations

- There is currently no evidence supporting a preferred first-line treatment strategy for patients who relapse 6-12 months after (neo)adjuvant treatment. Treatment options include a taxane in combination with dual HER2 blockade (trastuzumab plus pertuzumab) or T-DXd [I; A].

• What are the second and subsequent-line treatment options for patients with metastatic HER2-positive breast cancer?

The choice of subsequent-line therapies depends on the treatment previously received, patient clinical characteristics, the toxicity profile of available therapies, and treatment availability. Continuation of HER2-directed therapy beyond disease progression is the standard of care.

Second-line treatment

Recommendations

- -DXd is the recommended second-line treatment for patients with metastatic HER2-positive breast cancer, based on the results of the DESTINY-Breast03 trial [I; A].[279–281]

Third and subsequent-line treatments

Recommendations

- In the third-line setting, patients with metastatic HER2-positive breast cancer should receive a regimen not previously administered. Potential treatment options include:
  - Tucatinib plus trastuzumab plus capecitabine, based on the results of the HER2CLIMB trial (Refs. 38–40) [I; A].[282,283,40]
  - T-DXd, based on the results of the phase II DESTINY-Breast01 trial [II; A].[284]
  - T-DM1, based on the results of the TH3RESA trial [I; A].[285,286]

Beyond the third-line setting, there is no definitive data supporting a preferred treatment option. Treatment selection should consider treatment availability, cost, and toxicity profile; patient comorbidities; previous exposure to different anti-HER2 agents; sites of metastatic disease; and patient preferences.

Recommendations

- Beyond third line, continuation of anti-HER2 therapy (trastuzumab plus chemotherapy) or treatment with the combination of lapatinib plus trastuzumab may be considered

for patients with metastatic HER2-positive breast cancer287 [III; A].

• What is the recommended systemic treatment approach for patients with HER2-positive breast cancer who develop brain progression with controlled extracranial disease or isolated brain relapse?

Recommendations

- Continuation of the ongoing anti-HER2 systemic therapy is recommended after locoregional treatment of CNS metastases in patients with brain progression and controlled extracranial disease [I; A].
- Anti-HER2 systemic therapy is recommended for patients with isolated brain relapse who have previously received locoregional treatment and are not receiving active systemic therapy [II; B].

• What is the recommended treatment sequencing strategy for patients with metastatic TNBC (stage IV or recurrent disease)?

General principles and eligibility

Recommendations

- PD-L1 expression should be systematically assessed using the CPS in tumor tissue at diagnosis of metastatic disease. Germline *BRCA1/2* mutation status should also be assessed, and PALB2 status may be considered when targeted therapies become available, as these results influence first-line treatment selection and subsequent therapeutic strategies [I; A].[209]
- HER2-low status (IHC 1+ or IHC 2+/ISH-negative) should be assessed after at least one prior line of chemotherapy and, ideally, reassessed at disease progression, given potential inter-sample variability.[288] T-DXd may be considered for patients with HER2-low breast cancer after ≥1 prior lines of chemotherapy [I; A].[236]
- In patients with metastatic TNBC and PD-L1 CPS ≥10, pembrolizumab in combination with chemotherapy is the preferred first-line treatment option, based on the results of the KEYNOTE-355 trial, which demonstrated significant improvements in PFS (HR 0.65) and OS (median 23.0 *vs* 16.1 months; HR 0.73; 95% CI 0.55–0.95), with nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin as treatment backbones [I; A].[289]
- Evidence supporting the use of T-DXd in TNBC/HER2-low breast cancer remains limited, as prospective clinical trials included only small numbers of TNBC patients. In DESTINY-Breast03 and DESTINY-Breast01, approximately 72 patients with TNBC were included, whereas DESTINY-Breast04 included only 40 patients with HER2-low TNBC.[236,281,284] Further evidence is required to define the role of T-DXd after sacituzumab govitecan. Sequential ADC use may be considered in selected patients; however, sacituzumab govitecan should be prioritized in TNBC [III; C].[209,236,290]
- Combination cytotoxic chemotherapy regimens should generally be avoided outside the visceral crisis setting. In most cases, sequential single-agent chemotherapy provides a more favorable balance between clinical benefit and toxicity [III; B].[209,218]
- Chemotherapy remains an option for patients with metastatic TNBC, providing a modest but clinically meaningful survival benefit. The choice of cytotoxic agent should consider previous treatments, expected toxicity profile, comorbidities, and patient preferences [I; B].[209,218]

Treatment sequencing

Recommendations

- **Patients with *BRCA1/2* wild-type tumors and PD-L1 CPS ≥10**
  - First line: Pembrolizumab in combination with chemotherapy (weekly taxane or platinum-containing chemotherapy, according to patient characteristics and clinical profile) [I; A].[209,218,289]
  - Second line: Sacituzumab govitecan [I; A].[209,218,289]
  - Third line:
    - For patients with HER2-low tumors, T-DXd should be considered after ≥1 prior lines of chemotherapy [I; A].[209,236]
    - For patients with HER2 IHC 0 tumors, sequential single-agent chemotherapy (capecitabine, vinorelbine, gemcitabine, or platinum agents) should be considered according to patient preferences and expected toxicity profile [II; B].[209,218]

- **Patients with tumors harboring germline *BRCA1/2* mutations and PD-L1 CPS ≥10**
  - First-line: Pembrolizumab in combination with chemotherapy (pembrolizumab is currently approved only in the first-line setting) [I; A].[209,218,289]
  - Second line: PARP inhibitor therapy (preferably olaparib), if not previously administered [I; A].[224,225]
  - Third line: Sacituzumab govitecan [I; A].[209,218,290]
  - Fourth line:
    - For patients with HER2-low tumors, T-DXd should be considered after ≥1 prior lines of chemotherapy [I; A].[209,236]
    - For patients with HER2 IHC 0 tumors, sequential chemotherapy (capecitabine, vinorelbine, gemcitabine, or platinum agents) should be considered [II; B].[209,218]

- **Patients with *BRCA1/2* wild-type tumors and PD-L1 CPS <10**
  - First line: Single-agent chemotherapy (taxane, capecitabine, vinorelbine, gemcitabine, or platinum agents), according to disease characteristics, expected toxicity profile, and patient preferences [I; B].[209,218]
  - Second line: Sacituzumab govitecan [I; A].[209,218,290]
  - Third line:
    - T-DXd should be considered for patients with HER2-low tumors [I; A].[209,236]
    - Sequential chemotherapy should be considered for patients with HER2 IHC 0 tumors [II; B].[209,218]

- **Patients with tumors harboring germline *BRCA1/2* mutations and PD-L1 CPS <10**
  - First line: PARP inhibitor therapy (preferably olaparib; talazoparib as an alternative), provided that the patient has previously received anthracycline- and taxane-based chemotherapy in the (neo)adjuvant setting or that these agents are considered unsuitable [I; A].[209,224,225]
  - Second line: Sacituzumab govitecan [I; A].[209,218,290]
  - Third line:
    - T-DXd should be considered for patients with HER2-low tumors [I; A].[209,236]
    - Sequential chemotherapy should be considered for patients with HER2 IHC 0 tumors [II; B].[209,218]
- In patients with visceral crisis, initiation of cytotoxic chemotherapy may be considered, with subsequent sequencing of PARP inhibitor therapy when appropriate [III; C].[209,218,224,225]

Considerations regarding treatment sequencing

Recommendations

- Sacituzumab govitecan should generally be prioritized in the second- or third-line setting, given the robust and consistent clinical benefit demonstrated following prior exposure to chemotherapy [I; A].[209,218,290]
- T-DXd may be considered in patients with HER2-low metastatic TNBC after at least one prior line of chemotherapy [I; A].[209,236]
- The combination of PARP inhibitors with platinum agents or immune checkpoint inhibitors is not recommended outside the clinical trial setting, due to uncertainty regarding clinical benefit and the potential for increased toxicity [II; C].[209,218]
- In Portugal, talazoparib is reimbursed for metastatic TNBC and metastatic luminal breast cancer, whereas olaparib is currently reimbursed only for metastatic TNBC [IV; B].[291,292]

• What is the role of PARP inhibitors in locally advanced or metastatic TNBC?

Recommendations

- PARP inhibitors (olaparib or talazoparib) are therapeutic options for patients with metastatic TNBC harboring germline *BRCA1/2* mutations.[293,294] When a PARP inhibitor is selected in the first-line setting, olaparib is preferred based on the evidence from the OlympiAD trial [I; A].[294]

  Patients should have previously received anthracycline- and taxane-based therapy in the (neo)adjuvant or metastatic setting, unless these agents are considered unsuitable or contraindicated.
- There are no direct comparative data between PARP inhibitors and platinum-based chemotherapy in the first-line setting. Therefore, treatment selection should be individualized according to patient characteristics, disease biology, prior treatments, and treatment goals.
- The recommended first-line treatment for patients with metastatic TNBC and PD-L1 CPS ≥10 is pembrolizumab in combination with chemotherapy. In patients with concomitant germline *BRCA1/2* mutations, there are no data to define the optimal therapeutic sequence. As pembrolizumab is currently approved only in the first-line setting, initiation of treatment with pembrolizumab plus chemotherapy is recommended, with PARP inhibitor therapy considered at subsequent treatment lines when appropriate.
- When feasible, olaparib may be considered for patients with metastatic breast cancer harboring *PALB2* mutations, based on the results of the phase II TBCRC 048 trial.[260] However, this indication is currently not approved or reimbursed in Portugal [II; C].

• What is the role of PARP inhibitors in metastatic HER2-positive breast cancer?

Recommendations

- There is currently no robust clinical evidence supporting the use of PARP inhibitors in patients with metastatic HER2-positive breast cancer harboring germline *BRCA1/2* mutations outside the clinical trial setting [IV; C].

9. ARTIFICIAL INTELLIGENCE

Since the publication of the last Portuguese Society of Senology Consensus in 2022, the application of artificial intelligence (AI) in healthcare has evolved rapidly. The use of generative AI, exemplified by tools such as ChatGPT, has become increasingly widespread across both clinical practice and the patient experience. At the same time, significant advances have been made in the application of AI to medical imaging, pathology, and healthcare digital infrastructure.

• How can Portugal develop a robust, interoperable, and ethical digital health infrastructure aligned with the European Health Data Space, while simultaneously promoting digital literacy among healthcare professionals?

In Portugal, although significant progress has been made in the digitalization of clinical records and the implementation of platforms such as the Electronic Health Record (EHR), substantial barriers remain to building a data ecosystem fully prepared for European integration. In this context, the harmonization and integration of hospital data infrastructures represent a strategic priority, particularly within the framework of the European Health Data Space (EHDS) implementation.

The EHDS aims to ensure secure, transparent, and equitable access to electronic health data for both healthcare delivery and secondary uses, including research, public policy development, and innovation. For Portugal to actively participate in this new framework, it is essential that hospitals adopt models of syntactic and semantic interoperability, ensuring the harmonization of clinical data according to international standards.

The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) is one of the most widely adopt-

ed models for this purpose, enabling the mapping of heterogeneous data from consultations, diagnoses, medications, diagnostic tests, and other healthcare information sources into a common structure, thereby facilitating longitudinal and multicentre analyses. Adoption of the OMOP CDM across Portuguese healthcare institutions would ensure compatibility with European initiatives within the EHDS framework and promote Portugal's integration into international research and technological development consortia.

An interoperable health data infrastructure should be based on the implementation of secure and trusted research environments (TREs). A relevant example is the implementation of the Breast SPS clinical registry, which ensures semantic interoperability across institutions, enabling the consistent and comparable use of data across different clinical and research settings.

Portugal can leverage ongoing initiatives, such as the Longitudinal Electronic Health Record (RES Longitudinal) and Oncology Registries, to develop OMOP-based pilot models, assessing the technical, organizational, and regulatory feasibility of data harmonization.

• What is the impact of generative AI in healthcare, and what are its main opportunities and risks?

Generative AI (GenAI) represents a major technological transformation in the way digital tools are developed and applied in healthcare, particularly in oncology and breast cancer care.[295–297] While only a few years ago predictive models relied primarily on supervised algorithms and static datasets,[298,299] there is now a rapid emergence of systems capable of generating clinical content,[300] supporting medical education,[301] developing educational materials,[302] and synthesizing scientific information.[303] These advances are enabled by different forms of GenAI that are already being used by physicians, researchers, and students across various stages of their clinical, academic, and scientific activities.

Despite the existing challenges, concrete advances have already been achieved in the safe and responsible application of GenAI in breast health.[300] One example is the use of synthetic datasets,6 which have demonstrated utility in training algorithms when real-world data are scarce or when patient privacy needs to be protected.

Another promising application is the automated generation of personalized clinical reports, adapted to clinicians' needs or to different stages of the patient journey. The ability to summarize relevant findings and translate technical information into accessible formats for patients represents a significant advance in improving communication and health literacy.

The use of large language models (LLMs), such as ChatGPT, is becoming increasingly common in medical practice; however, it raises important concerns. Many healthcare professionals may have limited ability to recognize when models "hallucinate" (i.e., generate inaccurate information or fabricated references), may be unaware of the legal risks associated with entering sensitive data into public platforms, and may lack clear guidance regarding clinical responsibility in AI-assisted decision-making. This gap between AI adoption and digital literacy highlights the need for educational initiatives and the development of dedicated, clinically validated, and regulated AI tools that ensure reliability, auditability, and accountability — essential requirements for the ethical and safe integration of AI into medical practice.

• In which areas will GenAI have the greatest clinical impact, and how can safe, ethical, and effective implementation be ensured?

GenAI is expected to have the greatest clinical impact in the following areas:

- **Clinical decision support**, through the analysis of large volumes of clinical data and medical-scientific literature, supporting diagnosis, therapeutic decision-making, and treatment planning.

Implementation challenges: The current limitations in GenAI reliability, which may manifest as inaccurate information, "hallucinations" (i.e., the generation of unsupported or false information), or omission of critical data.

Recommendations

- Continuously monitor developments in GenAI and its applications in healthcare.
- Critically evaluate the evidence, performance, and clinical value of AI-based tools before adoption.
- Recognize and mitigate the risks associated with AI-generated errors and omissions.
- Actively collaborate with researchers in the design and development of AI tools to improve their performance, safety, and clinical applicability.

- **Optimization of healthcare systems**, through the automation of administrative tasks, such as clinical documentation, clinical history drafting, and summarization of clinical records for multidisciplinary team meetings, as well as support for large-scale data extraction and structuring.

Implementation challenges: The need to redesign workflows, ensure appropriate resource allocation, and establish infrastructures capable of continuous monitoring of AI performance and safety.

Recommendations

- Remain open to evaluating and adopting GenAI tools that demonstrate the potential to improve the quality, efficiency, and safety of clinical practice.
- Explore the use of these tools for large-scale data extraction and structuring to enable population-level analyses and support the monitoring of healthcare quality indicators.

- **Improvement of the physician-patient relationship**, through the development and implementation of tools that automate routine tasks, thereby freeing healthcare professionals' time for direct patient care and more personalized communication.

Implementation challenges: Ensuring that efficiency gains achieved through GenAI do not result in increased workload due to additional monitoring, validation, or administrative tasks, or in the use of AI primarily as a productivity or revenue-enhancing tool rather than as a means of improving patient care.

Recommendations

- Explore the use of GenAI to automate administrative tasks, thereby creating more time for meaningful patient interactions and improving the quality of care.

• What is the role of AI in breast imaging, and what are the requirements for its safe integration?

In Portugal, AI can play a role in two main contexts related to breast cancer detection and early diagnosis:

- **Organized population-based screening**, through AI-assisted interpretation of mammography and digital breast tomosynthesis, an application supported by an increasing body of evidence from the scientific literature.
- **Opportunistic/personalized screening and early diagnosis**, where AI acts as an AI-assisted second reader, providing standardized and efficient support based on algorithms trained on large mammography datasets (an application that is less extensively documented in the scientific literature).

Several commercial applications for mammography screening and assessment are currently available with European certification, including Lunit INSIGHT MMG®, Mia® Reader, and Transpara®.[50]

Transpara® has been validated in multiple clinical studies, demonstrating improvements in reader performance metrics, including sensitivity, specificity, and area under the curve (AUC), when used as a second reader.[304–306] The national experience with Transpara® in the early diagnosis setting follows a sequential reading workflow, in which the radiologist initially interprets the examination without access to the AI analysis and reviews the AI output only after completing the initial assessment. This approach is supported by several European teams[305,306] and endorsed by the European Society of Radiology.[307]

It is essential to establish local validation protocols and continuous performance monitoring of AI systems. Key indicators, including sensitivity, specificity, cancer detection rate, recall rate, interval cancer rate, false-positive rate, and performance across different breast density categories, should be systematically assessed.

• What is the role of AI in Pathology, and what are the main challenges to its implementation?

Digital pathology enables the digitization of conventional glass slides through high-resolution scanners, generating whole-slide images (WSIs) — digital representations of histological slides that allow microscopic evaluation on digital platforms — and facilitating the integration of computational tools and AI-based models.

Among the deep learning models applied to digital pathology, convolutional neural networks (CNNs) are particularly relevant due to their ability to process and analyze complex images. These networks can identify complex tissue patterns, including tumor morphology, mitotic figures, and lymphocytic infiltration, forming the basis of many clinical and research applications in breast pathology.[308]

CNN-based models can automatically differentiate benign, in situ, and invasive lesions in hematoxylin and eosin (H&E)-stained slides, potentially improving diagnostic consistency and efficiency while reducing the time required for slide evaluation.[309]

In immunohistochemical assessment, AI can significantly improve the quantification of biomarkers such as ER, PR, HER2, and Ki-67, particularly in heterogeneous cases or those with borderline values close to established diagnostic cut-off thresholds.

Beyond tumor cell assessment, AI can also support analysis of the tumor microenvironment. Quantification of TILs can be performed using AI models capable of distinguishing lymphocytes from other inflammatory cells based on morphology and spatial relationships with tumor cells. This approach enables a more objective and consistent assessment, potentially reducing interobserver variability.[310,311]

• How can AI contribute to more structured, accurate, and efficient clinical documentation?

AI can contribute to optimizing clinical documentation through two main approaches:

- AI-powered dictation systems, which convert speech into structured clinical documentation with direct integration into electronic health records.
- AI-powered ambient listening technologies, capable of automatically capturing verbal communication in clinical environments (e.g., consultations and examinations), extracting, synthesizing, and structuring relevant information to generate clinical notes and structured reports.

The implementation of these approaches can significantly improve efficiency by reducing the time spent on manual documentation and automating repetitive administrative tasks. This allows clinical teams to dedicate more time to meaningful patient interactions.

• What are the ethical and legal implications of AI use in breast health, and what changes with the new European Artificial Intelligence Act?

The use of AI in breast health — as in other areas of medicine — is subject to a legal and ethical framework encompassing both legal and ethical dimensions.

Legal dimensions

Fundamental rights – The European Artificial Intelligence Act (AI Act) aims to ensure that AI systems respect fundamental rights while promoting applications that generate benefits for individuals. Its provisions can be used to assess the regulatory framework applicable to AI systems in breast health, evaluating their compliance with established requirements. An example of work already developed in this context, involving AI systems applied to breast health, is the Cinderella project, coordinated by the Champalimaud Foundation, which used AI algorithms to support clinical decision-making and improve aesthetic and functional outcomes after breast cancer surgery.[312]

Medical liability and liability for device failure – The AI Act does not directly regulate medical liability. The Medical Device Regulation (MDR) provides the European regulatory framework for addressing failures associated with medical de-

vices and software incorporating technological components. Therefore, AI-based medical devices (or clinical decision-support software/electronic health record [EHR] systems incorporating AI functionalities) are subject to the MDR.

Technical and legal responsibilities associated with AI use – These responsibilities are shaped by requirements established under the AI Act, the MDR, applicable cybersecurity legislation, the General Data Protection Regulation (GDPR), and other national privacy and data protection laws. In Portugal, there is currently no comprehensive national framework specifically addressing the governance, implementation, monitoring, and accountability of AI systems in healthcare. Clarifying this regulatory framework and issuing national guidance for the development, evaluation/approval, implementation, monitoring, and auditing of AI-based systems in healthcare should be considered a priority.

Ethical dimensions

Bioethical aspects – In breast health, the bioethical issues raised by AI use are particularly relevant due to the increased sensitivity surrounding physical and psychological integrity, given the relationship between the breast and personal, body, and sexual identity. Although some concerns may reflect cultural or moral values, they are relevant to many individuals and should therefore be explicitly considered in any AI implementation strategy.

Ethical aspects associated with the use of digital health solutions – During the French Presidency of the Council of the European Union, 16 ethical principles for digital health were established.33 Among these, transparency and explainability of AI systems are particularly relevant, with important legal implications: (i) determining responsibilities between manufacturers/implementers and physicians using AI systems or their generated inferences, and (ii) ensuring accountability towards patients, thereby strengthening trust, safety, and informed control over the use of technology.

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