

## SPECIAL ARTICLE

# Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up<sup>†</sup>

F. Cardoso<sup>1</sup>, S. Kyriakides<sup>2</sup>, S. Ohno<sup>3</sup>, F. Penault-Llorca<sup>4,5</sup>, P. Poortmans<sup>6,7</sup>, I. T. Rubio<sup>8</sup>, S. Zackrisson<sup>9</sup> & E. Senkus<sup>10</sup>, on behalf of the ESMO Guidelines Committee\*

<sup>1</sup>Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; <sup>2</sup>Europa Donna Cyprus, Nicosia, Cyprus; <sup>3</sup>Breast Oncology Center, Cancer Institute Hospital, Tokyo, Japan; <sup>4</sup>Department of Pathology, Centre Jean Perrin, Clermont-Ferrand; <sup>5</sup>UMR INSERM 1240, IMoST Université d'Auvergne, Clermont-Ferrand; <sup>6</sup>Department of Radiation Oncology, Institut Curie, Paris; <sup>7</sup>Paris Sciences & Lettres – PSL University, Paris, France; <sup>8</sup>Breast Surgical Oncology Unit, Clinica Universidad de Navarra, Madrid, Spain; <sup>9</sup>Department of Translational Medicine, Diagnostic Radiology, Lund University and Skåne University Hospital Malmö, Malmö, Sweden; <sup>10</sup>Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland

\*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

<sup>†</sup>Approved by the ESMO Guidelines Committee: August 2003, last update April 2019. This publication supersedes the previously published version—*Ann Oncol* 2015; 26(Suppl 5): v8–v30.

For the purpose of the ESMO guidelines, inoperable locally advanced breast cancer is considered part of advanced breast cancer (ABC) and is discussed in the ABC guidelines; it will not be addressed in the present manuscript.

**Key words:** early breast cancer, diagnosis, treatment, follow-up

## Incidence and epidemiology

In 2018, the predicted number of new breast cancers in 28 European Union (EU) countries was 404 920, with estimated age-adjusted annual incidence of breast cancer of 144.9/100 000 and mortality of 32.9/100 000, with 98 755 predicted deaths [1]. Worldwide, there was about 2.1 million newly diagnosed female breast cancer cases in 2018, accounting for almost one in four cancer cases among women, and ~630 000 died of it [2]. Breast cancer incidence has increased since the introduction of mammography screening and continues to grow with the ageing of the population.

The most important risk factors include: genetic predisposition, exposure to oestrogens [endogenous and exogenous, including long-term hormone replacement therapy (HRT)], ionising radiation, low parity, high breast density and a history of atypical hyperplasia. The Western-style diet, obesity and the consumption of alcohol also contribute to the rising incidence of breast cancer [3].

There is a steep age gradient, with about a quarter of breast cancers occurring before age 50, and <5% before age 35.

The estimated 5-year prevalence of breast cancer (people with a diagnosis within the last 5 years and still alive, with or without disease) in Europe in 2012 was 1 814 572 cases [1] and a staggering

6 875 099 cases worldwide [2]. Prevalence is increasing, due to increased incidence and improvements in treatment outcomes.

In most Western countries, the mortality rate has decreased in recent years, especially in younger age groups, because of improved treatment and earlier detection [4, 5]. However, breast cancer is still the leading cause of cancer-related deaths for women in Europe and worldwide, although the mortality of lung cancer in women is overcoming breast cancer mortality in some countries.

Breast cancer in males is rare, contributing to ~1% of cases. The major risk factors include clinical disorders carrying hormonal imbalances (especially gynaecomastia and cirrhosis), radiation exposure, a positive family history and genetic predisposition [6].

## Breast cancer screening

Out of the 28 member states of the EU, 25 were planning, piloting or rolling out (ongoing or completed) national or regional population-based mammography screening programmes, to detect breast cancers at a pre-clinical stage [7]. The European Guidelines for quality assurance in breast cancer screening and diagnosis recommend performance parameters and indicators that should be monitored in any screening programme [8]. The

European Commission Initiative on Breast Cancer (ECIBC) has produced evidence-based recommendations for mammography screening, with the strongest recommendation for women aged 50–69 years and with conditional recommendations for women in younger and older age groups [9]. The greatest mortality reduction benefit has been shown in the 50- to 69-year-old age group, while evidence for effectiveness of mammography screening in women aged 40–49 years is more limited, especially for women aged between 40 and 44 years [10]. This was also the conclusion in the 2015 breast cancer screening report from the International Agency for Research on Cancer (IARC) [11]. There is no consensus about the exact effect of mammography screening on breast cancer mortality reduction, as the reported estimates vary. In a UK review of the randomised controlled mammography trials, a 20% relative breast cancer mortality reduction was estimated in women aged between 50 and 70 years [12]. It must be noted that the review stresses the importance of taking into account the risk of over-diagnosis and over-treatment, as well as false-positive screening, when balancing the benefits and harms of screening. Screening programmes carry the risk of false-negative results; consequently, a false feeling of security among patients and doctors may be instilled. Nevertheless, mammography screening and population-based awareness programmes, together with improved treatment, contribute to mortality reduction in breast cancer. There is also controversy and no consensus regarding the use of ultrasound (US) as a supplementary screening method. Risk-adapted screening is currently being evaluated in clinical trials.

In women with familial breast cancer, with or without proven *BRCA* mutations, annual screening with magnetic resonance imaging (MRI) of the breast, in combination with mammography, can detect the disease at a more favourable stage compared with mammography screening alone (70% lower risk of being diagnosed with breast cancer stage II or higher). However, it is not known whether breast cancer mortality is lowered [13]. There is no consensus for the use of US.

#### Recommendations:

- Regular (annual or every 2 years) mammography is recommended in women aged 50–69 years [I, A]. Regular mammography may also be done for women aged 40–49 and 70–74 years, although the evidence for benefit is less well established [II, B].
- In women with a strong familial history of breast cancer, with or without proven *BRCA* mutations, annual MRI and annual mammography (concomitant or alternating) are recommended [III, A].

### Diagnosis and pathology/molecular biology

The diagnosis of breast cancer is based on clinical examination in combination with imaging and confirmed by pathological assessment (Table 1). Clinical examination includes bimanual palpation of the breasts and regional lymph nodes and assessment for distant metastases (bones, liver and lungs; a neurological examination is only required when symptoms are present).

**Table 1. Diagnostic work-up for early breast cancer**

Assessment of general health status	History Menopausal status Physical examination Full blood count Liver, renal and cardiac (in patients planned for anthracycline and/or trastuzumab treatment) function tests, alkaline phosphatase and calcium
Assessment of primary tumour	Physical examination Mammography Breast US Breast MRI in selected cases Core biopsy with pathology determination of histology, grade, ER, PgR, HER2 and Ki67
Assessment of regional lymph nodes	Physical examination US US-guided biopsy if suspicious
Assessment of metastatic disease	Physical examination Other tests are not routinely recommended, unless high tumour burden, aggressive biology or when symptoms suggestive of metastases are present

ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; PgR, progesterone receptor; US, ultrasound.

Imaging includes bilateral mammography and US of the breast and regional lymph nodes [8]. An MRI of the breast is not routinely recommended, but should be considered in cases of:

- familial breast cancer associated with *BRCA* mutations [I, A];
  - lobular cancers [I, A];
  - dense breasts [II, B];
  - suspicion of multifocality/multicentricity (particularly in lobular breast cancer) [I, A];
  - large discrepancies between conventional imaging and clinical examination [III, B];
  - before neoadjuvant systemic therapy, and to evaluate the response to this therapy [II, A]; and
  - when the findings of conventional imaging are inconclusive (such as a positive axillary lymph node status with an occult primary tumour in the breast) [III, A] [14].
- It may also be considered in case of breast implants.

Several new techniques are being tested for screening and diagnostic imaging, such as three-dimensional (3D) mammography (digital breast tomosynthesis), 3D US, shear wave elastography and contrast-enhanced mammography/spectral mammography. None of these are yet routinely implemented but they have the potential to increase diagnostic accuracy, especially in women with dense breasts.

It is imperative to collect complete personal medical history, family history relating to breast/ovarian and other cancers and the menopausal status of the patient (if in doubt, measure serum oestradiol and follicle-stimulating hormone levels), and to carry out a full physical examination.

Apart from imaging, pretreatment disease evaluation includes pathological examination of the primary tumour and cytology/histology of the axillary nodes, if involvement is suspected.

Pathological diagnosis should be based on a core needle biopsy, preferably obtained by US or stereotactic guidance. A core needle biopsy (if this is not possible, at least a fine-needle aspiration indicating carcinoma) must be obtained before any type of treatment is initiated. If preoperative systemic therapy is planned, a core needle biopsy is mandatory to ensure a diagnosis of invasive disease and assess biomarkers [I, A]. It is recommended that at least 2–3 cores are obtained. In case of multifocal and multicentric tumours, all lesions should be biopsied [I, A]. A marker (e.g. surgical clip, carbon) should be placed into the tumour at biopsy, to ensure resection of the correct site and to enable pathological assessment of the surgical specimen [V, A]. As a minimum, US-guided fine-needle aspiration or core biopsy of suspicious lymph nodes should be carried out, preferably followed by clip or carbon marking of biopsied lymph nodes [III, A]. An excisional biopsy should not be carried out, except in rare cases of repeated negative core biopsies.

Final pathological diagnosis should be made according to the World Health Organization (WHO) classification [15] and the eighth edition of the American Joint Committee on Cancer (AJCC) tumour, node, metastasis (TNM) staging system [16]. This staging system, apart from purely anatomical information, includes also prognostic information related to tumour biology [tumour grade, oestrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2) and gene expression data if available]. The two most frequent subtypes are invasive carcinoma of the breast, not otherwise specified (NOS, previously named ductal carcinoma) (70%–75%) and lobular carcinoma (12%–15%). The other 18 subtypes exhibit specific morphological traits and are rare (from 0.5% to 5%). Each of these specific subtypes shows a particular prognosis. Of note, a neuroendocrine differentiation can be observed in some cases, without any prognostic or therapeutic consequences for the patient [15]. The pathological report should include presence/absence of ductal carcinoma *in situ* (DCIS), the histological type, grade, immunohistochemistry (IHC) evaluation of ER status (using a standardised assessment methodology, e.g. Allred score or *H*-score) and, for invasive cancer, IHC evaluation of PgR and HER2 expression or *HER2* gene amplification. *HER2* gene amplification status may be determined directly from all invasive tumours using *in situ* hybridisation (ISH) (fluorescent, chromogenic or silver), replacing IHC or only for tumours with an ambiguous (2+) IHC score [II, B] [17]. HER2 testing should be carried out according to the American Society of Clinical Oncology–College of American Pathologists (ASCO-CAP) guidelines. HER2 is defined as positive by IHC (3+) when more than 10% of the cells harbour a complete membrane staining, and by ISH if the number of *HER2* gene copies is  $\geq 6$ , or the *HER2*/chromosome 17 (CEP17) ratio is  $\geq 2$  and *HER2* copies  $\geq 4$ , or *HER2*/CEP17  $< 2$  and *HER2* copies  $\geq 6$  [18].

Proliferation markers such as the Ki67 labelling index may supply additional useful information, particularly if the assay can be standardised [III, A] [19, 20].

Alternatively, these biological markers can be assessed in the definitive surgical specimen if primary systemic therapy (PST) is

**Table 2. Surrogate definitions of intrinsic subtypes of breast cancer [23]**

Intrinsic subtype	Clinicopathological surrogate definition
Luminal A	'Luminal A-like' ER-positive HER2-negative Ki67 low <sup>a</sup> PgR high <sup>b</sup> Low-risk molecular signature (if available)
Luminal B	'Luminal B-like (HER2-negative)' ER-positive HER2-negative and either Ki67 high or PgR low High-risk molecular signature (if available)  'Luminal B-like (HER2-positive)' ER-positive HER2-positive Any Ki67 Any PgR
HER2	'HER2-positive (non-luminal)' HER2-positive ER and PgR absent
'Basal-like'	'Triple-negative' <sup>c</sup> ER and PgR absent <sup>c</sup> HER2-negative <sup>c</sup>

Adapted from the 2013 St Gallen Consensus Conference [23].

<sup>a</sup>Ki-67 scores should be interpreted in light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in receptor-positive disease of 20%, values of 30% or above could be considered clearly high; those of 10% or less clearly low.

<sup>b</sup>Suggested cut-off value is 20%; quality assurance programmes are essential for laboratories reporting these results.

<sup>c</sup>There is ~80% overlap between 'triple-negative' and intrinsic 'basal' subtype, but 'triple-negative' also includes some special histological types such as carcinoma with a rich lymphocytic stroma (former medullary), secretory carcinoma, low-grade metaplastic carcinoma and adenoid cystic carcinoma. ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor.

not planned. However, fixation is better controlled for core biopsies, allowing safer antigen preservation for IHC [21].

In case of negativity of ER/PgR and HER2 in the biopsy specimen, it is advisable to retest for them in the surgical specimen to account for the putative tumour heterogeneity [III, A] [22]. In case of discrepancy, the results from the surgical specimen are considered definite. In case of a HER2-positive test on biopsy, retesting for HER2 on the surgical specimen is mandatory for invasive carcinoma NOS grade I, ER- and PgR-positive (including special types such as tubular, mucinous, cribriform) or adenoid cystic carcinoma or secretory carcinoma (both usually triple-negative) [18].

For the purpose of prognostication and treatment decision making, tumours should be grouped into surrogate intrinsic subtypes, defined by routine histology and IHC data [III, A] (Table 2) [23, 24]. Luminal A-like tumours are typically low

grade, strongly ER-positive/PgR-positive, HER2-negative and have low proliferative fraction. Luminal B-like tumours are ER-positive but may have variable degrees of ER/PgR expression, are higher grade and have higher proliferative fraction [23].

Tumour-infiltrating lymphocyte (TIL) scoring is demonstrated to have a prognostic value in triple-negative breast cancer (TNBC) and HER2-positive breast cancer. It has been described as a predictor of pathological complete response (pCR) to chemotherapy (ChT) in many prospective neoadjuvant clinical trials and its increase appears linked to an improved prognosis after adjuvant therapy. TIL scoring can be used as a prognostic marker, as shown in a variety of clinical trials (e.g. BIG-2-98, FinHER, Cleopatra), providing a typically 15%–20% relative improvement in survival per 10% increase in TILs [25–27] and its use as a prognostic factor is endorsed by the 2019 St Gallen Consensus. However, TIL scoring should not be used to take treatment decisions nor to escalate or de-escalate treatment.

Genetic counselling and testing for germline *BRCA1* and *BRCA2* mutations should be offered to breast cancer patients in high-risk groups, i.e. those with:

- strong family history of breast, ovarian, pancreatic and/or high grade/metastatic prostate cancer;
- diagnosis of breast cancer before the age of 50;
- diagnosis of TNBC before the age of 60; and
- personal history of ovarian cancer or second breast cancer or male sex [II, A] [28, 29].

Other high-risk mutations may also be tested, if deemed appropriate by the treating physician/genetic counsellor.

For details regarding genetic testing and management of *BRCA* carriers, please refer to the appropriate ESMO Clinical Practice Guidelines [29].

#### Recommendations:

- Breast imaging should involve bilateral mammogram and US of breasts and axillae in all cases [I, A]; MRI is recommended in case of uncertainties following standard imaging and in special clinical situations [I, A].
- Pathological evaluation includes histology from the primary tumour and cytology/histology of the axillary nodes (if involvement is suspected) [I, A].
- Pathological report should include histological type, grade, IHC evaluation of ER, PgR (for invasive cancer), HER2 (for invasive cancer) and some form of proliferation markers (e.g. Ki67 for invasive cancer) [I, A]. Tumours should be grouped into surrogate intrinsic subtypes, defined by routine histology and IHC data [I, A].
- TIL scoring is of prognostic value and may be used to add on information on patient's prognosis. It should not, however, be used to take treatment decisions nor to escalate or de-escalate treatment.
- Genetic counselling and testing for germline *BRCA1* and *BRCA2* mutations should be offered to breast cancer patients in high-risk groups [II, A].

## Staging and risk assessment

Disease stage should be assessed according to the eighth edition of the AJCC TNM staging system [16]. In early breast cancer, routine staging evaluations are directed at locoregional disease. Asymptomatic distant metastases are rare, and most patients do not benefit from comprehensive laboratory tests (including tumour markers [30]) and radiological staging [III, D]. Minimum blood work-up (a full blood count, liver and renal function tests, alkaline phosphatase and calcium levels) is recommended before surgery and systemic (neo)adjuvant therapy [V, A].

A computed tomography (CT) scan of the chest, abdominal imaging (US, CT or MRI scan) and a bone scan can be considered for patients with:

- clinically positive axillary nodes;
- large tumours (e.g.  $\geq 5$  cm);
- aggressive biology; and
- clinical signs, symptoms or laboratory values suggesting the presence of metastases [III, A].

Dual imaging methods combining functional and anatomical information such as fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT may be useful when conventional methods are inconclusive [V, A]. PET-CT scanning can also replace traditional imaging for staging in high-risk patients [V, B] [31], although in cases of lobular cancers and low-grade tumours, PET-CT may be less sensitive. Current evidence does not support the use of FDG-PET-CT in the staging of locoregional disease, due to its limited sensitivity when compared with the gold standard, sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) [32].

In patients planned for (neo)adjuvant systemic treatment with anthracyclines and/or trastuzumab, evaluation of cardiac function with a cardiac US or a multigated acquisition (MUGA) scan is essential [I, A].

The postoperative pathological assessment of the surgical specimens should be made according to the pathological TNM system [16]. This assessment should include:

- the number, location and maximum diameter of the tumours removed;
- the total number of removed and positive lymph nodes, as well as the extent of metastases in the lymph nodes [isolated tumour cells, micrometastases (0.2–2 mm), macrometastases];
- the histological type and grade of the tumour(s) using a standard grading system;
- evaluation of the resection margins, including the location and minimum distance of the margin;
- vascular invasion; and
- a biomarker analysis, as described above [I, A].

For small tumours diagnosed by core biopsy, measuring only the residual tumour in the excision may result in understaging. It is recommended to correlate imaging, clinical and gross findings to microscopic observation if necessary [16].

The most important prognostic factors in early breast cancer are the expression of ER/PgR, HER2 and proliferation markers (e.g. Ki67), the number of involved regional lymph nodes, tumour histology, the size, grade and the presence of peritumoral

vascular invasion. Additionally, in patients undergoing breast-conserving therapy (BCT), the ipsilateral breast recurrence risk is related to the status of the surgical margins and the presence of DCIS.

Immunohistochemically detected tumour markers known to have great practical treatment importance are now incorporated into the eighth edition of the AJCC TNM staging system to refine prognosis, which also uses genomic assays, when available, to downstage some ER-positive, lymph node-negative tumours [16]. Clinical parameters (age, tumour stage, ER, PgR and HER2 expression and histological grade) have also been integrated into scoring systems, allowing a relatively accurate estimation of the probability of recurrence and death from breast cancer; examples include the Nottingham Prognostic Index (NPI), the PREDICT score and Adjuvant! Online (currently temporarily unavailable) [33–35].

UPA/PAI-1 (FEMTELLE; Sekisui Diagnostics, Lexington, MA) is an enzyme-linked immunosorbent assay (ELISA) evaluating the metastatic potential of a breast tumour. Despite its level [I, A] of prognostic value in node-positive and node-negative breast cancer patients, this test is not extensively used, probably due to the requirement for a substantial amount of fresh-frozen tissue [36].

Gene expression profiles, such as MammaPrint (Agendia, Amsterdam, The Netherlands), Oncotype DX Recurrence Score (Genomic Health, Redwood City, CA), Prosigna (PAM 50; NanoString Technologies, Seattle, WA), Endopredict (Myriad Genetics Salt Lake City, UT) and Breast Cancer Index (Biotheranostics, Inc., San Diego, CA), may be used to gain additional prognostic and/or predictive information to complement pathology assessment and to predict the benefit of adjuvant ChT [19]. All tests except MammaPrint were designed for patients with ER-positive early breast cancer only. The clinical utility of MammaPrint and Oncotype DX has been or is still being prospectively evaluated in large randomised clinical trials such as MINDACT for MammaPrint, West German Study Group (WSG) PLAN B trial, TAILORx and RxPONDER (SWOG 1007) for Oncotype DX [37–39]. A level of evidence (LoE) and grade of recommendation (GoR) of [I, A] have been achieved through the prospective MINDACT trial for the prognostic value and clinical utility (for ChT decision making) of MammaPrint (for clinical high risk, low genomic score) and for Oncotype DX through the TailorX and Plan B trials. A score of [I, B] according to biomarker LoE guidelines [40] has been achieved from retrospective analyses of data from prospective trials regarding the prognostic value of Prosigna and Endopredict, in ER-positive breast cancers [36, 41]. In addition, the prognostic value of MammaPrint has been validated in the RASTER trial, a prospective but non-randomised, clinical trial [42]. The OPTIMA Prelim Trial has recently shown that the use of molecular tests has an 86% probability of being cost-effective [43], along with several other published studies. Furthermore, both MammaPrint and Oncotype DX are able to identify patients with an ultra-low risk of death from breast cancer at 10 or 20 years [44, 45].

ER/PgR and HER2 are the only validated predictive factors allowing the selection of patients for endocrine therapy (ET) and anti-HER2 therapies, respectively. High ER expression is usually associated with lesser absolute benefit of ChT [46]. It must be stressed that IHC/ISH determination of intrinsic phenotype does

not have a 100% concordance with the molecular determination. The prerequisite for using such a surrogate assessment is the use of standardised assays and a meticulous quality control.

After neoadjuvant systemic treatment, the response to treatment and the amount of residual disease are important prognostic factors but need as much standardisation as any of the other biological markers. A multidisciplinary international working group developed practical recommendations for the systematic, standardised evaluation of the post-neoadjuvant surgical breast cancer specimen [47]. Systematic sampling of areas identified by intelligent mapping of the specimen and close correlation with radiological findings is preferable to overly exhaustive sampling and permits the collection of tissue samples for translational research. If a pCR was achieved (defined as no invasive disease both in the breast and axilla), this must be clearly stated [48]. In addition, the presence or absence of residual DCIS must be described. In case of residual invasive carcinoma, a comment must be made as to the presence or absence of ChT effect in the breast and the lymph nodes. The Residual Cancer Burden (RCB) is the preferred method for quantifying residual disease in clinical trials; other methods can be used according to regional preference [49]. Post-treatment tumour staging, using the TNM system, should also be included [16].

#### Recommendations:

- Disease stage should be assessed according to the AJCC TNM staging system [I, A].
- Comprehensive laboratory testing including tumour markers and radiological staging is not necessary for all patients [III, D].
- Minimum blood work-up (a full blood count, liver and renal function tests, alkaline phosphatase and calcium levels) is recommended before surgery and systemic (neo)adjuvant therapy [V, A].
- Imaging of chest, abdomen and bone is recommended for higher-risk patients (high tumour burden, aggressive biology, signs, symptoms or laboratory values suggesting the presence of metastases) [III, A].
- FDG-PET-CT scanning may be useful when conventional methods are inconclusive [V, A] and may replace traditional imaging for staging in high-risk patients [V, B].
- Postoperative pathological assessment of the surgical specimens should be made according to the pathological TNM system [I, A].
- Validated gene expression profiles may be used to gain additional prognostic and/or predictive information to complement pathology assessment and help in adjuvant ChT decision making [I, A].

## Treatment

### General rules

**Organisation of care.** Treatment of breast cancer in the setting of specialised breast units/centres defined as specialised institutions/departments that care for a high volume of breast cancer patients (a minimum of 150 new early breast cancer cases per year) leads to improved outcomes [both in terms of disease-free

survival (DFS) and overall survival (OS)], functional outcomes and quality of life (QoL) of patients, and is highly recommended [III, A]. The breast unit/centre should preferably be certified by an accredited body [III, A]. Treatment of breast cancer patients within specialised units is recommended by the European Parliament and European Commission, reviewed in Ref. [50].

#### Recommendations:

- Treatment should be carried out in specialised breast units/centres and provided by a multidisciplinary team specialised in breast cancer, consisting of at least medical oncologists, breast surgeons, radiation oncologists, breast radiologists, breast pathologists and breast nurses (or similarly trained and specialised health care practitioners) [III, A] [50, 51].
- The breast unit/centre should have or be able to refer patients to plastic/reconstructive surgeons, psychologists, physiotherapists and geneticists when appropriate [III, A].
- A breast nurse or a similarly trained and specialised health care practitioner should be available to act as a patient navigator [III, B] [50, 51].

**Patient information and involvement in decision making.** Following a diagnosis of breast cancer, a patient finds herself/himself in a new and unfamiliar landscape. This creates different levels of stress that vary from patient to patient and need to be addressed individually and tailored to each patient's needs. Most will remember the information provided to them in a fragmented way. Patients need space, both physical and timewise, to process and comprehend the information about their diagnosis, so they can cope psychologically with the treatment plan.

#### Recommendations:

- Information on diagnosis and treatment choice should be given repeatedly (both verbally and in writing) in a comprehensive and easily understandable form [V, A].
- The use of reliable, patient-centred websites or similar sources of information is recommended [V, A].
- Patients should be actively involved in all management decisions [V, A].

Treatment of early breast cancer is complex and involves combination of local modalities [surgery, radiotherapy (RT)], systemic anticancer treatments (ChT, ET, molecularly targeted therapies) and supportive measures, delivered in diverse sequences. The use of predictive biomarkers such as ER, PgR, HER2 and Ki67 and approved genomic signatures is well established to help in determining the treatment of choice (see Figure 1).

Particular attention must be paid to treatment of early breast cancer in special populations, e.g. very young or elderly patients. However, age is a continuous variable and its cut-offs in clinical trials are always arbitrarily chosen. 'Younger' patients should not be overtreated because they are 'young', just as 'older' patients should not be undertreated solely based on their calendar age.

In younger premenopausal patients, possible fertility issues should be discussed and guidance about fertility-preservation techniques should be provided, before the initiation of any

systemic treatment [52–56]. For details about fertility preservation, please refer to the appropriate ESMO Clinical Practice Guidelines [56].

#### Recommendations:

- The choice of treatment strategy should be based on the tumour burden/location (size and location of primary tumour, number of lesions, extent of lymph node involvement) and biology (pathology, including biomarkers and gene expression), as well as the age, menopausal status, general health status and preferences of the patient [V, A].
- Age should be taken into consideration in conjunction with other factors and should not be the sole determinant for withholding or recommending a treatment [V, A].
- In younger premenopausal patients, fertility issues and, when desired by the patient, fertility-preservation techniques should be discussed, before the initiation of any systemic treatment [V, A].

### Local treatment

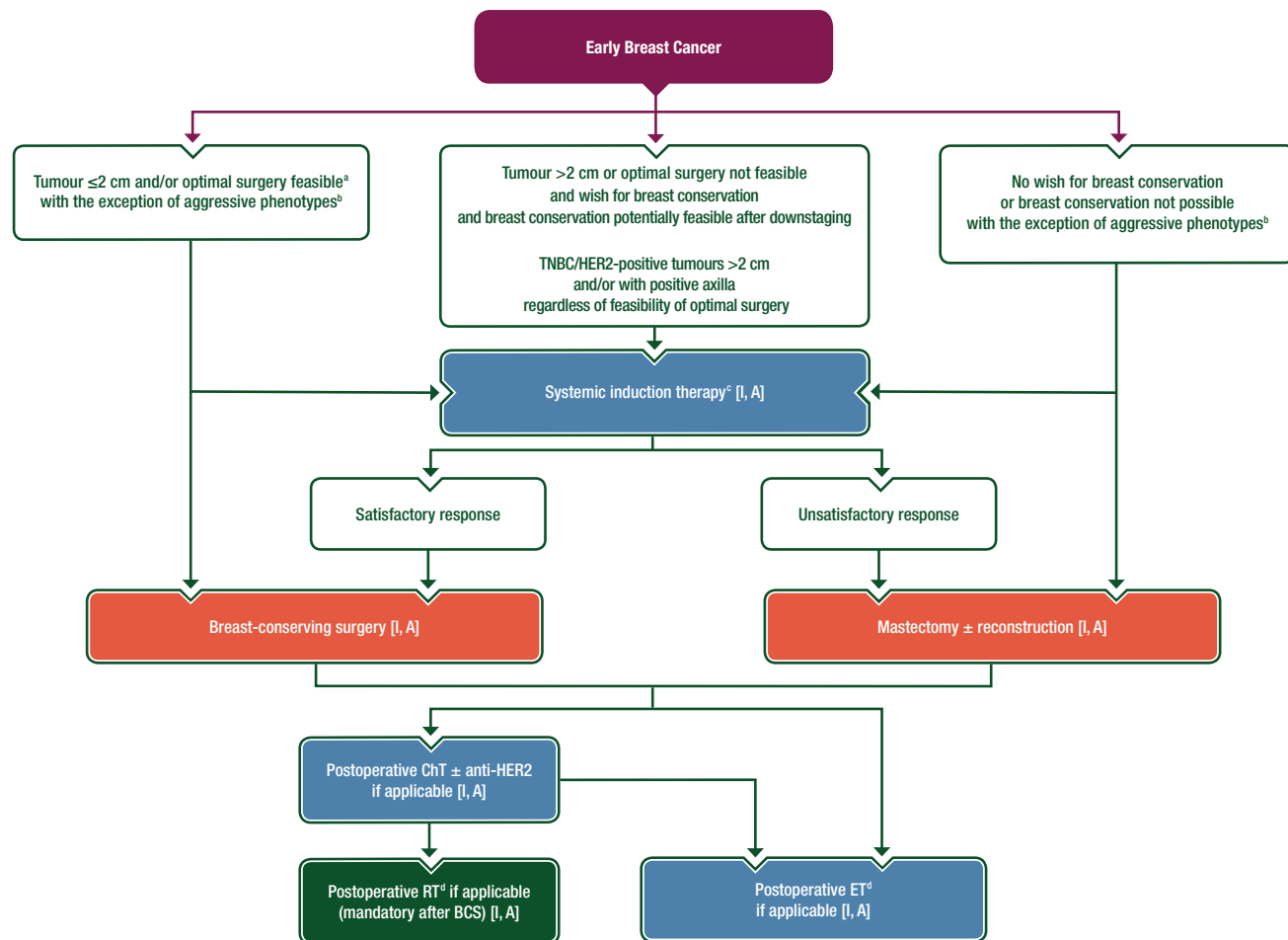
**Surgery.** The major change in the surgical treatment of primary breast cancer has been a shift towards breast conservation techniques, which started >30 years ago. Currently, in western Europe, 60%–80% of newly diagnosed cancers are amenable to breast conservation (wide local excision and RT), at diagnosis or after PST. A neoadjuvant approach should be preferred in subtypes highly sensitive to ChT, such as triple-negative and HER2-positive, in tumours >2 cm [II, A] and/or a positive axilla (see Figure 1).

In some patients, mastectomy is still carried out due to:

- tumour size (relative to breast size);
- tumour multicentricity;
- inability to achieve negative surgical margins after multiple resections;
- prior radiation to the chest wall/breast or other contraindications to RT;
- unsuitability for oncoplastic breast conservation; and
- patient choice [57].

**Breast-conserving surgery.** Breast-conserving surgery (BCS) is the primary surgical choice for breast cancer. For patients undergoing wide local excision, greater emphasis is now placed on achieving acceptable cosmesis, and breast surgeons are trained to undertake oncoplastic approaches to reduce the impact of local tumour excision on cosmesis, often using tissue displacement techniques. Oncoplastic procedures can result in better cosmetic outcomes, especially in patients with large breasts, a less favourable tumour/breast size ratio or a cosmetically challenging (central or inferior) location of the tumour within the breast.

Despite the overall trend towards breast conservation, increasing numbers of breast cancer patients are opting for bilateral mastectomy (incorporating contralateral risk-reducing surgery) rather than the preferred breast conservation and mammographic surveillance of the irradiated breast [58]. This must be confronted with data demonstrating that patients with



**Figure 1.** Early breast cancer treatment algorithm.

<sup>a</sup>Biology that requires ChT (TNBC, HER2-positive, luminal B-like), to assess response and prognosis and eventually decide on postoperative therapies, should preferentially receive preoperative ChT.

<sup>b</sup>Aggressive phenotypes: TNBC or HER2-positive breast cancer.

<sup>c</sup>If ChT is planned, it should all be given as neoadjuvant.

<sup>d</sup>Concomitant postoperative RT, postoperative ET and anti-HER2 therapy.

BCS, breast-conserving surgery; ChT, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; RT, radiotherapy, TNBC, triple-negative breast cancer.

early-stage breast cancer who opt for BCT might have an even better survival compared with those who have a mastectomy [59–62].

Margin status should be reported according to the recommendations of the College of American Pathologists (CAP); for example, a margin is positive and should be reported as such, when there is ink touching invasive cancer or DCIS; the anatomic location of the positive margin should be specified in oriented specimens. For negative margins (i.e. ink not touching invasive cancer or DCIS), the distance of invasive cancer and/or DCIS from the margin(s) should be reported. No tumour at the inked margin is required and >2 mm for *in situ* disease is preferred [63–66].

Marking the tumour bed with clips in a standardised way facilitates accurate planning of the radiation boost if indicated.

Currently achievable low local recurrence rates [ $<0.5\%$  per year (with a target of  $<0.25\%$ ) and  $\leq 10\%$  overall at very long-term follow-up] should be maintained.

**Recommendations:**

- BCS is the preferred local treatment option for the majority of early breast cancer patients, with the use of oncoplastic techniques, to maintain good cosmetic outcomes in technically challenging cases, when needed [I, A].
- Careful histological assessment of resection margins is essential. No tumour at the inked margin is required and  $>2$  mm for *in situ* disease is preferred [I, A].

**Mastectomy:** Besides simple mastectomy and skin-sparing mastectomy (SSM) that preserves the skin envelope, nipple-sparing mastectomy (NSM) has been increasingly used in the last decade. NSM has been shown to be safe from an oncological point of view in selected patients and to improve cosmetic outcomes for therapeutic and prophylactic surgeries [II, B] [67, 68]. Because data on NSM cannot be achieved with randomised

Downloaded from https://academic.oup.com/annonc/article-abstract/30/8/1194/5499075 by guest on 13 December 2019

studies, the use of prospective data registries will further aid in evaluation of the technique.

Immediate reconstruction in most women can make the prospect of losing a breast easier to accept [51]. The only oncological reason to advise against immediate reconstruction is the case of inflammatory breast cancer. However, some women may decline or defer reconstruction because of personal preferences. There is no evidence that reconstruction makes detection of local recurrence more difficult, and no basis for the outdated view that patients should wait 1–2 years after mastectomy before being offered reconstruction. The autologous tissue-based techniques generally tolerate postoperative RT well. Implant-based reconstruction may result in an unfavourable aesthetic outcome, following postoperative RT [69, 70]. If post-mastectomy radiotherapy (PMRT) is indicated, use of a temporary expander before RT may facilitate RT planning in some cases.

For women undergoing breast reconstruction, whether immediate or delayed, many surgical options are available. Silicone gel implants are safe and acceptable components of the reconstructive armamentarium [III, A]. Advances in gel cross-linking have reduced silicone bleed, and cohesive gel implants are likely to have fewer problems relating to capsular rupture. When considering implant-based reconstruction, patients should be informed about risk of anaplastic large cell lymphoma [71]. Autologous tissue flaps can replace relatively large volumes of breast tissue. Tissue can be taken from the latissimus dorsi muscle, transverse rectus abdominis muscle, or deep inferior epigastric perforator flap, among others.

#### Recommendations:

- Breast reconstruction should be available and proposed to all women requiring mastectomy [V, A].
- Immediate breast reconstruction should be offered to the vast majority of patients, except for those presenting with inflammatory cancer [V, A].
- The optimal reconstruction technique for each patient should be discussed individually taking into account anatomic, treatment- and patient-related factors and preferences [V, A].

**Advances in axillary management:** Regional lymph node status remains one of the strongest predictors of long-term prognosis in primary breast cancer. ALND is associated with lymphoedema affecting the upper limb in up to 25% of women following surgery (up to 15% following axillary RT without surgical clearance and below 10% following SLNB) [72, 73]. The incidence of lymphoedema rises significantly (to 40%) when axillary clearance is combined with RT to the axilla. SLNB delivers less morbidity in terms of shoulder stiffness and arm swelling and allows for a reduced hospital stay [I, A]. With appropriate training in the dual radiocolloid/blue dye technique or others (indocyanine green fluorescence technique or superparamagnetic iron oxide), high identification rates (over 97%), low false-negative rates and favourable axillary recurrence rates following SLNB are achievable [74].

There is no definite consensus for the pathological assessment of SLNB. The significance of occult micrometastases in terms of surgical management and patient outcome appears to be negligible [75]. Thus, the authors do not recommend routine IHC or

polymerase chain reaction (PCR) for the evaluation of sentinel lymph nodes (SLNs) in patients unexposed to preoperative systemic therapy, in agreement with other guidelines [V, E] [76–79].

Micrometastatic spread and isolated tumour cells are prognostically equivalent to N0 disease, with local as well as systemic treatment options selected based on other tumour- and patient-based parameters. Based on the results of the IBCSG 23–01 trial, further axillary treatment is not required when an SLN has micrometastasis (0.2–2 mm) [79]. For cases with macrometastatic spread in the SLN, the randomised controlled trial ACOSOG-Z0011 (10 years of median follow-up) reported non-inferior rates of OS, DFS and locoregional recurrence-free survival when ALND was avoided, for patients with clinical T1–T2 cN0 invasive breast cancer and 1–2 SLNs containing metastases (treated with BCS, tangential adjuvant RT including part of the axilla and adjuvant systemic therapy) [80, 81]. Therefore, all patients with micrometastatic spread and patients with limited involvement of the SLN, who are undergoing tangential breast RT and adjuvant systemic treatment and meet the criteria of the randomised trials, do not need any further axillary surgery [II, A]. For patients who do not meet those criteria, a level I/II ALND needs to be considered. Another option in patients with cN0 and SLN metastases (irrespective of the risk factors) is axillary RT, as demonstrated by the AMAROS study [72].

#### Recommendations:

- SLNB, rather than full nodal clearance, is the standard of care for axillary staging in early, clinically node-negative breast cancer [II, A].
- Further axillary surgery following positive SLNB is not required in case of low axillary disease burden (micrometastases or 1–2 SLNs containing metastases, treated with postoperative tangential breast RT) [II, A].
- Axillary radiation is a valid alternative in patients with positive SLNB, irrespective of the type of breast surgery [II, A].

**Surgery for *in situ* malignancy (intraepithelial neoplasia):** DCIS may be treated with total mastectomy or BCT, provided that clear resection margins can be achieved. There is no general agreement on what is considered an optimal margin; however, recent consensus has determined that a 2-mm margin is adequate in DCIS treated with whole-breast radiotherapy (WBRT) [64], because it is associated with lower rates of ipsilateral local recurrences and improved cosmetic outcomes [II, B].

Axillary node evaluation with SLNB is not required with *in situ* malignancy but may be reasonable in large and/or high-grade tumours, especially when mastectomy is required (in case an incidental invasive cancer is subsequently identified in the surgical specimen). The risk of a positive SLN with pure DCIS is small (7%–9%) and most of the metastases found are micrometastases or isolated tumour cells, detected by IHC [82, 83]. The decision to carry out an SLNB procedure should be based on the underlying risk of invasion. The invasive breast cancer underestimation rate is reported to be 20%–38%, and increases with the presence of:

- a palpable mass;
- an associated density on the mammogram;
- poorly differentiated DCIS in the biopsy;

- younger age; and
- larger extent of microcalcifications [84, 85].

If invasive cancer appears in the specimen, SLNB after conservative surgery is feasible and accurate for staging the axilla.

Lobular neoplasia [formerly called lobular carcinoma *in situ* (LCIS)], unlike DCIS, is considered a non-obligate precursor to invasive cancer. It is regarded as a risk factor for future development of invasive cancer in both breasts [relative risk (RR): 5.4–12] and does not require active treatment. The pleomorphic variant of lobular neoplasia may behave similarly to DCIS and should be treated accordingly, after multidisciplinary discussion.

#### Recommendations:

- BCS followed by WBRT or total mastectomy are acceptable treatment options for DCIS [I, A].
- When treated with BCS, a 2-mm margin is adequate in DCIS treated with WBRT [II, B].
- SLNB should not be routinely carried out in DCIS, apart from patients with large and/or high-grade tumours, especially when mastectomy is required [V, D].

**Management of occult breast cancer:** Occult breast cancer is a tumour presenting as lymph node metastases without identifiable primary lesion within the breast. It constitutes <0.5% of all new diagnosed breast cancer cases [86]. Routine diagnosis, apart from standard breast and axillary imaging, requires breast MRI and PET-CT (to exclude another primary tumour site). Management includes ALND, although axillary RT in the case of a low axillary disease burden might be an option. Local treatment options include WBRT and/or mastectomy, but there is no benefit in doing both [IV, B] [86, 87].

#### Recommendation:

- The preferred locoregional management of occult breast cancer is ALND and WBRT [IV, B].

**Risk-reducing mastectomy:** The lifetime risk of breast cancer in a *BRCA1* mutation carrier varies between 65% and 90%, with a 10-year actuarial risk of contralateral breast cancer ranging from 25% to 31% [88]. With bilateral mastectomy, the risk for subsequent breast cancer is reduced by 90%–95%, whereas improved survival has not yet been demonstrated in healthy *BRCA1* and *BRCA2* mutation carriers [III, A] [89], although significant improvement in survival was observed among *BRCA1/2* mutation carriers with a history of unilateral breast cancer [90].

#### Recommendations:

- Risk-reducing surgery (with prophylactic bilateral mastectomy and reconstruction) may be offered to women at very high risk, such as *BRCA1* or *BRCA2* mutation carriers or those who have had previous chest RT at young age. Careful genetic assessment and psychological counselling are mandatory before undertaking such surgery, and the option of intense surveillance should also be discussed [III, A].
- Non-high-risk patients who opt for bilateral mastectomy (incorporating contralateral risk-reducing surgery) rather

than the preferred breast conservation should be counselled that survival outcomes in patients with early-stage breast cancer treated with BCS might be even better (and certainly not worse) than those treated with mastectomy [V, A].

**Surgery after PST:** PST should be followed by surgery according to the principles outlined above. Patients need to be evaluated considering the baseline tumour characteristics as well as the post-treatment outcomes to decide on surgical treatment. Downsizing of a large unifocal primary tumour with PST will allow BCS to be undertaken in a substantial proportion of patients, even in tumours that were unresectable at diagnosis. With multifocal disease or where reduction of the primary tumour size is more limited, patients may still be eligible for BCS or oncoplastic conservative surgery, and if not, mastectomy will be required. Breast MRI is the most accurate modality for assessing the extent of residual disease following PST. Breast MRI should also be carried out before the start of PST for proper comparative evaluation. When BCS is anticipated, it is necessary to mark the primary site (using a marker clip or carbon localisation, under US guidance) to facilitate accurate surgery [V, A].

In patients with clinically and imaging-negative axilla, although SLNB can be carried out before or after preoperative systemic therapy [91, 92], a post-systemic therapy SLNB is preferable [II, A] as it obviates the need for two separate surgeries and facilitates the final definition of pCR of the axilla. In patients with limited initial (biopsy proven) nodal involvement (cN1) who convert to negative, results from the SENTINA and ACOSOG Z1071 studies have shown that SLNB can be carried out in selected cases. In these studies, false-negative rates of SLN post-systemic therapy range from 8% to 14.2% [93, 94]. False-negative rates can be improved by marking the biopsied positive node(s) to verify their removal, as well as using dual tracer and removing  $\geq 3$  SLNs [II, B] [95–97]. It should be stressed that any tumour deposits in SLNs prompt ALND in these patients. Available data do not support the routine use of SLNB in patients with initial bulky nodal involvement (cN2–3) [II, E].

#### Recommendations:

- Surgery following PST should be carried out according to general rules for early breast cancer and considering the baseline tumour characteristics as well as the post-treatment outcomes [II, A].
- If BCS is anticipated, marking of the tumour site must be carried out [V, A] and pre- and post-treatment breast MRI should be carried out [II, A].
- In clinically negative axilla, although SLNB may be carried out either pre- or post-PST, post-PST SLNB is preferred [II, A].
- In patients with baseline axillary involvement converting to negative, SLNB may be carried out in selected cases, and, if negative, further axillary surgery may be avoided [II, B].
- Identification of any tumour deposits in post-PST SLNB prompts ALND [II, B].

#### Radiotherapy.

**Whole-breast RT after BCS:** Postoperative RT is strongly recommended after BCS [I, A]. WBRT alone reduces the 10-year risk of any first recurrence (including locoregional and distant)

by 15% and the 15-year risk of breast cancer-related mortality by 4% [98]. Boost RT gives a further 50% RR reduction and is indicated for most patients who have unfavourable risk factors for local control such as age <50 years, grade 3 tumours, presence of vascular invasion or extensive intraductal component and non-radical tumour excision (focally—otherwise further surgery should be advocated) [I, A] [99, 100].

#### Recommendations:

- Postoperative RT is strongly recommended after BCS [I, A].
- Boost RT is recommended to reduce the risk of in-breast relapse in patients at higher risk of local recurrence [I, A].

**Accelerated partial-breast RT after BCS:** The concept of accelerated partial-breast irradiation (APBI) is an appealing approach to substantially shorten the overall treatment time. The rationale for APBI is that the majority of local failures occur in the vicinity of the primary tumour site, while so-called ‘elsewhere’ in-breast failures may represent a new primary tumour. Excellent results with low local recurrence rates equivalent to WBRT are reported for partial-breast irradiation (accelerated and conventionally fractionated) using external beam techniques [101, 102] and brachytherapy [103]. However, for intraoperative RT, as used in the ELIOT (single dose with electrons) and TARGIT (single dose with 50-kV X-rays) randomised trials, the ipsilateral breast cancer recurrence rate was significantly higher in the APBI groups, compared with the WBRT [104, 105]. Based on these results, APBI might be considered an acceptable treatment option in patients with a low risk for local recurrence, for example those who are at least 50 years old, with unicentric, unifocal, node-negative, non-lobular breast cancer, up to 3 cm without the presence of extensive intraductal components or vascular invasion and with negative margins, especially if they will receive adjuvant endocrine treatment [III, C] [106]. APBI may also be considered for low-grade DCIS [III, C]. More and long-term results of several past and ongoing prospective randomised APBI trials are awaited.

#### Recommendation:

- APBI is an acceptable treatment option in patients with a low risk for local recurrence [III, C].

**Post-mastectomy RT:** PMRT in node-positive patients reduces the 10-year risk of any recurrence (including locoregional and distant) by 10% and the 20-year risk of breast cancer-related mortality by 8% [107]. The benefits of PMRT are independent from the number of involved axillary lymph nodes and the administration of adjuvant systemic treatment. Therefore, although PMRT is always recommended for high-risk patients, including those with involved resection margins,  $\geq 4$  involved axillary lymph nodes [I, A] and T3–T4 tumours independent of the nodal status [II, B], it should also be considered for routine use in patients with 1–3 positive axillary lymph nodes [I, A] [107].

#### Recommendation:

- PMRT is recommended for high-risk patients, including those with involved resection margins, involved axillary

lymph nodes and T3–T4 tumours [I, A]; it should also be considered in patients with 1–3 positive axillary lymph nodes [I, A].

**Regional RT:** Older randomised trials have used extended comprehensive locoregional RT encompassing the chest wall and all lymph nodes. Recently presented results support this approach, especially for patients with involved axillary lymph nodes [108–110]. Therefore, although clinically apparent lymph node relapses (especially axillary and internal mammary) are rare, nodal RT remains indicated for patients with involved lymph nodes [I, B] [111]. The authors cannot discriminate which part of the regional lymph nodes is most important to irradiate. The recent Danish population-based study, in which left-sided node-positive breast cancer patients received medial supraclavicular RT and right-sided patients received the same treatment including the internal mammary nodes, points to the importance of including the internal mammary lymph nodes in the regional target volume. Regarding the supraclavicular part of the target volume, the authors agree with the European Society for Radiotherapy and Oncology (ESTRO) guidelines for target volume delineation in breast cancer that advise to include only the most caudal lymph nodes surrounding the subclavicular arch and the base of the jugular vein [112]. After ALND, the resected part of the axilla should not be irradiated, except in cases of clear residual disease after surgery. After a positive SLNB without subsequent ALND, regional RT is advised. Which axillary lymph node levels should be irradiated can be defined based on the presence of other risk factors including extent of nodal involvement, tumour diameter, tumour grade, vascular invasion and tumour site (i.e. in the lowest-risk cases, no RT; in the intermediate-risk cases, exclusive level 1–2 RT; in the highest-risk cases, full level 1–4 treatment, including the internal mammary nodes) [98, 107].

#### Recommendations:

- Comprehensive nodal RT is recommended for patients with involved lymph nodes (the role of irradiating particular nodal volumes is poorly defined; see details in text) [I, B].
- After ALND, routine axillary irradiation should not be done to the operated part of the axilla [I, E].

**RT and breast reconstruction:** Many patients who have a clinical indication for mastectomy are eligible for PMRT. In the case of breast reconstruction, either immediate or delayed, a close collaboration between reconstructive surgeons and radiation oncologists is an absolute requirement to define the most appropriate timing, type of reconstruction and RT target volumes. Based on several patient- and treatment-related factors, individualisation of the approach towards the combination of RT and reconstruction is required to obtain satisfactory results, irrespective of the sequence and the reconstructive method used. Better outcomes in patients with an indication for PMRT, both in terms of cosmesis and complication risks, are usually obtained with autologous tissue reconstruction [113–115].

#### Recommendations:

- Postoperative RT, if indicated, can be administered after immediate breast reconstruction [III, A].

- An intensive multidisciplinary and interactive patient-involving approach is required to individualise the best combination of the sequence and type of breast reconstruction and RT [V, A].

**RT doses and fractionation:** Doses used for local and/or regional adjuvant irradiation have traditionally been 45–50 Gy in 25–28 fractions of 1.8–2.0 Gy with a typical boost dose of 10–16 Gy in 2 Gy single doses. Shorter fractionation schemes (e.g. 15–16 fractions with 2.5–2.67 Gy single dose) have shown similar effectiveness and comparable side-effects [I, A] [116–118]. These data are not separately validated in young patients and in patients with mastectomy and/or additional regional RT, as these patients were either not included or underrepresented in the relevant trials. As hypofractionation in many places is being introduced for all patient subgroups, the authors advise to carefully monitor, evaluate and compare outcomes in patients treated with hypofractionation outside of the inclusion criteria of the published studies. Further hypofractionation (up to five fractions in 1 week) is currently the subject of an ongoing prospective clinical trial.

#### **Recommendation:**

- Moderate hypofractionation schedules (15–16 fractions of  $\leq 3$  Gy/fraction) are recommended for routine postoperative RT of breast cancer [I, A].

**RT for in situ malignancy (intraepithelial neoplasia):** WBRT after BCS for DCIS decreases the risk of local recurrence, with survival equal to that after mastectomy [I, A] [119]. The decrease in the risk of local recurrence by RT is evident in all subtypes of DCIS. WBRT is recommended in the majority of women with DCIS, on the basis of the substantial reduction in disease recurrence leading to a higher rate of long-term breast conservation and the inability to define subsets of women who do not benefit from RT [120–122]. However, in some patients with low-risk DCIS (tumour size  $< 10$  mm, low/intermediate nuclear grade, adequate surgical margins), the risk of local recurrence following excision only is low and omitting radiation can be an option. Tumour bed boost can be considered for patients at higher risk for local failure [III, B]. APBI should only be considered for highly selected low-risk patients, provided that patients are monitored [123]. Total mastectomy with clear margins in DCIS is curative, and PMRT is not recommended. RT is not warranted for lobular intraepithelial neoplasia, with the exception of the pleomorphic subtype that should be considered from a treatment-perspective point of view as high-grade DCIS.

#### **Recommendations:**

- WBRT is recommended for the majority of women with DCIS treated with BCS [I, A].
- In patients with low-risk DCIS, omitting radiation is an option [V, B].
- Tumour bed boost can be considered for patients at higher risk for local failure [III, B].
- PMRT is not recommended for DCIS [I, E].

## **(Neo)Adjuvant systemic treatment**

**General recommendations.** The decision on (neo)adjuvant systemic treatment should be based on the predicted sensitivity to particular treatment types, the benefit from their use and an individual's risk of relapse (Tables 2–4, Figure 2) [V, A]. The final decision should also incorporate the predicted treatment short- and long-term toxicities, the patient's biological age, general health status, comorbidities and preferences [V, A]. Adjuvant systemic therapy should be started without undue delays, as data show an important decrease in efficacy when it is administered  $> 12$  weeks after surgery [I, A] [124].

ET should be used in all luminal-like cancers [I, A]. Indications for ChT within this subtype depend on the individual's risk of relapse, taking into account the tumour burden and features suggestive of biological aggressiveness (grade, proliferation, vascular invasion), presumed responsiveness to ET and patient preferences [I, A]. Features associated with lower endocrine responsiveness include low steroid receptor expression, lack of PgR expression, high tumour grade and high expression of proliferation markers.

The majority of luminal A-like cancers do not require ChT, except those with high disease burden [I, A]. Data from neoadjuvant studies have demonstrated that ChT sensitivity depends on the intrinsic phenotype, the highest being for HER2-positive (when combined with anti-HER2 therapy) and TNBC. However, even assuming the relative benefit would be similar, the absolute benefit derived from adjuvant ChT varies substantially, depending on the individual risk of relapse, which is determined by both the biology and the burden of the disease. For example, the absolute benefit of adjuvant ChT for a low-burden, luminal A-like breast cancer is extremely small. When balanced against the known short- and long-term side-effects, ChT is not recommended in this setting.

Several decision-making tools such as PREDICT Plus, NPI and Adjuvant! Online (the last is currently temporarily unavailable) exist to help predict recurrence risk and potential benefit from systemic treatments [33–35]. In cases of uncertainty regarding indications for adjuvant ChT, urokinase plasminogen activator–plasminogen activator inhibitor 1 (uPA-PAI1) [I, A] [125] or gene expression assays, such as MammaPrint, Oncotype DX, Prosigna, Endopredict or Breast Cancer Index, may be used (see LoE/GoR recommendations in 'Diagnosis and pathology/molecular biology' section and in Table 4). These assays can help determine the individual's recurrence risk and potentially predict the benefit of ChT in general [I, A] [19, 126], albeit not for specific cytotoxic agents. Genomic tests are not recommended for patients with:

- clinicopathological low-risk tumours (pT1a, pT1b, G1, ER high, pN0); and/or
- patients with comorbid health conditions who are not candidates for adjuvant ChT; and/or
- special types of luminal-like breast cancer such as low-grade encapsulated papillary carcinoma and solid papillary carcinoma (which should be considered as DCIS for the sake of treatment decisions [127]), and invasive tubular carcinoma may be treated with locoregional treatment only, as the prognosis is excellent; or

**Table 3. Systemic treatment recommendations for early breast cancer subtypes**

Subtype	Recommended therapy	Comments
Luminal A-like	ET alone in the majority of cases	Consider ChT if high tumour burden ( $\geq 4$ LNs, T3 or higher)
Luminal B-like (HER2-negative)	ChT followed by ET for the majority of cases	
Luminal B-like (HER2-positive)	ChT + anti-HER2 followed by ET for all patients	If contraindications for the use of ChT, one may consider ET + anti-HER2 therapy, although no randomised data exist
HER2-positive (non-luminal)	ChT + anti-HER2	
Triple-negative (ductal)	ChT	

For special histological types, the authors recommend following the St Gallen recommendations [23] that propose ET for endocrine-responsive histologies (cribriform, tubular and mucinous), ChT for high-risk endocrine-nonresponsive histologies (medullary, metaplastic) and no systemic therapy for low-risk endocrine nonresponsive histologies (adenoid cystic and apocrine).  
ChT, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; LN, lymph node.

- 1–3 involved nodes coexisting with many other high-risk factors, or with  $\geq 4$  positive nodes for whom adjuvant ChT is indicated [126].

#### Recommendations:

- Adjuvant systemic treatment should preferably start within 3–6 weeks after surgery [I, A] and neoadjuvant systemic therapy should start as soon as diagnosis and staging is completed (ideally within 2–4 weeks) [V, A].
- The decision on adjuvant systemic therapies should be based on an individual's risk of relapse (which depends on tumour burden and tumour biology), the predicted sensitivity to particular types of treatment, the benefit from their use and their associated short- and long-term toxicities, the patient's biological age, general health status, comorbidities and preferences [V, A].
- All luminal-like cancers should be treated with ET [I, A].
- Most luminal A-like tumours do not require ChT, except those with high disease burden [I, A].
- ChT use in luminal B-like HER2-negative patients depends on individual risk of recurrence, presumed responsiveness to ET and patient preferences [V, A].
- In cases of uncertainty regarding indications for adjuvant ChT (after consideration of all clinical and pathological factors), expression of uPA-PAI1 [I, A] or gene expression assays, such as MammaPrint [I, A], Oncotype DX [I, A], Prosigna, Endopredict or Breast Cancer Index, can be used.
- Luminal B-like HER2-positive tumours should be treated with ChT, ET and anti-HER2 therapy [I, A]. In selected low-risk patients (T1abN0), the combination of anti-HER2 therapy and ET alone may be used [III, B].
- Patients with TNBC should receive ChT, with the possible exception of low-risk 'special histological subtypes' such as secretory or adenoid cystic carcinomas or very early (T1aN0) tumours [I, A].
- HER2-positive cancers should be treated with ChT plus anti-HER2 therapy, with the possible exception of selected cases with very low risk, such as T1aN0 tumours [I, A].

- ChT should not be used concomitantly with ET [II, D], with the exception of gonadotropin-releasing hormone (GnRH) analogues used for ovarian protection [I, A] [128].
- Anti-HER2 therapy may routinely be combined with non-anthracycline-based ChT, ET and RT [I, A].
- RT may be delivered safely during anti-HER2 therapy, ET and non-anthracycline, non-taxane-based ChT [III, B].
- If ChT and RT are to be used, ChT should usually precede RT [V, A].

#### Recommendations:

- For premenopausal women, tamoxifen for 5–10 years is a standard of care [I, A].
- In patients becoming postmenopausal during the first 5 years of tamoxifen, a switch to letrozole should be considered, depending on predicted risk of late recurrence [II, A].
- In patients requiring ChT and who recover menses (in particular in the first year but acceptable within the first 2 years), addition of OFS to ET should be strongly considered [I, A].
- The role of replacing tamoxifen with an AI can be considered in high-risk patients; if used, it mandates effective OFS, with regular biochemical control of oestrogen levels [I, A].
- The role of OFS in patients <35 years not requiring ChT is not clear, but inferior outcomes of young luminal early breast cancer patients suggest the use of the most effective ET (i.e. combination with OFS) [III, A].
- OFS during ChT provides some protection of ovarian function and has no negative impact on oncological outcomes; thus, it should be proposed to patients [I, A]. It should not, however, be the sole fertility preservation method used, in case of desired pregnancy [I, A].

**Postmenopausal patients:** AIs compared with tamoxifen allow for about 4% absolute benefit in DFS, with no significant impact on OS (1%–2%, depending on the choice of an upfront or sequential strategy) [139–141]. DFS benefit was demonstrated for their use upfront (non-steroidal AI and exemestane), after 2–

Table 4. Summary of biomarkers used in treatment decision making

Biomarker	Method	Use	LoE	GoR
ER	IHC Positive if $\geq 1\%$	Essential to the characterisation of the IHC luminal-like group Poor prognostic marker if negative Predictive marker for ET Mandatory for ET prescription	I	A
PgR	IHC Positive if $\geq 1\%$	If negative tumour classified as IHC luminal B-like Strong poor prognostic marker if negative Predictive marker for ET	I	A
HER2	IHC Positive if $>10\%$ complete membrane staining (3+) ISH <u>Single probe</u> if $HER2 \geq 6$ copies <u>Dual probe</u> Positive if $HER2/CEP17 \geq 2$ and $HER2$ copies $\geq 4$ Or $HER2/CEP17 < 2$ and $HER2$ copies $\geq 6$	Essential to the characterisation of: HER2-enriched (ER-negative) Luminal B-like, HER2-positive Prognostic marker Predictive marker for anti-HER2 treatment Mandatory for anti-HER2 therapy regardless of treatment line	I  I	A  A
Ki67	IHC No final consensus on cut-off but values $<10\%$ are considered low and $>30\%$ are considered high <sup>a</sup>	Absence of international consensus for scoring and threshold Prognostic value in ER-positive, HER2-negative tumours (primary tumours and post-neoadjuvant residual tumour) Absence of prognostic value in HER2-positive or triple-negative tumours Predictive of response to neoadjuvant ET <sup>b</sup> Predictive of response to neoadjuvant ChT If elevated, ChT is often prescribed in ER-positive, HER2-negative tumours Part of the IHC definition of luminal-like tumours Ki67 low, luminal A-like Ki67 high, luminal B-like	I  I  I  Expert opinion  Expert opinion  II	A  A  A  A  A  B
Intrinsic subtypes	Gene expression profile, N-Counter <sup>TM</sup> technology	Prognostic Predictive: Different responses to neoadjuvant ChT and anti-HER2 therapy according to the subtype	II and III  I	B  B
First-generation signatures (Mamma Print, Oncotype DX)	Gene expression profile, RT-PCR	For ER-positive, HER2-negative tumours Prognostic (Neo)Adjuvant ChT is indicated if high risk or high score	I	A

Continued

Table 4. Continued

Biomarker	Method	Use	LoE	GoR
Second-generation signatures (Prosigna <sup>®</sup> , Endopredict <sup>®</sup> )	N-Counter <sup>™</sup> technology, RT-PCR	Can be carried out in biopsy or surgical specimen For ER-positive, HER2-negative tumours, include T size and N status in their final score Prognostic (Neo)Adjuvant ChT is indicated if high risk or high score Can be carried out in biopsy or surgical specimen	I	B

<sup>a</sup>According to the International Ki67 Working Group Guidelines [215].

<sup>b</sup>A decrease in Ki67 expression during neoadjuvant ET is highly predictive of response.

ChT, chemotherapy; ER, oestrogen receptor; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridisation; LoE, level of evidence; PgR, progesterone receptor; RT-PCR, reverse transcription polymerase chain reaction.

3 years of tamoxifen (non-steroidal AI and exemestane) or as extended adjuvant therapy, after 5 years of tamoxifen (letrozole and anastrozole) [142–144]. Numerous studies demonstrated an advantage of 10 years rather than 5 years of ET, although the optimal duration and regimen of adjuvant ET are currently unknown and there is a minimal benefit for the use of AIs for more than 5 years [I, C] [142, 145].

The use of tamoxifen is associated with an increased risk of thromboembolic complications and endometrial hyperplasia (including a small risk of endometrial cancer). Caution should be exercised in patients with risk factors for these conditions, and appropriate diagnostic tests should be carried out in the presence of symptoms suggestive of these complications. Patients on tamoxifen should be advised to avoid the use of strong and moderate CYP2D6 inhibitors (although there are no unequivocal data on their detrimental effects). If such drugs cannot be replaced, a switch to alternative treatment, i.e. AIs, should be considered [IV, B] [146, 147]. The study of CYP2D6 polymorphisms as a decision aid regarding the use of adjuvant tamoxifen is not proven and should not be done outside a clinical trial.

Patients undergoing OFS and those taking AIs are at an increased risk of bone loss and musculoskeletal pain often affecting their treatment compliance.

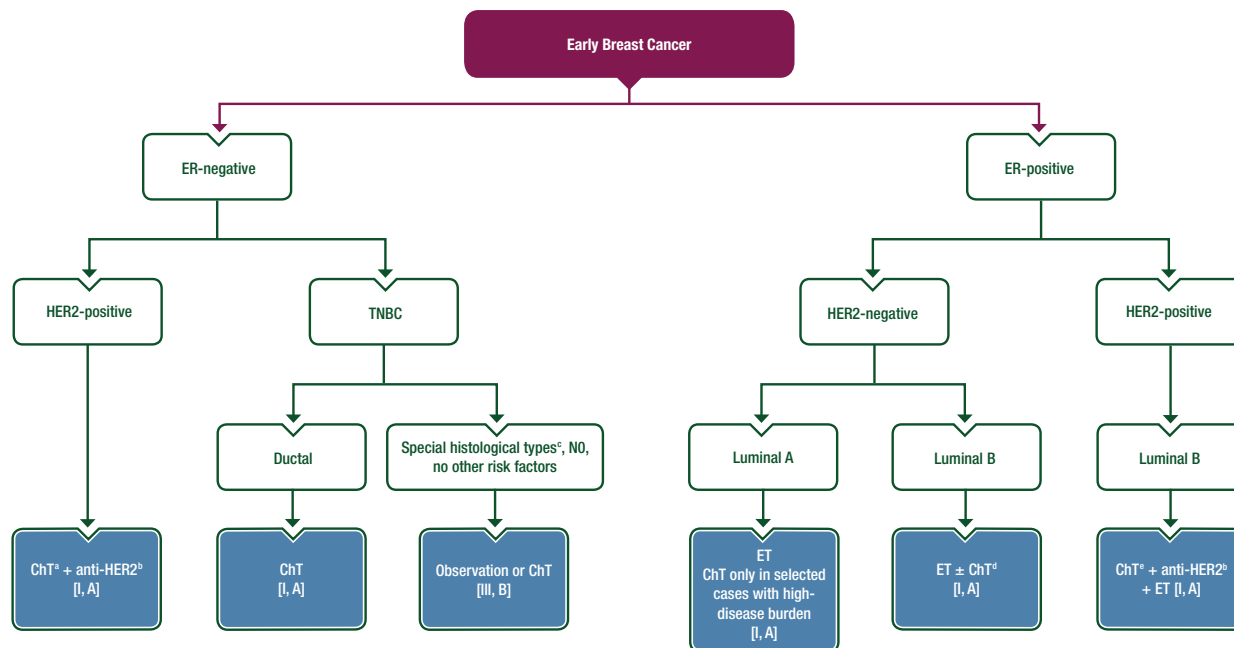
#### Recommendations:

- For postmenopausal women, AIs (both non-steroidal and steroidal) and tamoxifen are considered standard treatments [I, A].
- AIs can be used upfront (non-steroidal AI and exemestane), after 2–3 years of tamoxifen (non-steroidal AI and exemestane) or as extended adjuvant therapy, after 5 years of tamoxifen (letrozole and anastrozole) [I, A].
- Extended adjuvant therapy should be discussed with all patients, except those with a very low risk of relapse [I, A], but the optimal duration and regimen of adjuvant ET are currently unknown. There is only a minimal benefit for the use of AIs for more than 5 years [I, C].

- Patients undergoing OFS and those taking AIs should be advised to have adequate calcium and vitamin D3 intake and undergo periodic assessment of bone mineral density [by dual energy X-ray absorption (DEXA) scan] [I, A].
- The study of CYP2D6 polymorphisms as a decision aid regarding the use of adjuvant tamoxifen is not proven and should not be done [I, E].

**Chemotherapy.** ChT is recommended in the vast majority of triple-negative, HER2-positive breast cancers and in high-risk luminal-like HER2-negative tumours [I, A]. The absolute benefit of ChT is more pronounced in ER-negative tumours [148, 149]. The most frequently used regimens contain anthracyclines and/or taxanes, although in selected patients cyclophosphamide/methotrexate/5-fluorouracil (CMF) may still be used. Four cycles of doxorubicin and cyclophosphamide (AC) are considered to have equal efficacy to 6 cycles of CMF. There is no place for routine use of 6 cycles of three-drug anthracycline-based regimens, possibly except in patients with strong contraindications to taxanes [I, D] [150, 151]. Randomised phase III data have shown that 5-fluorouracil (5-FU) can be dropped from anthracycline-based regimens because it does not add efficacy and it increases toxicity; therefore, the standard anthracycline-based regimens are AC or epirubicin plus cyclophosphamide (EC) [I, A] [152].

The addition of taxanes slightly improves the efficacy of ChT, independently of age, nodal status, tumour size or grade, steroid receptor expression or tamoxifen use, but at the cost of increased non-cardiac toxicity; most importantly it allows for the use of a lower total dose of anthracyclines through the use of sequential regimens [I, A] [150, 153]. Sequential use of anthracyclines and taxanes is superior to concomitant use [154] and is also much less toxic [I, A]. Some data suggest that a taxane/anthracycline sequence may be slightly more effective than the traditionally used anthracycline/taxane order [155] but both are acceptable [I, A]. Overall, ChT regimens based on anthracyclines and taxanes reduce breast cancer mortality by about one-third [129, 150]. Non-



**Figure 2.** (Neo)-adjuvant systemic treatment choice by marker expression and intrinsic phenotype.

<sup>a</sup>With possible exception of selected cases with very low risk T1abN0.

<sup>b</sup>Anti-HER2: trastuzumab ± pertuzumab.

<sup>c</sup>Adenoid cystic or apocrine, secretory carcinoma, low-grade metaplastic carcinoma.

<sup>d</sup>Depending on level of ER and PgR expression, proliferation, genomically assessed risk, tumour burden and/or patient preference.

<sup>e</sup>Except for very low-risk patients T1abN0 for whom ET/anti-HER2 therapy alone can be considered.

ChT, chemotherapy; ER, oestrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; N0, node-negative; PgR, progesterone receptor; TNBC, triple-negative breast cancer.

anthracycline, taxane-based regimens, such as 4 cycles of docetaxel and cyclophosphamide (TC), may be used as an alternative to 4 cycles of anthracycline-based ChT [I, A] [156], although such an approach has proven inferior to a combination of anthracyclines and taxanes [157]. No robust, prospective randomised data exist on the use of platinum compounds in the adjuvant setting, either in unselected triple-negative tumours or in *BRCA1/2* mutation carriers and they cannot therefore be recommended [V, E].

The advantages and potential complications of the use of implanted devices (like Port-a-Cath) providing venous access for administration of systemic therapy should be discussed with all patients (for detail, please refer to the ESMO Clinical Practice Guidelines on central venous access in oncology [158]).

High-dose ChT with stem cell support should not be used [I, E].

**Recommendations:**

- ChT should be administered for 12–24 weeks (4–8 cycles) [I, A].
- Sequential anthracycline/taxane-based regimen is the standard for the majority of patients [I, A].
- In selected lower-risk patients, 4 cycles of anthracycline- or taxane-based ChT or CMF may be used [II, B].
- Non-anthracycline regimens may be used in patients at risk of cardiac complications [I, A].
- Anthracycline-based regimens should not include 5-FU (EC or AC is standard) [I, A].

- Platinum compounds should not be used routinely in the adjuvant setting [V, E].
- The use of dose-dense schedules [with granulocyte colony-stimulating factor (G-CSF) support] should be considered, particularly in highly proliferative tumours [I, A] [159, 160].

**Anti-HER2 therapy.** Trastuzumab combined with ChT in patients with HER2 overexpression/amplification approximately halves the recurrence and mortality risk, compared with ChT alone, translating into a 10% absolute improvement in long-term DFS and 9% increase in 10-year OS [I, A] [161–163] (see Figure 3). Trastuzumab is approved in patients with node-positive disease and in N0 patients with tumours >1 cm. Due to the relatively high relapse risk, even in patients with N0 tumours <1 cm, it should also be considered in this patient group, particularly in ER-negative disease [IV, B] [164]. If a HER2 test result is ultimately deemed to be equivocal, even after reflex testing with an alternative assay, HER2-targeted therapy may also be considered, although the true benefit from trastuzumab in those patients is still unknown [V, B].

In most studies, trastuzumab was administered for 1 year, although in the FinHER trial a similar improvement was obtained with only 9 weeks of treatment [II, A] [165]. No additional benefit was demonstrated for 2-year trastuzumab administration in the HERA trial [166]. A few studies compared shorter versus standard 12-month administration of trastuzumab, but only the largest Persephone trial was able to show the non-inferiority of

Downloaded from https://academic.oup.com/annonc/article-abstract/30/8/1194/5499075 by guest on 13 December 2019

the shorter 6-month regimen, although this could not be demonstrated in the other studies [167–170]. Therefore, a duration of 1 year remains the standard, although in highly selected low-risk patients, who receive anthracycline/taxane-based ChT, shortening trastuzumab duration to 6 months may be discussed [I, B]. Further data and longer follow-up are needed and several questions are still open regarding de-escalation of anti-HER2 therapy, ChT or both in HER2-positive early breast cancer. Trastuzumab is usually well-tolerated, although cardiac dysfunction may occur, usually reversible. Baseline cardiac function (expressed by the left ventricular ejection fraction) is indispensable before the start of treatment and periodic monitoring of cardiac function (usually every 3–4 months) during treatment is necessary.

Due to its cardiotoxicity, trastuzumab should not be routinely administered concomitantly with anthracyclines [I, D]. Combination with taxanes is safe and has been demonstrated to be more effective than sequential treatment [I, A] [162]. Trastuzumab may also be safely combined with RT and ET.

In the neoadjuvant setting, dual anti-HER2 blockade associated with ChT (trastuzumab/lapatinib, trastuzumab/pertuzumab) has led to improvements in the pCR rate when compared with ChT associated with one anti-HER2 agent [171–173]. However, this did not translate into statistically significant improvement in long-term outcomes for the combination of trastuzumab/lapatinib, and such a treatment cannot be recommended [I, E] [174]. For the trastuzumab/pertuzumab combination, after reviewing potential risks and benefits (including the financial impact), in selected higher-risk cases it is an acceptable option as PST [II, B]. In the adjuvant setting, the addition of pertuzumab resulted in a very small (0.9%) improvement in invasive DFS [175] in the intention-to-treat (ITT) population and a higher benefit (2.5%) in the high-risk population (defined as N-positive or ER-negative), leading to its approval in the latter setting by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA). This combination can therefore be considered in high-risk patients (as per above definition) [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: B] (see Table 5). It is currently unknown if dual blockade in the neoadjuvant setting should be continued for a total of 1 year in patients for whom a pCR is achieved or if this treatment should be stopped at surgery. For this reason, and until new trials are concluded, it is recommended to decide on the administration of 1 year of trastuzumab/pertuzumab based on the risk assessment at diagnosis; the treatment may start before or after the surgery, in accordance with the approval wording by the regulators.

For patients with HER2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant ChT combined with anti-HER2 therapy, substitution of adjuvant trastuzumab with trastuzumab emtansine (T-DM1) decreases the risk of recurrence of invasive breast cancer or death by 50% and is recommended, once approved and where available [176].

Extended adjuvant anti-HER2 therapy with neratinib in patients who completed 1 year of trastuzumab demonstrated additional improvement in DFS, in particular in the ER-positive/HER2-positive subgroup, albeit at the cost of significant toxicity, mostly diarrhoea [177]. It can be considered in some selected high-risk patients, with appropriate diarrhoea prophylaxis and management [I, B; ESMO-MCBS v1.1 score: A]. It is unknown,

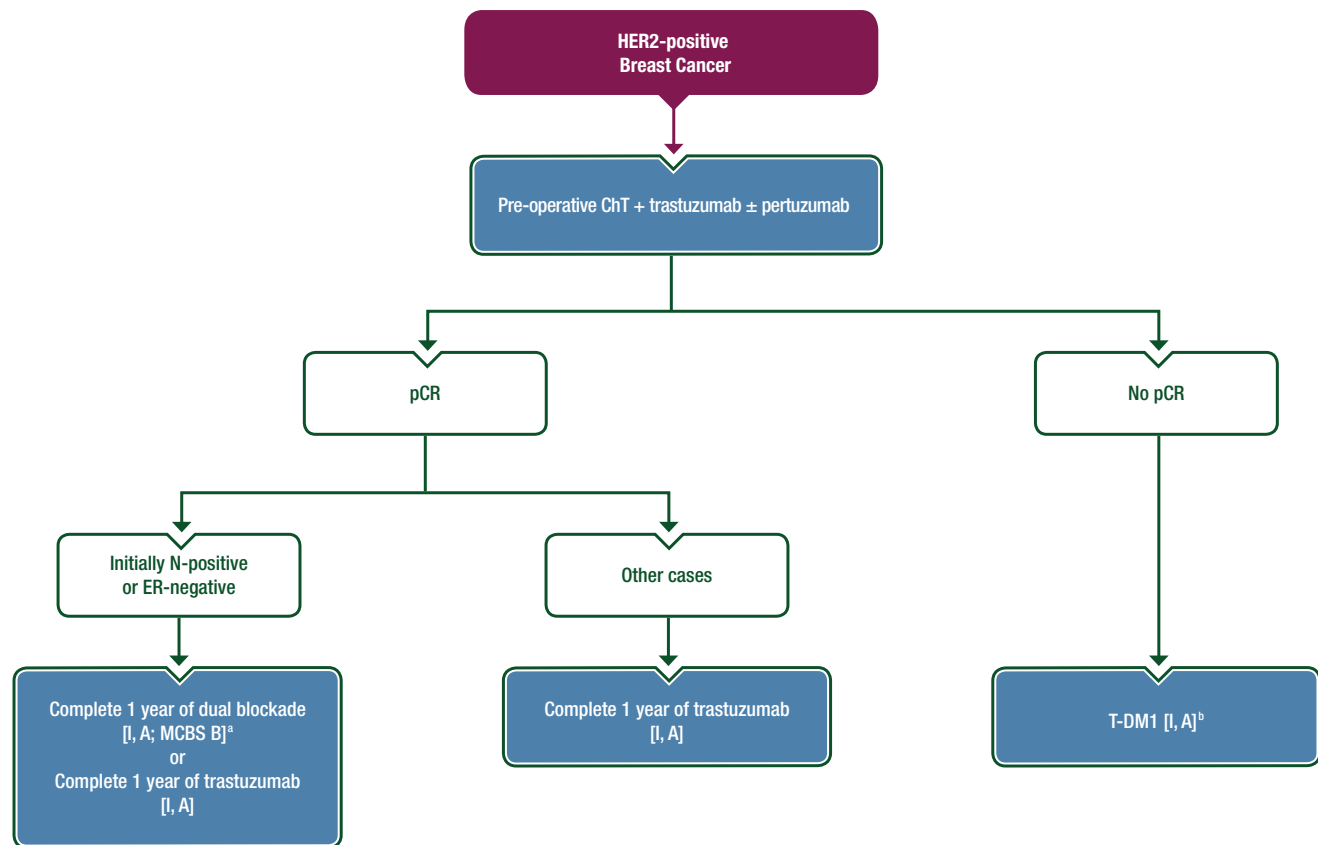
however, if this benefit is maintained for patients who have previously received dual blockade with trastuzumab/pertuzumab.

In small, node-negative, mostly ER-positive, HER2-positive tumours with no other risk factors, the combination of single-agent paclitaxel and trastuzumab provided excellent outcomes in a single-arm phase II study [178]. No randomised data exist to support omission of ChT in this group. However, in cases of contraindications for ChT or patient refusal, it is acceptable to offer the combination of targeted agents (ET and trastuzumab) [V, A].

#### Recommendations:

- (Neo)Adjuvant trastuzumab is highly effective and should be given to all HER2-positive early breast cancer patients who do not have contraindications for its use, with the possible exception of selected cases with very low risk, such as T1aN0 tumours [I, A].
- If a HER2 test result is ultimately deemed to be equivocal, even after reflex testing with an alternative assay, HER2-targeted therapy may also be considered [V, B].
- One year of (neo)adjuvant trastuzumab remains a standard for the vast majority of HER2-positive patients [I, A].
- In highly selected, low-risk patients who receive anthracycline/taxane-based ChT, shortening trastuzumab duration to 6 months may be discussed [I, A].
- Trastuzumab should usually not be given concomitantly with anthracycline-based ChT [I, D]; it can be safely combined with non-anthracycline-based ChT (i.e. taxanes) and its concomitant use is more effective than sequential treatment [I, A].
- Regular cardiac monitoring is mandatory before starting and during trastuzumab treatment [I, A].
- Dual blockade with trastuzumab/lapatinib has not led to improved long-term outcomes and cannot therefore be recommended [I, E].
- Dual blockade with trastuzumab/pertuzumab can be considered in high-risk patients, defined as N-positive or ER-negative, for the duration of 1 year, starting before or after surgery [I, A; ESMO-MCBS v1.1 score: B].
- In cases of residual invasive disease after completion of neoadjuvant ChT combined with anti-HER2 therapy, adjuvant trastuzumab should be replaced by adjuvant T-DM1, once approved and where available [I, A].
- Extended anti-HER2 therapy with neratinib may be considered in selected high-risk patients, not previously treated with dual blockade, and with appropriate diarrhoea prophylaxis and management [I, B; ESMO-MCBS v1.1 score: A].

**Primary (neoadjuvant) systemic therapy.** In locally advanced and large ‘operable’ cancers, in particular when mastectomy is required due to tumour size, PST is recommended to decrease the extent of surgery needed [I, A]. In operable cases, the timing of treatment (pre- versus postoperative) has no effect on long-term outcomes, except a possible small increase in locoregional recurrences in the PST group, but without impact on survival [II, A] [153, 179–181]. Additionally, PST allows for assessment of therapy response, which is of well-established prognostic value and may guide choice of postoperative treatment. Thus, in subtypes highly sensitive to ChT, such as triple-negative and HER2-positive, a



**Figure 3.** HER2-positive breast cancer treatment.

<sup>a</sup>ESMO-MCBS v1.1 scores for new therapies/indications approved by the EMA since 1 January 2016. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.

<sup>b</sup>Not yet EMA-approved.

ChT, chemotherapy; EMA, European Medicines Agency; ER, oestrogen receptor; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; HER2, human epidermal growth factor receptor 2; N-positive, node-positive; pCR, pathological complete response; T-DM1, trastuzumab emtansine.

neoadjuvant approach should be preferred, in tumours >2 cm [II, A] (see Figure 1).

All modalities (ChT, ET and targeted therapy) used in adjuvant treatment may also be used preoperatively. If ChT is used, it is recommended to deliver all planned treatment without unnecessary breaks, i.e. without dividing it into preoperative and postoperative periods, irrespective of the magnitude of tumour response [II, A]. This will increase the probability of achieving a pCR, which is a proven factor for a good prognosis. Unfortunately, there are no validated predictive markers to allow the tailoring of the regimen to the individual patient. The addition of a platinum compound (usually carboplatin) to preoperative ChT allows for an increase in the pCR rate in triple-negative tumours. Data on the effect of those compounds on long-term outcomes are conflicting, in particular in patients with deleterious *BRCA1/2* mutations [I, C] [182–185], thus strong recommendations regarding selection of patients who may benefit from addition of carboplatin cannot be given (see Figure 2).

After delivery of the standard 4–8 cycles of anthracyclines and taxanes, in the absence of pCR, addition of 6–8 cycles of capecitabine resulted in improvement of DFS and OS (in particular in triple-negative tumours) in one trial run in Asian patients [186]. Although more data are necessary in non-Asian patients, this

option may be offered to triple-negative patients who do not achieve a pCR after optimal neoadjuvant ChT [I, B]. The value of adjuvant capecitabine after the use of a platinum compound in the neoadjuvant setting is currently unknown.

ER-positive/HER2-negative carcinomas, especially of the lobular histology and luminal A-like subtype, are generally less responsive to primary ChT and may benefit more from primary ET [187]. In postmenopausal patients, primary (neoadjuvant) ET is usually given for 4–8 months before surgery or until maximum response and continued postoperatively. AIs are more effective than tamoxifen in decreasing the tumour size and facilitating less extensive surgery [I, A] [188–190]. Good response to preoperative ET, expressed by Ki67 drop or preoperative endocrine prognostic index (PEPI) score, may, in combination with other clinical factors, guide in selecting patients with favourable prognosis not requiring adjuvant ChT [191–193].

Due to paucity of data from randomised trials, preoperative ET is not routinely recommended in premenopausal patients, outside clinical trials. However, in highly selected patients with luminal A-like tumours and no indication for ChT, who are not candidates for optimal surgery, preoperative ET consisting of OFS plus an aromatase inhibitor can be considered [II, C] [194].

Table 5. ESMO-MCBS table for new therapies/indications in early breast cancer<sup>a</sup>

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score <sup>b</sup>
Pertuzumab + standard adjuvant ChT + 1 year of treatment with trastuzumab	Early breast cancer adjuvant	Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer (APHINITY: a randomised placebo-controlled phase III study) [174] Phase III NCT01358877	Placebo + standard adjuvant ChT + 1 year of treatment with trastuzumab	OS not yet reported; 0.9% improvement in 3-year iDFS (94.1% versus 93.2%) in the ITT population <sup>c</sup>	iDFS HR: 0.81 (0.66–1.00) in the ITT population <sup>c</sup>	Increased grade 3 diarrhoea (9.8% versus 3.7%)	B (Form 1)
Neratinib (1 year of oral therapy, 240 mg/day)	Early breast cancer adjuvant	Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase III trial [176] Phase III NCT00878709	1 year of oral placebo	OS not yet reported; 2.5% improvement in 5-year iDFS (90.2% versus 87.7%) in the ITT population	iDFS HR: 0.73 (0.57–0.92) in the ITT population	Increased grade $\geq 3$ diarrhoea (40% versus 2%)	A (Form 1)

<sup>a</sup>EMA approvals since January 2016.

<sup>b</sup>ESMO-MCBS version 1.1 [214]. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.

<sup>c</sup>High-risk population defined as N-positive or ER-negative; corresponds to the regulatory approval setting (by the EMA and the FDA).

ChT, chemotherapy; CI, confidence interval; EMA, European Medicines Agency; ER, oestrogen receptor; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; iDFS, invasive disease-free survival; ITT, intention to treat; N-positive, node-positive; OS, overall survival; QoL, quality of life.

**Recommendations:**

- PST should be used to reduce the extent of surgery in locally advanced and large operable cancers, in particular when mastectomy is required due to tumour size [I, A]. It should also be considered in all patients with tumours > 2 cm for which ChT is deemed necessary, in particular with triple-negative and HER2-positive subtypes [I, B].
- Drugs and drug regimens used in the preoperative setting should be selected according to rules identical to those in the postoperative setting [I, A]. A sequential regimen of anthracyclines and taxanes is recommended for the vast majority of patients [I, B].
- The addition of a platinum compound may be considered in triple-negative tumours and/or in patients with deleterious *BRCA1/2* mutations [I, C].
- If PST is used, all ChT should be delivered preoperatively [I, B].
- In high-risk, triple-negative patients not achieving pCR after standard neoadjuvant ChT, the addition of 6–8 cycles of capecitabine postoperatively may be considered [I, C].
- In postmenopausal patients with ER-positive/HER2-negative cancers requiring PST and without a clear indication for ChT, preoperative ET (4–8 months or until maximum response) should be considered and continued postoperatively [I, A].

**Bisphosphonates for early breast cancer.** Prophylactic use of bisphosphonates in women with a low-oestrogen status (postmenopausal or undergoing OFS) leads to prolongation of DFS and breast cancer-specific survival [135, 195–197]. In patients with treatment-related bone loss, bisphosphonates decrease the risk of skeletal complications [I, A] [198, 199].

**Recommendations:**

- Bisphosphonates for early breast cancer are recommended in women with low-oestrogen status (undergoing OFS or postmenopausal), especially if at high risk of relapse [I, A].
- Bisphosphonates are also recommended in patients with treatment-related bone loss [I, A].

**Treatment of elderly patients.** Due to the limited data from randomised studies, strong recommendations cannot be made regarding the use of (neo)adjuvant systemic therapies in this population. Full doses of drugs should be used, whenever feasible [V, A]. In patients suitable for standard ChT, single-agent capecitabine or docetaxel has been demonstrated to be inferior to the standard multidrug regimen (AC or CMF) [II, D] [200, 201]. In frail elderly patients, the use of a single-agent pegylated liposomal doxorubicin and metronomic cyclophosphamide plus methotrexate is feasible and demonstrates similar activity, although their efficacy in comparison to standard ChT remains unknown [II, B] [202].

A geriatric assessment should be carried out before treatment decisions; the G8 tool can be used as a screening tool to select patients needing a full geriatric assessment [II, A] [203].

**Recommendations:**

- Treatment of elderly early breast cancer patients should be adapted to biological (not chronological) age, with

consideration of less aggressive regimens in frail patients. In patients suitable for standard ChT, a standard multidrug regimen should be used [II, B].

- A geriatric assessment should be carried out before making treatment decisions [II, A].

**Treatment of male breast cancer.** The vast majority of breast cancer cases in male patients are ductal invasive carcinomas of the luminal-like type. Tamoxifen is the standard adjuvant systemic therapy [IV, A]; AIs should not be used alone in this setting, due to lower efficacy [IV, E] [189, 190]. ChT and anti-HER2 therapy indications and regimens should follow the same recommendations as those for breast cancer in female patients [IV, A] [190–191].

**Recommendations:**

- Tamoxifen is the standard adjuvant ET for male breast cancer patients [IV, A].
- If a strong contraindication exists for the use of tamoxifen, a combination of an AI plus a luteinizing hormone-releasing hormone (LHRH) agonist may be considered, but its higher toxicity must be discussed with the patient to avoid compliance issues [IV, B].
- An AI alone should not be used as adjuvant ET in male breast cancer patients [IV, E].
- ChT and anti-HER2 therapy indications and regimens should follow the same recommendations as those for breast cancer in female patients [IV, A].

**Systemic adjuvant therapy for DCIS.** In patients treated conservatively for ER-positive DCIS, both tamoxifen and AIs decrease the risk of invasive and non-invasive recurrences and reduce the incidence of second primary (contralateral) breast cancer, albeit without an effect on OS [204–206].

**Recommendations:**

- Both tamoxifen and AIs may be used after conservative local treatment of DCIS to prevent local recurrence and to decrease the risk of development of a second primary breast cancer [I, B].
- Following mastectomy for DCIS, tamoxifen or AIs might be considered to decrease the risk of contralateral breast cancer in patients who are at a high risk of new breast tumours [II, B].

## Personalised medicine

Breast cancer was the pioneer of personalised medicine in oncology. ER, PgR and HER2 status have been used for many years as predictive factors to select patients for targeted ET or anti-HER2 treatment [I, A]. In recent years, surrogate intrinsic tumour phenotypes, based on biomarker expression, have also been used for treatment individualisation [I, A]. Additionally, uPA-PAI1, a marker of tumour invasiveness, has been validated in prospective clinical trials as a prognostic marker for both node-negative and node-positive breast cancer [I, A] and can be used in treatment decision making for early breast cancer [125]. Molecular signatures for ER-positive breast cancer such as MammaPrint,

Oncotype DX, EndoPredict, Prosigna and Breast Cancer Index are commercially available and may help with (neo)adjuvant ChT decision making, in conjunction with all clinicopathological factors, in cases where decisions are challenging, such as luminal B-like/HER2-negative and node-negative/nodes 1–3-positive breast cancer [126, 192]. Results from large phase III prospective clinical trials, such as MINDACT [37], TAILORx [39] and Plan B [38] have identified molecularly defined groups of patients where adjuvant CT can be safely spared. Results from the phase III adjuvant RxPONDER trial in N-positive patients are awaited. A biomarker summary is shown in Table 4.

#### Recommendations:

- ER, PgR and HER2 status should guide all systemic treatment decisions [I, A].
- Surrogate intrinsic tumour phenotypes, based on expression of ER, PgR, HER2 and Ki67, should be used to define subpopulations of breast cancers [I, A].
- Expression of uPA-PAI1 or multigene panels, such as MammaPrint, Oncotype DX, EndoPredict, Prosigna or Breast Cancer Index, may be used in conjunction with all clinicopathological factors to guide systemic treatment decisions in patients where these decisions are challenging, such as luminal B-like/HER2-negative and node-negative/nodes 1–3-positive breast cancer [I, A].

### Follow-up, long-term implications and survivorship

The aims of follow-up are:

- to detect early local recurrences or contralateral breast cancer;
- to evaluate and treat therapy-related complications (such as menopausal symptoms, osteoporosis and second cancers);
- to motivate patients continuing adjuvant ET; and
- to provide psychological support and information in order to enable a return to normal life after breast cancer.

Ten-year survival of breast cancer exceeds 70% in most European regions, with 89% survival for local and 62% for regional disease [207]. The annual hazard of recurrence peaks in the second year after diagnosis but remains at 2%–5% in years 5–20 [208]. Patients with node-positive disease tend to have higher annual hazards of recurrence than patients with node-negative cancers. In the first years the risk of recurrence is higher in patients with ER-negative cancers, but 5–8 years after diagnosis their annual hazard of recurrence drops below the level of ER-positive tumours [III, B] [209]. Relapse of breast cancer may occur as late as >20 years after the initial diagnosis, particularly in patients with ER/PgR-positive disease [208].

Despite the fact that no randomised data exist to support any particular follow-up sequence or protocol, balancing patient needs, follow-up costs and burden is necessary [V, A]. Every visit should include a thorough history, eliciting of symptoms and a physical examination. Apart from routine mammography ± breast US, an MRI of the breast may be indicated for young patients, especially in cases of dense breast tissue and genetic or familial predispositions. US can also be considered in the follow-up of lobular invasive carcinomas [III, B]. In asymptomatic

patients, there are no data to indicate that other laboratory or imaging tests (e.g. blood counts, routine chemistry tests, chest X-rays, bone scans, liver US exams, CT scans, FDG-PET-CT) or any tumour markers such as cancer antigen 15-3 (CA15-3) or carcinoembryonic antigen (CEA) produce a survival benefit [I, A]. However, routine blood tests may be indicated as follow-up for patients on ET due to the potential side-effects of these drugs, namely in the lipid profile, although the impact of these changes on the risk of cardiovascular complications has not been fully demonstrated [V, B]. For patients on tamoxifen, an annual gynaecological examination by an experienced gynaecologist is recommended [V, B]. Routine transvaginal US is not recommended, as it leads to unacceptably high numbers of false-positive findings [210].

Very importantly, most available data for follow-up recommendations come from an era of less sophisticated diagnostic procedures and less efficacious treatment of advanced disease, and new trials are urgently needed to reassess this question. In symptomatic patients or in the case of abnormal findings on examination, appropriate tests should be carried out immediately [V, A].

In addition to adequate local and systemic treatments, epidemiological evidence points towards lifestyle factors having an effect on the prognosis of patients with breast cancer. For example, regular exercise provides functional and psychological benefits [II, B] [211] and possibly reduces the risk of recurrence. Regular exercise is therefore a relatively simple and effective recommendation that should be made to all suitable patients after treatment of breast cancer [II, B] [211]. Weight gain and obesity are likely to adversely affect the prognosis of breast cancer [212]. Nutritional counselling should be recommended as part of the survivor care for all obese patients [III, B]. The use of HRT increases the risk of recurrence and is usually contraindicated [I, D] [213].

Specialised rehabilitation facilities and services are indispensable to decrease the physical, psychological and social sequelae of breast cancer treatment. The main aims of physiotherapy should include the prevention and treatment of lymphoedema, assuring full range of movements of arm and shoulder, and prevention or correction of postural defects resulting from mastectomy. There are no data indicating that any type of physiotherapy may increase the risk of recurrence. When indicated, patients should not be denied access to rehabilitation services [I, A].

Available data, albeit with some limitations, confirm the safety of pregnancy after treatment of breast cancer. Pregnancy may be considered after completion of ChT, RT and anti-HER2 therapy; for ER-positive disease, it is also recommended to complete at least 18 months of ET. Women desiring pregnancy should be encouraged to join prospective clinical trials/registries, such as the POSITIVE trial.

There are no data to support advising patients who have undergone axillary clearance to avoid cannulation, venesection and blood pressure monitoring in the ipsilateral arm [V, D]. Prompt initiation of antibiotic treatment of potentially infected wounds on the ipsilateral arm is advised, in particular after ALND [I, A].

Follow-up cannot and should not be seen exclusively from the physical perspective. Patients often have increased levels of anxiety after the completion of treatment, when close contact with

**Table 6. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America–United States Public Health Service Grading System<sup>a</sup>)**

#### Levels of evidence

- I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
- II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
- III Prospective cohort studies
- IV Retrospective cohort studies or case–control studies
- V Studies without control group, case reports, expert opinions

#### Grades of recommendation

- A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
- B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
- C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
- D Moderate evidence against efficacy or for adverse outcome, generally not recommended
- E Strong evidence against efficacy or for adverse outcome, never recommended

<sup>a</sup>By permission of the Infectious Diseases Society of America [216].

the treatment team decreases. Depression and intense fatigue frequently occur in the months following the end of adjuvant ChT and/or RT. This is also aggravated by long-term survivorship issues involving work, family and sexuality, which are often not closely addressed during follow-up and result in some patients not being able to cope effectively. Long-term survivorship needs to be addressed as a different set of challenges and realities, to encompass the psychosocial needs of patients once treatment ends [V, A]. Follow-up clinics should focus not only on late side-effects but also on issues that deal with the long-term implications of living with breast cancer. Assessing the various QoL issues, particularly for patients under long-term ET, is an important aspect of follow-up care. The role of a specialised breast nurse (or equivalent dedicated health professional acting as a patient navigator) throughout a patient's diagnosis, treatment and follow-up is crucial [V, A]. All countries should develop the necessary educational structure and infrastructure required to provide the help of specialised breast nurses within the multidisciplinary team to all breast cancer patients [V, A].

#### Recommendations:

- Regular follow-up visits are recommended every 3–4 months in the first 2 years (every 6 months for low-risk and DCIS patients), every 6–8 months from years 3 to 5 and annually thereafter. The interval of visits should be adapted to the risk of relapse and patients' needs [V, A].
- Annual bilateral (after BCT) and/or a contralateral mammography (after mastectomy), with US and breast MRI when needed (see 'Diagnosis and pathology/molecular biology' section), is recommended [II, A].

- In asymptomatic patients, other laboratory or imaging tests (e.g. blood counts, routine chemistry tests, chest X-rays, bone scans, liver US exams, CT scans, FDG-PET-CT) or any tumour markers such as CA15-3 or CEA are not recommended [I, D].
- Regular bone density evaluation is recommended for patients on AIs or undergoing OFS [I, A].
- Patients should be encouraged towards adopting a healthy lifestyle, including diet modification and exercise [II, A].
- HRT should usually not be used [I, D].
- Patients should have unlimited access to specialised rehabilitation facilities and services [V, A].
- Long-term survivorship problems including psychological needs and issues related to work, family and sexuality should be addressed [V, A].

## Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (<http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>). The relevant literature has been selected by the expert authors. An ESMO-MCBS table with MCBS scores is included in Table 5. ESMO-MCBS v1.1 [214] was used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. Levels of evidence and grades of recommendation have been applied using the system shown in Table 6. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

## Acknowledgements

The ESMO Guidelines Committee would like to thank the ESMO Faculty and other experts who provided critical reviews of these ESMO Clinical Practice Guidelines.

## Funding

No external funding has been received for the preparation of these guidelines. Production costs have been covered by ESMO from central funds.

## Disclosure

FC has reported consultancy/research grants from Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Medscape, MacroGenics, Merck Sharp & Dohme, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME, Roche, Sanofi, Seattle Genetics and Teva; SO has reported honoraria from AstraZeneca, Chugai, Eisai, Novartis, Pfizer, Eli Lilly, Taiho and Kyowa Hakko Kirin and research grants from Daiichi Sankyo, Eisai and Taiho; FP-L has reported consultancy/honoraria from Roche, Pfizer, Novartis, AstraZeneca, Genomic

Health, Agendia, Myriad and NanoString; ITR has reported honoraria from Roche; SZ has reported travel support from Siemens AG and speaker's fees from Siemens AG and AstraZeneca; ES has reported honoraria from Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Clinigen, EGIS Pharmaceuticals, Eli Lilly, Janssen, Novartis, Pfizer, Pierre Fabre, prIME, Roche, Sandoz and Teva, travel support from Amgen, AstraZeneca, EGIS Pharmaceuticals, Novartis, Pfizer and Roche and clinical research fees from Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer, Eli Lilly, Janssen, Merck, Novartis, Pfizer, Roche and Samsung; SK and PP have declared no potential conflicts of interest.

## References

- ECIS—European Cancer Information System. <https://ecis.jrc.ec.europa.eu> (25 March 2019, date last accessed).
- Bray F, Ferlay J, Soerjomataram I. et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68(6): 394–424.
- McTiernan A. Behavioral risk factors in breast cancer: can risk be modified? *Oncologist* 2003; 8(4): 326–334.
- Autier P, Boniol M, La Vecchia C. et al. Disparities in breast cancer mortality trends between 30 European countries: retrospective trend analysis of WHO mortality database. *BMJ* 2010; 341(Aug 11): c3620.
- Allemani C, Weir HK, Carreira H. et al. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet* 2015; 385(9972): 977–1010.
- Ottini L, Palli D, Rizzo S. et al. Male breast cancer. *Crit Rev Oncol Hematol* 2010; 73(2): 141–155.
- Report on the implementation of the Council Recommendation on Cancer Screening in the European Union. <https://ecis.jrc.ec.europa.eu> (25 March 2019, date last accessed).
- Perry N, Broeders M, de Wolf C. et al. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition—summary document. *Ann Oncol* 2007; 19(4): 614–622.
- European guidelines for breast cancer screening and diagnosis. <https://publications.europa.eu/s/jPcX> (25 March 2015, 2019, date last accessed).
- Gotzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2011; 1: CD001877.
- Lauby-Secretan B, Scoccianti C, Loomis D. et al. Breast-cancer screening—viewpoint of the IARC Working Group. *N Engl J Med* 2015; 372(24): 2353–2358.
- Independent UK, Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012; 380(9855): 1778–1786.
- Warner E, Messersmith H, Causer P. et al. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. *Ann Intern Med* 2008; 148(9): 671–679.
- Sardanelli F, Boetes C, Borisch B. et al. Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. *Eur J Cancer* 2010; 46(8): 1296–1316.
- Lakhani SR, Ellis IO, Schnitt SJ. et al. WHO Classification of Tumours of the Breast. WHO Classification of Tumours, Vol. 4, 4th edition. Geneva: IARC Press 2012.
- Giuliano AE, Connolly JL, Edge SB. et al. Breast cancer—major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017; 67(4): 290–303.
- Hammond ME. ASCO-CAP guidelines for breast predictive factor testing: an update. *Appl Immunohistochem Mol Morphol* 2011; 19(6): 499–500.
- Wolff AC, Hammond MEH, Allison KH. et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *J Clin Oncol* 2018; 36(20): 2105–2122.
- Duffy MJ, Harbeck N, Nap M. et al. Clinical use of biomarkers in breast cancer: updated guidelines from the European Group on Tumor Markers (EGTM). *Eur J Cancer* 2017; 75: 284–298.
- Penault-Llorca F, Radosevic-Robin N. Ki67 assessment in breast cancer: an update. *Pathology* 2017; 49(2): 166–171.
- Mann GB, Fahey VD, Feleppa F, Buchanan MR. Reliance on hormone receptor assays of surgical specimens may compromise outcome in patients with breast cancer. *J Clin Oncol* 2005; 23(22): 5148–5154.
- Chen X, Yuan Y, Gu Z, Shen K. Accuracy of estrogen receptor, progesterone receptor, and HER2 status between core needle and open excision biopsy in breast cancer: a meta-analysis. *Breast Cancer Res Treat* 2012; 134(3): 957–967.
- Goldhirsch A, Winer EP, Coates AS. et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol* 2013; 24(9): 2206–2223.
- Dai X, Li T, Bai Z. et al. Breast cancer intrinsic subtype classification, clinical use and future trends. *Am J Cancer Res* 2015; 5(10): 2929–2943.
- Dieci MV, Radosevic-Robin N, Fineberg S. et al. Update on tumor-infiltrating lymphocytes (TILs) in breast cancer, including recommendations to assess TILs in residual disease after neoadjuvant therapy and in carcinoma in situ: a report of the International Immuno-Oncology Biomarker Working Group on Breast Cancer. *Semin Cancer Biol* 2018; 52 (Pt 2): 16–25.
- Wein L, Savas P, Luen SJ. et al. Clinical validity and utility of tumor-infiltrating lymphocytes in routine clinical practice for breast cancer patients: current and future directions. *Front Oncol* 2017; 7: 156.
- Loi S, Drubay D, Adams S. et al. Tumor-infiltrating lymphocytes and prognosis: a pooled individual patient analysis of early-stage triple-negative breast cancers. *J Clin Oncol* 2019; 37(7): 559–569.
- National Comprehensive Cancer Network guidelines for treatment of breast cancer. [http://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf) (12 February 2019, date last accessed).
- Paluch-Shimon S, Cardoso F, Sessa C. et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Ann Oncol* 2016; 27(Suppl 5): v103–v110.
- Krop I, Ismaila N, Andre F. et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *J Clin Oncol* 2017; 35(24): 2838–2847.
- Koolen BB, Vrancken Peeters MJ, Aukema TS. et al. 18F-FDG PET/CT as a staging procedure in primary stage II and III breast cancer: comparison with conventional imaging techniques. *Breast Cancer Res Treat* 2012; 131(1): 117–126.
- Robertson IJ, Hand F, Kell MR. FDG-PET/CT in the staging of local/regional metastases in breast cancer. *Breast* 2011; 20(6): 491–494.
- Blamey RW, Pinder SE, Ball GR. et al. Reading the prognosis of the individual with breast cancer. *Eur J Cancer* 2007; 43(10): 1545–1547.
- Ravdin PM, Siminoff LA, Davis GJ. et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. *J Clin Oncol* 2001; 19(4): 980–991.
- Wishart GC, Bajdik CD, Azzato EM. et al. A population-based validation of the prognostic model PREDICT for early breast cancer. *Eur J Surg Oncol* 2011; 37(5): 411–417.
- Harbeck N, Sotlar K, Wuerstlein R, Doisneau-Sixou S. Molecular and protein markers for clinical decision making in breast cancer: today and tomorrow. *Cancer Treat Rev* 2014; 40(3): 434–444.
- Cardoso F, van't Veer LJ, Bogaerts J. et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med* 2016; 375(8): 717–729.
- Nitz U, Gluz O, Christgen M. et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West

- German Study Group (WSG) PlanB trial. *Breast Cancer Res Treat* 2017; 165(3): 573–583.
39. Sparano JA, Gray RJ, Makower DF et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med* 2018; 379(2): 111–121.
  40. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Inst* 2009; 101(21): 1446–1452.
  41. Wazir U, Mokbel K. Emerging gene-based prognostic tools in early breast cancer: first steps to personalised medicine. *World J Clin Oncol* 2014; 5(5): 795–799.
  42. Drukker CA, Bueno-de-Mesquita JM, Retel VP et al. A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study. *Int J Cancer* 2013; 133(4): 929–936.
  43. Hall PS, Smith A, Hulme C et al. Value of information analysis of multi-parameter tests for chemotherapy in early breast cancer: the OPTIMA prelim trial. *Value Health* 2017; 20(10): 1311–1318.
  44. Petkov VI, Miller DP, Howlader N et al. Breast-cancer-specific mortality in patients treated based on the 21-gene assay: a SEER population-based study. *NPJ Breast Cancer* 2016; 2: 16017.
  45. Esserman LJ, Yau C, Thompson CK et al. Use of molecular tools to identify patients with indolent breast cancers with ultralow risk over 2 decades. *JAMA Oncol* 2017; 3(11): 1503–1510.
  46. Harris LN, Ismaila N, McShane LM, Hayes DF. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline summary. *J Oncol Pract* 2016; 12(4): 384–389.
  47. Bossuyt V, Provenzano E, Symmans WF et al. Recommendations for standardized pathological characterization of residual disease for neo-adjuvant clinical trials of breast cancer by the BIG-NABCG collaboration. *Ann Oncol* 2015; 26(7): 1280–1291.
  48. Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014; 384(9938): 164–172.
  49. Symmans WF, Peintinger F, Hatzis C et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol* 2007; 25(28): 4414–4422.
  50. Cardoso F, Cataliotti L, Costa A et al. European Breast Cancer Conference manifesto on breast centres/units. *Eur J Cancer* 2017; 72: 244–250.
  51. Wilson AR, Marotti L, Bianchi S et al. The requirements of a specialist breast centre. *Eur J Cancer* 2013; 49(17): 3579–3587.
  52. Senkus E, Gomez H, Dirix L et al. Attitudes of young patients with breast cancer toward fertility loss related to adjuvant systemic therapies. *EORTC Study 10002 BIG 3-98. Psychooncology* 2014; 23(2): 173–182.
  53. Lee SJ, Schover LR, Partridge AH et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006; 24(18): 2917–2931.
  54. Paluch-Shimon S, Pagani O, Partridge AH et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). *Breast* 2017; 35: 203–217.
  55. Cardoso F, Loibl S, Pagani O et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. *Eur J Cancer* 2012; 48(18): 3355–3377.
  56. Peccatori FA, Azim HA Jr, Orecchia R et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; 24(Suppl 6): vi160–vi170.
  57. Association of Breast Surgery at Baso 2009. Surgical guidelines for the management of breast cancer. *Eur J Surg Oncol* 2009; 35(Suppl 1): 1–22.
  58. Alborno CR, Matros E, Lee CN et al. Bilateral mastectomy versus breast-conserving surgery for early-stage breast cancer: the role of breast reconstruction. *Plast Reconstr Surg* 2015; 135(6): 1518–1526.
  59. Hwang ES, Lichtensztajn DY, Gomez SL et al. Survival after lumpectomy and mastectomy for early stage invasive breast cancer: the effect of age and hormone receptor status. *Cancer* 2013; 119(7): 1402–1411.
  60. van Maaren MC, de Munck L, de Bock GH et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. *Lancet Oncol* 2016; 17(8): 1158–1170.
  61. Lagendijk M, van Maaren MC, Saadatmand S et al. Breast conserving therapy and mastectomy revisited: breast cancer-specific survival and the influence of prognostic factors in 129,692 patients. *Int J Cancer* 2018; 142(1): 165–175.
  62. Gentilini OD, Cardoso MJ, Poortmans P. Less is more. Breast conservation might be even better than mastectomy in early breast cancer patients. *Breast* 2017; 35: 32–33.
  63. Schnitt SJ, Moran MS, Houssami N, Morrow M. The Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer: perspectives for pathologists. *Arch Pathol Lab Med* 2015; 139(5): 575–577.
  64. Morrow M, Van Zee KJ, Solin LJ et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. *J Clin Oncol* 2016; 34(33): 4040–4046.
  65. Houssami N, Macaskill P, Marinovich ML et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. *Eur J Cancer* 2010; 46(18): 3219–3232.
  66. Moran MS, Schnitt SJ, Giuliano AE et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *J Clin Oncol* 2014; 32(14): 1507–1515.
  67. De La Cruz L, Moody AM, Tappy EE et al. Overall survival, disease-free survival, local recurrence, and nipple-areolar recurrence in the setting of nipple-sparing mastectomy: a meta-analysis and systematic review. *Ann Surg Oncol* 2015; 22(10): 3241–3249.
  68. Wei CH, Scott AM, Price AN et al. Psychosocial and sexual well-being following nipple-sparing mastectomy and reconstruction. *Breast J* 2016; 22(1): 10–17.
  69. Chatterjee JS, Lee A, Anderson W et al. Effect of postoperative radiotherapy on autologous deep inferior epigastric perforator flap volume after immediate breast reconstruction. *Br J Surg* 2009; 96(10): 1135–1140.
  70. Senkus-Konefka E, Wełnicka-Jaśkiewicz M, Jaśkiewicz J, Jassem J. Radiotherapy for breast cancer in patients undergoing breast reconstruction or augmentation. *Cancer Treat Rev* 2004; 30(8): 671–682.
  71. Cardoso MJ, Wyld L, Rubio IT et al. EUSOMA position regarding breast implant associated anaplastic large cell lymphoma (BIA-ALCL) and the use of textured implants. *Breast* 2019; 44: 90–93.
  72. Donker M, van Tienhoven G, Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014; 15(12): 1303–1310.
  73. Gebruers N, Verbelen H, De Vrieze T et al. Incidence and time path of lymphedema in sentinel node negative breast cancer patients: a systematic review. *Arch Phys Med Rehabil* 2015; 96(6): 1131–1139.
  74. Krag DN, Anderson SJ, Julian TB et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol* 2010; 11(10): 927–933.
  75. Giuliano AE, Hawes D, Ballman KV et al. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. *JAMA* 2011; 306(4): 385–393.
  76. Lyman GH, Somerfield MR, Bosserman LD et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2017; 35(5): 561–564.

77. National Comprehensive Cancer Network guidelines for treatment of breast cancer. [http://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf) (25 March, 2019, date last accessed).
78. Weaver DL. Pathology evaluation of sentinel lymph nodes in breast cancer: protocol recommendations and rationale. *Mod Pathol* 2010; 23(Suppl 2): S26–S32.
79. Galimberti V, Cole BF, Zurrada S et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol* 2013; 14(4): 297–305.
80. Giuliano AE, Ballman KV, McCall L et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA* 2017; 318(10): 918–926.
81. Jagsi R, Chadha M, Moni J et al. Radiation field design in the ACOSOG Z0011 (Alliance) Trial. *J Clin Oncol* 2014; 32(32): 3600–3606.
82. Leidenius M, Salmenkivi K, von Smitten K, Heikkilä P. Tumour-positive sentinel node findings in patients with ductal carcinoma in situ. *J Surg Oncol* 2006; 94(5): 380–384.
83. Moore KH, Sweeney KJ, Wilson ME et al. Outcomes for women with ductal carcinoma-in-situ and a positive sentinel node: a multi-institutional audit. *Ann Surg Oncol* 2007; 14(10): 2911–2917.
84. Meijnen P, Oldenburg HS, Loo CE et al. Risk of invasion and axillary lymph node metastasis in ductal carcinoma in situ diagnosed by core-needle biopsy. *Br J Surg* 2007; 94(8): 952–956.
85. Yen TW, Hunt KK, Ross MI et al. Predictors of invasive breast cancer in patients with an initial diagnosis of ductal carcinoma in situ: a guide to selective use of sentinel lymph node biopsy in management of ductal carcinoma in situ. *J Am Coll Surg* 2005; 200(4): 516–526.
86. Hessler LK, Molitoris JK, Rosenblatt PY et al. Factors influencing management and outcome in patients with occult breast cancer with axillary lymph node involvement: analysis of the National Cancer Database. *Ann Surg Oncol* 2017; 24(10): 2907–2914.
87. Wu SG, Zhang WW, Sun JY et al. Comparable survival between additional radiotherapy and local surgery in occult breast cancer after axillary lymph node dissection: a population-based analysis. *J Cancer* 2017; 8(18): 3849–3855.
88. Kuchenbaecker KB, Hopper JL, Barnes DR et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA* 2017; 317(23): 2402–2416.
89. Ludwig KK, Neuner J, Butler A et al. Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. *Am J Surg* 2016; 212(4): 660–669.
90. Heemskerk-Gerritsen BA, Rookus MA, Aalfs CM et al. Improved overall survival after contralateral risk-reducing mastectomy in BRCA1/2 mutation carriers with a history of unilateral breast cancer: a prospective analysis. *Int J Cancer* 2015; 136(3): 668–677.
91. El Hage Chehade H, Headon H, El Tokhy O et al. Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving 3,398 patients. *Am J Surg* 2016; 212(5): 969–981.
92. Galimberti V, Ribeiro Fontana SK, Maisonneuve P et al. Sentinel node biopsy after neoadjuvant treatment in breast cancer: five-year follow-up of patients with clinically node-negative or node-positive disease before treatment. *Eur J Surg Oncol* 2016; 42(3): 361–368.
93. Kuehn T, Bauerfeind I, Fehm T et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol* 2013; 14(7): 609–618.
94. Boughey JC, Suman VJ, Mittendorf EA et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA* 2013; 310(14): 1455–1461.
95. Donker M, Straver ME, Wesseling J et al. Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients: the MARI procedure. *Ann Surg* 2015; 261(2): 378–382.
96. Caudle AS, Yang WT, Krishnamurthy S et al. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. *J Clin Oncol* 2016; 34(10): 1072–1078.
97. Siso C, de Torres J, Esgueva-Colmenarejo A et al. Intraoperative ultrasound-guided excision of axillary clip in patients with node-positive breast cancer treated with neoadjuvant therapy (ILINA trial): a new tool to guide the excision of the clipped node after neoadjuvant treatment. *Ann Surg Oncol* 2018; 25(3): 784–791.
98. Darby S, McGale P, Correa C et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10, 801 women in 17 randomised trials. *Lancet* 2011; 378(9804): 1707–1716.
99. van Werkhoven E, Hart G, van Tinteren H et al. Nomogram to predict ipsilateral breast relapse based on pathology review from the EORTC 22881-10882 boost versus no boost trial. *Radiother Oncol* 2011; 100(1): 101–107.
100. Bartelink H, Maingon P, Poortmans P et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol* 2015; 16(1): 47–56.
101. Coles CE, Griffin CL, Kirby AM et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet* 2017; 390(10099): 1048–1060.
102. Livi L, Meattini I, Marrazzo L et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer* 2015; 51(4): 451–463.
103. Polgár C, Ott OJ, Hildebrandt G et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2017; 18(2): 259–268.
104. Veronesi U, Orecchia R, Maisonneuve P et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* 2013; 14(13): 1269–1277.
105. Vaidya JS, Wenz F, Bulsara M et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014; 383(9917): 603–613.
106. Polgár C, Van Limbergen E, Potter R et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). *Radiother Oncol* 2010; 94(3): 264–273.
107. McGale P, Taylor C, Correa C et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; 383(9935): 2127–2135.
108. Poortmans PM, Collette S, Kirkove C et al. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med* 2015; 373(4): 317–327.
109. Whelan TJ, Olivetto IA, Levine MN. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015; 373(19): 1878–1879.
110. Thorsen LB, Offersen BV, Danø H et al. DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. *J Clin Oncol* 2016; 34(4): 314–320.
111. Poortmans P. Postmastectomy radiation in breast cancer with one to three involved lymph nodes: ending the debate. *Lancet* 2014; 383(9935): 2104–2106.

112. Offersen BV, Boersma LJ, Kirkove C et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. *Radiother Oncol* 2015; 114(1): 3–10.
113. Spear SL, Boehmler JH, Bogue DP, Mafi AA. Options in reconstructing the irradiated breast. *Plast Reconstr Surg* 2008; 122(2): 379–388.
114. Momoh AO, Ahmed R, Kelley BP et al. A systematic review of complications of implant-based breast reconstruction with prereconstruction and postreconstruction radiotherapy. *Ann Surg Oncol* 2014; 21(1): 118–124.
115. Kelley BP, Ahmed R, Kidwell KM et al. A systematic review of morbidity associated with autologous breast reconstruction before and after exposure to radiotherapy: are current practices ideal? *Ann Surg Oncol* 2014; 21(5): 1732–1738.
116. Whelan TJ, Pignol JP, Levine MN et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; 362(6): 513–520.
117. Bentzen SM, Agrawal RK, Aird EG et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008; 371(9618): 1098–1107.
118. Bentzen SM, Agrawal RK, Aird EG et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008; 9: 331–341.
119. Goodwin A, Parker S, Ghersi D, Wilcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast—a systematic review of the randomised trials. *Breast* 2009; 18(3): 143–149.
120. Morrow M, Schnitt SJ, Norton L. Current management of lesions associated with an increased risk of breast cancer. *Nat Rev Clin Oncol* 2015; 12(4): 227–238.
121. Barbour S, Moore J, Dunn N et al. Patterns of care for ductal carcinoma in situ of the breast: Queensland's experience over a decade. *Breast* 2017; 35: 169–176.
122. Rakovitch E, Nofech-Mozes S, Hanna W et al. Omitting radiation therapy after lumpectomy for pure DCIS does not reduce the risk of salvage mastectomy. *Breast* 2018; 37: 181–186.
123. Correa C, Harris EE, Leonardi MC et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol* 2017; 7(2): 73–79.
124. Lohrisch C, Paltiel C, Gelmon K et al. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol* 2006; 24(30): 4888–4894.
125. Harbeck N, Kates RE, Look MP et al. Enhanced benefit from adjuvant chemotherapy in breast cancer patients classified high-risk according to urokinase-type plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (n = 3424). *Cancer Res* 2002; 62(16): 4617–4622.
126. Curigliano G, Burstein HJ, Winer EP et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Ann Oncol* 2017; 28(8): 1700–1712.
127. Wei S. Papillary lesions of the breast: an update. *Arch Pathol Lab Med* 2016; 140(7): 628–643.
128. Albain KS, Barlow WE, Ravdin PM et al. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 2009; 374(9707): 2055–2063.
129. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 365(9472): 1687–1717.
130. Goss PE, Ingle JN, Martino S et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003; 349(19): 1793–1802.
131. Swain SM, Jeong JH, Wolmark N. Amenorrhoea from breast cancer therapy—not a matter of dose. *N Engl J Med* 2010; 363(23): 2268–2270.
132. Pagani O, O'Neill A, Castiglione M et al. Prognostic impact of amenorrhoea after adjuvant chemotherapy in premenopausal breast cancer patients with axillary node involvement: results of the International Breast Cancer Study Group (IBCSG) Trial VI. *Eur J Cancer* 1998; 34(5): 632–640.
133. Francis PA, Regan MM, Fleming GF et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2015; 372(5): 436–446.
134. Francis PA, Pagani O, Fleming GF et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med* 2018; 379(2): 122–137.
135. Gnant M, Mlineritsch B, Schippinger W et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009; 360(7): 679–691.
136. Pagani O, Regan MM, Walley BA et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014; 371(2): 107–118.
137. Moore HC, Unger JM, Phillips KA et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med* 2015; 372(10): 923–932.
138. Lambertini M, Moore HCF, Leonard RCF et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient-level data. *J Clin Oncol* 2018; 36(19): 1981–1990.
139. Bliss JM, Kilburn LS, Coleman RE et al. Disease-related outcomes with long-term follow-up: an updated analysis of the intergroup exemestane study. *J Clin Oncol* 2012; 30(7): 709–717.
140. Regan MM, Neven P, Giobbie-Hurder A et al. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8.1 years median follow-up. *Lancet Oncol* 2011; 12(12): 1101–1108.
141. Cuzick J, Sestak I, Baum M et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol* 2010; 11(12): 1135–1141.
142. Goss PE, Ingle JN, Pater JL et al. Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. *J Clin Oncol* 2008; 26(12): 1948–1955.
143. Burstein HJ, Prestrud AA, Seidenfeld J et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncol* 2010; 28(23): 3784–3796.
144. Dowsett M, Cuzick J, Ingle J et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol* 2010; 28(3): 509–518.
145. Davies C, Pan H, Godwin J et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013; 381(9869): 805–816.
146. Leyland-Jones B, Regan MM, Bouzyk M et al. Abstract S1-8: outcome according to CYP2D6 genotype among postmenopausal women with endocrine-responsive early invasive breast cancer randomized in the BIG trial. *Cancer Res* 2011; 70(Suppl 24): S1–S8.
147. Sideras K, Ingle JN, Ames MM et al. Coprescription of tamoxifen and medications that inhibit CYP2D6. *J Clin Oncol* 2010; 28(16): 2768–2776.
148. Berry DA, Cirrincione C, Henderson IC et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. *JAMA* 2006; 295(14): 1658–1667.
149. Clarke M, Coates AS, Darby SC et al. Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials. *Lancet* 2008; 371(9606): 29–40.
150. Peto R, Davies C, Godwin J et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet* 2012; 379(9814): 432–444.

151. Samuel JA, Wilson JW, Bandos H et al. Abstract S3-02: nSABP B-36: a randomized phase III trial comparing six cycles of 5-fluorouracil (5-FU), epirubicin, and cyclophosphamide (FEC) to four cycles of adriamycin and cyclophosphamide (AC) in patients (pts) with node-negative breast cancer. *Cancer Res* 2015; 75 (Suppl 9): S3-02.
152. Nitz U, Gluz O, Huober J et al. Final analysis of the prospective WSG-AGO EC-doc versus FEC phase III trial in intermediate-risk (pN1) early breast cancer: efficacy and predictive value of Ki67 expression. *Ann Oncol* 2017; 28(11): 2899.
153. Gianni L, Baselga J, Eiermann W et al. Phase III trial evaluating the addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil, as adjuvant or primary systemic therapy: European Cooperative Trial in Operable Breast Cancer. *J Clin Oncol* 2009; 27(15): 2474–2481.
154. Shao N, Wang S, Yao C et al. Sequential versus concurrent anthracyclines and taxanes as adjuvant chemotherapy of early breast cancer: a meta-analysis of phase III randomized control trials. *Breast* 2012; 21(3): 389–393.
155. Earl HM, Vallier AL, Hiller L et al. Effects of the addition of gemcitabine, and paclitaxel-first sequencing, in neoadjuvant sequential epirubicin, cyclophosphamide, and paclitaxel for women with high-risk early breast cancer (Neo-tAnGo): an open-label, 2x2 factorial randomised phase 3 trial. *Lancet Oncol* 2014; 15(2): 201–212.
156. Jones S, Holmes FA, O'Shaughnessy J et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. *J Clin Oncol* 2009; 27(8): 1177–1183.
157. Blum JL, Flynn PJ, Yothers G et al. Anthracyclines in early breast cancer: the ABC trials-USOR 06-090, NSABP B-46-1/USOR 07132, and NSABP B-49 (NRG Oncology). *J Clin Oncol* 2017; 35(23): 2647–2655.
158. Sousa B, Furlanetto J, Hutka M et al. Central venous access in oncology: ESMO Clinical Practice Guidelines. *Ann Oncol* 2015; 26(Suppl 5): v152–v168.
159. Citron ML, Berry DA, Cirincione C et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003; 21(8): 1431–1439.
160. Gray R, Bradley R, Braybrooke J et al. Abstract GS1-01: increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality: an EBCTCG meta-analysis of 21,000 women in 16 randomised trials. *Cancer Res* 2018; 78(Suppl 4): GS1–01.
161. Cameron D, Piccart-Gebhart MJ, Gelber RD et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 2017; 389(10075): 1195–1205.
162. Perez EA, Romond EH, Suman VJ et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol* 2014; 32(33): 3744–3752.
163. Slamon D, Eiermann W, Robert N et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; 365(14): 1273–1283.
164. Gonzalez-Angulo AM, Litton JK, Broglio KR et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. *J Clin Oncol* 2009; 27(34): 5700–5706.
165. Joensuu H, Bono P, Kataja V et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. *J Clin Oncol* 2009; 27(34): 5685–5692.
166. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet* 2013; 382(9897): 1021–1028.
167. Pivrot X, Romieu G, Debled M et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol* 2013; 14(8): 741–748.
168. Joensuu H, Fraser J, Wildiers H et al. Effect of adjuvant trastuzumab for a duration of 9 weeks vs 1 year with concomitant chemotherapy for early human epidermal growth factor receptor 2-positive breast cancer: the SOLD randomized clinical trial. *JAMA Oncol* 2018; 4(9): 1199–1206.
169. Conte PF, Bisagni G, Frassoldati A et al. 9 weeks vs 1 year adjuvant trastuzumab in combination with chemotherapy: results of the phase III multicentric Italian study Short-HER. *J Clin Oncol* 2017; 35(Suppl 15): 501.
170. Earl HM, Hiller L, Vallier A-L et al. PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): randomised phase 3 non-inferiority trial with definitive 4-year (yr) disease-free survival (DFS) results. *J Clin Oncol* 2018; 36(Suppl 15): 506.
171. Baselga J, Bradbury I, Eidtmann H et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet* 2012; 379(9816): 633–640.
172. Guarneri V, Frassoldati A, Bottini A et al. Preoperative chemotherapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2-positive operable breast cancer: results of the randomized phase II CHER-LOB study. *J Clin Oncol* 2012; 30(16): 1989–1995.
173. Gianni L, Pienkowski T, Im YH et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; 13(1): 25–32.
174. Piccart-Gebhart M, Holmes E, Baselga J et al. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. *J Clin Oncol* 2016; 34(10): 1034–1042.
175. von Minckwitz G, Procter M, de Azambuja E et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med* 2017; 377(2): 122–131.
176. von Minckwitz G, Huang CS, Mano MS et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med* 2019; 380(7): 617–628.
177. Martin M, Holmes FA, Ejlertsen B et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017; 18(12): 1688–1700.
178. Tolane SM, Barry WT, Dang CT et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med* 2015; 372(2): 134–141.
179. Rastogi P, Anderson SJ, Bear HD et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol* 2008; 26(5): 778–785.
180. von Minckwitz G, Schneeweiss A, Loibl S et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol* 2014; 15(7): 747–756.
181. Sikov WM, Berry DA, Perou CM et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J Clin Oncol* 2015; 33(1): 13–21.
182. Loibl S, O'Shaughnessy J, Untch M et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrightNess): a randomised, phase 3 trial. *Lancet Oncol* 2018; 19(4): 497–509.
183. Hahnen E, Lederer B, Hauke J et al. Germline mutation status, pathologic complete response, and disease-free survival in triple-negative

- breast cancer: secondary analysis of the GeparSixto randomized clinical trial. *JAMA Oncol* 2017; 3(10): 1378–1385.
184. Masuda N, Lee SJ, Ohtani S et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med* 2017; 376(22): 2147–2159.
  185. von Minckwitz G, Untch M, Nüesch E et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. *Breast Cancer Res Treat* 2011; 125(1): 145–156.
  186. Cataliotti L, Buzdar AU, Noguchi S et al. Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer: the Pre-Operative “Arimidex” Compared to Tamoxifen (PROACT) trial. *Cancer* 2006; 106(10): 2095–2103.
  187. Smith IE, Dowsett M, Ebbs SR et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. *J Clin Oncol* 2005; 23: 5108–5116.
  188. Eiermann W, Paepke S, Apfelstaedt J et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicenter study. *Ann Oncol* 2001; 12(11): 1527–1532.
  189. Eggemann H, Ignatov A, Smith BJ et al. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. *Breast Cancer Res Treat* 2013; 137(2): 465–470.
  190. Korde LA, Zujewski JA, Kamin L et al. Multidisciplinary meeting on male breast cancer: summary and research recommendations. *J Clin Oncol* 2010; 28(12): 2114–2122.
  191. Sousa B, Moser E, Cardoso F. An update on male breast cancer and future directions for research and treatment. *Eur J Pharmacol* 2013; 717(1–3): 71–83.
  192. Cardoso F, Bartlett JMS, Slaets L et al. Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. *Ann Oncol* 2018; 29(2): 405–417.
  193. Azim HA Jr, Michiels S, Zagouri F et al. Utility of prognostic genomic tests in breast cancer practice: the IMPAKT 2012 Working Group Consensus Statement. *Ann Oncol* 2013; 24(3): 647–654.
  194. Masuda N, Sagara Y, Kinoshita T et al. Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2012; 13(4): 345–352.
  195. Coleman R, Cameron D, Dodwell D et al. Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial. *Lancet Oncol* 2014; 15(9): 997–1006.
  196. Early Breast Cancer Trialists’ Collaborative Group (EBCTCG). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet* 2015; 386(10001): 1353–1361.
  197. Dhesy-Thind S, Fletcher GG, Blanchette PS et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2017; 35(18): 2062–2081.
  198. Eidtmann H, de Boer R, Bundred N et al. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. *Ann Oncol* 2010; 21(11): 2188–2194.
  199. Hadji P, Aapro MS, Body JJ et al. Management of aromatase inhibitor-associated bone loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. *J Bone Oncol* 2017; 7: 1–12.
  200. Muss HB, Berry DA, Cirincione CT et al. Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med* 2009; 360(20): 2055–2065.
  201. Perrone F, Nuzzo F, Di Rella F et al. Weekly docetaxel versus CMF as adjuvant chemotherapy for older women with early breast cancer: final results of the randomized phase III ELDA trial. *Ann Oncol* 2015; 26(4): 675–682.
  202. Crivellari D, Gray KP, Dellapasqua S et al. Adjuvant pegylated liposomal doxorubicin for older women with endocrine nonresponsive breast cancer who are NOT suitable for a “standard chemotherapy regimen”: the CASA randomized trial. *Breast* 2013; 22(2): 130–137.
  203. Biganzoli L, Wildiers H, Oakman C et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012; 13(4): e148–e160.
  204. Staley H, McCallum I, Bruce J. Postoperative tamoxifen for ductal carcinoma in situ. *Cochrane Database Syst Rev* 2012; 10: CD007847.
  205. Forbes JF, Sestak I, Howell A et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. *Lancet* 2016; 387(10021): 866–873.
  206. Margolese RG, Cecchini RS, Julian TB et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. *Lancet* 2016; 387(10021): 849–856.
  207. Allemani C, Minicozzi P, Berrino F et al. Predictions of survival up to 10 years after diagnosis for European women with breast cancer in 2000–2002. *Int J Cancer* 2013; 132(10): 2404–2412.
  208. Pan H, Gray R, Braybrooke J et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med* 2017; 377(19): 1836–1846.
  209. Park S, Koo JS, Kim MS et al. Characteristics and outcomes according to molecular subtypes of breast cancer as classified by a panel of four biomarkers using immunohistochemistry. *Breast* 2012; 21(1): 50–57.
  210. Committee Opinion No. 601: tamoxifen and uterine cancer. *Obstet Gynecol* 2014; 123(6): 1394–1397.
  211. Mustian KM, Alfano CM, Heckler C et al. Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. *JAMA Oncol* 2017; 3(7): 961–968.
  212. Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. *J Clin Oncol* 2002; 20(4): 1128–1143.
  213. Holmberg L, Iversen OE, Rudenstam CM et al. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *J Natl Cancer Inst* 2008; 100(7): 475–482.
  214. Cherny NI, Dafni U, Bogaerts J et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Ann Oncol* 2017; 28(10): 2340–2366.
  215. Dowsett M, Nielsen TO, A’Hern R et al. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. *J Natl Cancer Inst* 2011; 103(22): 1656–1664.
  216. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2001; 33(2): 139–144.