clinical practice guidelines

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Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence and epidemiology

In 2012, the estimated age-adjusted annual incidence of breast cancer in 40 European countries was 94.2/100 000 and the mortality 23.1/100 000 [1]. The incidence increased after 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), ionising radiation, low parity 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 [2]. 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 in Europe in 2012 was 1 814 572 cases [1]. Prevalence is increasing, as a consequence of increased incidence and due to 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 [3, 4]. However, breast cancer is still the leading cause of cancer-related deaths in European women.

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 and, in particular, a positive family history and genetic predisposition [5].

breast cancer screening

Eighteen European countries have established national or regional population-based mammography screening programmes, to detect breast cancers at a pre-clinical stage [6]. 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 [7]. Mammography screening, every 2 years, has shown the greatest mortality reduction benefit in the age group of 50–69 years and is recommended by the European Union and numerous individual countries [8]. The evidence for effectiveness of mammography screening in women aged 40–49 years is limited [9]. This was also the conclusion in the recent breast cancer screening report from the International Agency for Research on Cancer [10]. 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 old [11]. 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, may contribute to mortality reduction in breast cancer. Therefore, we recommend (after a discussion of the benefits and risks with the woman who is to be screened) regular mammography in women aged 50–69 years [I, A]. There is controversy and no consensus regarding the role of screening in women aged 40–49 years, or for the use of ultrasound.

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 [12]. We recommend annual MRI concomitantly or alternating every 6 months with mammography, starting 10 years younger than the youngest case in the family [III,A]. There is no consensus for the use of ultrasound.

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 locoregional lymph nodes and

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Table 1. Diagnostic workup 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 ultrasound Breast MRI Core biopsy with pathology determination of histology, grade, ER, PgR, HER-2 and Ki67
Assessment of regional lymph nodes	Physical examination Ultrasound Ultrasound-guided biopsy if suspicious
Assessment of metastatic disease	Physical examination Other tests are not routinely recommended, unless locally advanced or when symptoms suggestive of metastases are present

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

assessment for distant metastases (bones, liver and lungs; a neurological examination is only required when symptoms are present). Imaging includes bilateral mammography and ultrasound of the breast and regional lymph nodes [7]. An MRI of the breast is not routinely recommended, but should be considered in cases of: familial breast cancer associated with *BRCA* mutations, breast implants, lobular cancers, suspicion of multifocality/multicentricity (particularly in lobular breast cancer), or large discrepancies between conventional imaging and clinical examination [III, B]. MRI may also be recommended before neoadjuvant chemotherapy, when evaluating the response to primary systemic therapy or 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] [13]. Several new techniques are being tested for screening and diagnostic imaging, such as: 3D mammography (breast tomosynthesis), 3D ultrasound, shear wave elastography and contrast-enhanced mammography/spectral mammography. None of these are routinely implemented as yet, but they have the potential to increase diagnostic accuracy, especially in women with dense breasts.

Apart from imaging, pre-treatment disease evaluation includes pathological examination of the primary tumour and cytology/histology of the axillary nodes, if involvement is suspected. Other assessments include: complete personal medical history, family history relating to breast/ovarian and other cancers, physical examination, a full blood count, liver and renal function tests, alkaline phosphatase and calcium levels. Assessing the menopausal status of the patient is imperative, if in doubt measure serum oestradiol and follicle-stimulating hormone levels. In patients planned for (neo)adjuvant treatment, with anthracyclines and/or trastuzumab, evaluation of cardiac function with a cardiac ultrasound or a multigated acquisition scan is essential [I, A].

Pathological diagnosis should be based on a core needle biopsy, obtained preferably by ultrasound 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 [III, A]. A marker (e.g. surgical clip, carbon) should be placed into the tumour at biopsy, to ensure surgical resection of the correct site [V, A]. As a minimum, ultrasound-guided fine needle aspiration or core biopsy of suspicious lymph nodes should be carried out [III, A]. In patients with clinically and imaging negative axilla, the best timing to carry out sentinel lymph node biopsy (SLNB), i.e. before or after preoperative systemic therapy, remains controversial [II, C]. The recently published SENTINA and ACOSOG Z1071 studies demonstrated lower detection rates and higher rates of false-negatives when SLNB is carried out after systemic therapy, compared with SNLB that is carried out before neoadjuvant chemotherapy [14, 15]. However, if the axilla is negative on ultrasound and/or positron emission tomography (PET)/computed tomography (CT) scanning, carried out before the start of systemic therapy, a post-systemic therapy SNLB can be considered [V, B].

Final pathological diagnosis should be made according to the World Health Organization (WHO) classification [16] and the tumour–node–metastases (TNM) staging system. The pathological report should include the histological type, grade, immunohistochemical (IHC) evaluation of oestrogen receptor (ER) status (using a standardised assessment methodology, e.g. Allred or H-score) and, for invasive cancer, IHC evaluation of progesterone receptor (PgR) and human epidermal growth factor 2 receptor (HER2) gene expression. HER2 gene amplification status may be determined directly from all invasive tumours using *in situ* hybridisation (fluorescent, chromogenic or silver), replacing IHC or only for tumours with an ambiguous (2+) IHC score [II, B] [17]. The guidelines for HER2 testing have recently been updated by the American Society of Clinical Oncology–College of American Pathologists (ASCO-CAP) group. There is a change in the definition of HER2 positivity by

IHC (3+ when more than 10% of the cells, instead of 30%, harbour a complete membrane staining), and by *in situ* hybridisation (positive if the number of HER2 gene copies is ≥6 or the ratio HER2/chromosome 17 is ≥2, instead of 2.2). The definition of equivocal cases is broader; if a case is defined as equivocal after two tests it is eligible for trastuzumab, and should be discussed in multidisciplinary tumour boards [V, B] [18].

Proliferation markers such as the Ki67 labelling index may supply additional useful information, particularly if the assay can be standardised [V, A] [19, 20]. Alternatively, these biological markers can be assessed in the definitive surgical specimen if primary systemic therapy is 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].

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].

staging and risk assessment

Disease stage should be assessed according to the TNM system (Tables 3 and 4). In early breast cancer, routine staging evaluations are directed at locoregional disease (Figure 1). Asymptomatic distant metastases are very rare and patients do not benefit from comprehensive laboratory (including tumour markers [25]) and radiological staging [III, D]. Minimum blood workup (a full blood count, liver and renal function tests, alkaline phosphatase and calcium levels) is recommended before surgery and systemic (neo)adjuvant therapy [V, B]. A CT scan of the chest, an abdominal ultrasound or CT scan and a bone scan can be considered for patients with: clinically positive axillary nodes, large tumours (e.g. ≥5 cm), aggressive biology or clinical signs, symptoms or laboratory values suggesting the presence of metastases [III, B]. Dual imaging methods combining functional and anatomical information such as fluorodeoxyglucose positron emission tomography (FDG-PET)/CT may be useful when conventional methods are inconclusive [V, A]. PET/CT scanning can replace traditional imaging for staging in high-risk patients who are candidates for neoadjuvant chemotherapy, as well as those with locally advanced and/or inflammatory disease due to their high risk of having metastatic disease [V, B] [26]. Current evidence does not support the use of FDG-PET/CT in the staging of local/regional disease, due to its limited specificity when compared with the gold standard, SLNB and axillary lymph node dissection [27].

The postoperative pathological assessment of the surgical specimens should be made according to the pathological TNM system (Tables 3 and 4). This assessment should include: the number, location and maximum diameter of the tumours removed, the total number of removed and positive lymph

Table 2. Surrogate definitions of intrinsic subtypes of breast cancer according to the 2015 St Gallen Consensus Conference [23] and also recommended by the ESMO Clinical Practice Guidelines

Intrinsic subtype	Clinicopathologic surrogate definition	Notes
Luminal A	'Luminal A-like' ER-positive HER2-negative Ki67 low* PgR high** low-risk molecular signature (if available)	*Ki-67 scores should be interpreted in the 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, **Suggested cut-off value is 20%; quality assurance programmes are essential for laboratories reporting these results.
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 overexpression	'HER2-positive (non-luminal)' HER2-positive ER and PgR absent	
'Basal-like'	'Triple-negative (ductal)' ER and PgR absent HER2-negative	There is ~80% overlap between 'triple-negative' and intrinsic 'basal-like' subtype, but 'triple-negative' also includes some special histological types such as (typical) medullary and adenoid cystic carcinoma with low risks of distant recurrence.

ER, oestrogen receptor; HER2, human epidermal growth factor 2 receptor; PgR, progesterone receptor.

Table 3. Tumour–node–metastases (TNM) staging system for carcinoma of the breast

Primary tumour (T)[a,b,c,d]	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
Tis (DCIS)	Ductal carcinoma *in situ*
Tis (LCIS)	Lobular carcinoma *in situ*
Tis (Paget's)	Paget's disease (Paget disease) of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorised based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted.
T1	Tumour ≤20 mm in greatest dimension
T1mi	Tumour ≤1 mm in greatest dimension
T1a	Tumour >1 mm but ≤5 mm in greatest dimension
T1b	Tumour >5 mm but ≤10 mm in greatest dimension
T1c	Tumour >10 mm but ≤20 mm in greatest dimension
T2	Tumour >20 mm but ≤50 mm in greatest dimension
T3	Tumour >50 mm in greatest dimension
T4	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)[e]
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or oedema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma[f]
Regional lymph nodes (N) Clinical (cN)[g,h,i,j,k]	
NX	Regional lymph nodes cannot be assessed (e.g. previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected[k] ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected[k] ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected[k] ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)
Regional lymph nodes (N) Pathological (pN)[h,i,j,k]	
pNX	Regional lymph nodes cannot be assessed (e.g. previously removed or not removed for pathological study)
pN0	No regional lymph node metastasis identified histologically
pN0(i−)	No regional lymph node metastases histologically, negative immunohistochemistry (IHC)
pN0(i+)	Malignant cells in regional lymph node(s) not >0.2 mm [detected by haematoxylin and eosin (H&E) staining or IHC including isolated tumour cell clusters (ITCs)]
pN0(mol−)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in one to three axillary lymph nodes; and/or in internal mammary nodes with metastases detected by SLNB but not clinically detected[l]
pN1mi	Micrometastases (>0.2 mm and/or >200 cells, but none >2.0 mm)
pN1a	Metastases in one to three axillary lymph nodes, at least one metastasis >2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by SLNB but not clinically detected[l]
pN1c	Metastases in one to three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by SLNB but not clinically detected[l]
pN2	Metastases in four to nine axillary lymph nodes; or in clinically detected[k] internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in four to nine axillary lymph nodes (at least one tumour deposit >2.0 mm)

Continued

Table 3. *Continued*

pN2b	Metastases in clinically detected[k] internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	Metastases in ≥10 axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected[k] ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by SLNB but not clinically detected[l]; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ≥10 axillary lymph nodes (at least one tumour deposit >2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected[k] ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by SLNB but not clinically detected[l]
pN3c	Metastases in ipsilateral supraclavicular lymph nodes
Distant metastasis (M)	
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumour cells in circulating blood, bone marrow or other non-regional nodal tissue that are not >0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm

[a]DCIS; LCIS. Post-treatment ypT: The use of neoadjuvant therapy does not change the clinical (pre-treatment) stage. Clinical (pre-treatment) T will be defined by clinical and radiographic findings, while y pathological (post-treatment) T will be determined by pathological size and extension. The ypT will be measured as the largest single focus of invasive tumour, with the modifier 'm' indicating multiple foci. The measurement of the largest tumour focus should not include areas of fibrosis within the tumour bed.

[b]The T classification of the primary tumour is the same regardless of whether it is based on clinical or pathological criteria, or both. Designation should be made with the subscript 'c' or 'p' modifier to indicate whether the T classification was determined by clinical (physical examination or radiological) or pathological measurements, respectively. In general, pathological determination should take precedence over clinical determination of T size.

[c]Size should be measured to the nearest millimetre.

[d]Multiple simultaneous ipsilateral primary carcinomas are defined as infiltrating carcinomas in the same breast, which are grossly or macroscopically distinct and measurable. T stage is based only on the largest tumour. The presence and sizes of the smaller tumour(s) should be recorded using the '(m)' modifier.

[e]Invasion of the dermis alone does not qualify as T4; dimpling of the skin, nipple retraction or any other skin change except those described under T4b and T4d may occur in T1, T2 or T3 without changing the classification. The chest wall includes ribs, intercostal muscles and serratus anterior muscle, but not the pectoralis muscles.

[f]Inflammatory carcinoma is a clinical–pathological entity characterised by diffuse erythema and oedema (peau d'orange) involving a third or more of the skin of the breast. These skin changes are due to lymphoedema caused by tumour emboli within dermal lymphatics. Although dermal lymphatic involvement supports the diagnosis of inflammatory breast cancer, it is neither necessary nor sufficient, in the absence of classical clinical findings, for the diagnosis of inflammatory breast cancer.

[g]Classification is based on axillary lymph node dissection with or without SLNB. Classification based solely on SLNB without subsequent axillary lymph node dissection is designated (sn) for 'sentinel node', e.g. pN0(sn).

[h]Isolated tumour cell clusters (ITCs) are defined as small clusters of cells not >0.2 mm, or single tumour cells, or a cluster of <200 cells in a single histological cross section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

[i]Post-treatment yp 'N' should be evaluated as for pre-treatment 'N'. The modifier 'sn' is used if a sentinel node evaluation was carried out. If no subscript is attached, it is assumed that the axillary nodal evaluation was by axillary node dissection.

[j]ypN categories are the same as those for pN.

[k]Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathological macrometastasis based on fine needle aspiration biopsy with cytological examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, e.g. cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, e.g. cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy or sentinel lymph node biopsy. Pathological classification (pN) is used for excision or SLNB only in conjunction with a pathological T assignment.

[l]'Not clinically detected' is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

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SLNB, sentinel lymph node biopsy; RT-PCR, reverse transcription polymerase chain reaction; DCIS, ductal carcinoma *in situ*; LCIS, called lobular carcinoma *in situ*.

Table 4. Stage grouping system for carcinoma of the breast

Anatomic stage/prognostic groups[a]		
Stage 0		
Tis	N0	M0
Stage IA		
T1[b]	N0	M0
Stage IB		
T0	N1mi	M0
T1[b]	N1mi	M0
Stage IIA		
T0	N1[c]	M0
T1[b]	N1[c]	M0
T2	N0	M0
Stage IIB		
T2	N1	M0
T3	N0	M0
Stage IIIA		
T0	N2	M0
T1[b]	N2	M0
T2	N2	M0
T3	N1	M0
T3	N2	M0
Stage IIIB		
T4	N0	M0
T4	N1	M0
T4	N2	M0
Stage IIIC		
Any T	N3	M0
Stage IV		
Any T	Any N	M1

[a]Anatomic stage: M0 includes M0(i+). The designation pM0 is not valid; any M0 should be clinical. If a patient presents with M1 before neoadjuvant systemic therapy, the stage is considered stage IV and remains stage IV regardless of response to neoadjuvant therapy. Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy. Post-neoadjuvant assessment is designated with a 'yc' or 'yp' prefix. Of note, no stage group is assigned if there is a complete pathological response (pCR) to neoadjuvant therapy, e.g. ypT0ypN0cM0.

[b]T1 includes T1mi.

[c]T0 and T1 tumours with nodal micrometastases only are excluded from stage IIA and are classified stage IB.

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nodes, as well as the extent of metastases in the lymph nodes [isolated tumour cells, micrometastases (0.2–2 mm), macrometastases]. The report should also include: 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 [III, A].

The most important prognostic factors in early breast cancer are: expression of ER/PgR, HER2 and proliferation markers, the number of involved regional lymph nodes, tumour histology, the size, grade and the presence of peri-tumoural vascular invasion. Additionally, in patients undergoing breast-conserving therapy (BCT), the ipsilateral breast recurrence risk is related to the status of the surgical margins.

Clinical parameters (age, tumour stage, ER expression and histological grade) have 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), Adjuvant! Online (www.adjuvantonline.com) or the PREDICT score [28–30]. Urokinase plasminogen activator–plasminogen activator inhibitor 1 (uPA-PAI1) (FEMTELLE, Sekisui Diagnostics) is an Elisa test evaluating the metastatic potential of a breast tumour. Despite its level IA prognostic value, this test is not extensively used outside Germany, probably due to the requirement for a substantial amount of fresh-frozen tissue [31].

Gene expression profiles, such as MammaPrint (Agendia, Amsterdam, the Netherlands), Oncotype DX Recurrence Score (Genomic Health, Redwood City, CA), Prosigna (Nanostring technologies, Seattle, WA) and Endopredict (Myriad Genetics), may be used to gain additional prognostic and/or predictive information to complement pathology assessment and to predict the benefit of adjuvant chemotherapy. The three latter tests are designed for patients with ER-positive early breast cancer only. The clinical utility of Mammaprint and Oncotype DX is still being prospectively evaluated in large randomised clinical trials such as MINDACT for Mammaprint, WSG PLAN B trial, TAILORx and RxPONDER for Oncotype DX. A IB evidence level has been achieved from retrospective analyses of data from prospective trials regarding the prognostic value of MammaPrint, Oncotype DX, Prosigna and Endopredict, in ER-positive breast cancers [31, 32]. In addition, the prognostic value of MammaPrint has been validated in the Raster trial, a prospective but non-randomised, clinical trial [33].

ER/PgR and HER2 are the only validated predictive factors, allowing the selection of patients for endocrine therapies (ETs) and anti-HER2 treatments, respectively. High ER expression is usually associated with lesser absolute benefit of chemotherapy.

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 in clinical trials [34]. 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 pathologic complete response (pCR) was achieved, both in the breast and axilla, this must be clearly stated. In addition, the presence or absence of residual ductal carcinoma *in situ* (DCIS) must be described. In case of residual invasive carcinoma, a comment must be made as to the presence or absence of chemotherapy effect in the breast and the lymph nodes. The Residual Cancer Burden is the preferred method for quantifying residual disease in clinical trials; other methods can be used according to regional preference. Post-treatment tumour staging, using the TNM system,

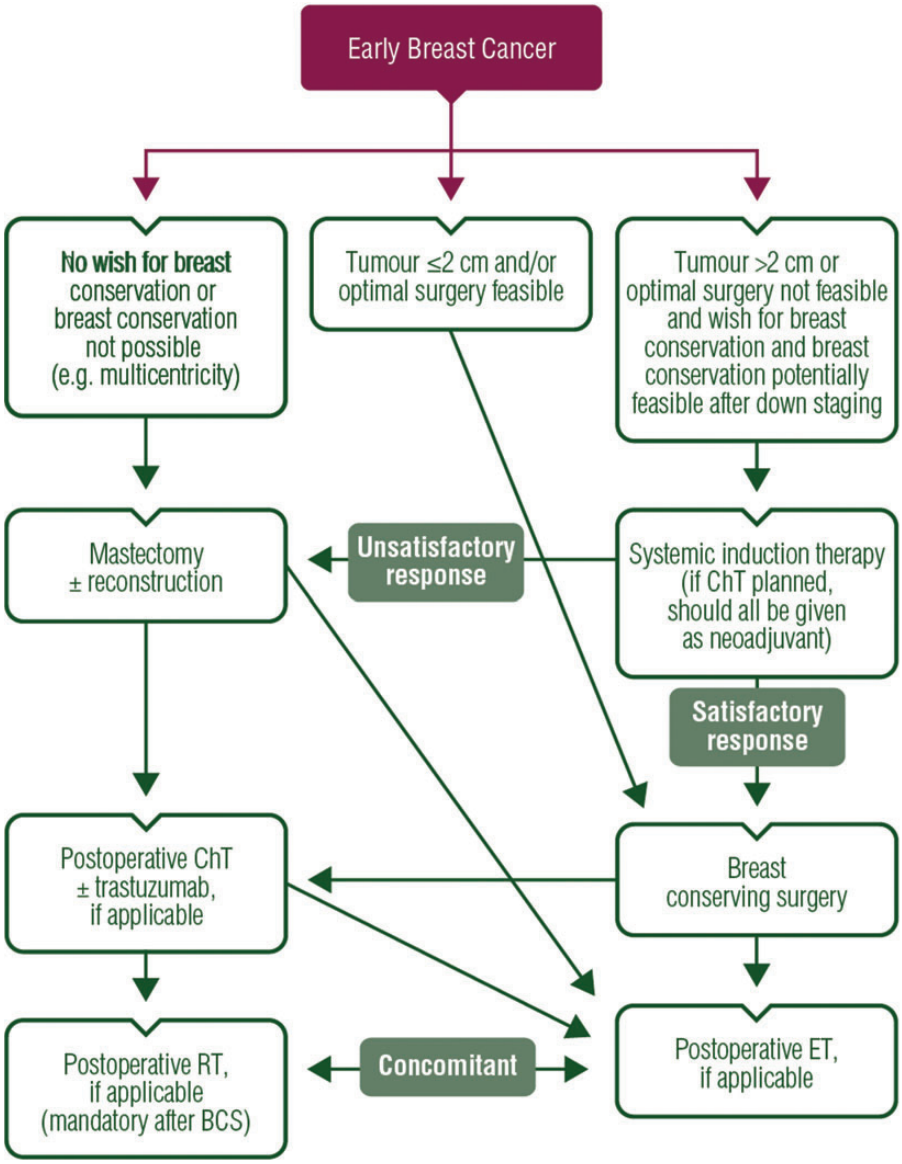

Figure 1. Early breast cancer treatment algorithm. Cht, chemotherapy; BCS, breast-conserving surgery; ET, endocrine therapy; RT, radiotherapy.

should also be included. Some guidance is also provided by the United States Food and Drug Administration recommendation for accelerated drug approval in neoadjuvant treatment of breast cancer [35].

management of local/locoregional disease

Treatment should be carried out in 'breast units' defined as specialised institutions/departments that care for a high volume of breast cancer patients (a minimum of 150 early breast cancer cases per year). Treatment should be provided by a multidisciplinary team, which includes: at least one surgeon, radiation oncologist, medical oncologist, radiologist and pathologist, who are specialised in breast cancer [IV, A] [36–38]. A breast nurse, or a similarly trained and specialised health care practitioner, acting as a patient navigator, is also important [III, B] [36, 37]. Depending on the local situation and availability, other members of the breast team may include plastic/reconstructive surgeons, psychologists, physiotherapists and geneticists. Following a diagnosis of breast cancer, a patient finds herself in a new and unfamiliar landscape. This creates different levels of stress that vary from patient to patient, and needs to be addressed individually and tailored to each patient's needs. Most will remember the information provided to them in a fragmented way. They will need space and time to process and comprehend their diagnosis, so they can cope psychologically with the diagnosis and treatment plan. To accommodate for this, information on diagnosis and treatment choice should be given repeatedly (both verbally and in writing) in a comprehensive and easily understandable form. The use of reliable, patient-centred websites or similar sources of information, is important and very useful.

The choice of treatment strategy must be extensively discussed with the patient and take into account the patient's preferences. It 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 and general health status of the patient. Age should be taken into consideration in conjunction with other factors and should not be the sole determinant for withholding or recommending a treatment. Age is a continuous variable and its cut-offs in clinical trials are always arbitrarily chosen. Overall, we strongly recommend that 'younger' patients should not be over-treated because they are 'young', just as 'older' patients should not be under-treated, because they are deemed to be old. Patients should be actively involved in all management decisions. The possibility of hereditary cancer should be explored and, if needed, prophylactic procedures discussed following appropriate genetic counselling and testing of the patient [IV, D] [39]. In younger premenopausal patients, possible fertility issues should be discussed and guidance about fertility-preservation techniques should be provided, before the initiation of treatment [40–43].

local treatment

surgery. Arguably the major change in the surgical treatment of primary breast cancer has been a shift towards breast-conservation treatment, which started >30 years ago. Currently, in Western Europe, 60%–80% of newly diagnosed cancers are amenable to breast conservation [wide local excision and radiation therapy (RT)]. 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, or patient choice [44].

breast-conservation surgery: 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. A careful histological assessment of resection margins is essential. Margin status should be reported according to the recommendations of the 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 [45]. No tumour at the inked margin is required and >2 mm (for *in situ* disease) is preferred [46, 47].

Marking the tumour bed with clips in a standardised way facilitates accurate planning of the radiation boost field, if it is indicated. Currently, achievable low local recurrence rates [<0.5% per year (with a target of <0.25%) and ≤10% overall at very long-term follow-up] should be maintained [48].

mastectomy: Breast reconstruction should be available to those women requiring mastectomy [37]. Immediate reconstruction in most women can make the prospect of losing a breast easier to accept, but not all women will be suitable for immediate reconstruction. Some women may decline or defer reconstruction because of personal preference. Others will be advised against immediate reconstruction for oncological reasons, particularly in the case of inflammatory breast cancer. The autologous tissue-based techniques generally tolerate postoperative RT well. Implant-based reconstruction can result in an unfavourable aesthetic outcome, following postoperative RT [49, 50]. Skin-sparing mastectomy allows the skin envelope to be conserved for use in the breast reconstruction. If post-mastectomy radiotherapy (PMRT) is indicated, a temporary implant should be positioned before RT.

For women undergoing breast reconstruction, whether immediate or delayed, a wide range of surgical options are available. The best technique for each patient should be discussed individually taking into account anatomic, treatment and patient preference. 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.

Autologous tissue flaps can replace relatively large volumes of breast tissue. Tissue can be taken from the latissimus dorsi muscle from the back, transverse rectus abdominis muscle, the free deep inferior epigastric perforator flap from the lower abdomen, superior gluteal artery-based perforator flap or free gracilis-based flap.

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.

advances in axillary staging: Regional lymph node status remains one of the strongest predictors of long-term prognosis in primary breast cancer. Axillary clearance 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) [51, 52]. The incidence of lymphoedema rises significantly (to 40%) when axillary clearance is combined with RT to the axilla. SLNB, rather than full nodal clearance, is now accepted as the standard of care for axillary staging in early, clinically node-negative breast cancer [II, A], unless axillary node involvement is proven on ultrasound-guided biopsy [53]. With appropriate training in the dual radiocolloid/blue dye or indocyanine green fluorescence technique, high identification rates (over 97%), low false-negative rates and favourable axillary recurrence rates following SLNB are achievable [54]. SLNB delivers less morbidity in terms of shoulder stiffness and arm swelling and allows for a reduced hospital stay [I, A].

There is no definite consensus for the pathologic assessment of SLNB. The significance of occult micrometastases in terms of surgical management and patient outcome appears to be negligible [55]. Thus, the authors of this manuscript agree with the guidelines published by ASCO [53], the National Comprehensive Cancer Network [56] and others [57, 58], that routine IHC or polymerase chain reaction is not recommended for the evaluation of sentinel lymph nodes.

The optimal management of micrometastatic spread and isolated tumour cells is the subject of ongoing research. Based on the results of the IBCSG 23–01 trial, further axillary treatment does not seem to be required when a sentinel node (SN) has micrometastasis (0.2–2 mm) [59]. The presence of macrometastatic spread in the SN traditionally mandated conventional axillary lymph node clearance. Recent results of a randomised, controlled trial (6.3 years of median follow-up) for patients with clinical T1–T2 cN0 invasive breast cancer and one to two sentinel lymph nodes containing metastases [treated with breast-conservation surgery (BCS) and tangential adjuvant RT], reported non-inferior rates of overall survival (OS), disease-free survival (DFS) and locoregional recurrence-free survival [60]. Another option in patients with cN0 and sentinel lymph node metastases (irrespective of the risk factors) is axillary irradiation, as demonstrated by the AMAROS study [51]. Therefore, all patients with micrometastatic spread or isolated tumour cells (<0.2 mm) in the SN and patients with limited involvement of the sentinel lymph node, undergoing tangential breast irradiation and adjuvant systemic treatment, may not need to have any further axillary procedure [II, B]. However, these results need to be confirmed and cannot be extended to patients with different characteristics than those of the trial's patient population.

surgery for in situ *malignancy (intraepithelial neoplasia):* DCIS may be treated with total mastectomy or BCT, provided clear resection margins can be achieved. There is no general consensus on what is considered an adequate margin; however, circumferential margins <2 mm are considered less adequate and no DCIS on inked margins is a minimal requirement [47]. 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). Lobular neoplasia (formerly called lobular carcinoma *in situ*), 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.

The risk of a positive SN with pure DCIS is small (7%–9%) and most of the metastases found are micrometastases or isolated tumour cells, detected by immunohistochemistry [61, 62]. The decision to perform an SN procedure should be based on the underlying risk of invasion. This 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 a larger extent of microcalcifications [63, 64]. Generally, an SN procedure is usually done if there is an associated mass, or if an ablative treatment is chosen.

risk-reducing mastectomy: Risk-reducing surgery (with prophylactic bilateral mastectomy and reconstruction) may be offered to women at very high risk, such as those who have had previous chest irradiation for lymphoma or *BRCA1* or *BRCA2* gene mutation carriers. 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% [65–67]. With bilateral mastectomy, the risk for both subsequent breast cancer incidence and mortality is reduced by 90%–95% [III, A]. Careful genetic assessment and psychological counselling are mandatory before undertaking such surgery.

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. These patients should be properly counselled and informed that patients with early-stage breast cancer, who opt for BCT, might have an even better outcome compared with those who have a mastectomy [68].

surgery after primary systemic therapy: Primary systemic therapy should be followed by surgery, according to the principles outlined above. Downsizing of a large unifocal primary tumour with neoadjuvant therapy will allow BCT to be undertaken in a substantial proportion of patients, even in tumours that were unresectable at diagnosis. This includes those with HER2 overexpression and triple-negative breast cancers who, at presentation, would have otherwise required mastectomy. With multifocal disease, or where reduction of the primary tumour size is more limited, mastectomy will still be required. Breast MRI is the most accurate modality for assessing the extent of residual disease following neoadjuvant treatment. Breast MRI should also be carried out before the start of systemic therapy for proper comparative evaluation. When a breast-conserving procedure is anticipated, it is necessary to mark the primary site (using a marker clip or carbon localisation, under ultrasound guidance) to facilitate accurate surgery.

radiation therapy

invasive carcinoma:

RT after BCS:

whole breast radiation therapy: Postoperative RT is strongly recommended after BCS [I, A] [69]. Whole breast radiation therapy (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% [69]. Boost irradiation gives a further 50% RR reduction. It is indicated for patients who have unfavourable risk factors for local control such as: age <50 years, grade 3 tumours, extensive DCIS, vascular invasion or non-radical tumour excision (focally—otherwise further surgery should be advocated) [I, A] [70, 71].

accelerated partial breast irradiation only: The concept of accelerated partial breast irradiation (APBI) is an appealing approach to shorten the overall treatment time substantially. 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. However, in the ELIOT (single dose of electrons) and TARGIT (single intra-operative dose 50 kV X-rays) randomised trials, the ipsilateral breast recurrence rate was significantly higher in the APBI groups, compared with the WBRT trial [72, 73]. Notwithstanding these negative 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 hormonal treatment [III, C] [74]. In the meantime, long-term results of several past and still on-going prospective randomised APBI trials are eagerly awaited.

radiation after mastectomy: 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% [75]. The benefits of PMRT are independent from the number of involved axillary lymph nodes and the administration of adjuvant systemic treatment. Therefore, while PMRT was always recommended for high-risk patients, including involved resection margins, four or more involved axillary lymph nodes [I, A], and T3–T4 tumours independent of the nodal status [II, B], we should now also consider routine use of PMRT for patients with one to three positive axillary lymph nodes [I, A] [75, 76].

regional irradiation: Older randomised trials have used large comprehensive locoregional RT encompassing the chest wall and all regional lymph nodes. Recently presented results support this approach, especially for patients with involved axillary lymph nodes [77–79]. Therefore, although clinically apparent lymph node relapses (especially axillary and internal mammary) are rare, nodal irradiation remains indicated for patients with involved lymph nodes [I, B] [80]. We 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, while right-sided patients received the same 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 of this manuscript agree with the new European Society for Radiotherapy and Oncology (ESTRO) guidelines for target volume delineation in breast cancer. The ESTRO guidelines advise to include only the most caudal lymph nodes surrounding the sub-clavicular arch and the base of the jugular vein [81]. After axillary lymph node dissection, the resected part of the axilla should not be irradiated, except in cases of residual disease after surgery.

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] [82–85]. Strictly speaking, these data are not fully validated in young patients and in patients with mastectomy and/or additional regional irradiation. These patients were either not included or under-represented in the relevant trials. As hypofractionation in many places is being introduced for all patient subgroups, and in the unlikelihood of prospective, randomised trials that will test this, we advise to carefully monitor, evaluate and compare outcomes in those patients. Further hypofractionation (to five fractions) is currently the subject of ongoing prospective clinical trials.

patients with unresectable disease: Most patients who present with unresectable non-metastatic disease will first be treated with primary systemic therapy. If rendered resectable, this should be followed by surgery and RT, according to the principles outlined for locoregional advanced disease.

If the disease remains unresectable, RT should be considered to treat all sites of the original tumour extension, with a boost to residual disease. Most durable remissions can be expected with an elective dose up to an equivalent of 50 Gy to regions with a high likelihood of bearing subclinical disease and a boost up to 60–76 Gy (depending on the dose to the organs at risk) to all sites of macroscopic disease. Regular evaluation during the course of RT is advised, to select patients that might become amenable for resection after 45–50 Gy.

Interesting, but early, reports are published on combined radiation and chemotherapy, which should be further evaluated in prospective trials.

It is advisable that patients are seen by the radiation oncologist preceding initiation of primary systemic therapy. If judged relevant, a CT scan should be taken in the treatment position, for later image co-registration to improve localisation of the target volumes (e.g. enlarged lymph nodes that might not be resectable).

non-invasive carcinoma (intraepithelial neoplasia): WBRT after BCS for DCIS decreases the risk of local recurrence, with survival equal to that after mastectomy [I, A] [86]. 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, and the inability to define subsets of women who do not benefit from radiotherapy [56, 87]. 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 may be an option. Randomised data on additional dose to the tumour bed (boost) are lacking, but a boost can be considered for patients at higher risk for local failure [III, B]. APBI should only be carried out within a clinical trial. Total mastectomy with clear margins in DCIS is curative, and PMRT is not recommended. Lobular neoplasia is a risk factor for future development of invasive cancer in both breasts; RT is not warranted, with exception of the pleomorphic subtype.

adjuvant systemic treatment

The decision on systemic adjuvant treatment should be based on the predicted sensitivity to particular treatment types, the benefit from their use and an individual's risk of relapse. The final decision should also incorporate the predicted treatment sequelae, the patient's biological age, general health status, co-morbidities and preferences. Treatment should start preferably within 2–6 weeks after surgery. The data show an important decrease in systemic therapy efficacy when it is administered more than 12 weeks after surgery [88].

The most recent publication of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview states the relative benefit of chemotherapy is similar in all the subgroups independent of age, stage, histopathological grade and ER status [89]. This seems to be in contradiction with the results from individual trials, both in the adjuvant and neoadjuvant settings, as well as knowledge of breast cancer biology. One also needs to take into account that many trials included in the EBCTCG overview have incomplete data on ER expression, in particular quantitative immunohistochemistry. Furthermore, these trials have included patients with generally higher risk of recurrence than those seen today and often used suboptimal ETs (by current standards). However, these views can be conciliated when acknowledging that, even if the relative benefit would be similar, the absolute benefit derived from adjuvant chemotherapy varies substantially. The risk to the individual patient is determined by the biology and the burden of the disease, for example the absolute benefit of adjuvant chemotherapy for a low burden luminal-A-like breast cancer, is extremely small and needs to be balanced against the known short- and long-term side-effects.

The authors of this manuscript agree with the 2013 and 2015 St Gallen guidelines, which recommend, for luminal cases with unclear chemotherapy indications, that the decision on systemic adjuvant therapies should be based on the surrogate intrinsic phenotype (Figure 2), that is determined by ER/PgR, HER2 and Ki67 assessment (Tables 2 and 5), with the selective help of genomic tests when available (particularly MammaPrint, Oncotype DX, Prosigna ROR and Endopredict) [23, 33].

It must be stressed that IHC/fluorescence *in situ* hybridisation determination of intrinsic phenotype, is not fully accurate. The prerequisite for using such a surrogate assessment is the use of standardised assays and a meticulous quality control.

All luminal cancers should be treated with ET. Most luminal A tumours, except those with the highest risk of relapse (extensive nodal involvement), require no chemotherapy [I, A] whereas luminal B HER2-negative cancers constitute a population of the highest uncertainty regarding chemotherapy indications [I, C]. Indications for chemotherapy within this subtype depend on the individual's risk of relapse, taking into account

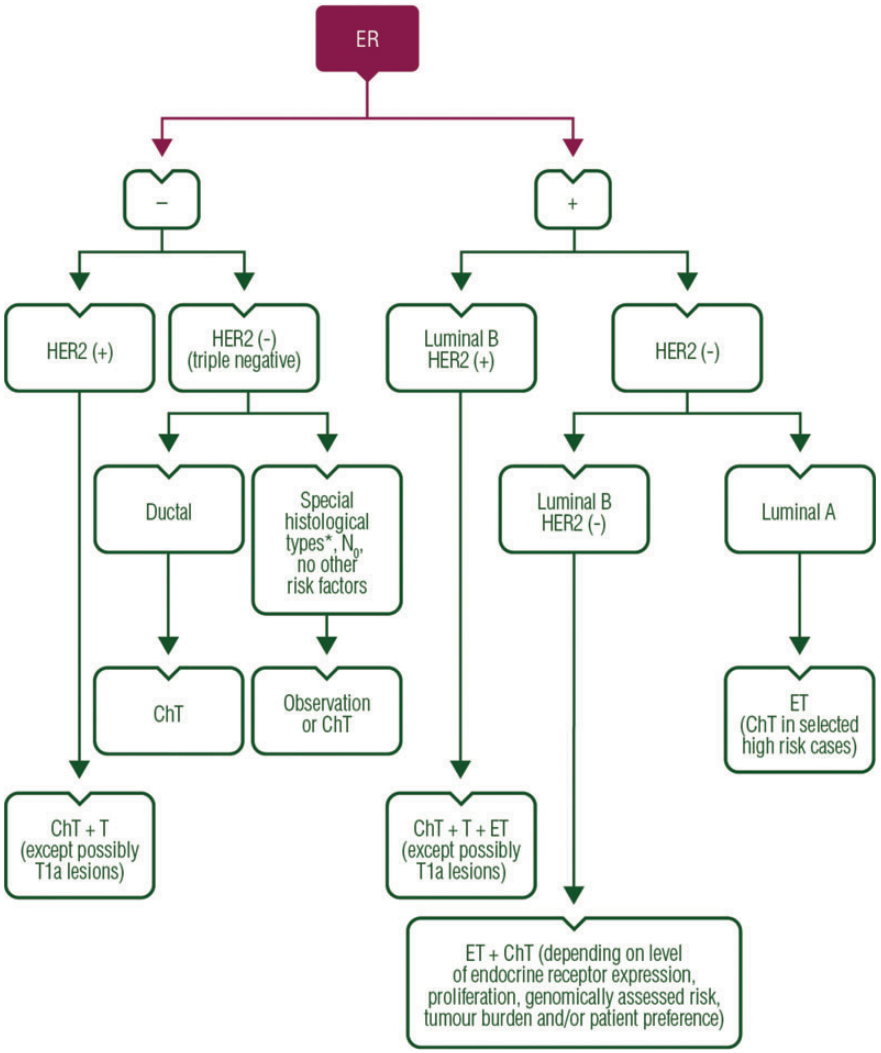

Figure 2. (Neo)adjuvant systemic treatment choice by biomarker expression and intrinsic phenotype. ER, oestrogen receptor; HER2, human epidermal growth factor 2 receptor; ChT, chemotherapy; ET, endocrine therapy; T, trastuzumab.

Table 5. 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 (four or more positive LN, T3 or higher) grade 3
Luminal B-like (HER2-negative)	ET + ChT for the majority of cases	
Luminal B-like (HER2-positive)	ChT + anti-HER2 + 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, we recommend following the St Gallen 2013 recommendations [23] that propose ET for endocrine responsive histologies (cribriform, tubular and mucinous), ChT for high-risk endocrine nonresponsive (medullary, metaplastic) and no systemic therapy for low-risk endocrine nonresponsive (secretory juvenile, adenoid cystic and apocrine).
ET, endocrine therapy; ChT, chemotherapy; LN, lymph node; HER2, human epidermal growth factor 2 receptor.

the tumour extent and features suggestive of its aggressiveness (grade, proliferation, vascular invasion), presumed responsiveness to ET and patient preferences. Features associated with lower endocrine responsiveness include, low steroid receptor expression, lack of PgR expression, high tumour grade and high expression of proliferation markers. Several decision-making tools such as Adjuvant! Online, PREDICT and the Nottingham Prognostic Index exist to help in predicting recurrence risks and benefits from particular treatments [28–30]. uPA-PAI1 tumour markers have level I evidence as prognostic factors and can be used to aid treatment decision making in early breast cancer [I, A] [90]. In cases of uncertainty regarding indications for adjuvant chemotherapy (after consideration of other tests), gene expression assays, such as MammaPrint, Oncotype DX, Prosigna and Endopredict, may be used, where available. These assays can determine the individuals recurrence risk as well as, potentially predict the benefit of chemotherapy [IV, A] [23, 33, 91–94]. Luminal B HER2-positive tumours are treated with chemotherapy, ET and trastuzumab [I, A]. No randomised data exist to support omission of chemotherapy in this group. However, in small, node-negative tumours, combination of single-agent paclitaxel and trastuzumab provides excellent results [95]. Additionally, in cases of contraindications for chemotherapy or patient refusal, in selected cases it may be acceptable to offer the combination of targeted agents (ET and trastuzumab) [V, A]. Triple-negative tumours benefit from adjuvant chemotherapy, with the possible exception of low-risk 'special histological subtypes' such as, secretory juvenile, apocrine or adenoid cystic carcinomas [I, A]. HER2 (non-luminal) cancers are treated with chemotherapy plus trastuzumab, apart from selected cases with very low risk, such as T1aN0 [I, A].

In general, chemotherapy should not be used concomitantly with ET [II, D] [96]. Trastuzumab may routinely be combined with non-anthracycline-based chemotherapy and ET [I, A]. Concomitant use with anthracyclines is not routinely recommended outside of clinical trials. For most patients, the use of a sequential anthracycline-based followed by taxane–trastuzumab-based regimen is the preferred choice. RT may be delivered safely during trastuzumab, ET and non-anthracycline–non-taxane-based chemotherapy [III, B]. If chemotherapy and RT are to be used separately, chemotherapy usually precedes RT.

endocrine therapy. ET is indicated in all patients with detectable ER expression (defined as ≥1% of invasive cancer cells) irrespective of the use of chemotherapy and/or targeted therapy [I, A] [97, 98]. The choice of agent is primarily determined by the patient's menopausal status. Other factors include differences in efficacy and side-effect profiles.

premenopausal patients: Tamoxifen 20 mg/day for 5–10 years is a standard [I, A]. In patients becoming postmenopausal during the first 5 years of tamoxifen, a switch to letrozole, an aromatase inhibitor (AI), seems to be particularly beneficial [99]. The value of adding ovarian suppression [by gonadotropin-releasing hormone (GnRH) agonists or ovarian ablation] has long been a matter of controversy, particularly in chemotherapy-treated patients, who frequently develop ovarian failure as a consequence of cytotoxic treatment [II, B] [100, 101]. Chemotherapy-induced amenorrhoea has been demonstrated to be related to improved long-term outcomes [97, 102, 103].

The SOFT trial demonstrated no significant overall DFS improvement in patients undergoing ovarian suppression. Treatment effect was most pronounced among those treated with adjuvant chemotherapy. The data on OS is not yet mature. Not all clinical situations have been adequately represented in the SOFT trial and a case-by-case decision should be taken, after careful discussion with the patient regarding potential benefits and substantially different side-effect profiles [I, B] [104]. Less clear is the value of combining ovarian suppression and AI, as contradictory results were obtained in the ABCSG-12 and combined SOFT-TEXT trials [I, C] [105, 106]. Combination of ovarian ablation and tamoxifen in ER-positive patients is at least as effective as cyclophosphamide/methotrexate/fluorouracil (CMF)-type chemotherapy and may be used as an alternative [II, A] [100, 107]. The optimal duration of ovarian suppression is not known, although it is usually administered for 2–5 years [V, B].

For patients with contraindications to tamoxifen, a GnRH agonist in combination with an AI should be used. In rare cases where both tamoxifen and AI are not tolerated, a GnRH agonist alone may be considered. The role of GnRH agonists in preventing chemotherapy-related ovarian failure has been recently supported by the efficacy data (less premature ovarian failures and more pregnancies) from the POEMS trial (ER-negative patients) and safety data from TEXT trial (ER-positive patients) [II, B] [106, 108]. However, due to contradictory results from previous trials, the decision must be taken in a case-by-case manner and after careful discussion with the patient regarding benefits and risks of such an approach.

postmenopausal patients: AIs (both non-steroidal and steroidal) and tamoxifen are valid options. AIs allow for prolongation of the DFS, with no significant impact on OS (1%–2%, depending on the choice of an upfront or sequential strategy) [I, B] [109–112]. They 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) [113, 114]. There is no proven benefit for the routine use of AIs for >5 years. The recently published ATLAS study demonstrated an advantage of 10 years rather than 5 years of tamoxifen. With this in mind, extended adjuvant therapy should be discussed with all patients, except the ones with a very low risk, although the optimal duration and regimen of adjuvant ET is currently unknown [I, C] [115].

The use of tamoxifen is associated with an increased risk of thromboembolic complications and endometrial hyperplasia (including endometrial cancer). Caution should be exercised in patients with conditions predisposing to these sequela. Appropriate diagnostic tests should be carried out in those presenting with symptoms that are 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] [116, 117]. Patients undergoing ovarian suppression and those taking AIs, are at an increased risk of bone loss and should be advised to have adequate calcium and vitamin D3 intake. In addition, periodic assessment of their bone mineral density (by dual energy X-ray absorption [DEXA] scan) should be undertaken [I, A].

chemotherapy. Chemotherapy is recommended in the vast majority of triple-negative, HER2-positive breast cancers and in high-risk luminal HER2-negative tumours [I, A]. The absolute benefit from chemotherapy is more pronounced in ER-negative tumours [118, 119]. In ER-positive tumours, chemotherapy at least partially exerts its effect by induction of ovarian failure [97, 102]. The most frequently used regimens contain anthracyclines and/or taxanes, although in selected patients CMF may still be used. Four cycles of doxorubicin and cyclophosphamide (AC) are considered equal to six cycles of CMF. The added value of six cycles of three-drug anthracycline-based regimens is controversial [I, C] [89, 120]. Data on topoisomerase IIα as a predictive factor for anthracycline-based chemotherapy have not been confirmed in prospective studies. A large meta-analysis suggested that, although it may have some predictive value and its use may be related to a small clinical benefit, it cannot be recommended for clinical practice [I, C] [121].

The addition of taxanes improves the efficacy of chemotherapy, independently of age, nodal status, tumour size or grade, steroid receptor expression or tamoxifen use, but at the cost of increased non-cardiac toxicity [I, A] [89, 122]. Sequential use of anthracyclines and taxanes is superior to concomitant use [I, B] [123]. Some data suggest that a taxane-anthracycline sequence may be more effective than the traditionally used anthracycline-taxane order [124]. Overall, chemotherapy regimens based on anthracyclines and taxanes reduce breast cancer mortality by about one-third [89, 98]. Non-anthracycline, taxane-based regimens, such as four cycles of docetaxel and cyclophosphamide (TC), may be used as an alternative to four cycles of anthracycline-based chemotherapy in selected patients (i.e. those at risk of cardiac complications) [I, A] [125]. No robust, prospective randomised data exist on the use of platinum compounds in the adjuvant setting, either in unselected triple-negative tumours or *BRCA 1/2* mutation carriers. Therefore, its use cannot be recommended for routine use.

Chemotherapy is usually administered for 12–24 weeks (four to eight cycles), depending on the individual recurrence risk and the selected regimen. The use of dose-dense schedules (with granulocyte colony-stimulating factor [G-CSF] support) should be considered, particularly in highly proliferative tumours [I, B] [126]. High-dose chemotherapy with stem cell support should not be used [I, E].

HER2-directed therapy. Trastuzumab combined with chemotherapy in patients with HER2 overexpression/amplification approximately halves the recurrence risk, compared with chemotherapy alone, translating into a 10% absolute improvement in long-term DFS and 9% increase in 10-year OS [I, A] [127–129]. Trastuzumab is approved in patients with node-positive disease and in N0 patients with tumours >1 cm. Due to the relatively high failure 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] [130]. In line with the new ASCO HER2 guidelines, if an HER2 test result is ultimately deemed to be equivocal, even after reflex testing with an alternative assay, HER2-targeted therapy may also be considered [18].

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] [131]. No additional benefit was demonstrated for 2-year trastuzumab administration in the HERA trial [132]. The PHARE trial compared 6 and 12 months of trastuzumab, where the non-inferiority of 6 months of trastuzumab could not be demonstrated. Therefore, a duration of one year remains the standard [133]. Trastuzumab is usually well-tolerated, although (usually reversible) cardiac dysfunction may occur. Patient selection should be founded on the baseline cardiac function (expressed by the left ventricular ejection fraction). Periodic (usually every 3–4 months) monitoring of cardiac function during treatment is necessary.

Due to its cardiotoxicity, trastuzumab should not be routinely administered concomitantly with anthracyclines [I, B]. Combination with taxanes is safe and has been demonstrated

to be more effective than sequential treatment [I, A] [128]. Trastuzumab may also be safely combined with RT and ET.

In the neoadjuvant setting, dual anti-HER2 blockade associated with chemotherapy (trastuzumab + lapatinib, trastuzumab + pertuzumab) has led to improvements in the pCR rate when compared with chemotherapy associated with one anti-HER2 agent. However, this did not translate into improvement in long-term outcomes for the combination of trastuzumab + lapatinib, and such a treatment cannot be recommended [134–137]. For the trastuzumab + pertuzumab combination, the results of the large adjuvant Aphinity trial are needed before this can be recommended for routine use. However, after reviewing potential risks and benefits (including the financial impact), in selected higher risk cases it can be considered an acceptable option as neoadjuvant therapy.

bisphosphonates. Prophylactic use of bisphosphonates, although not formally approved in most countries, may be discussed in women with a low-oestrogen status (undergoing ovarian suppression or postmenopausal), as prolongation of DFS and breast cancer specific survival was demonstrated in these populations [I, B] [105, 138, 139]. In patients with treatment-related bone loss, bisphosphonates decrease the risk of skeletal complications [I, A] [140, 141].

treatment of elderly patients. Due to the limited data from randomised studies, strong recommendations cannot be made regarding the use of adjuvant systemic therapies in this population. In general, treatment decisions should be based on biological rather than formal age, and 'fit' elderly patients should receive identical treatments to their younger counterparts. Full doses of drugs should be used, whenever feasible [V, A]. In patients suitable for standard chemotherapy, single-agent capecitabine or docetaxel have been demonstrated to be inferior to the standard multidrug regimen (AC or CMF) and therefore, a standard multidrug regimen should be used [II, D] [142, 143]. 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 chemotherapy remains unknown [II, B] [144].

systemic adjuvant therapy for DCIS. In patients treated conservatively for ER-positive DCIS, tamoxifen decreases the risk of both invasive and non-invasive recurrences, and reduces the incidence of second primary (contralateral) breast cancer, without an effect on OS [I, B] [145]. Following mastectomy, tamoxifen 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]. AIs are being investigated for use in adjuvant therapy for DCIS, but they should not be used in routine care at this time.

primary (neoadjuvant) systemic therapy. In locally advanced and large 'operable' cancers, in particular when mastectomy is required due to tumour size, primary systemic therapy (used before local treatment) may 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 [II, C] [122, 146]. All modalities (chemotherapy, ET and targeted therapy) used in adjuvant treatment may also be used preoperatively. If chemotherapy 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 [V, B]. This will increase the probability of achieving a pCR, which is a proven factor for a good prognosis. For the same reason, in HER2-positive breast cancer, trastuzumab therapy should be started in the neoadjuvant setting, in association with the taxane part of the chemotherapy regimen. This increases the probability of achieving a pCR. The role of dual HER2 blockade (including a combination of trastuzumab and pertuzumab) is not well proven and such treatment is not recommended for routine use, although it may be discussed on a case-by-case basis. The addition of platinum compound (carboplatin) to neoadjuvant chemotherapy allows for an increase in the pCR rate in triple-negative tumours, particularly in those carrying deleterious *BRCA 1/2* or *RAD* mutations or in patients with a family history of breast/ovarian cancer. But the effect of those compounds on long-term outcomes is unknown (I, B) [147–149]. The chemotherapy regimens to be used in the neoadjuvant setting are the same ones used in the adjuvant setting. Unfortunately, there are no validated predictive markers to allow the tailoring of the regimen to the individual patient. Therefore, it is recommended that a sequential regimen of anthracyclines and taxanes is used for the vast majority of patients [I, B]. For *BRCA 1/2* or *RAD* mutations it is acceptable to add a platinum compound, after discussion with the patient.

After delivery of the standard 4 to 8 cycles of anthracyclines and taxanes, even in the absence of pCR, no additional chemotherapy should be administered in the adjuvant setting, since such an approach has no proven benefit.

ER-positive, HER2-negative carcinomas, especially of the lobular subtype, are generally less responsive to primary chemotherapy than ER-negative and HER2-positive tumours, and may benefit more from primary ET [150]. In post-menopausal patients 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] [151–153]. Due to paucity of data from randomised trials, preoperative ET is not routinely recommended in premenopausal patients outside clinical trials.

The vast majority of breast cancer cases in male patients are ductal invasive carcinoma of the luminal type. Tamoxifen is the standard adjuvant systemic therapy, AIs should not be used alone in this setting, as they are less effective [154, 155]. Chemotherapy indications and regimens should, for the moment, follow the same recommendations as those for luminal-like breast cancer in female patients [155–157].

personalised medicine

Breast cancer is the pioneer of personalised medicine in oncology. ER and/or PgR and HER2 status have been used for many years as predictive factors to select patients for targeted ET or anti-HER2 treatment. In recent years, surrogate intrinsic tumour phenotypes, based on biomarker expression, have also

Table 6. Summary of biomarkers used in treatment decision making

Biomarker	Prognostic	Predictive	Technical validation	Clinical validation	Test and scoring recommendations	Patient selection
ER	++	+++	Yes LOE IB	Yes	IHC	Hormonal treatment
PgR	+++	+	Yes LOE IB	No	IHC	If negative, chemotherapy in some cases
HER2	++	+++	Yes LOE IB	Yes	IHC ≥10% cells with complete membrane staining ISH: number of HER2 gene copies ≥6 or the ratio HER2/chromosome 17 ≥2	Anti-HER2 treatment
Ki67	++	+	No	No	IHC no final consensus on cut-off but values below 10% are considered low and above 30% are high	Chemotherapy if elevated
Intrinsic subtypes	++	++	Yes	Yes	Gene expression profile (not for IHC surrogates)	Different responses to neoadjuvant chemotherapy according to the subtype
First generation signatures (MammaPrint, Oncotype Dx)	+++	++	Yes	Validated retrospectively in prospective clinical trials, prospective clinical validation ongoing	Gene expression profile, RT-PCR	Chemotherapy if high risk or high score
Second generation signatures (Prosigna®, Endopredict®)	++	++	Yes	Validated retrospectively in prospective clinical trials	N-Counter TM technology, RT-PCR	Prognosis, chemotherapy if high risk or high score

ER, oestrogen receptor; IHC, immunohistochemistry; RT-PCR, reverse transcription polymerase chain reaction; LOE, level of evidence; PgR, progesterone receptor; ISH, *in situ* hybridisation; HER2, human epidermal growth factor 2 receptor.

been used for treatment individualisation. 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] [92] and can be used in treatment decision making for early breast cancer. In cases when decisions might be challenging, such as luminal B HER2-negative and node-negative breast cancer, commercially available molecular signatures for ER-positive breast cancer, such Oncotype DX, EndoPredict, Prosigna, and for all types of breast cancer (pN0–1), such as MammaPrint and Genomic Grade Index, may be used in conjunction with all clinicopathological factors, to help in treatment decision making [23, 92]. Results from large phase III prospective clinical trials (MINDACT, Plan B, TAILORx and RxPONDER) are eagerly awaited for an optimal and accurate use of these new tools in clinical practice. A biomarker summary is shown in Table 6.

follow-up and long-term implications

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 ET.
- 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 [158]. The annual hazard of recurrence peaks in the second year after diagnosis but remains at 2%–5% in years 5–20. Patients with node-positive disease tend to have higher annual hazards of recurrence than patients with node-negative cancers. In the first few 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] [159]. Relapse of breast cancer may occur as late as >20 years after the initial diagnosis, particularly in patients with ER/PgR-positive disease.

Despite the fact that no randomised data exist to support any particular follow-up sequence or protocol, balancing patient needs and follow-up costs, we recommend regular visits every 3–4 months in the first 2 years, every 6 months from years 3–5 and annually thereafter [V, A]. Every visit should include a thorough history, eliciting of symptoms and a physical examination. Annual ipsilateral (after BCT) and/or a contralateral mammography with ultrasound is recommended [II, A]. An MRI of the breast may be indicated for young patients, especially in cases of dense breast tissue and genetic or familial predispositions.

Table 7. Summary of recommendations

Screening and diagnosis

- Mammography screening in the 50- to 70-year age group reduces breast cancer mortality.
- In women with familial breast cancer, with or without proven BRCA mutations, annual screening with MRI of the breast, in combination with mammography is recommended [III, A].
- Diagnosis and treatment should be carried out in 'breast units': specialised institutions caring for a high volume of breast cancer patients, and provided by a multidisciplinary team including at least a surgeon, radiation oncologist, medical oncologist, radiologist, pathologist and a breast nurse (or another trained and specialised health care practitioner)—all specialised in and dedicated to breast cancer [IV, A]. The patients should be provided with full, preferably written, culturally adapted information about their disease and treatment [V, A].
- The diagnosis of breast cancer is based on clinical examination in combination with imaging, and confirmed by pathological assessment. Other assessments include complete personal and family medical history, including evaluation of menopausal status, a physical examination, a full blood count, liver and renal function tests, alkaline phosphatase and calcium levels.
- Imaging includes bilateral mammography and ultrasound of the breast and regional lymph nodes. An MRI of the breast is not routinely recommended, but should be considered in cases of: familial breast cancer associated with BRCA mutations, breast implants, lobular cancers, suspicion of multifocality/multicentricity (particularly in lobular breast cancer) or large discrepancies between conventional imaging and clinical examination, and before and during neoadjuvant chemotherapy [III, A].
- Pathological diagnosis should be based on core needle biopsy obtained (preferably) by ultrasound or stereotactic guidance. If preoperative systemic therapy is planned, a core needle biopsy is mandatory to ensure a diagnosis of invasive disease and assess biomarkers [III, A].
- The pathological report should include the histological type, grade, ER status and, for invasive cancer, PgR status, HER2 status and a proliferation measure such as Ki67 [III, A]. 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]. 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].
- A marker (e.g. surgical clip, carbon) should be placed into the tumour at biopsy, to ensure surgical resection of the correct site [V, A].

Staging and risk assessment

- Lymph nodes should be assessed by clinical examination and ultrasound, supplemented by ultrasound-guided fine needle aspiration or core biopsy of suspicious lymph nodes [III, A].
- Routine staging evaluations are directed at locoregional disease, as in early breast cancer asymptomatic distant metastases are very rare and patients do not profit from comprehensive laboratory and radiological staging.
- Asymptomatic distant metastases are very rare and most patients do not benefit from comprehensive laboratory (including tumour markers [25]) and radiological staging [III, D].
- Additional investigations such as chest CT abdominal ultrasound or CT scan and bone scan should be considered for patients with clinically positive axillary nodes, large tumours (e.g. ≥5 cm), aggressive biology or clinical signs, symptoms or laboratory values suggesting the presence of metastases [III, B]. Dual imaging methods combining functional and anatomical information such as FDG-PET/CT may be useful when conventional methods are inconclusive [V, A]. PET/CT scanning can replace traditional imaging for staging in high-risk patients who are candidates for neoadjuvant chemotherapy, as well as those with locally advanced and/or inflammatory disease due to their high risk of having metastatic disease [V, B].
- In patients planned for (neo)adjuvant treatment, with anthracyclines and/or trastuzumab, evaluation of cardiac function with a cardiac ultrasound or a multigated acquisition scan is essential [I, A].
- The postoperative pathological assessment of the surgical specimen should be made according to the pTNM system to include: number, location and maximum diameter of tumour(s) removed, histological type and grade of the tumour(s), vascular invasion, biomarker analysis, evaluation of the resection margins, the total number of removed and number of positive lymph nodes and the extent of metastases in the lymph nodes [III, A].
- HER2 gene amplification status may be determined directly from all invasive tumours using *in situ* hybridisation (fluorescent, chromogenic or silver), replacing IHC or only for tumours with an ambiguous (2+) IHC score [II, B].
- Proliferation markers such as the Ki67 labelling index may supply additional useful information, particularly if the assay can be standardised [V, A].

Treatment

- The choice of treatment strategy is based on biology (pathology including biomarkers, gene expression) and tumour extent/location (size and location of primary tumour, number of lesions, number and extent of lymph node involvement) as well as on the age, body habitus and general health status of the patient and her/his preferences.
- The possibility of hereditary cancer should be explored and, if needed, prophylactic procedures discussed, following appropriate genetic counselling and testing [IV, D]. Risk-reducing surgery with prophylactic bilateral mastectomy and reconstruction may be offered to women with a very high risk of breast cancer, such as those carrying the BRCA1 or BRCA2 gene mutations or those with previous chest irradiation for lymphoma. With bilateral mastectomy, the risk for both subsequent breast cancer incidence and mortality is reduced by 90%–95% [III, A].
- DCIS may be treated with BCS, provided clear resection margins can be achieved, or with mastectomy.
- WBRT after BCS for DCIS decreases the risk of local recurrence with survival equal to that after mastectomy [I, A].
- Following mastectomy for DCIS, tamoxifen 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].

Continued

Table 7. *Continued*

- Randomised data on additional dose to the tumour bed (boost) in DCIS patients are lacking, but a boost can be considered for patients at higher risk for local failure [III, B].
- Breast conservation (wide local excision and RT) is the local treatment of choice in the majority of patients with invasive cancer. In some circumstances, mastectomy may still be carried out because of tumour size (relative to breast size), tumour multicentricity, prior radiation to the chest or breast, or patient choice.
- Oncoplastic procedures can achieve better cosmetic outcomes, especially in patients with large breasts, with a less favourable tumour/breast size ratio or with a cosmetically difficult location of the tumour in the breast.
- Breast reconstruction, preferably immediate, should be available to women requiring mastectomy.
- Silicone gel implants are safe and acceptable components of the reconstructive armamentarium [III, A].
- SLNB rather than full axillary nodal clearance, is now the standard of care, unless axillary node involvement is proven [II, A].
- Patients with isolated tumour cells (<0.2 mm) in the sentinel node and patients with limited involvement of the sentinel lymph nodes undergoing tangential breast irradiation may not need to have any further axillary procedure [II, B].
- In patients undergoing preoperative systemic therapy, SLNB carried out after systemic therapy demonstrated lower detection rates and higher rates of false-negatives. However, if the axilla is negative on ultrasound and/or PET/CT scanning, carried out before the start of systemic therapy, a post-systemic therapy SNLB can be considered [V, B].
- Postoperative RT is strongly recommended after BCS [I, A]. Boost irradiation gives a further 50% risk reduction and is indicated for patients with unfavourable risk factors for local control [I, A].
- Partial breast irradiation may be considered carefully as an acceptable treatment option in selected patients at least 50 years old, with unicentric, unifocal, node-negative, non-lobular breast cancer up to 3 cm in size without the presence of an extensive intraductal component or vascular invasion, and with negative margins [III, C].
- Post-mastectomy RT is recommended for patients with involved axillary nodes and/or with T3–T4 tumours, especially in the presence of additional risk factors [I, A].
- Although clinically apparent lymph node relapses (especially axillary and internal mammary) are rare, nodal irradiation remains indicated for patients with involved lymph nodes [I, B].
- Shorter fractionation schemes (e.g. 15–16 fractions with 2.5–2.67 Gy single dose) have been validated in large prospective studies and are generally recommended [I, A].
- The decision on systemic adjuvant therapies is based on the surrogate intrinsic phenotype determined by ER/PgR, HER2 and Ki67 assessment or on the genomic-based intrinsic subtype.
- All patients with detectable ER expression, defined as ≥1% of invasive cancer cells, should be offered ET [I, A]. For premenopausal patients, tamoxifen is a standard [I, A] and ovarian suppression may improve DFS in patients remaining premenopausal after having received chemotherapy. For some premenopausal patients, the combination of an AI and ovarian suppression can be an option, although long-term follow-up and survival data are still lacking. For postmenopausal patients, AIs (both non-steroidal and steroidal) and tamoxifen are valid options [I, B].
- Extended adjuvant therapy should be discussed with all postmenopausal patients, except the ones with a very low risk, although the optimal duration and regimen of adjuvant ET is currently unknown [I, C].
- Patients on tamoxifen should be advised to avoid the use of strong and moderate CYP2D6 inhibitors. If such drugs cannot be replaced, a switch to AIs (in premenopausal patients in combination with ovarian suppression) should be considered [IV, B].
- Patients undergoing ovarian suppression and those taking AIs are at an increased risk of bone loss and should be advised to have adequate calcium and vitamin D3 intake. In addition, periodic assessment of their bone mineral density should be undertaken [I, A].
- Chemotherapy is recommended in the vast majority of triple-negative, HER2-positive breast cancers and in high-risk luminal HER2-negative tumours [I, A].
- The added value of six cycles of three-drug anthracycline-based regiments is controversial [I, C]. The addition of taxanes improves the efficacy of chemotherapy, independently of age, nodal status, tumour size or grade, steroid receptor expression or tamoxifen use, but at the cost of increased non-cardiac toxicity [I, A]. Non-anthracycline, taxane-based regimens, such as four cycles of docetaxel and cyclophosphamide, may be used as an alternative to four cycles of anthracycline-based chemotherapy in selected patients (i.e. those at risk of cardiac complications) [I, A].
- Most luminal A tumours, except those with the highest risk of relapse (extensive nodal involvement), require no chemotherapy [I, A].
- For luminal HER2(−) cancers, the indications for chemotherapy depend on the individual risk of relapse presumed responsiveness to ET and patient preferences. In general, chemotherapy should not be used concomitantly with ET [II, D].
- Luminal B HER2(+) tumours are treated with chemotherapy, ET and trastuzumab [I, A]; no data exist to support omission of chemotherapy in this group. In cases of contraindications for chemotherapy or patient refusal, in selected cases it may be acceptable to offer the combination of targeted agents (ET and trastuzumab) [V, A].
- uPA-PAI1 tumour markers have level I evidence as prognostic factors and can be used to aid treatment decision making in early breast cancer [I, A].
- In cases of uncertainty regarding indications for adjuvant chemotherapy (after consideration of other tests), gene expression assays, such as MammaPrint, Oncotype DX, Prosigna and Endopredict, may be used, where available. These assays can determine the individual's recurrence risk as well as potentially predict the benefit of chemotherapy [IV, A].
- HER2(+) (non-luminal) cancers should be treated with chemotherapy plus trastuzumab [I, A].
- Triple-negative tumours benefit from adjuvant chemotherapy, with possible exclusion of low-risk 'special histological subtypes' such as secretory juvenile, apocrine or adenoid cystic carcinomas [I, A].

Continued

Table 7. *Continued*

- Chemotherapy usually consists of four to eight cycles of anthracycline- and/or taxane-based regimen. Sequential use of anthracyclines and taxanes, instead of concomitant, is recommended [I, B].
- The use of dose-dense schedules (with G-CSF support) should be considered particularly in highly proliferative tumours [I, B].
- High-dose chemotherapy with stem cell support should not be used [I, E].
- Trastuzumab combined with chemotherapy in patients with HER2 overexpression/amplification approximately halves the recurrence risk and improves overall survival, compared with chemotherapy alone [I, A].
- Trastuzumab is approved in patients with node-positive disease and in N0 patients with tumours >1 cm. Due to the relatively high failure 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].
- Due to its cardiotoxicity, trastuzumab should not be routinely administered concomitantly with anthracyclines [I, B]. Combination with taxanes is safe and has been demonstrated to be more effective than sequential treatment [I, A].
- RT may be delivered safely during trastuzumab, ET and non-anthracycline–non-taxane-based chemotherapy [III, B].
- Prophylactic use of bisphosphonates may be discussed in women with a low-oestrogen status (undergoing ovarian suppression or postmenopausal) [I, B]. In patients with treatment-related bone loss, bisphosphonates decrease the risk of skeletal complications [I, A].
- In elderly patients, full doses of drugs should be used, whenever feasible [V, A]. In patients suitable for standard chemotherapy a standard multidrug regimen should be used [II, D].
- In locally advanced and large 'operable' cancers, in particular when mastectomy is required due to tumour size, primary systemic therapy (used before local treatment) may allow for achieving operability or decreasing the extent of surgery [I, A]. All modalities (chemotherapy, ET and targeted therapy) used in adjuvant treatment may also be used preoperatively. In operable cases, the timing of treatment (pre- versus postoperative) has no effect on long-term outcomes [II, C]. If chemotherapy is used, it is recommended to deliver all planned treatment without unnecessary breaks, irrespective of the magnitude of tumour response [V, B].

Follow-up and survivorship

- The aims of follow-up are to detect early local recurrences or contralateral breast cancer, to evaluate and treat therapy-related complications, to motivate patients continuing hormonal treatments and to provide psychological support and information in order to enable a return to normal life.
- Regular visits every 3–4 months in the first 2 years, every 6 months from years 3–5 and annually thereafter are recommended [V, A].
- Annual ipsilateral (after BCT) and/or contralateral mammography with ultrasound is recommended [II, A]. In asymptomatic patients, there are no data to indicate that other laboratory or imaging tests produce a survival benefit but available data come from old studies and new trials are needed.
- Ultrasound can be considered in the follow-up of lobular invasive carcinomas [III, B].
- Routine blood tests are usually indicated to follow-up patients on ET due to the potential side-effects of these drugs, namely in the lipid profile [V, A].
- For patients on tamoxifen, an annual gynaecological examination, possibly with a gynaecological ultrasound, by an experienced gynaecologist is recommended [V, B].
- Regular bone density evaluation is recommended for patients on AIs [I, A].
- Regular exercise should be recommended to all suitable patients after treatment of breast cancer [II, B].
- Nutritional counselling should be recommended as part of the survivor care for all obese patients [III, B].
- The use of hormone replacement therapy increases the risk of recurrence and should be discouraged [I, A].

MRI, magnetic resonance imaging; ER, oestrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor 2 receptor; CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; IHC, immunohistochemistry; DCIS, ductal carcinoma in situ; BCS, breast-conserving surgery; WBRT, whole breast radiation therapy; G-CSF, granulocyte colony-stimulating factor; BCT, breast-conserving therapy; RT, radiotherapy; SLNB, sentinel lymph node biopsy; DFS, disease-free survival; AI, aromatase inhibitor; ET, endocrine therapy; uPA-PAI1, urokinase plasminogen activator-plasminogen activator inhibitor 1.

Ultrasound 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 ultrasound exams, CT scans, PET/FDG CT or any tumour markers such as CA15–3 or CEA) produce a survival benefit [I, A]. However, routine blood tests are usually indicated to follow-up patients on ET due to the potential side-effects of these drugs, namely in the lipid profile [V, A]. For patients on tamoxifen, an annual gynaecological examination, possibly with a gynaecological ultrasound, by an experienced gynaecologist is recommended [V, B]. Regular bone density evaluation is recommended for patients on AIs [I, A]. 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.

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] 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] [160]. Weight gain and obesity are likely to adversely affect the prognosis of breast cancer [161].

Table 8. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

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 the control group, case reports, experts 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, …), optional
D	Moderate evidence against the efficacy or for adverse outcomes, generally not recommended
E	Strong evidence against the efficacy or for adverse outcomes, never recommended

[a]By permission of the Infectious Diseases Society of America [163].

Nutritional counselling should be recommended as part of the survivor care for all obese patients [III, B]. The use of hormone replacement therapy increases the risk of recurrence and should be discouraged [I, A] [162].

Patients should have unlimited access to specialised rehabilitation facilities and services, to decrease the physical, psychological and social sequela 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.

It is uncertain whether women who have undergone axillary clearance should be advised 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 axillary lymph node dissection.

Follow-up cannot and should not be seen exclusively from the physical perspective. Women often have increased levels of anxiety after the completion of treatment, when close contact with the treatment team decreases. Depression and intense fatigue frequently occur in the months following the end of adjuvant chemotherapy 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 women 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 women once treatment ends. 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 quality-of-life issues, particularly for women 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. 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.

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 7. Levels of evidence and grades of recommendation have been applied using the system shown in Table 8. 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.

conflict of interest

ES has reported honoraria from Astellas, Janssen, Bayer, Roche, AstraZeneca, GlaxoSmithKline and Amgen; advisory board for Astellas, Pierre Fabre, Amgen, Janssen, Roche and Teva; travel support from Roche, Novartis, Janssen, Astellas, Amgen and Sandoz. FP-L has reported consultancy/honoraria from Roche, GlaxoSmithKline, Genomic Health and Nanostring.

SZ has reported travel support from Siemens AG; speaker's fees from Siemens AG and AstraZeneca. FC has reported consultancy/research grants from Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Merck-Sharp, Merus, Novartis, Pfizer, Roche and Sanofi. The other authors have declared no potential conflicts of interest.

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