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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 2008, the estimated age-adjusted annual incidence of breast cancer in Europe (40 countries) was 88.4/100 000 and the mortality 24.3/100 000. The incidence increased after the introduction of mammography screening and continues to do so with the aging of the population. The most important risk factors include genetic predisposition, exposure to estrogens (endogenous and exogenous) and ionising radiation, low parity and history of atypical hyperplasia. The Western-style diet, obesity and 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 prevalence of breast cancer in Europe in 2010 was 3 763 070 cases [3] and is increasing, both as a consequence of increased incidence and of improvements in treatment outcomes. In most Western countries, the mortality rate has decreased in recent years, especially in younger age groups because of improved treatment and earlier detection [4]. However, breast cancer is still the leading cause of cancer-related deaths in European women.

Breast cancer in males is rare, contributing ~1% of cases. The major risk factors include clinical disorders carrying hormonal imbalances, radiation exposure and, in particular, a positive family history and genetic predisposition [5].

## diagnosis and pathology/molecular biology

Eighteen European countries have established national or regional population-based mammography screening programmes with the purpose of detecting breast cancers at a pre-clinical stage, in order to improve the chance of survival [6]. The European Guidelines for quality assurance in breast cancer screening and diagnosis recommend standards and describe performance parameters and indicators that should be monitored in any screening programme [7]. Biannual mammography screening has been shown to have the greatest effect on breast cancer mortality reduction in the age group of 50–69 years and mammography screening in this age group is recommended by the European Union and numerous countries [8], while the effect in women aged 40–49 years is disputed [9]. There is no consensus about the exact effect of mammography screening on breast cancer mortality reduction, and the estimates reported vary. In a recent UK review of the randomised, controlled mammography trials, a 20% relative breast cancer mortality reduction was estimated in women invited to screening in the age group of 50–70 years [10], although the review stresses the importance of taking into account the risk of overdiagnosis and overtreatment as well as false-positive screening when balancing the benefits and harms of screening. Additionally, screening programmes carry the risk of false-negative results and consequently a false feeling of security among patients and doctors.

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 to be diagnosed with breast cancer stage II or higher). It is not known, however, whether breast cancer mortality is lowered [11].

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 assessment for distant metastases (bones, liver, lungs and neurological examination in the case of symptoms). Imaging includes bilateral mammography and ultrasound of the breast and regional lymph nodes. The added value of ultrasound is well proven. An MRI of the breast is not

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

| | |
|---|---|
| Assessment of general health status | History<br>Menopausal status<br>Physical examination<br>Full blood count<br>Liver and renal function tests, alkaline phosphatase and calcium |
| Assessment of primary tumour | Physical examination<br>Mammography<br>Breast ultrasound<br>Breast MRI[a]<br>Biopsy |
| Assessment of regional lymph nodes | Physical examination<br>Ultrasound<br>Ultrasound-guided biopsy if suspicious |
| Assessment of metastatic disease | Physical examination<br>Other tests are not routinely recommended, unless locally advanced or when symptoms suggestive of metastases are present |

[a]Not routinely recommended, but may be considered in cases of familial breast cancer associated with *BRCA* mutations, breast implants, for lobular cancers, before neoadjuvant chemotherapy or when the findings of conventional imaging are inconclusive (see the text).

routinely recommended, but may be considered in cases of familial breast cancer associated with *BRCA* mutations, breast implants, for lobular cancers, before neoadjuvant chemotherapy or when the findings of conventional imaging are inconclusive such as positive axillary lymph node status with occult primary tumour in the breast, suspicion of multifocality/multicentricity (in particular in lobular breast cancer) and for evaluating response to primary systemic therapy [12]. 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 them is routinely implemented as yet, but all show promising preliminary results and could increase diagnostic accuracy, especially in women with dense breasts [13].

Apart from imaging, pretreatment disease evaluation includes pathological examination of the primary tumour and cytology/histology of axillary nodes if involvement is suspected. Other assessments include complete personal medical history, family history relating to breast/ovarian and other cancers, physical examination, full blood count, liver and renal function tests, alkaline phosphatase and calcium. Assessing the menopausal status is imperative, if in doubt by measuring serum estradiol and follicle-stimulating hormone levels.

Pathological diagnosis should be based on a core needle biopsy obtained manually or, preferably, by ultrasound or stereotactic guidance. A core needle biopsy (or, if that is not possible, at least a fine needle aspiration indicating carcinoma) must be obtained before any type of treatment. If preoperative systemic therapy is planned, a core needle biopsy is mandatory to ensure a diagnosis of invasive disease and assess biomarkers, and a marker (e.g. surgical clip, carbon) should be placed into the tumour at biopsy to facilitate evaluation of tumour response during treatment and 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. In patients with clinically and imaging negative axilla, the best timing to carry out sentinel lymph node biopsy (SLNB), before or after preoperative systemic therapy, remains controversial.

Final pathological diagnosis should be made according to the World Health Organization (WHO) classification [14] and the tumour–node–metastases (TNM) staging system analysing all tissue removed. The pathological report should include the histological type, grade, immunohistochemical (IHC) evaluation of estrogen receptor (ER) status using a standardised assessment methodology (e.g. Allred or H-score), and, for invasive cancer, IHC evaluation of PgR and HER2 receptor expression. HER2 gene amplification status may be determined directly from all tumours using *in situ* hybridisation (fluorescent or chromogenic or silver *in situ* hybridisation), replacing IHC or only for tumours with an ambiguous (2+) IHC score [II, B] [15]. Proliferation markers such as the Ki67 labelling index may supply additional useful information, particularly if the assay can be standardised [V, A] [16, 17]. Alternatively, these biological markers can be assessed in the definitive surgical specimen if primary systemic therapy is not planned, although fixation is better controlled for core biopsies, allowing safer antigen preservation for IHC [18]. In case of negativity of ER/PgR and HER2 in the biopsy specimen, it is advisable to retest them in the surgical specimen, to account for the putative tumour heterogeneity [19].

For the purpose of prognostication and treatment decision-making, tumours are grouped into surrogate intrinsic subtypes defined by routine histology and IHC data (Table 2) [20].

## 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, as asymptomatic distant metastases are very rare and patients do not benefit from comprehensive laboratory (including tumour markers [21]) and radiological staging [III, D]. Additional investigations such as chest computed tomography (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) 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. Current evidence does not support the use of FDG-PET/CT in the staging procedure of local/regional disease, due to limited specificity compared with the gold standard methods for axillary staging —SLNB and axillary lymph node dissection [22].

The postoperative pathological assessment of the surgical specimen should be made according to the primary TNM (pTNM) system (Tables 3 and 4) to include number, location

**Table 2.** Surrogate definitions of intrinsic subtypes of breast cancer according to the 2013 St Gallen Consensus Conference and also recommended by the ESMO Clinical Practice Guidelines [20]

| Intrinsic subtype | Clinicopathologic surrogate definition | Notes |
|---|---|---|
| Luminal A | 'Luminal A-like'<br>• ER-positive<br>• HER2-negative<br>• Ki67 low*<br>• PgR high** | *The cut-off point between high and low values for Ki67 varies between laboratories.<br>**Suggested values are 20% for both PgR and Ki67, but laboratory specific cut-off points can be used to distinguish between low and high values for Ki67 and PgR; quality assurance programmes are essential for laboratories reporting these results. |
| Luminal B | 'Luminal B-like (HER2-negative)'<br>• ER-positive<br>• HER2-negative<br>• and either<br>  • Ki67 high or<br>  • PgR low | |
| | 'Luminal B-like (HER2-positive)'<br>• ER-positive<br>• HER2-positive<br>• any Ki67<br>• any PgR | |
| HER2 overexpression | 'HER2-positive (non-luminal)'<br>• HER2-positive<br>• ER and PgR absent | |
| 'Basal-like' | 'Triple-negative (ductal)'<br>• ER and PgR absent<br>• 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. |

and maximum diameter of tumours removed, the total number of removed and number of positive lymph nodes, and 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 and lymphovascular invasion and biomarker analysis, as described above.

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

Clinical parameters (age, tumour stage, ER expression and histological grade) have been integrated into scoring systems that allow 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 PREDICT score [23–25]. Gene expression profiles such as MammaPrint® (Agendia, Amsterdam, the Netherlands) or Onco*type* DX® Recurrence Score (Genomic Health, Redwood City, USA) may be used to gain additional prognostic and/or predictive information to complement pathology assessment and to predict response to adjuvant chemotherapy. This is particularly true in patients with ER-positive early breast cancer; however, their true clinical utility is still being evaluated in large randomised clinical trials such as MINDACT, TAILORx and RxPONDER.

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

After neoadjuvant systemic treatment, the response to treatment and amount of residual disease are important prognostic factors but need as much standardisation as any of the other biological markers, and no uniform guidelines exist for the evaluation of response to neoadjuvant treatment, although some guidance is provided by the FDA recommendation for accelerated drug approval in neoadjuvant treatment of breast cancer [26].

## management of local/locoregional disease

According to the international recommendations, treatment should be carried out in 'breast units' defined as specialised

**Table 3.** Tumour–node–metastases (TNM) staging system for carcinoma of the breast [27]

| | |
|---|---|
| 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)[l] |
| pN0(mol+) | Positive molecular findings (RT–PCR)[l], but no regional lymph node metastases detected by histology or IHC |
| pN1 | Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by SLNB but not clinically detected[m] |
| pN1mi | Micrometastases (>0.2 mm and/or >200 cells, but none >2.0 mm) |
| pN1a | Metastases in 1–3 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[m] |
| pN1c | Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by SLNB but not clinically detected[m] |
| pN2 | Metastases in 4–9 axillary lymph nodes; or in clinically detected[k] internal mammary lymph nodes in the absence of axillary lymph node metastases |
| pN2a | Metastases in 4–9 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[m]; 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[m] |
| 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, ductal carcinoma *in situ*; LCIS, called lobular carcinoma *in situ*. 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]RT–PCR: reverse transcription–polymerase chain reaction.

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

From [112]. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Handbook, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

institutions/departments caring for a high volume of breast cancer patients and provided by multidisciplinary teams, including at least a surgeon, radiation oncologist, medical oncologist, radiologist and pathologist specialised in breast cancer [III, B] [28, 29]. Depending on the local situation and availability, other members of the breast team may include plastic surgeons, psychologists, physiotherapists, geneticists and specialised breast nurses. Following a diagnosis of breast cancer, a woman finds herself in a new and unfamiliar landscape. This creates different levels of stress that vary from patient to patient, and need to be addressed individually and tailored to every woman's needs. Most women will remember the information

**Table 4.** Stage grouping system for carcinoma of the breast [27]

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

From [112]. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Handbook, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

provided to them in a fragmented way. They will need space and time to process and comprehend their diagnosis, so that they can cope better psychologically with the diagnosis and treatment plan. To accommodate for that, information on diagnosis and treatment choice should also be provided in written form.

The choice of treatment strategy is based on the tumour extent/location (size and location of primary tumour, number of lesions, number and extent of lymph node involvement) and biology (pathology including biomarkers, gene expression) as well as on the age and general health status of the patient and personal preferences. Age should be taken into consideration in conjunction with other factors and should not be the determinant reason 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 are not overtreated and that 'older' patients are not undertreated because of age alone. 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] [30]. In younger premenopausal patients, possible fertility issues should be discussed and guidance about fertility-preservation techniques provided before initiation of treatment [31, 32].

## local treatment

### surgery

Arguably the major change in the surgical treatment of primary breast cancer has been the 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)], but in some patients mastectomy is still carried out because of tumour size (relative to breast size), tumour multicentricity, inability to achieve negative surgical margins after multiple resections, prior radiation to the chest wall or breast and other contraindications to RT, or patient choice [33].

*breast-conservation surgery (BCS).* 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 local volume deficit with adjacent tissue displacement flaps. 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 (central or inferior) location of the tumour in the breast. A careful histological assessment of resection margins is essential, with no tumour at the inked margin required and a minimum 1 mm margin preferred for the invasive component and >2 mm of normal tissue required for *in situ* disease [34]. Marking the tumour bed with clips facilitates accurate planning of the radiation boost field, where appropriate. Acceptably low local recurrence rates remain the major quality assurance target. Current guidelines recommend that local recurrence rates after wide excision and RT should be <1% per year (with a target of <0.5%), and should not exceed 10% overall.

*mastectomy.* European treatment guidelines recommend that breast reconstruction should be available to those women requiring mastectomy [29]. Immediate reconstruction in some 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. Some women will be advised against

immediate reconstruction for oncological reasons, particularly in case of inflammatory breast cancer. The autologous tissue-based techniques appear to tolerate postoperative RT well, but implant-based reconstruction may result in an unfavourable aesthetic outcome following postoperative RT [35, 36]. Skin-sparing mastectomy allows the skin envelope to be conserved for use in the breast reconstruction; if post-mastectomy radiotherapy (PMRT) is indicated, at least 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 and should take into account several anatomic, treatment and patient preference factors. 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 using 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 can replace relatively large volumes of breast tissue. 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 to 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 3%–5% of women following surgery alone (similar to the incidence following axillary RT without surgical clearance), but 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 breast cancer [II, A], unless axillary node involvement is proven on ultrasound-guided biopsy. With appropriate training in the dual radiocolloid/blue dye or indocyanine green fluorescence technique, acceptably low false-negative rates and favourable axillary recurrence rates following SLNB are achievable [37]. SLNB delivers less morbidity in terms of shoulder stiffness and arm swelling and allows for a reduced hospital stay [I, A]. Training and quality assurance in SLNB have been rolled out to breast units across Europe in the last 10 years.

There is no consensus for the pathologic assessment of SLNB. The significance of occult micrometastases in terms of surgical management and patient outcome appears to be negligible [38]. Thus, routine IHC or PCR is not recommended for the evaluation of sentinel lymph nodes in guidelines published by the American Society of Clinical Oncology, the National Comprehensive Cancer Network and others [39], and is also not recommended by the authors of this manuscript.

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 has micrometastasis (0.2–2 mm) [40]. The presence of macrometastatic spread in the sentinel node 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 1 to 2 sentinel lymph nodes containing metastases, treated with BCS and tangential adjuvant RT reported non-inferior rates of overall survival (OS), disease-free survival (DFS) and locoregional recurrence-free survival [41]. Thus, patients with isolated tumour cells (<0.2 mm) in the sentinel node and patients with limited involvement of the sentinel lymph node undergoing tangential breast irradiation 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 inadequate [34]. Axillary node evaluation with SLNB is not required with *in situ* malignancy but may be reasonable in the context of large and/or high grade tumours, especially when they require mastectomy (in case an incidental invasive cancer is subsequently identified in the surgical specimen). Lobular neoplasia (formerly called LCIS), unlike DCIS, is considered a non-obligate precursor to invasive cancer and is best regarded as a risk factor for future development of invasive cancer in both breasts [relative risk (RR) 5.4–12] and thus does not require active treatment. The pleomorphic variant of lobular neoplasia may behave similarly to DCIS and should be treated accordingly.

*risk-reducing mastectomy.* Risk-reducing surgery with prophylactic bilateral mastectomy and reconstruction may be offered to women at very high risk, such as those with previous chest wall irradiation for lymphoma or carrying the *BRCA1* or *BRCA2* gene mutations. The lifetime risk of breast cancer in a *BRCA1* carrier is 80%–85%, with a 10-year actuarial risk of contralateral breast cancer ranging from 25% to 31% [42]. 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) in preference to breast conservation and mammographic surveillance of the irradiated breast. These patients should be counselled properly and should be informed of the finding that patients with early-stage breast cancer might have an even better outcome after BCT compared with after mastectomy [43].

*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 BCS to be undertaken in some patients who, at presentation, would have

otherwise required mastectomy. With multifocal disease, or where the primary tumour size reduction 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. 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] [34]. Whole breast radiation therapy (WBRT) alone reduces the risk of local recurrence by two-thirds (for low-risk patients—to below 0.5% per year). Furthermore, RT has a beneficial effect on survival [44]. Boost irradiation gives a further 50% risk reduction and is indicated for patients with unfavourable risk factors for local control including age <50, grade 3 tumours, vascular invasion and (focally—otherwise further surgery should be advocated) non-radical tumour excision [I, A] [45].

*accelerated partial breast irradiation only:* Accelerated partial breast irradiation (APBI) is an attractive approach to shorten the overall treatment time substantially. The rationale for APBI is that the majority of local failures occur in the index quadrant, and some of so-called 'elsewhere' in-breast failures often represent a new primary tumour. Several randomised trials utilising various irradiation techniques are ongoing or have been published. An intraoperative single RT fraction yielded acceptable but increased local recurrence and fewer side-effects, but the follow-up is too short to give a general recommendation for APBI [46]. Nevertheless, APBI might be considered an acceptable treatment option in 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 lymphovascular invasion, and with negative margins of at least 2 mm [III, C] [47].

*radiation after mastectomy:* PMRT in node-positive patients reduces the local recurrence risk fourfold, which translates into 5% reduction in 15-year breast cancer mortality [48]. It is always recommended for patients with positive deep margins and four or more positive axillary nodes [I, A], and is indicated for patients with T3–T4 tumours independent of the nodal status [II, B]. The evidence supporting the use of PMRT for patients with one to three positive axillary lymph nodes is at least as strong as for patients with more involved lymph nodes, however less accepted [20, 49]. It should, however, be considered, especially in the presence of additional risk factors such as young age, vascular invasion and a low number of examined axillary lymph nodes. The value of PMRT in such patients is being investigated in clinical trials.

*regional irradiation:* Most older randomised trials have used large comprehensive locoregional RT encompassing the chest wall and all regional lymph nodes. Therefore, although clinically apparent lymph node relapses (especially axillary and internal mammary) are rare, until the results from the recent trials evaluating regional RT within the framework of BCT become available, regional RT remains indicated for patients with involved lymph nodes [I, B]. 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] [50–52]. Strictly speaking, these data are not fully validated in young patients and in patients with mastectomy and/or additional regional irradiation, as these patients were either not included or underrepresented in the relevant trials. As hypofractionation in many places is being introduced for all patient subgroups, 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 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 locoregionally advanced disease.

If 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 high doses up to an equivalent of 50 Gy and a boost up to 60–76 Gy, depending on the dose to the organs at risk. Regular evaluation during the course of RT is advised to select patients that might become amenable for resection after 45–50 Gy with a higher dose (boost) spared for the postoperative situation based on the pathology findings.

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 including, if judged relevant, a CT scan 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] [53]. The decrease in the risk of local recurrence by RT is evident in all subtypes of DCIS. 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 so low that omitting radiation may be an option, although the annual recurrence rate amounts to >1% [IV, C]. 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 RT is not recommended. Lobular neoplasia is a risk factor for future development of invasive cancer in both breasts; RT is not warranted, perhaps with an exception for the pleomorphic subtype.

## adjuvant systemic treatment

The decision on systemic adjuvant treatment should be based on (i) predicted sensitivity to particular treatment methods and benefit from their use and (ii) individual risk of relapse. Final decision should also incorporate the predicted treatment sequelae, the patient's biological age, general health status, comorbidities and preferences. The treatment should start preferably within 2–6 weeks after surgery; data show an important decrease in systemic therapy efficacy when administered more than 12 weeks after surgery [54].

The most recent publication of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Overview states that the relative benefit of chemotherapy is similar in all the subgroups independent of age, stage, histopathological grade and ER status [55]. This seems to be in contradiction with the results from individual trials, both in the adjuvant and in 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 with the risk of the individual patient that is determined by the biology and the burden of the disease (e.g. 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).

According to the 2011 and 2013 St Gallen guidelines, the decision on systemic adjuvant therapies should be based on the surrogate intrinsic phenotype determined by ER/PgR, HER2 and Ki67 assessment (Tables 2 and 5) with the selective help of first-generation genomic tests when available (such as MammaPrint® or Onco*type* DX®) for luminal cases with unclear chemotherapy indications [20, 56]. It must be stressed that IHC/fluorescence *in situ* hybridisation determination of intrinsic phenotype is not fully accurate and that 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 highest risk of relapse (extensive nodal involvement), require no chemotherapy [II, 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 risk of relapse, taking into account 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 [23–25]. Urokinase plasminogen activator–plasminogen activator inhibitor 1 (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] [57]. In case of uncertainty regarding indications for adjuvant chemotherapy (after consideration of other tests), gene expression assays, such as MammaPrint® or Onco*type* DX®, may be used where available to determine the individual recurrence risk and predict the benefit from chemotherapy [IV, A] [20, 58–61]. Luminal B HER2(+) tumours are treated with chemotherapy, ET and trastuzumab [I, A]; no randomised data exist to support omission of chemotherapy in this group; however, in cases of contraindications for chemotherapy or patient refusal, it is 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 medullary or adenoid cystic carcinomas [I, A]. HER2 (non-luminal) cancers, apart

**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 CT if<br>(i) high tumour burden (four or more positive LN, T3 or higher)<br>(ii) grade 3 |
| Luminal B-like (HER2-negative) | ET + CT for the majority of cases | |
| Luminal B-like (HER2-positive) | CT + anti-HER2 + ET for all patients | If contraindications for the use of CT, one may consider ET + anti-HER2 therapy,although no randomised data exist. |
| HER2-positive (non-luminal) | CT + anti-HER2 | |
| Triple-negative (ductal) | CT | |

For special histological types, we recommend following the St Gallen 2013 recommendations [20] that propose ET for endocrine responsive histologies (cribriform, tubular and mucinous) and CT for endocrine nonresponsive (apocrine, medullary, adenoid cystic and metaplastic).

from selected cases with very low risk, such as T1aN0, are treated with chemotherapy plus trastuzumab [I, A].

In general, chemotherapy should not be used concomitantly with ET [II, D] [62]. 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, although may be considered in selected patients treated in experienced centres. 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-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 chemotherapy and/or targeted therapy [I, A] [63, 64]. The choice of medication is primarily determined by patient's menopausal status. Other factors include (minor) differences in efficacy and side effect profile.

*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 [65]. The value of addition of ovarian suppression [by gonadotropin-releasing hormone (GnRH) agonists or ovarian ablation] is not well-defined, in particular in chemotherapy-treated patients, who frequently develop ovarian failure as a consequence of cytotoxic treatment [II, B] [66, 67]. 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] [66, 68]. The optimal duration of ovarian suppression is not known, although it is usually administered for 2–5 years [V, B]. Combining ovarian suppression and AI demonstrated no benefit compared with combination with tamoxifen in the ABCSG-12 trial, and cannot be recommended outside clinical trials [II, C] [69]. For patients with contraindications to the use of tamoxifen, a GnRH agonist alone or in combination with an AI can be used. The role of GnRH agonists in preventing chemotherapy-related ovarian failure is not well-established and contradictory data exist [II, C].

*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 if upfront or sequential strategy) [I, B] [70–73]. They can be used upfront (non-steroidal AI and exemestane), after 2 to 3 years of tamoxifen (non-steroidal AI and exemestane) or as extended adjuvant, after 5 years of tamoxifen (letrozole and anastrozole) [74, 75]. There is no proven benefit for the routine use of AIs for >5 years. In view of the recently published ATLAS study demonstrating an advantage of 10 rather than 5 years of tamoxifen, extended adjuvant should be discussed with all patients, except the ones with very low risk, although the optimal duration and regimen of adjuvant ET is currently unknown [I, C] [76].

The use of tamoxifen is associated with increased risk of thromboembolic complications and endometrial hyperplasia (including endometrial cancer). Caution should be exercised in patients with conditions predisposing to these sequelae and appropriate diagnostic tests carried out in those presenting with symptoms suggestive of these complications. Although there are no unequivocal data on their detrimental effects, patients on tamoxifen should be advised to avoid the use of strong and moderate CYP2D6 inhibitors or, if such drugs cannot be replaced, a switch to alternative treatment, i.e. AIs, should be considered [IV, B] [77, 78]. Patients undergoing ovarian suppression and AI users are at increased risk of bone loss and should be advised to assure adequate calcium plus vitamin D3 supply and to assess periodically the bone mineral density [by dual energy X-ray absorption (DEXA) scan] [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 benefit from chemotherapy is more pronounced in ER-negative tumours [79, 80]. In ER-positive tumours, chemotherapy at least partially exerts its effect by induction of ovarian failure [63, 81]. Most frequently used regimens contain anthracyclines and/or taxanes, although in selected patients CMF may still be used. Four cycles of AC (doxorubicin, cyclophosphamide) are considered equal to six cycles of CMF, whereas six cycles of three-drug anthracycline-based regimens are superior [I, A] [55]. Data on topoisomerase IIα as a predictive factor for anthracycline-based chemotherapy have not been confirmed in prospective studies. A largemeta-analysis suggested that although it may have a small clinical benefit, it is not recommended for clinical practice [82]. Thus, a routine use of this biomarker is not currently advised [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-cardiotoxicity [I, A] [55, 83]. Sequential rather than the concomitant use of anthracyclines and taxanes is superior [I, B] [84]. Overall, chemotherapy regimens based on anthracyclines and taxanes reduce breast cancer mortality by about one-third [55, 64]. Non-anthracycline, taxane-based regimens (such as four cycles of TC) may in selected patients (such as those at risk of cardiac complications) be used as an alternative to four cycles of anthracycline-based chemotherapy [I, A] [85]. 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, in particular in highly proliferative tumours [I, B] [86]. High-dose chemotherapy with stem cell support is not recommended [I, E].

## HER2-directed therapy

Trastuzumab combined with chemotherapy in patients with HER2 overexpression/amplification approximately halves the recurrence risk, compared with chemotherapy alone; this translates into ∼10% absolute improvement in 3-year DFS and 3% increase in 3-year OS [I, A] [87–89]. Trastuzumab is

approved in patients with node-positive disease and in N0 patients with tumours >1 cm, although—due to relatively high failure risk even in patients with N0 tumours <1 cm—it should also be considered in this patient group, in particular in ER-negative disease [IV, B] [90]. 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] [91]. No additional benefit was demonstrated for 2-year trastuzumab administration [92] in the HERA trial. The PHARE trial compared 6 and 12 months of trastuzumab: the non-inferiority of 6 months of trastuzumab could not be demonstrated, and hence 1 year duration should remain the standard [93]. Trastuzumab is usually well-tolerated, although (usually reversible) cardiac dysfunction may occur and selection of patients based on the baseline cardiac function (expressed by the left ventricular ejection fraction) and periodic monitoring during treatment are 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] [88]. 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, long-term outcomes are not known and such a treatment cannot be recommended outside of clinical trials [94–96].

### bisphosphonates

Some data suggest a beneficial anticancer effect of bisphosphonates, especially when used in a low-estrogen environment (women undergoing ovarian suppression or postmenopausal), although study results are equivocal and such a treatment cannot be routinely recommended in women with normal bone mineral density [I, C] [69, 97]. In patients with treatment-related bone loss, bisphosphonates decrease the risk of skeletal complications [I, A] [98, 99].

### treatment of elderly patients

Limited data on elderly patients from randomised studies do not allow strong recommendations to 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 get treatments identical to their younger counterparts. Full doses of drugs should be used, whenever feasible [V, A]. In patients suitable for standard chemotherapy, single-agent capecitabine was demonstrated to be inferior to the standard multidrug regimen (AC or CMF) and therefore, a standard multidrug regimen should be used [II, D] [100]. In elderly patients, single-agent pegylated liposomal doxorubicin and metronomic cyclophosphamide plus methotrexate are feasible and demonstrate similar activity, although their efficacy in comparison to standard chemotherapy remains unknown [II, B] [101].

### 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 effect on OS [I, B] [102]. Following mastectomy, tamoxifen may also be considered to decrease the risk of contralateral breast cancer [II, B]. AIs are being investigated for the adjuvant therapy of DCIS but should not be used in routine care.

### 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 allow for achieving operability or decreasing the extent of surgery [I, A]. In operable cases, the timing of treatment (pre- versus postoperative) has no effect on long-term outcomes [II, C] [83, 103]. 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 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, thus increasing the probability of achieving a pCR. 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. It is therefore recommended that a sequential regimen of anthracyclines and taxanes is used [I, B].

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 [104]. ET is usually given for 4–6 months before surgery and continued postoperatively; for post-menopausal patients, AIs are more effective than tamoxifen in decreasing the tumour size and facilitating less extensive surgery [I, A] [105–107].

## 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 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] [57] and can be used in treatment decision-making for early breast cancer. Molecular signatures for ER-positive breast cancer such Onco*type* DX®, EndoPredict®, Breast Cancer Index™ or for all types of breast cancer (pN0-1) such as MammaPrint® and

**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% cell + | Anti-HER2 treatment |
| Ki67 | ++ | + | NO | NO | IHC no consensus | 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, prospective validation ongoing | Gene expression profile, RT-pCR | Chemotherapy if high risk or high score |
| Second generation signatures | + | + | NO | NO | Gene expression profile | None yet |

Genomic Grade Index® are commercially available, but none of them have proven robust clinical utility so far. In some cases of difficult decision, such as grade 2 ER-positive HER2-negative and node-negative breast cancer, MammaPrint® and Onco*type* DX® may be used in conjunction with all clinicopathological factors, to help in treatment decision-making [20, 61]. Results from large phase III prospective clinical trials (MINDACT, TAILORx and RxPONDER) are eagerly awaited for an optimal and accurate use of these new tools in clinical practice. A biomarker summary table 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 and to provide psychological support and information in order to enable a return to normal life after breast cancer.

Ten-year survival of breast cancer exceeds 70% in most European regions, with 89% survival for local and 62% for regional disease [108]. 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 years the risk of recurrence is higher in patients with ER-negative cancers, but after ~5–8 years after diagnosis, the annual hazards of recurrence drop below the level of ER-positive tumours [III, B] [109]. Relapses 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 to 4 months in the first 2 years, every 6 months from years 3–5 and annually thereafter [V, A]. Every visit should include thorough history taking, eliciting of symptoms and physical examination. Ipsilateral (after BCS) and contralateral mammography is recommended every 1 to 2 years [II, A]. An MRI of the breast may be indicated for young patients, especially in the case of dense breast tissue and genetic or familial predispositions [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 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 by an experienced gynaecologist is recommended [V, A]. For patients on AIs, regular bone density evaluation is recommended [I, A]. Very importantly, most available data for follow-up recommendations come from an era of less sophisticated diagnostic procedures and less efficacious treatment for advanced disease, and new trials are urgently needed to reassess this question nowadays. 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 affecting the prognosis of patients with breast cancer: regular exercise provides functional and psychological benefits [II, B], possibly reduces the risk of recurrence and should be recommended to all suitable patients after treatment for breast cancer [II, B] [110]. Weight gain and obesity are likely to adversely affect the prognosis of breast cancer [111]; nutritional counselling should be recommended as part of survivor care for all obese patients [III, B]. The use of hormone replacement therapy (HRT) increases the risk of recurrence and should be discouraged [I, A].

Patients should have unlimited access to specialised rehabilitation facilities and services, to decrease the physical, psychological and social sequelae of breast cancer treatment. The main aims of physiotherapy should include prevention and treatment of lymphoedema, assuring full range of movements of arm and shoulder, and prevention and correction of postural defects resulting from mastectomy. There are no data indicating that any type of physiotherapy may increase the risk of

**Table 7.** Summary of recommendations

| |
|---|
| **Screening and diagnosis** |
| Mammography screening in the 50–70 year age group reduces breast cancer mortality. |
| Diagnosis and treatment should be carried out in 'breast units': specialised institutions caring for a high volume of breast cancer patients, and provided by multidisciplinary teams including at least a surgeon, radiation oncologist, medical oncologist, radiologist and pathologist—all specialised in breast cancer. The patients should be provided with full, preferably written information about their disease and treatment. |
| 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, physical examination, full blood count, liver and renal function tests, alkaline phosphatase and calcium. |
| Pathological diagnosis should be based on core needle biopsy obtained by manual, or preferably by ultrasound or stereotactic, guidance. The pathological report should include the histological type, grade, ER and, for invasive cancer, PgR and HER2. |
| Routine staging evaluations are directed at locoregional disease, as asymptomatic distant metastases are very rare and patients do not profit from comprehensive laboratory and radiological staging. |
| 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 and lymphovascular 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. |
| **Treatment** |
| The choice of treatment strategy is based on the tumour extent/location (size and location of primary tumour, number of lesions, number and extent of lymph node involvement) and biology (pathology including biomarkers, gene expression) as well as on the age, body habitus and general health status of the patients and their preferences. |
| The possibility of hereditary cancer should be explored and, if needed, prophylactic procedures discussed, following appropriate genetic counselling and testing of the patient. |
| 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 with previous chest wall irradiation for lymphoma or carrying the *BRCA1* or *BRCA2* gene mutations. |
| Ductal carcinoma *in situ* may be treated with BCT, 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. |
| 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 wall 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 should be available to women requiring mastectomy. |
| Sentinel lymph node biopsy (SLNB), rather than full axillary nodal clearance, is now the standard of care, unless axillary node involvement is proven. |
| 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. |
| Postoperative RT is strongly recommended after BCS. Boost irradiation gives a further 50% risk reduction and is indicated for patients with unfavourable risk factors for local control. |
| Partial breast irradiation may be considered an acceptable treatment option in 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 lymphovascular invasion, and with negative margins of at least 1 mm. |
| Postmastectomy RT is recommended for patients with four or more positive axillary nodes and/or with T3–T4 tumours, and should be considered for patients with one to three positive axillary lymph nodes, especially in the presence of additional risk factors. |
| Shorter fractionation schemes (e.g. 15 to 16 fractions with 2.5–2.67 Gy single dose) have been validated in large prospective studies and are generally recommended. |
| The decision on systemic adjuvant therapies is based on the intrinsic phenotype determined by ER/PgR, HER2 and Ki67 assessment. |
| All patients with detectable ER expression, defined as ≥1% of invasive cancer cells, should be offered ET. For premenopausal patients, tamoxifen is a standard and the value of ovarian suppression is not well-defined. For postmenopausal patients, AIs (both non-steroidal and steroidal) and tamoxifen are valid options. |
| For luminal HER2(−) cancers, the indications for chemotherapy depend on the individual risk of relapse, presumed responsiveness to ET and patient preferences. |
| Luminal B HER2(+) tumours are treated with chemotherapy, ET and trastuzumab; no data exist to support omission of chemotherapy in this group. |
| HER2(+) (non-luminal) cancers, should be treated with chemotherapy plus trastuzumab. |
| Triple-negative tumours benefit from adjuvant chemotherapy, with possible exclusion of low-risk 'special histological subtypes' such as medullary or adenoid cystic carcinomas. |
| Chemotherapy usually consists of 4–8 cycles of anthracycline- and/or taxane-based regimen. Sequential use of anthracyclines and taxanes, instead of concomitant, is recommended. |
| Trastuzumab combined with chemotherapy in patients with HER2 overexpression/amplification approximately halves the recurrence risk and improves overall survival (OS), compared with chemotherapy alone. |

*Continued*

**Table 7.** *Continued*

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|---|
| 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. All modalities (chemotherapy, ET and targeted therapy) used in adjuvant treatment may also be used preoperatively. |
| **Follow up and survivorship** |
| The aims of follow-up were 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. |
| Ipsilateral (after BCS) and contralateral mammography is recommended every 1 to 2 years. 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. |

**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]Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

recurrence; hence, patients should not be denied access to this rehabilitation service, when indicated.

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 for 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 as women often have increased levels of anxiety after treatment completion, when close contact with the treatment team decreases. Depression and intense fatigue very often occur in the months following the end of adjuvant chemotherapy and/or RT. This is also aggravated by the fact that long-term survivorship issues involving work, family and sexuality, are often not closely addressed during follow-up, resulting in 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 after 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 and assessing the various quality-of-life issues. The role of a specialised breast nurse throughout a patient's diagnosis, treatment and follow-up is crucial. All countries should develop the necessary educational and infrastructure requirements to be able to provide the help of specialised breast nurses, within the multidisciplinary team, to all breast cancer patients.

## note

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.

## conflict of interest

Dr Senkus has reported the advisory board for GlaxoSmithKline and AstraZeneca; travel support from Roche and Amgen. Prof. Penault-Llorca has reported consultancy/honoraria from Roche, GlaxoSmithKline and Genomic Health. Prof. Thompson has reported honoraria from Roche. Dr Zackrisson has reported travel support from Siemens AG; speaker's fees from Siemens AG and AstraZeneca. Dr Cardoso has reported consultancy/research grants from Eisai, Roche, GlaxoSmithKline, Celgene, AstraZeneca, Novartis, Pfizer, Astellas, GE Oncology, Merck-Sharp, Merus, BV, Genentech; speaker's bureau from Novartis, GlaxoSmithKline. The other authors have declared no potential conflicts of interest.

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