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

In 2008 the estimated age-adjusted annual incidence of breast cancer in Europe (40 countries) was 88.4/100 000 and the mortality 24.3/100000. The incidence is increasing due to mammographic screening and an aging population; postmenopausal hormone replacement therapy, Western-style diet, obesity and consumption of alcohol and tobacco contribute to the rising incidence of breast cancer. There is a steep age gradient, with about a quarter of breast cancers occurring before age 50, and <5% before age 35. In most Western countries, the mortality rate has decreased in recent years, especially in younger age groups because of improved treatment and earlier detection. However, breast cancer is still the leading cause of cancer-related deaths in European women.

## diagnosis

The diagnosis is based on clinical, radiological and pathological examinations. Clinical examination includes bimanual palpation of the breasts and locoregional lymph nodes. Radiological examinations include bilateral mammography and ultrasound of the breasts (and regional lymph nodes depending on local expertise). Magnetic resonance imaging (MRI) of the breast is not needed as a routine procedure, but may be considered in cases involving diagnostic challenges arising, for example, because of dense breast tissue especially in young women, in cases of familial breast cancer associated with *BRCA* mutations, silicone gel implants, or positive axillary lymph node status with occult primary tumor in the breast, or where multiple tumor foci are suspected, in particular with lobular breast cancer [78]. Pathological diagnosis should be based on core needle biopsy obtained by manual, 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 surgical operation. If preoperative chemotherapy is anticipated, a core needle biopsy is preferred, and a surgical clip should be placed into the tumor at biopsy to facilitate the later surgical resection [V]. Final pathological diagnosis should be made according to the World Health Organization (WHO) classification [86] and the tumor–node–metastases (TNM) staging system analyzing all tissue removed.

## staging and risk assessment

Patient-related staging assessment includes complete personal medical history, family history relating to breast/ovarian and other cancers, physical examination, performance status, 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 (FSH) levels].

Preoperative disease-related staging includes clinical TNM staging (Table 1), pathological examination of the core needle biopsy with a pathologist's report on histological type and grade, needle cytology of axillary nodes if involvement is suspected clinically or on ultrasound, and determination of estrogen receptor (ER), progesterone receptor (PgR) and HER2 receptor status by immunohistochemistry (IHC) or fluorescence *in situ* hybridization (FISH)/chromogenic *in situ* hybridization (CISH) test [III, B]. Alternatively, these biological markers can be assessed on the definitive surgical specimen if primary systemic therapy is not planned.

If preoperative (neoadjuvant) systemic therapy is planned, additional investigations such as chest X-ray, abdominal ultrasound or CT scan and bone scintigraphy should be considered to exclude metastatic disease. These investigations are also recommended for patients with clinically positive axillary nodes, large tumors (e.g. ≥5 cm) or clinical signs, symptoms or laboratory values indicating the presence of

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**Table 1.** Tumor node metastases (TNM) staging system for carcinoma of the breast

| | |
|---|---|
| **Primary tumor (T)**[a,b,c] | |
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma *in situ* (called intraepithelial neoplasia) |
| 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 categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted. |
| T1 | Tumor ≤20 mm in greatest dimension |
| T1mi | Tumor ≤1 mm in greatest dimension |
| T1a | Tumor >1 mm but ≤5 mm in greatest dimension |
| T1b | Tumor >5 mm but ≤10 mm in greatest dimension |
| T1c | Tumor >10 mm but ≤20 mm in greatest dimension |
| T2 | Tumor >20 mm but ≤50 mm in greatest dimension |
| T3 | Tumor >50 mm in greatest dimension |
| T4[d] | Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules) |
| T4a | Extension to the chest wall, not including only pectoralis muscle adherence/invasion |
| T4b | Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma |
| T4c | Both T4a and T4b |
| T4d | Inflammatory carcinoma[e] |
| *Post-treatment ypT.*[f] The use of neoadjuvant therapy does not change the clinical (pretreatment) stage. Clinical (pretreatment) 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 tumor, with the modifier 'm' indicating multiple foci. The measurement of the largest tumor focus should not include areas of fibrosis within the tumor bed. | |
| **Regional lymph nodes (N)** | |
| *Clinical* | |
| 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[g] 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[g] 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[g] 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) |
| *Pathological (pN)*[h,i] | |
| 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) no greater than 0.2 mm [detected by H&E or IHC including isolated tumor cell clusters (ITCs)] |
| pN0(mol–) | No regional lymph node metastases histologically, negative molecular findings (RT–PCR)[j] |
| pN0(mol+) | Positive molecular findings (RT–PCR)[j], 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 sentinel lymph node biopsy but not clinically detected[k] |
| pN1mi | Micrometastases (>0.2 mm and/or >200 cells, but none greater than 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 sentinel lymph node biopsy but not clinically detected[k] |
| pN1c | Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected |

**Table 1.** (*Continued*)

| | |
|---|---|
| pN2 | Metastases in 4–9 axillary lymph nodes; or in clinically detected[l] internal mammary lymph nodes in the *absence* of axillary lymph node metastases |
| pN2a | Metastases in 4–9 axillary lymph nodes (at least one tumor deposit >2.0 mm) |
| pN2b | Metastases in clinically detected[l] 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[l] 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 sentinel lymph node biopsy but not clinically detected[k]; or in ipsilateral supraclavicular lymph nodes |
| pN3a | Metastases in ≥10 axillary lymph nodes (at least one tumor deposit >2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes |
| pN3b | Metastases in clinically detected[l] 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 sentinel lymph node biopsy but not clinically detected[k] |
| pN3c | Metastases in ipsilateral supraclavicular lymph nodes |
| *Post-treatment ypN* | |
| Post-treatment yp 'N' should be evaluated as for clinical (pretreatment) 'N' methods above. The modifier 'sn' is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed that the axillary nodal evaluation was by axillary node dissection (AND) | |
| The X classification will be used (ypNX) if no yp post-treatment SN or AND was performed | |
| N categories are the same as those for pN | |
| **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 tumor cells in circulating blood, bone marrow or other non-regional nodal tissue that are no larger than 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 |
| *Post-treatment yp M classification.* The M category for patients treated with neoadjuvant therapy is the category assigned in the clinical stage, prior to initiation of neoadjuvant therapy. Identification of distant metastases after the start of therapy in cases where pretherapy evaluation showed no metastases is considered progression of disease. If a patient was designated to have detectable distant metastases (M1) before chemotherapy, the patient will be designated as M1 throughout. | |

**Anatomic stage/prognostic groups[m]**

| | | | |
|---|---|---|---|
| 0 | Tis | N0 | M0 |
| IA | T1[n] | N0 | M0 |
| IB | T0 | N1mi | M0 |
| | T1[n] | N1mi | M0 |
| IIA | T0 | N1[o] | M0 |
| | T1[n] | N1[o] | M0 |
| | T2 | N0 | M0 |
| IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| IIIA | T0 | N2 | M0 |
| | T1[n] | 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]The T classification of the primary tumor 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 radiologicalo) or pathological measurements, respectively. In general, pathological determination should take precedence over clinical determination of T size.

[b]Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cut-off for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cut-off.

[c]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 tumor. The presence and sizes of the smaller tumor(s) should be recorded using the '(m)' modifier.

[d]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

metastases, even if preoperative systemic treatment is not planned [III, B]. Patients with early stage (e.g. N0) breast cancer do not profit from comprehensive laboratory (including tumor markers [45]) and radiological staging [III, B].

The postoperative pathological assessment of the surgical specimen should be made according to the pTNM system (Table 2) to include: number, location and maximum diameter of tumors removed, the total number of removed and number of positive lymph nodes, and the extent of metastases in the lymph nodes [isolated tumor cells, micrometastases (0.2–2 mm), macrometastases]. The report should also include histological type and grade of the tumor (using a standard grading system), evaluation of the resection margins including the location and minimum distance of the margin, vascular and lymphovascular invasion; immunohistochemical evaluation of ER and PgR using a standardized assessment methodology (e.g. Allred or H-score), and immunohistochemical evaluation of HER2 receptor expression. HER2 gene amplification status may be determined directly from all tumors using *in situ* hybridization (FISH or CISH), replacing IHC, or only from tumors with an ambiguous (2+) IHC score [II, B] [91]. Proliferation markers such as the Ki67 labeling index may supplement additional useful information, particularly if the assay can be standardized.

Clinical parameters 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) or Adjuvant! (www.adjuvantonline.com). Gene expression profiles such as Mammaprint™ or Oncotype Dx Recurrence Score™ may be used to gain additional prognostic and/or predictive information to complement pathology assessment and to predict response to adjuvant chemotherapy, in particular in patients with ER-positive early breast cancer [II, A] [1, 54, 67]. The accurate integration of these new genomic tools into current clinical practice and their added value is still unknown and is currently being evaluated in two large prospective phase III trials (MINDACT and TAILORx).

## treatment by disease stage

Multidisciplinary treatment planning involving at least a breast surgeon, radiologist, pathologist, and medical and radiation oncologists should be used to integrate local and systemic therapies and their sequence [III, B]. The possibility of hereditary cancer should be explored and, if needed, prophylactic procedures discussed following adequate genetic counseling and testing of the patient [IV, D].

### 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 about two-thirds of newly diagnosed cancers are amenable to breast conservation (wide local excision and radiotherapy), but in the remaining third mastectomy is still

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.

[e]Inflammatory carcinoma is a clinical–pathological entity characterized by diffuse erythema and edema (peau d'orange) involving a third or more of the skin of the breast. These skin changes are due to lymphedema caused by tumor 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.

[f]If a cancer was designated as inflammatory before neoadjuvant chemotherapy, the patient will be designated to have inflammatory breast cancer throughout, even if the patient has complete resolution of inflammatory findings.

[g]*Clinically detected* is defined as detecting 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 sentinel lymph node biopsy only in conjunction with a pathological T assignment.

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

[i]Isolated tumor cell clusters (ITCs) are defined as small clusters of cells not greater than 0.2 mm, or single tumor 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.

[j]RT–PCR: reverse transcription–polymerase chain reaction.

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

[l]'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.

[m]Anatomic stage: M0 includes M0(i+). The designation pM0 is not valid; any M0 should be clinical. If a patient presents with M1 prior to 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. Postneoadjuvant therapy is designated with a 'yc' or 'yp' prefix. Of note, no stage group is assigned if there is a complete pathological response (CR) to neoadjuvant therapy, e.g. ypT0ypN0cM0.

[n]T1 includes T1mi.

[o]T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

Modified from NCI [64].

**Table 2.** Selected current adjuvant chemotherapy regimens

| Regimen | No. of cycles | Duration of cycles (weeks) | Reference |
|---|---|---|---|
| AC | 4 | 3 | [32] |
| CMF (oral or i.v. days 1+8) | 6 | 4 | [10] |
| $FE_{100}C$ | 6 | 3 | [35] |
| $CE_{1,8}F$ | 6 | 4 | [13, 56] |
| A (or E) → CMF | 4 → 4 (–8) | 3 → 4 | [14, 71] |
| AP → CMF | 4 → 4 | 3 → 4 | [37] |
| DC | 4 | 3 | [53] |
| AC → P(H) qwk | 4 → 4 | 3 → 3 | [76, 84] |
| AC → D(H) | 4 → 4 | 3 → 3 | [84] |
| DCarboH | 6 | 3 | [82] |
| ddAC → ddP (G-CSF) | 4 → 4 | 2 → 2 | [16] |
| DAC | 6 | 3 | [60] |
| $FEC_{100}$ → D | 3 → 3 | 3 → 3 | [75] |

A, doxorubicin; C, cyclophosphamide; D, docetaxel; E, epirubicin; F, fluorouracil; G-CSF, granulocyte colony-stimulating factor, e.g. filgrastim; M, methotrexate; P, paclitaxel; Carbo, carboplatin; H, trastuzumab, may be given with a taxane; qwk, weekly; dd, dose-dense; →, followed by.

recommended because of tumor size (e.g. >4 cm diameter), or tumor multifocality/multicentricity, central tumor site within the breast and prior radiation to the chest wall or breast [2].

*breast conservation surgery (BCS).* For patients undergoing wide local excision, greater emphasis is now placed on achieving acceptable cosmesis, and breast surgeons are now trained to undertake glanduloplasty to reduce the local volume deficit with adjacent tissue displacement flaps. Newer oncoplastic procedures such as therapeutic mammoplasty (breast reduction at the same time as wide local tumor excision) can achieve better cosmetic outcomes in patients with large breasts. The role of breast MRI in assessing tumor multifocality and planning surgery is currently the subject of intense debate.

Careful histological assessment of resection margins is essential, and marking the tumor bed with clips will facilitate accurate planning of the radiation boost field where appropriate. Postoperative radiotherapy is strongly recommended after BCS [I, A] [27]. Acceptably low local recurrence rates remain the major quality assurance target, and current guidelines recommend that local recurrence rates after wide excision and radiotherapy should be <1% per year and should not exceed 10% overall.

*mastectomy.* European treatment guidelines recommend that breast reconstruction should be available to those women requiring mastectomy [31]. 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. Many women will decline or defer reconstruction because of personal preference. For oncological reasons, particularly when postmastectomy radiation therapy is anticipated, some women will be advised against immediate reconstruction. Skin-sparing mastectomy allows the skin envelope to be conserved for use in the breast reconstruction. Endoscopic breast surgery is an emerging technique which is currently being performed in the context of clinical trials.

For women undergoing breast reconstruction, whether immediate or delayed, a wide range of surgical options is available. Silicone gel implants are safe and effective 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 from extracapsular rupture.

Myocutaneous tissue flaps using the *latissimus dorsi* muscle from the back or transverse *rectus abdominis* muscle, or the free DIEP (deep inferior epigastric perforator) flap from the lower abdomen 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 2 years after mastectomy before being offered reconstruction.

*advances in axillary staging.* Regional lymph node status remains the strongest predictor of long-term prognosis in primary breast cancer. Sentinel lymph node biopsy (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 suspected clinically or on ultrasound. With appropriate training in the technique, acceptably low false-negative rates and favorable axillary recurrence rates following SLNB are achievable [55].

SLNB delivers less morbidity in terms of shoulder stiffness and arm swelling, and allows for 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.

The presence of macrometastatic spread in the sentinel node traditionally mandates conventional axillary lymph node clearance. Axillary clearance is associated with lymphedema affecting the upper limb in 3–5% of women following surgery alone (similar to the incidence following axillary radiotherapy without surgical clearance), but the incidence of lymphedema rises significantly to ~40% when axillary clearance is combined with radiotherapy to the axilla. Women who have undergone axillary clearance are advised to avoid cannulation, venesection and blood pressure monitoring in the ipsilateral arm, and to start antibiotic treatment promptly for potentially infected wounds on the ipsilateral arm [V, D]. Once established, lymphedema should be treated by trained therapists using a combination of compression bandaging, manual lymphatic drainage and graduated compression garments.

The optimal management of micrometastatic spread and isolated tumor cells is the subject of ongoing research. Whether further axillary treatment is required when a sentinel node has micrometastasis (0.2–2 mm) is being debated. Recent results of a randomized controlled trial (6.3 years of median follow-up) for patients with clinical T1–T2 cN0 invasive breast cancer, 1–2 sentinel lymph nodes containing metastases, treated with BCS and tangential adjuvant radiation therapy reported non-inferior rates of overall, disease-free, and locoregional recurrence-free survival [38]. Currently, patients with isolated tumor cells (<0.2 mm) in the sentinel node and patients with the above characteristics may not need to have any further axillary procedure [II, B].

*surgery for in situ* malignancy (intraepithelial neoplasia). Ductal carcinoma *in situ* (DCIS, ductal intraepithelial neoplasia) may

be treated with BCS providing clear resection margins can be achieved. There is no general consensus on what is regarded as an adequate margin; however, margins <2 mm are considered inadequate [61]. Adjuvant breast irradiation after BCS decreases the risk of local recurrence but has no effect on survival [I, A]. Total mastectomy with clear margins in DCIS is curative, and radiation therapy is not recommended. Axillary node evaluation with SLNB is not required with *in situ* malignancy but may be reasonable in the context of large tumors requiring mastectomy. Lobular neoplasia (formerly called lobular carcinoma *in situ*, 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]. 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 60% chance that the cancer will be bilateral. The risk for both subsequent breast cancer incidence and mortality is reduced by ∼90–95%, but surgery cannot guarantee prevention of developing breast cancer in the future [III, A]. Careful genetic assessment and psychological counseling is mandatory before undertaking such surgery.

For those women diagnosed with breast cancer where the risk of contralateral disease is likely to be higher, such as with multifocal lobular carcinoma, or where invasive carcinoma is associated with widespread LCIS or hyperplasia with atypia in the surrounding breast tissue, contralateral risk-reducing mastectomy is increasingly being requested by patients despite no significant survival advantage.

The increasing sophistication and knowledge of patients facing surgery, both for breast cancer treatment and for risk reduction, mean that the range of surgical options are now discussed in great depth by breast surgeons and nurses. Despite the overall trend towards breast conservation over the last 30 years, breast specialists in both Europe and the USA are noting increasing numbers of younger women with breast cancer opting for bilateral mastectomy (incorporating contralateral risk-reducing surgery) in preference to breast conservation and mammographic surveillance of the irradiated breast.

## radiation therapy

### invasive carcinoma

*radiation therapy after BCS.* whole breast radiotherapy (WBRT). Postoperative radiotherapy is strongly recommended after BCS [I, A] [27]. Whole breast radiotherapy reduces the risk of local recurrence by two-thirds and an additional boost gives a further 50% risk reduction. Furthermore, radiotherapy has a beneficial effect on survival. In general, boost irradiation is indicated, too, in older patients [I, A], but optional in patients with presumed low risk for local failure (wide margins, node-negative, no vessel invasion) [III, B]. In patients >70 years of age who have endocrine-responsive invasive breast cancer with maximum stage pT1N0 and clear margins, it may be possible to omit radiation therapy without compromising survival [II, B] [36, 48].

*accelerated partial breast irradiation (PBI) only.* PBI is an attractive approach to shorten the overall treatment time substantially. The rationale for PBI 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 tumor. Several randomized trials in selected patients with different, non-comparable techniques are ongoing or have been recently published, e.g. the TARGIT A tria. An intraoperative single radiation therapy fraction yielded excellent results in regard to local failure and side effects, but follow-up is too short to give a general recommendation for PBI [87]. Nevertheless, PBI is 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 and lymphovascular invasion, and with negative margins of at least 2 mm [II,B] [70].

*radiation after mastectomy.* Postmastectomy radiotherapy (PMRT) is always recommended for patients with four or more positive axillary nodes [II, B], and indicated for patients with T3–T4 tumors independent of the nodal status [III, B]. PMRT may also be considered in patients with 1–3 positive axillary lymph nodes [27] in the presence of additional risk factors, such as young age, vessel invasion and low number of examined axillary lymph nodes; the worth of PMRT in such patients is being investigated in clinical trials.

*additional regional irradiation.* Randomized trials have used large comprehensive fields encompassing the chest wall and all regional lymph nodes, but axillary relapses after axillary dissection and relapses in the mammary internal region are rare, and irradiation of these sites is not routinely recommended unless there is suspicious residual tumor.

Supraclavicular lymph nodes should be considered for inclusion in the target volume in the case of extensive involvement of axillary and supraclavicular lymph nodes (N ≥2); internal mammary lymph nodes should be included in the target volume in cases of metastatic spread to this area.

*radiation therapy doses and fractionation.* Adjuvant doses used for local and/or regional irradiation are 45–50 Gy in 25–28 fractions of 1.8–2.0 Gy. The typical boost dose is 10–16 Gy in 2 Gy single doses. As an option, shorter fractionation schemes (e.g. 16 fractions with 2.66 Gy single dose) have shown similar effectiveness and comparable side effects [90] [I, B], but caution is needed in patients with G3 differentiated tumors, in young patients and in patients with mastectomy and/or additional regional irradiation, as these patients were either not included or were underrepresented in the relevant trials.

### non-invasive carcinoma (intraepithelial neoplasia)

Adjuvant whole breast irradiation after BCS of DCIS decreases the risk of local recurrence but has no effect on survival [I, A]. Randomized data about additional dose to the tumor bed

(boost) are lacking, but a boost can be considered for patients at higher risk for local failure, e.g. for young patients [III, B]. PBI should only be performed within a clinical trial. The decrease in risk of local recurrence by radiotherapy is evident in all subtypes of DCIS. However, in some patients with low-risk DCIS (tumor 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. In ER-positive DCIS tamoxifen may be considered following BCS (with or without adjuvant radiation) [II, A]. Total mastectomy with clear margins in DCIS is curative, and radiation therapy is not recommended. In this group of patients tamoxifen may also be considered to decrease the risk of contralateral breast cancer [II, B]. Lobular neoplasia (formerly called LCIS) is a risk factor for future development of invasive cancer in both breasts; radiotherapy is not warranted, perhaps with an exception for the pleomorphic subtype.

## systemic therapy

### adjuvant systemic therapy

Treatment is recommended if a relevant reduction of the estimated risk of recurrence and death can be expected with an acceptable level of treatment-related adverse effects. ER and HER2 status are the most relevant predictive factors for the choice of treatment modality. Tumors with any detectable (≥1%) expression of ER and/or PgR by IHC are considered hormone-receptor positive.. Tumors with no detectable expression of ER and PgR are considered hormone receptor negative or endocrine non-responsive [44]. Features indicative of uncertainty of endocrine responsiveness include low levels of steroid hormone receptor immunoreactivity, lack of PgR, poor differentiation (G3), high proliferation markers (Ki67), HER2 overexpression and high gene expression score results (e.g. Oncotype Dx Recurrence Score, Mammaprint). In the absence of all these features, tumors are considered highly endocrine responsive [41].

Patients with tumors of different degrees of endocrine responsiveness may receive endocrine treatment alone, or a combination of chemotherapy and endocrine therapy, the choice being determined by factors outlined in Table 3. Patients with tumors of uncertain endocrine responsiveness are usually treated with a combination of endocrine therapy and chemotherapy.

Patients with endocrine-non-responsive tumors benefit from chemotherapy and should not receive endocrine therapy. In addition to endocrine therapy and chemotherapy, patients with tumors indicative of HER2 overexpression or amplification should be considered for adjuvant treatment with trastuzumab and chemotherapy (see below). For each individual, the choice of adjuvant therapy must take into account the potential benefit, possible side effects and patient preference. Several decision-making tools have been developed to help doctor–patient communication for adjuvant treatment decisions.

*endocrine therapy.* Patients with tumors considered of high or uncertain responsiveness (ER ≥1%) should be treated with endocrine therapy.

In premenopausal patients tamoxifen alone (20 mg daily for 5 years) or the combination of ovarian function suppression with tamoxifen are standard therapies [II, A] in particular after chemotherapy [19, 24]; ovarian function suppression and tamoxifen is at least as effective as chemotherapy without further hormonal therapy [I, A] [22]. Longer term therapy may be effective in patients with node-positive disease [68]. Ovarian function ablation may be achieved by bilateral oophorectomy which leads to irreversible ablation of ovarian function. Gonadotropin-releasing hormone analogs (GnRHAs) lead to reversible ovarian suppression sufficient for therapeutic activity. GnRHAs should be given for at least 2 years, although the optimal duration for this treatment has not been established [III, D]. Combining GnRHAs and aromatase inhibitors (AIs) in premenopausal patients is not indicated outside clinical trials, as is the use of AIs alone. Tamoxifen should not be used simultaneously with chemotherapy [I, A], whereas the best use of GnRHAs (concurrent or sequential with chemotherapy) is unknown.

In postmenopausal patients AIs can be used upfront [3, 20] for 5 years, with one trial [20] reporting a modest survival benefit as compared with tamoxifen; or AIs can be prescribed sequentially after 2–3 years of tamoxifen [I, A] [21]. For patients who are being treated with tamoxifen, a switch to an AI after 2–3 years is recommended [I, A] [25]. In postmenopausal patients, 5 years of tamoxifen alone is still a viable option for certain patients at very low risk of recurrence. For patients who have completed 5 years of tamoxifen the addition of an AI for a further period of 2–5 years is recommended especially for patients with node-positive disease [I, A] [25, 43]. The total duration of optimal adjuvant endocrine treatment is between 5 and 10 years; there is no proven benefit for the routine use of AIs for >5 years. Sequential rather than concurrent administration of cytotoxic and endocrine therapies should be used [II, A]; while the concurrent use of tamoxifen and anthracyclines is detrimental, the concurrent use of AIs and chemotherapy has not been investigated.

*CYP2D6 (cytochrome P450 2D6).* Tamoxifen has major active metabolites (4-hydroxytamoxifen, *N*-desmethyltamoxifen, endoxifen); endoxifen is a potent competitor of estradiol and possibly a downregulator of ER expression. CYP2D6, a microsomal enzyme, limits the synthesis of endoxifen. The activity of CYP2D6 is determined by genotype and by inhibitor drugs (Table 4). While some retrospective studies point towards an unfavorable prognosis of patients with low activity genotypes ('poor metabolizer') of CYP2D6, two retrospective analyses of randomized controlled trials failed to detect a differential effect of CYP2D6 poor metabolizer genotypes on the efficacy of tamoxifen [57, 72]. Thus, routine genotyping is not recommended. However, it appears reasonable to recommend that moderate-to-potent inhibitors of CYP2D6 be avoided in patients on tamoxifen or, if such drugs cannot be replaced, that alternatives to tamoxifen, i.e. AIs, be considered [81].

*prevention of bone loss, bisphosphonate therapy.* Women treated with AIs should receive sufficient vitamin D and calcium, if necessary as nutritional supplements; further, a DEXA (dual energy X-ray absorption) scan is recommended to allow early treatment of osteoporosis. A DEXA scan should also be performed for women experiencing premature menopause (e.g. <45 years of age) [74].

**Table 3.** Threshold for treatment modalities according to the 2009 St. Gallen Consensus Conference

| | Relative indications for chemoendocrine therapy | Factors not useful for decision | Relative indications for endocrine therapy alone |
|---|---|---|---|
| Clinicopathological features | | | |
| ER and PgR | Lower ER and PgR level | | Higher ER and PgR level |
| Histological grade | Grade 3 | Grade 2 | Grade 1 |
| Proliferation | High[a] | Intermediate[a] | Low[a] |
| Nodes | Node positive (≥4 involved nodes) | Node positive (1–3 involved nodes) | Node negative |
| PVI | Presence of extensive PVI | | Absence of extensive PVI |
| pT size | >5 cm | 2.1–5 cm | ≤2 cm |
| Patient preference | Use all available treatments | | Avoid chemotherapy-related side effects |
| Multigene assays | | | |
| Gene signature[b] | High score | Intermediate score | Low score |

[a]Conventional measures of proliferation include assessment of Ki67 labeling index (e.g. low, ≤15%; intermediate, 16–30%; high, >30%) [77] and pathological description of the frequency of mitoses. The reliability of these measures will vary in different geographic settings. First-generation genetic signatures contain genes sampling the ER, HER2 and proliferative pathways [78, 79]. Meta-analysis indicates that much of the prognostic information in these signatures resides in their sampling of proliferative genes [80], but their respective total scores may be the only form in which information is provided at present and could be used in this component of assessment of relative indications for chemotherapy.

[b]The Panel agreed that validated multigene tests, if readily available, could assist in deciding whether to add chemotherapy in cases where its use was uncertain after consideration of conventional markers.

ER, estrogen receptor; PgR, progesterone receptor; pT, pathological tumour size (i.e. size of the invasive component); PVI, peritumoral vascular invasion. Adapted from Goldhirsch *et al.* [41].

Bisphosphonates prevent bone loss in patients with iatrogenic premature menopause [40, 46] and in postmenopausal patients treated with AIs [I, A] [11].

Some, but not all [18] studies indicate that adjuvant therapy with zoledronic acid and possibly other bisphosphonates lowers the risk of breast cancer recurrences in premenopausal patients treated with luteinizing hormone-releasing hormone (LHRH) analogs [39] and in selected postmenopausal patients treated with AIs [29]. Thus, the use of adjuvant zoledronic acid is still controversial and is not recommended as routine therapy [I, C].

*chemotherapy.* Adjuvant chemotherapy is recommended for patients with tumors of uncertain or absent [17] endocrine responsiveness and for patients with HER2-overexpressing or amplified tumors. A multiplicity of chemotherapy regimens are acceptable for adjuvant treatment (common examples are listed in Table 2). Standard chemotherapy regimens are superior to less intensive regimens even in elderly patients [II, B] [62].

At present, the use of anthracyclines may be recommended for most patients [I, A] [26] and especially for patients with HER2-positive disease [III, B]. However, anthracycline-free regimens with similar or superior efficacy are being developed [e.g. docetaxel–cyclophosphamide (DC)]. For some patients (elderly, cardiac contraindication, etc.), CMF (cyclophosphamide, methotrexate and fluorouracil) may still be appropriate [I, A] [10, 62].

Some retrospective analyses suggest that taxanes may be particularly effective in patients with ER-negative or HER2-positive early breast cancer; other trials did not replicate these findings [III, C]. Chemotherapy regimens combining anthracyclines and taxanes have been investigated mainly in patients with nodal-positive breast cancer. Some studies suggest that the sequential rather than the concomitant use of anthracyclines and taxanes may be superior [34, 85].

The optimal duration of adjuvant chemotherapy is not known. However, at least four cycles (12–16 weeks) should be administered, generally aiming for a total duration of chemotherapy of 18–24 weeks, in particular for patients with higher risk of recurrence (e.g. node-positive disease). The use of dose-dense schedules with prophylactic granulocyte colony-stimulating factor (G-CSF) is acceptable especially in highly proliferative tumors [8, 12] [I, A], whilst high-dose therapy requiring bone marrow progenitor cell support cannot be recommended at all [I, A].

*trastuzumab.* Patients with breast cancers that overexpress HER2 protein ($p185^{HER2}$, measured by IHC, e.g. 3+ using HercepTest, DAKO) or have HER2 gene amplification (measured by FISH or CISH) benefit from adjuvant treatment with trastuzumab [I, A]; the indication for adjuvant trastuzumab should be based on an average HER2:CEP17 ratio of ≥2 or—in the presence of polysomy 17—on ≥4 HER2 signals per cell [91]. Adjuvant trastuzumab lowers the hazard of recurrence by about a quarter to a half and the hazard of death by about one-sixth to one-third. While randomized trials have excluded patients with small primaries of <1 cm, overexpression of HER2 confers a poorer prognosis even in these small tumors, and the use of trastuzumab should be discussed with women with small, node-negative breast cancers. Based on pharmacokinetic analyses a 3-weekly schedule (6 mg/kg) is considered equivalent to a weekly schedule (2 mg/kg). The optimum duration of adjuvant trastuzumab has not yet been established, but for the time being 1 year is recommended.

**Table 4.** Important drug classes divided by known CYP2D6 inhibitory activity.

| Class | Moderate-to-potent inhibitors with clearly demonstrated or expected *in vivo* inhibition[a] | Weak-to-moderate inhibitors that have demonstrated or could potentially have some *in vivo* effect[b] | Alternative drugs expected to have little *in vivo* inhibition[c] |
|---|---|---|---|
| SSRI/SNRIs | Paroxetine[d] Fluoxetine[d] Bupropion Duloxetine | Sertraline[d] Citalopram[d] Fluvoxamine | Venlafaxine[d] Desvenlafaxine Reboxetine Escitalopram Mirtazapine |
| Tricyclic antidepressants | | Clomipramine Doxepin Desipramine Imipramine Amitriptyline Nortriptyline | |
| Antipsychotics | Thioridazine Perhenazine Pimozide | Chlorpromazine Fluphenazine Haloperidol | Thiothixene Clozapine Risperidone Clozapine Olanzapine Ziprasidone Quetiapine |
| Cardiac medications | Quinidine Ticlopidine | Amidarone Nicardipine Verapamil Amlodipine Felodipine Nifedipine | Diltiazem |
| Medications for infectious diseases | Terenadine Quinidine[e] | Ritonavir Halofantrine Choroquine | Indinavir Saquinavir Nelfinavir Delavirdine Nevirapine Efavirenz |
| H2 blockers | | Cimetidine | Ranitidine |
| H1 blockers[f] | | Clemastine Tripelennamine Promethazine Hydroxyzine Diphenylpyraline | Chorpheniramine Cetirine Loratadine |
| Miscellaneous medications | Cinacacet | Celecoxib | Galapentin |

[a]Medications in the *in vivo* data that demonstrate an effect on endoxifen concentrations when co-prescribed with tamoxifen.
[b]Medications classified as moderate-to-potent inhibitors have demonstrated *in vivo* inhibition of CYP2D6 substrates with an increase in the plasma AUC (area under the concentration–time curve) of the substrate by at least ≥2-fold and/or *in vitro* inhibition using human liver microsome systems with *in vitro* inhibition constant ($K_i$) values ≤1 μmol/l. These medications are expected to have or have demonstrated phenotypic conversion of extensive metabolizers to poor metabolizers and significant reduction in endoxifen levels. They should not be administered to women receiving tamoxifen for prolonged periods of time.
[c]Medications classified as weak-to-moderate inhibitors have demonstrated *in vivo* inhibition of CYP2D6 substrates with an increase in the plasma AUC of the substrate by <2fold and/or *in vitro* inhibition using human liver microsome systems with $K_i$ values in the range of 2–10 μmol/l. Although these medications have either demonstrated lesser reductions in endoxifen levels or could potentially result in reduction of endoxifen levels, it is unclear what the clinical importance of such reductions may be.
[d]Medications classified as 'alternative drugs expected to have little *in vivo* inhibition' are not expected to have any effect on endoxifen levels.
[e]Quinidine is mentioned both as a cardiac and an antimalarial medication.
[f]Not a comprehensive review of all antihistamines.
CYP2D6, cytochrome P450 2D6; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
From Sideras *et al.* [81].

Trastuzumab may be started in parallel with a taxane, but it should not be given concurrently with an anthracycline outside the context of a clinical trial. Even when given after an anthracycline-containing regimen trastuzumab may have cardiotoxic effects and cardiac function should be routinely monitored. It is important to avoid trastuzumab in patients with low left ventricular ejection fraction (LVEF, <50%) and in patients whose cardiac function deteriorates during therapy. The use of trastuzumab alone or with endocrine therapy, i.e. without chemotherapy, for early breast cancer is not yet supported by clinical trial evidence.

## systemic adjuvant therapy for ductal intraepithelial neoplasia (DCIS)

Tamoxifen reduces the risk of invasive and non-invasive recurrences after breast-conserving resection of ER-positive DCIS but has no impact on survival [I, A] [23, 33]. AIs are being investigated for the adjuvant therapy of DCIS but should not be used in routine care.

## primary (neoadjuvant) systemic therapy

Primary systemic therapy is indicated for locally advanced breast cancer (stages IIIA–B) including inflammatory breast cancer [III, B] and for large operable tumors for reducing tumor size in order possibly to perform BCS [I, A] [73] and to assess responsiveness to systemic therapy in clinical trials [89]. Prior to primary systemic therapy, a core needle biopsy and complete pathological assessment (i.e. histological type, grade, ER, PgR and HER2 status) is essential. In addition, full clinical staging to rule out gross metastatic disease is recommended. Many centers now undertake pretreatment SLNB to document axillary nodal status. As a minimum, fine needle aspiration of suspicions lymph nodes should be done. Chemotherapy should be chosen based on predictive factors similar to adjuvant treatment;
ER-positive, HER2-negative carcinoms may be less responsive to primary chemotherapy than ER-negative and HER2-positive tumors [89]; primary hormonal therapy is active, in particular with AIs [30, 83], but long-term recurrence and survival results

are not yet available. Trastuzumab should be added to primary chemotherapy in patients with HER2-positive tumors [II, B]; the concomitant use of anthracyclines and trastuzumab should be limited to clinical trials. Primary systemic therapy should be followed by both surgery and radiation therapy according to the principles outlined above. If neoadjuvant treatment is chosen, it is preferable to perform all chemotherapy in the preoperative setting; however, performing part of the chemotherapy as neoadjuvant and part as adjuvant is also acceptable [77].

*surgery after primary systemic therapy.* Down-sizing of a large unifocal primary tumor with neoadjuvant therapy will allow BCS to be undertaken in some patients who would at presentation have otherwise required mastectomy. With multifocal disease, or where the primary tumor 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. Where rapid tumor shrinkage indicates a likely complete or near-complete tumor response to treatment, it is necessary to mark the primary site (using a marker clip under ultrasound guidance, or skin tattooing) to facilitate accurate BCS. Detailed histological assessment of tumor resection margins is essential, and, if there is a discrepancy in receptor analysis, the receptor status from the pretreatment core biopsy is favored.

## prognosis

The prognosis of patients with breast cancer depends on biological characteristics of the cancer and the patient and on appropriate therapy. Age, anatomical stage, ER expression and histological grade can be integrated into prognostic models (e.g. Nottingham prognostic index, Adjuvant!) as outlined above (Staging and risk assessment). Molecular predictors of prognosis (e.g. the Amsterdam 70 gene signature, Mammaprint, or the 16-gene Recurrence Score, Oncotype Dx) may outperform the traditional prognostic markers in certain patient populations, but their integration into prognostic models is still under investigation.

In general terms, the annual hazard of recurrence peaks in the second year after diagnosis but remains at 2–5% in years 5–20 [77]; patients with node-positive disease tend to have higher annual hazards of recurrence than patients with node-negative cancers. The risk of recurrence is higher in patients with ER-negative cancers, but the annual hazards of recurrence drop below the level of ER-positive tumors ~5–8 years after diagnosis [III, B] [8, 52]. Relapses of breast cancer have been observed as late as >20 years after the initial diagnosis.

In addition to adequate local and systemic treatments, epidemiological evidence points towards lifestyle factors affecting the prognosis of patients with breast cancer [49]: Regular exercise provides functional and psychological benefits [II, B], possibly reduces the risk of recurrence [47] and should be recommended to all suitable patients after treatment for breast cancer [II, B] [59]; aerobic training and weight lifting do not negatively affect the development of lymphedema [79, 80]. Likewise, weight gain and obesity are likely to negatively affect the prognosis of breast cancer [15]; nutritional counseling should be recommended as part of survivor care for all obese patients [III, B]. Smoking cessation should be encouraged [III, C] [58].

## follow-up

There is no evidence from randomized trials supporting any particular follow-up sequence or protocol. The aims of follow-up are to detect early in-breast and local recurrences or contralateral breast cancer, to evaluate and treat therapy-related complications (such as menopausal symptoms, osteoporosis and second cancers) and to provide psychological support and information in order to enhance returning to normal life after breast cancer. Whatever the follow-up protocol and the frequency of visits, every visit should include history taking, eliciting of symptoms and physical examination. Ipsilateral (after BCS) and contralateral clinical mammography is recommended yearly for premenopausal women and for postmenopausal women [V, D]. 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 tumor markers such as CA15-3 or CEA) produce a survival benefit [I, A]. However, the available studies were performed in an era where treatment for advanced disease, both systemic and locoregional, was less efficacious, and new trials are needed to reassess this question nowadays.

## note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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