COLLEGE OF ONCOLOGY

National Clinical Practice Guidelines

Breast Cancer

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Breast Cancer Guidelines Expert Panel

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Reference: Wildiers H, Stordeur S, Vlayen J, Scholten R, van de Wetering F, Bourgain C, Carly B, Christiaens M-R, Cocquyt V, Lifrange E, Schobbens J-C, Van Goethem M, Villeirs G, Van Limbergen E, Neven P. Breast cancer in women: diagnosis, treatment and follow-up. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2013. KCE Reports 143 – 3rd EDITION. D/2013/10.273/38.

Stakeholders and validators

Stakeholders	Professional association
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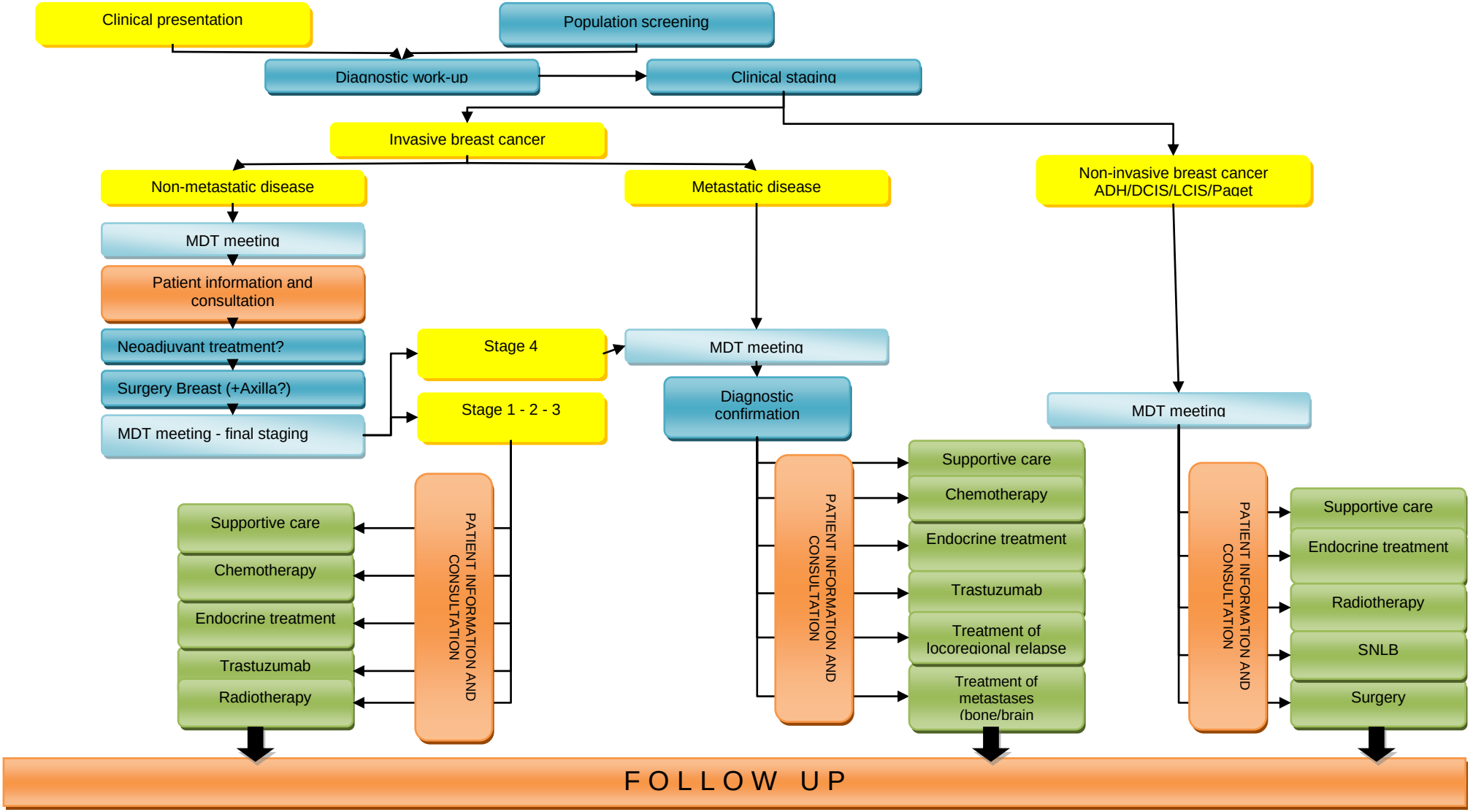
General algorithm



ADH: atypical ductal hyperplasia ; DCIS: ductal carcinoma in situ ; LCIS Lobular carcinoma in situ ; MDT: multidisciplinary team

National Guidelines Breast Cancer

INTRODUCTION [1-2]

This document presents the updated clinical practice guidelines on breast cancer which was first published in 2007 and completely updated in 2010. It covers a broad range of topics: diagnosis, staging, treatment, reconstructive surgery, supportive therapy and follow-up. The guidelines primarily concern women with early (DCIS and invasive) or advanced (locally or metastatic) breast cancer.

The 2013 update focuses on four therapeutic approaches, i.e. axillary surgery in women with positive sentinel nodes, the use of bevacizumab in women with metastatic breast cancer, the use of trastuzumab in women with HER2 positive invasive breast cancer, and the use of bisphosphonates in the adjuvant setting. Updated conclusions and recommendations are added to their respective sections with a special indication. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences. The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care.

For more in-depth information and the scientific background, we would like to ask the readers to consult the full scientific report at www.kce.fgov.be.

The guidelines are developed by a panel of experts (see 'expert panel') comprising clinicians of different specialties and were reviewed by relevant professional associations (see 'external reviewers and validators'). Guideline development and literature review expertise, support and facilitation were provided by the KCE Expert Team.

SEARCH FOR EVIDENCE

Sources [5-7]

The present guidelines were developed by adapting (inter)national clinical practice guidelines to the Belgian context using the ADAPTE methodology.

To identify published clinical practice guidelines on breast cancer, a broad search of electronic databases (Medline, PreMedline, EMBASE), specific guideline websites and websites of organisations in oncology was conducted. Both national and international clinical practice guidelines were searched. A language (English, Dutch, French) and date restriction (2006–2009) were used. Clinical practice guidelines without references were excluded, as were clinical practice guidelines without clear recommendations.

For each clinical question, the evidence - identified through the included CPGs - was updated by searching Medline, the Cochrane Database of Systematic Reviews and DARE.

For therapeutic interventions, systematic reviews and randomized controlled trials (RCT) were included. However, for diagnostic interventions we also searched for observational studies in case no systematic review or RCT was found. All searches were run between March and December 2009, and updated in January 2010.

The methodological quality of the identified clinical practice guidelines was assessed using the AGREE instrument. The quality of the systematic reviews, randomized controlled trials and prognostic studies was critically appraised using the checklists of the Dutch Cochrane Centre. The

methodological quality of the diagnostic accuracy studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies checklist.

The seventh edition of the TNM Classification of Malignant Tumours was used to describe and categorize cancer stages and progression.

Guideline update

A regular update of the full guideline takes a lot of time and is not cost-effective. Therefore, the decision was made to regularly update specific parts of the guideline based on alert messages given by the members of the guideline development group.

The following therapeutic approaches were addressed in this update:

RQ1 - The potential omission of axillary lymph node dissection (ALND) in women with breast cancer and positive sentinel nodes (isolated tumour cells / micrometastasis / macrometastasis)

RQ2 - The use of bisphosphonates in the adjuvant setting

RQ3 - The use of bevacizumab for patients with HER-2 negative metastatic breast cancer

RQ4 - The use of trastuzumab with non-anthracycline chemotherapy for patients with HER-2 positive breast cancer in the adjuvant setting.

Systematic reviews were searched from January 2010 onwards (the search date of the Guideline version 2010) for all research questions in OVID Medline, PreMedline, Embase, and The Cochrane Library (Cochrane Database of Systematic Reviews, DARE, HTA database). In addition, the protocols and reviews of the Cochrane Breast Cancer Group were browsed.

If a recent systematic review was included a search for randomised controlled trials (RCTs) published after the search date of the review was done in MEDLINE, PreMedline, Embase and CENTRAL. If no systematic review was available a full search for RCTs was performed from 2010 onwards in those databases. Members of the guideline development group were also consulted to identify relevant evidence that might have been missed during the search process. The risk of bias of identified RCTs was assessed by the Cochrane Collaboration's tool for assessing risk of bias.

Grade of recommendation

A grade of recommendation was assigned to each recommendation using the GRADE system (appendix 1).

PEER REVIEW AND VALIDATION

The guidelines prepared by the guideline development group were circulated to the relevant professional associations (see 'external reviewers'). Each association was asked to assign two key persons to discuss the recommendations during an open meeting. As a preparation of the meeting all invited experts were asked to score each recommendation on a 5-point Likert-scale to indicate their agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' indicating 'somewhat disagree', '3' indicating 'unsure', '4' indicating 'somewhat agree', and '5' indicating 'completely agree' (the experts were also able to answer 'not applicable' in case they were not familiar with the underlying evidence). In case an expert disagreed with the recommendation (score '1' or '2'), (s)he was asked to provide appropriate evidence. Scientific arguments reported by these experts were used to adapt the formulation or the strength of the clinical recommendations. The second and third rounds of evaluation focused on the adapted recommendations in order to reach a consensus.

Europa Donna Belgium was contacted to invite patients representatives to take part of a stakeholder meeting (22nd March 2013). A key role for patient representatives is to ensure that patient views and experiences inform the group's work.

As part of the standard KCE procedures, an external scientific validation of the report was conducted by three independent experts, making use of the AGREE II checklist. The validation process was chaired by CEBAM. The validation of the report results from a consensus or a voting process between the validators.

EPIDEMIOLOGY [3-4]

In Belgium, 9 908 new breast cancers were diagnosed in 2010. In Belgium as in Europe, breast cancer is the most frequent cause of death by cancer in women (20.2% of all cancer deaths). However, a favourable pattern in breast cancer mortality in the EU-25 was observed after 1989, leading to a fall in overall rates from 21.3/100 000 in 1990 to 18.9/100 000 in 2000. This decline has been attributed to the combined effect of earlier detection and improved adjuvant treatment.

Only 5% of breast carcinomas are diagnosed in women who are younger than 40 years of age, but this proportion increased to 47.5% in the 50-69 years age group. The highest age-standardised incidence rates were reported in the 60-64 years age group (415.8/100 000 person-years in 2010) and in the 65-69 years age group (413.4/100 000 person-years in 2010) 4.

Female breast cancer has a relatively good prognosis, with a 5-year relative survival rate of 88.0% (Belgium, 2004-2008). However, the survival rate declined at a longer follow-up period, reaching a 10-year relative survival of 78.9% (Flemish Region, 1999-2008) 4.

A favourable pattern in breast cancer mortality in the EU-25 was observed after 1989, leading to a fall in overall rates from 21.3/100 000 in 1990 to 18.9/100 000 in 2000 5.

DIAGNOSIS OF BREAST CANCER

Triple assessment [8-15]

The diagnosis of breast cancer relies on the so-called triple assessment, including clinical examination, imaging (comprising mammography and ultrasonography) and sampling of the lesion with a needle for histological/cytological assessment. The choice between core biopsy and/or a fine needle aspiration cytology depends on the clinician's, radiologist's and pathologist's experience.

- All patients should have a clinical examination (*1C evidence*).
- If a localised abnormality is detected, patients should have mammography and/or ultrasonography followed by core biopsy and/or fine needle aspiration cytology (*1C evidence*).
- If clinical examination and imaging are pathognomonic (BIRADS 2) of a benign lesion (i.e. a cyst), biopsy/cytology is not mandatory (*expert opinion*).
- A lesion considered malignant only on the basis of clinical examination, imaging or cytology should, where possible, have histopathological confirmation of malignancy before any surgical procedure takes place (*1C evidence*).
- Two-view mammography should be performed as part of triple assessment (clinical assessment, imaging and tissue sampling) in a unit specialized in breast imaging (*1C evidence*).

- Women presenting with breast symptoms and a strong suspicion of breast cancer should be evaluated by means of the triple assessment approach, whatever their age (*1C evidence*).

Magnetic resonance imaging (MRI) [16-23]

- There is insufficient evidence to recommend routine use of MRI for the diagnosis of breast cancer. MRI can be considered in specific clinical situations where other imaging modalities are not reliable, or have been inconclusive, and where there are indications that MRI is useful (clinically palpable and mammographically occult tumours, cT0N+ patients, BRCA-associated cancers, diagnosis of recurrence) (*1C evidence*).
- For definitive characterization of breast lesions, biopsy cannot yet be replaced by MRI (*1B evidence*).

99mTc-MIBI scintimammography (SMM) [16,17, 24-30]

- There is insufficient evidence to routinely use 99mTc-MIBI scintimammography for the diagnosis and staging of breast cancer. 99mTc-MIBI scintimammography can be considered in specific clinical situations where other imaging modalities are not reliable, or have been inconclusive, and where there are indications that 99mTc-MIBI scintimammography is useful (*1C evidence*).

PET-scan [31-35]

- PET scanning is insufficiently accurate to be recommended for diagnosis of breast cancer as an alternative to biopsy (*1B evidence*).

Hormonal receptor assessment [36-48]

- Estrogen receptors and progesterone receptors (ER/PgR) should be measured on all ductal carcinomas in situ (DCIS) and primary invasive breast cancers (*1B evidence*).
- Assessment of HER2 protein expression and, if positive, confirmation tests with gene amplification should be performed in every primary invasive breast cancer at the time of diagnosis and at the time of recurrence whenever possible (*1B evidence*).

Tumour markers [49-58]

- There is no good evidence to recommend the assessment of tumour markers (circulating tumour cells [CTC], CA 15-3, CA 27.29, CEA and Cathepsin D) in the diagnosis of primary breast cancer (*2C evidence*).

STAGING OF BREAST CANCER

TNM classification and stage grouping see appendix 2.

Routine staging tests [11, 49-52, 57-63]

- In women with stage I breast cancer, the routine use of bone scanning, liver ultrasonography and chest radiography has a very low yield and cannot be recommended (*2C evidence*).

- In asymptomatic women with DCIS, the routine use of bone scanning, liver ultrasonography and chest radiography cannot be recommended for baseline staging (*2C evidence*).

Magnetic resonance imaging [47, 64-74]

- Routine MRI of the breast is not recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or DCIS (*1C evidence*), except in the following situations:
  - if the estimates of the extent of the disease, needed for treatment planning, diverge between clinical examination, mammography and ultrasound (*2C evidence*);
  - in invasive lobular cancer (*1C evidence*);
  - if, due to high breast density, mammographic assessment does not allow to exclude multicentric or bilateral disease (*2C evidence*).
- For M-staging (visceral or bone metastases), MRI/CT can be considered (*2C evidence*).

Axillary ultrasonography [75-78]

- Axillary ultrasonography with fine needle aspiration cytology of axillary lymph nodes with suspected malignancy is recommended (*2C evidence*).

PET-scan [31, 79-86]

- Axillary lymph node PET scan is not recommended in the staging of breast cancer, because its sensitivity is inferior to sentinel node biopsy and a fortiori to axillary node dissection (*1B evidence*).
- PET scan can be useful for the evaluation of metastatic disease in locally advanced breast tumours with a high chance of (micro- or macro) metastatic disease (*expert opinion*).
- The evidence on the usefulness of PET for the detection of bone metastases was inconclusive and therefore, bone scan is still the technique of choice (*2C evidence*).

TREATMENT OF NON INVASIVE BREAST CANCER

Early precursor and high-risk lesions [59, 87-88]

Since precursor lesions, such as atypical lobular hyperplasia (ALH), atypical ductal hyperplasia (ADH) and (small cell) lobular carcinoma in situ (LCIS), have a small chance of progression and a very slow progression rate, they are usually considered as indicators of increased risk.

- Management of early precursor lesions is preferably discussed in a multidisciplinary team meeting (*expert opinion*).
- When atypical lobular hyperplasia or flat epithelial atypia is present near the margins of an excision specimen, re-excision is not necessary (*expert opinion*).
- When lobular carcinoma in situ or atypical ductal hyperplasia is present in the margins of an excision specimen, re-excision is not recommended (*expert opinion*).
- When atypical lobular hyperplasia / lobular carcinoma in situ, flat

epithelial atypia or an atypical intraductal proliferation reminiscent of atypical ductal hyperplasia, is found in a core biopsy, diagnostic excision is recommended (*expert opinion*).

- When pleomorphic lobular carcinoma in situ or lobular carcinoma in situ with comedonecrosis is found in a core biopsy, complete excision with negative margins is recommended, and anti-hormonal treatment and/or radiotherapy is an option (*expert opinion*).
- After a diagnosis of lobular carcinoma in situ or atypical ductal hyperplasia, annual follow-up mammography is indicated (*2C evidence*).

Ductal carcinoma in situ

DCIS or intraductal carcinoma is most commonly diagnosed as a result of detection of microcalcifications on mammography. It is usually not palpable. By definition, it is confined to the duct system of the breast, so it is not associated with metastases.

Surgery [11, 59, 75, 89- 97]

- Women with high-grade and/or palpable and/or large DCIS of the breast who are candidates for breast-conserving surgery should be offered the choice of local wide excision or mastectomy after having been correctly informed. In case of multicentricity local wide excision is not recommended (*1B evidence*).
- In women with DCIS, mastectomy with or without immediate reconstruction remains an acceptable choice for those preferring to minimize the risk of local recurrence or to avoid radiotherapy (*1B evidence*).
- Cosmetic repair should be offered to patients treated with breast-conserving surgery (*1C evidence*).
- Immediate breast reconstruction should be discussed with all patients being advised to have a mastectomy, except when significant comorbidities preclude this option (*1C evidence*).
- When local wide excision is performed in women with DCIS, a minimum radial excision margin of 2 mm is usually recommended, with pathological examination of the specimen (*1C evidence*).
- Axillary clearance is not recommended for women with DCIS (*1C evidence*).

Sentinel lymph node biopsy [75, 96, 98-99]

- Sentinel lymph node biopsy is not recommended in patients with a preoperative diagnosis of DCIS who are having breast-conserving surgery, unless they are considered to be at high risk of invasive disease. Patients at high risk include those with a palpable mass or extensive micro-calcifications (*1B evidence*).
- Sentinel lymph node biopsy is recommended for high-grade DCIS, when mastectomy with or without immediate reconstruction is planned (*1A evidence*).

Radiotherapy [100]

- After a breast-conserving surgery of DCIS, omitting radiotherapy could be considered when, after discussion in the multidisciplinary team meeting, the risk of local recurrence is estimated to be very low (*1A evidence*).

Endocrine therapy [44-46,101]

- Adjuvant hormonal therapy is recommended for patients with ER positive DCIS (*1A evidence*).

Paget's disease [75, 102-108]

- Breast-conserving surgery with removal of the nipple–areolar complex followed by radiotherapy should be offered as an alternative to mastectomy in patients with Paget's disease without underlying invasive breast cancer (*2C evidence*).
- Cosmetic repair should be offered to patients with Paget's disease treated with breast-conserving surgery (*1C evidence*).

TREATMENT OF EARLY INVASIVE BREAST CANCER [75]

- All cases of breast cancer should be discussed within a multidisciplinary team before any treatment is initiated (*expert opinion*).

Neoadjuvant treatment [109]

- In patients with unifocal operable tumours too large for breast-conserving surgery, downstaging with neoadjuvant systemic therapy can be considered (*1A evidence*).

Surgery to the breast [11, 75, 89, 92-94, 110-113]

- Breast-conserving surgery followed by radiotherapy offers the same survival benefits as modified radical mastectomy in women with stage I or II breast cancer who are candidates for breast-conserving surgery (*1A evidence*).
- Cosmetic repair should be offered to patients treated with breast conserving surgery (*1C evidence*).
- Immediate breast reconstruction after mastectomy offers the same survival benefits as mastectomy without reconstruction (*1C evidence*).
- The choice of surgery must be tailored to the individual patient with stage I or II breast cancer, who should be fully informed of the surgical options (*1A evidence*).

Surgery to the axilla [59, 75, 89, 98-99, 114]

- Sentinel lymph node biopsy is not recommended for (*1A evidence*):
  - large T2 (i.e. > 3 cm) or T3-4 invasive breast cancers;
  - inflammatory breast cancer;
  - patients with suspicious palpable axillary lymph nodes;
  - multiple tumours; and possibly disturbed lymph drainage after recent axillary surgery or a large biopsy cavity after tumour excision.
- In women with primary breast cancer of less than 3 cm and with clinically and ultrasonographically negative nodes, a sentinel lymph node biopsy should be performed (*1A evidence*).

Update 2013 [115-128]

Conclusions

In breast cancer patients with one or two positive sentinel nodes (micro- or macrometastases), treated with surgery and systemic therapy:

- There are indications that SLND alone is non-inferior to ALND with respect to 5-year overall survival and 5-year disease-free survival (Giuliano et al., 2011), low level of evidence; Yi 2010 and Yi 2013, *very low level of evidence*).
- A difference in axillary recurrence after 5 years between SLND alone and ALND in women with breast cancer and a positive sentinel lymph node could neither be demonstrated nor refuted (Giuliano et al., 2011 and Yi 2013; *very low level of evidence*).
- There are indications that SLND alone leads to less wound infections and axillary seromas 30 days after surgery than ALND in women with breast cancer and a positive sentinel lymph node (Lucci et al., 2007); *low level of evidence*).
- There are indications that SLND alone leads to less axillary paresthesias and subjectively reported lymphedema after 12 months than ALND in women with breast cancer and a positive sentinel lymph node (Lucci et al., 2007); *low level of evidence*).
- A difference in objectively assessed lymphedema after 12 months between SLND alone and ALND in women with breast cancer and a positive sentinel lymph node could neither be demonstrated nor refuted (Lucci et al., 2007); *low level of evidence*).
- Quality of life after SLND alone or after ALND in women with breast cancer and a positive sentinel lymph node has not been studied in the RCT (Giuliano et al., 2011).

In breast cancer patients with positive sentinel node (isolated tumour cells only), treated with surgery and systemic therapy:

- A difference in axillary recurrence after 5 years between SLND alone and ALND in women with breast cancer and a positive sentinel lymph node with isolated tumour cells could neither be demonstrated nor refuted. The risk difference of axillary recurrence between SLND alone and ALND in women with breast cancer and a positive sentinel lymph node with isolated tumour cells is +0.94% [95% CI -0.77% to 2.66%] (Calhoun 2005, Giobuin 2009, Pepels 2012; *very low level of evidence*).

In breast cancer patients with positive sentinel node (micrometastases only), treated with surgery and systemic therapy:

- A difference in 5-year overall survival between SLND alone and ALND in women with breast cancer and a positive sentinel lymph node with micrometastases could neither be demonstrated nor refuted (Bilimoria 2009, Cortesi 2012, Wasif 2010, Yi 2010; *very low level of evidence*).
- There are indications that axillary recurrence was slightly higher after SLND alone than after ALND women with breast cancer and a positive sentinel lymph node with micrometastases (risk difference, +1.51% [95%CI -1.59% to 4.62%]) (Bilimoria 2009, Bulte 2009, Cortesi 2012, Fan 2005, Pepels 2012, Yi 2010; *very low level of evidence*).

In breast cancer patients with positive sentinel node (macrometastases only), treated with surgery and systemic therapy:

- There are indications that 5-year overall survival of breast cancer women with nodal macrometastases is similar whether women are treated with SLND alone or ALND (Bilimoria 2009, Cortesi 2012, Wasif 2010, Yi 2010; *very low level of evidence*).
- A difference in axillary recurrence after 5 years between SLND alone

and ALND in women with breast cancer and a positive sentinel lymph node with macrometastases could neither be demonstrated nor refuted. The risk difference of axillary recurrence between SLND alone and ALND is +0.14% [95%CI -0.12% to 0.41%] (Bilimoria 2009, Fan 2005, Yi 2010; *very low level of evidence*).

Recommendations

- For women with a SLNB that shows isolated tumor cells, we recommend not to perform completion ALND (*strong recommendation*).
- For women treated with breast-conserving surgery and with one or two positive sentinel lymph nodes with micrometastases, completion ALND is not recommended (*strong recommendation*).
- For women treated with mastectomy and with one or two positive sentinel lymph nodes with micrometastases, completion ALND is not recommended (*weak recommendation*).
- For women treated with breast-conserving surgery and with one or two positive sentinel lymph nodes with macrometastases, completion ALND remains the standard treatment. However, for patients at low risk for axillary failure, completion ALND can be omitted (*strong recommendation*).
- For women treated with mastectomy and with one or two positive sentinel lymph nodes with macrometastases, completion ALND remains the standard treatment. However, for patients at low risk for axillary failure, completion ALND can be omitted (*weak recommendation*).
- For women with three or more positive sentinel lymph nodes with micro- or macrometastases, we recommend ALND (*strong recommendation*).
- Benefits and risks of each procedure have to be discussed with the patient (*strong recommendation*).

Adjuvant therapy

Sequencing of adjuvant therapy [129-134]

- If adjuvant chemotherapy and radiotherapy are indicated, the chemotherapy should be given first (*1A evidence*).
- It is recommended to start adjuvant chemotherapy or radiotherapy within 8 weeks of completion of surgery (*1C evidence*).

Radiotherapy [11, 38, 59, 75, 135-147]

- In patients with early breast cancer, adjuvant radiotherapy is indicated after breast-conserving surgery (*1A evidence*).
- Adjuvant chest wall radiotherapy after mastectomy should be offered to patients with early invasive breast cancer at high risk of local recurrence, i.e. with four or more positive axillary lymph nodes or involved resection margins (*1A evidence*).
- Until data from a large ongoing randomized trial become available, radiotherapy after mastectomy should be offered to patients with 1-3 positive nodes (*1A evidence*).
- Internal mammary chain irradiation should be discussed on a case by case basis in the multidisciplinary team meeting (*expert opinion*).
- The target volume of percutaneous adjuvant radiotherapy

encompasses the entire breast and the adjoining thoracic wall. The dose amounts to approximately 50 Gray fractionated in the conventional manner (1.8-2.0 Gray) with an additional local boost (*1A evidence*).

- An additional beam boost to the site of local excision can be offered to patients with early invasive breast cancer at high risk of local recurrence, following breast-conserving surgery with clear margins and whole-breast radiotherapy (*2A evidence*).
- Axillary radiotherapy should be discussed on a case by case basis in the multidisciplinary team meeting (*1A evidence*).

Systemic therapy [148-156]

- The choice of the adjuvant systemic treatment for invasive breast cancer should be driven by the hormonal sensitivity, risk profile of the tumour, age, menopausal status and comorbidities of the patient (*1A evidence*).

Table 1: Surrogate definitions of intrinsic subtypes of breast cancer

Intrinsic subtype	**Clinico-pathological definition**	**Notes**
Luminal A	**Luminal A** ER and/or PgR positive HER2 negative Ki-67 low (<14%)*	This cut-off point for Ki-67 labelling index was established by comparison with PAM50 intrinsic subtyping. Local quality control of Ki-67staining is important.
Luminal B**	**Luminal B (HER2 negative)** ER and/or PgR positive HER2 negative Ki-67 high	Genes indicative of higher proliferation are markers of poor prognosis in multiple genetic assays. If reliable Ki-67 measurement is not available, some alternative assessment of tumour proliferation such as grade may be used to distinguish between 'Luminal A' and 'Luminal B (HER2 negative)'.
	Luminal B (HER2 positive) ER and/or PgR positive Any Ki-67 HER2 over-expressed or amplified	Chemotherapy, endocrine and anti-HER2 therapy may be indicated.
Erb-B2 over-expression	**HER2 positive (nonluminal)** HER2 over-expressed or amplified ER and PgR absent	Quality of HER2 testing is of paramount importance
'Basal-like'	**Triple negative (ductal)** ER and PgR absent HER2 negative	Approximately 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(er) risks of distant recurrence. Staining for basal keratins although shown to aid selection of true basal-like tumours, is considered insufficiently reproducible for general use.

*This cut-off point is derived from comparison with gene array data as a prognostic factor. Optimal cut-points in Ki-67 labelling index for prediction of efficacy of endocrine or cytotoxic therapy may vary.
**Some cases over-express both luminal and HER2 genes.

*** The heterogeneous subtype includes adenoid cystic, juvenile secretory (good prognosis), medullary (intermediate prognosis), and metaplastic (either low grade, with good prognosis; or high grade, with poor prognosis) carcinomas, for which no generalizations can be proposed.

Table 2: Systemic treatment recommendations for subtypes

Subtype	Type of therapy	Notes on therapy
Luminal A	Endocrine therapy alone	Few require cytotoxics (e.g. high nodal status or other indicator of risk).
Luminal B (HER2 negative)	Endocrine ± cytotoxic therapy	Inclusion and type of cytotoxics may depend on tumour load and characteristics including level of endocrine receptor expression and patient preference.
Luminal B (HER2 positive)	Cytotoxics + anti-HER2 + endocrine therapy	No data are available to support the omission of cytotoxics in this group.
HER2 positive (non luminal)	Cytotoxics + anti-HER2	Patients at very low risk (e.g. pT1a and node negative) may be observed without systemic adjuvant treatment.
Triple negative (ductal)	Cytotoxics	
Special histological type*		
A. Endocrine responsive	Endocrine therapy	
B. Endocrine nonrespon-sive	Cytotoxics	Medullary** and adenoid cystic carcinomas may not require any adjuvant cytotoxics (if node negative).

*Special histological types: Endocrine responsive (cribriform, tubular, and mucinous); Endocrine nonresponsive (apocrine, medullary, adenoid cystic and metaplastic).

** Medullary carcinoma has a better outcome than other triple negative tumours, but this was mainly in cohorts where patients received chemotherapy. Medullary carcinoma is probably highly chemosensitive. One study of metaplastic tumours without adjuvant chemotherapy showed 10y overall survival around 65% which indicates intrinsic risk of relapse without chemotherapy. The value of adjuvant chemotherapy for these tumours is insufficiently studied.

Chemotherapy [37, 75, 157-176]

- For patients with Stage I-III breast cancer, preferred regimens are standard anthracycline-based regimens with or without a taxane (*1A evidence*).
- For patients with lymph node-positive breast cancer, preferred regimens are standard anthracycline and taxane-based regimens (*2A evidence*).
- For patients with HER-2 positive breast cancer who receive trastuzumab, a sequential regimen of anthracyclines and taxanes is recommended to decrease the total dose of anthracyclines and hence reduce the cardiotoxicity (*expert opinion*).
- Women receiving an adjuvant anthracycline–taxane regimen should be closely monitored for febrile neutropenia.
- Primary prophylactic G-CSF (granulocyte colony-stimulating factor) is recommended if risk of febrile neutropenia is 20% or higher (*1A*

evidence).

- Secondary prophylaxis with CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (*1A evidence*).
- In patients with breast cancer, high-dose chemotherapy with stem-cell transplantation cannot be recommended (*1A evidence*).
- For women of childbearing age, fertility issues should always be discussed before the induction of breast cancer therapy (*1C evidence*).
- Chemotherapy during pregnancy is not contraindicated after 14 weeks of gestation (*2C evidence*).

Endocrine therapy [37,75, 177-188]

- Premenopausal women with hormone-receptor positive breast cancer should receive adjuvant endocrine treatment with tamoxifen for 5 years, with or without an LHRH analogue (*1A evidence*).
- Premenopausal women with stage I or II breast cancer who cannot take tamoxifen, should receive a LHRH analogue (*1A evidence*).
- Postmenopausal women with hormone-receptor positive breast cancer should receive adjuvant endocrine treatment with either (*1A evidence*):
  - tamoxifen (for 5 years),
  - anastrozole (for 5 years) or letrozole (for 5 years),
  - or tamoxifen (for 2 - 3 years) followed by an aromatase inhibitor (up to a total of five years of hormone therapy),
  - or an aromatase inhibitor (for 2 years) followed by tamoxifen (up to a total of 5 years).
- Postmenopausal women with hormone receptor-positive tumours who have completed five years of adjuvant tamoxifen therapy should be considered for extended treatment with an aromatase inhibitor (for up to 5 years) if they were node-positive or high-risk node-negative (pT2 or grade III) (*1A evidence*).

Trastuzumab [75, 152, 161, 189-195]

Among breast cancer patients with HER-2 positive invasive (non-metastatic) breast cancer in the adjuvant setting, treated with trastuzumab with adjuvant non-anthracycline chemotherapy versus trastuzumab with adjuvant anthracycline–taxane chemotherapy:

- A difference in overall survival after 5 years (median follow-up 65 months) could neither be demonstrated nor refuted (Slamon 2011; *low level of evidence*).
- A difference in disease free survival after 5 years (median follow-up 65 months) could neither be demonstrated nor refuted (Slamon 2011; *low level of evidence*).
- There are indications that trastuzumab plus adjuvant non-anthracycline chemotherapy leads to less congestive heart failure (New York Heart Association grade 3 or 4) than trastuzumab with adjuvant anthracycline–taxane chemotherapy (Slamon 2011; *low level of evidence*).
- There are indications that trastuzumab plus adjuvant non-anthracycline chemotherapy leads to less >10% relative reduction in left ventricular ejection fraction than trastuzumab with adjuvant anthracycline–taxane chemotherapy (Slamon 2011; *low level of evidence*).

Recommendations 2013

- A one-year course of trastuzumab is indicated for women with HER2-positive, node-positive or high-risk node-negative breast cancer (tumour size > 1 cm) who received chemotherapy, and with a left ventricular ejection fraction of ≥ 55% and no important cardiovascular risk factors (*strong recommendation*).
- Trastuzumab can be combined either with a taxane in an anthracycline containing regimen or with a non-anthracycline regimen (TCH) (*weak recommendation*).
- In patients under trastuzumab, cardiac function should be monitored during treatment (e.g. every 3 months) and during follow-up (*strong recommendation*).
- Benefits and risks of each treatment have to be discussed with the patient (*strong recommendation*).

Bisphosphonates [196-206]

- In women with early non-metastatic breast cancer a difference in overall survival with bisphosphonates compared to no bisphosphonates could neither be demonstrated nor refuted (Wong 2012, Aft 2012, Coleman 2011, Gnant 2011, Paterson 2012; *low level of evidence*).
- In women with early non-metastatic breast cancer a difference in disease-free survival with bisphosphonates compared to no bisphosphonates could neither be demonstrated nor refuted (Wong 2012, Aft 2012, Coleman 2011, Gnant 2011, Paterson 2012; *low level of evidence*).
- Based on the results from randomized controlled trials it is plausible that adding zoledronic acid increases the occurrence of osteonecrosis of the jaw in women with early non-metastatic breast cancer (Wong 2012, Aft 2012, Coleman 2011, Gnant 2011; *moderate level of evidence*).
- There are indications that zoledronic acid increases the occurrence of bone pain in women with early non-metastatic breast cancer (Gnant 2011; *low level of evidence*).
- An effect of zoledronic acid on the occurrence of arthralgia in women with early non-metastatic breast cancer could neither be demonstrated nor refuted (Gnant 2011; *very low level of evidence*).
- There are indications that zoledronic acid increases the occurrence of pyrexia in women with early non-metastatic breast cancer (Gnant 2011; *very low level of evidence*).

Recommendation 2013

- In women with early non-metastatic breast cancer, bisphosphonates cannot be recommended as an adjuvant breast cancer therapy (*strong recommendation*).

TREATMENT OF METASTATIC BREAST CANCER

Multidisciplinary approach [47]

- The treatment of the metastatic breast cancer should be discussed

within a multidisciplinary team and patient preferences should always be taken into account (*expert opinion*).

Diagnosis of metastatic breast cancer

Tumour markers [36]

- For monitoring patients with metastatic disease during active therapy, CA 27.29, CA 15-3 or CEA can be used in conjunction with diagnostic imaging, history, and physical exam (*2C evidence*).

Biopsy of metastatic lesions [27, 197]

- Metastatic lesions should be biopsied whenever accessible and ER, PgR and HER2 should be reassessed (*1B evidence*).
- In both pre- and postmenopausal women, HER2 status should be used to identify patients most likely to benefit from Trastuzumab (*1B evidence*).

Systemic treatment

Endocrine therapy and ER antagonists [10, 59, 197, 207-212]

- In premenopausal women with hormone receptor-positive or hormone receptor-unknown metastatic breast cancer, suppression of ovarian function in combination with tamoxifen is the first-line hormonal therapy of choice (*1A evidence*).
- In postmenopausal women with hormone receptor-positive or hormone receptor-unknown metastatic breast cancer, first-line treatment consists of third-generation aromatase inhibitors (anastrozole, letrozole, exemestane) or Tamoxifen. In the choice of the agent, the adjuvant endocrine therapy received should be taken into consideration. As second-line treatment, a third-generation aromatase inhibitor or Fulvestrant is recommended (*1A evidence*).
- Fulvestrant may be considered as an alternative to third-generation aromatase inhibitors for metastatic breast cancer in postmenopausal women with hormone receptor-positive (ER+ and/or PgR+) breast cancer that has recurred after prior adjuvant tamoxifen therapy or progressed during prior tamoxifen therapy for advanced disease (*1B evidence*).

Chemotherapy [59, 168, 197, 213-223]

- Chemotherapy for patients with metastatic breast cancer is indicated for the following conditions (*expert opinion*):
  - hormone-refractory or HR- tumours
  - rapidly progressive disease or symptomatic disease
  - life-threatening disease
- The choice between polychemotherapy and sequential single-agent chemotherapy should take into account the prognosis, performance status, need for rapid symptom control and toxicity profiles, with the ultimate goal of optimizing quality and quantity of life (*expert opinion*).
- Anthracycline- and/or taxane-based regimens are to be preferred as first-line treatment (*1A evidence*).
- In patients with anthracycline resistance or failure and who are taxane-naive, and are considered for further chemotherapy, taxane-based

treatment (monotherapy or combination of a taxane with gemcitabine or capecitabine) should be used, taking into account quality of life, toxicity, characteristics of the disease and the ease of administration (*1A evidence*).

Biological therapy

Trastuzumab [47, 197, 224-226]

- Trastuzumab with/without non-anthracycline-based chemotherapy or endocrine therapy is the treatment of choice of HER2 positive metastatic breast cancer except in the presence of cardiac contra-indications (*1A evidence*).

Bevacizumab [227-232]

Among women with HER-2 negative metastatic breast cancer, treated with bevacizumab in combination with chemotherapy versus chemotherapy alone:

- A difference in overall survival between bevacizumab in combination with first-line chemotherapy and first-line chemotherapy alone could neither be demonstrated nor refuted (Wagner 2012; *low level of evidence*).
- A difference in overall survival between bevacizumab in combination with second-line chemotherapy and second-line chemotherapy alone could neither be demonstrated nor refuted (Wagner 2012; *moderate level of evidence*).
- It is plausible that bevacizumab in combination with first-line chemotherapy has a positive effect on progression free survival as compared to first-line chemotherapy alone (Wagner 2012; *moderate level of evidence*).
- It is demonstrated that bevacizumab in combination with second-line chemotherapy has a positive effect on progression free survival in women with HER-2 negative metastatic breast cancer as compared to second-line chemotherapy alone (Wagner 2012; *high level of evidence*)
- It is plausible that bevacizumab in combination with first-line chemotherapy leads to more grade 3 or higher adverse events as compared to first-line chemotherapy alone (Wagner 2012; *moderate level of evidence*)
- There are indications that bevacizumab in combination with first or second-line chemotherapy leads to more serious adverse events as compared to first or second-line chemotherapy alone (Wagner 2012; *low level of evidence*)

Recommendation 2013

- In women with metastatic breast cancer, adding bevacizumab to a systemic chemotherapy, either in first-line or in second-line therapy, cannot be recommended (*weak recommendation*).

Treatment of bone metastases [11, 47, 59, 196, 197]

- Bisphosphonates should be routinely used in combination with other systemic therapy in patients with metastatic breast cancer with multiple or symptomatic lytic bone metastases (*1A evidence*).
- In patients with painful or threatening bone metastases, radiotherapy is the treatment of choice, if feasible (*1A evidence*).

Treatment of brain metastases [47]

- Patients with a single or small number of potentially resectable brain metastases can be treated with radiosurgery or with surgery followed by whole-brain radiotherapy. Whole-brain radiotherapy should only be offered to patients for whom surgery or radiosurgery is not appropriate (*2C evidence*).

TREATMENT OF LOCOREGIONAL RELAPSE [10, 59]

- A local recurrence in the thoracic wall should be treated preferentially with surgery and adjuvant radiotherapy whenever possible (*1C evidence*).
- A local recurrence after breast-conserving treatment should be treated by mastectomy (*1C evidence*).
- Systemic treatment for a completely excised locoregional recurrence should be discussed on a case by case basis in the multidisciplinary team meeting (*expert opinion*).

SUPPORTIVE CARE FOR PATIENTS WITH BREAST CANCER [11, 47, 59, 233-238]

- Women with breast cancer should be informed about the risk of developing lymphoedema following surgery or radiotherapy and should be offered rapid access to a specialist lymphoedema service (*1A evidence*).
- Physiotherapy for mobility after axillary clearance should be recommended (*1A evidence*).
- Physical training, including specific exercises for cancer-related fatigue, can be considered after treatment for breast cancer (*1A evidence*).
- Menopausal hormonal replacement therapy is contraindicated in women with breast cancer (*1B evidence*).
- Psychological support should be available to all patients diagnosed with breast cancer (*1A evidence*).
- A palliative care team should assess all patients with uncontrolled disease in order to plan a symptom-management strategy (*1C evidence*).

SURVEILLANCE OF PATIENTS WITH BREAST CANCER [3,18,62,64,238]

- Yearly mammography with/without ultrasound should be used during the first 10 years to detect recurrence or second primaries in patients who have undergone previous treatment for breast cancer, including DCIS (*1C evidence*).
- Intensive surveillance (CBC testing, tumour markers, chest x-ray, bone scans, liver ultrasound or computed tomography) is not recommended for routine breast cancer surveillance (*1A evidence*).
- MRI should not be offered routinely as a post-treatment surveillance test in patients who have been treated for early invasive breast cancer or DCIS, except in the following situations (*1C evidence*):
  - Lobular invasive cancer
  - Very young patients (< 35 years)
  - BRCA associated cancers
  - If initial tumour was not seen at mammography/ultrasound
  - In specific clinical situations where other imaging modalities are not reliable, or have been inconclusive
- Follow-up consultations can be provided every 3 to 4 months in the first two years after diagnosis, every 6 months until 5 years after diagnosis, and every year after 5 years (*expert opinion*).

MULTIDISCIPLINARY APPROACH OF PATIENTS WITH BREAST CANCER [11,258]

- All women with a potential or known diagnosis of breast cancer should have access to a breast care nurse specialist for information and support at every stage of diagnosis, treatment and follow- up (*1B evidence*).

BREAST CANCER AND PREGNANCY [260,261]

- Breast cancer is not a contraindication for later pregnancy or breastfeeding, but should be individually discussed (*2C evidence*).

PARTICIPATION IN CLINICAL TRIALS

- In view of the rapidly changing evidence in the field of breast cancer, clinicians should encourage women with breast cancer to participate in clinical trials (*expert opinion*).

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Appendix 1: GRADE system

Grade of recommendation / description	Benefit vs Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/ Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/ Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/ Strong recommendation, low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, can apply to most patients in most circumstances without reservation
2A/ Weak recommendation, high quality evidence	Benefits closely balanced with risk and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/ Weak recommendation, moderate quality evidence	Benefits closely balanced with risk and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/ Weak recommendation, low quality evidence	Benefits closely balanced with risk and burden	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

Appendix 2: TNM classification and stage grouping (7th edition)

cTNM Clinical Classification

T – Primary tumour

Tx Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ

- Tis (DCIS) Ductal carcinoma in situ
- Tis (LCIS) Lobular carcinoma in situ
- Tis (Paget) 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 disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.

T1 Tumor 2 cm or less in greatest dimension

- T1mi Microinvasion 0.1 cm or less in greatest dimension

Microinvasion is the extension of cancer cells beyons the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion (do not use the sum of all individual foci). The presence of multiple foci of microinvasion should be noted, as it is with multiple larger invasive carcinomas.

- T1a More than 0.1 cm but not more than 0.5 cm in greatest dimension
- T1b More than 0.5 cm but not more than 1 cm in greatest dimension
- T1c More than 1 cm but not more than 2 cm in greatest dimension

T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension

T3 Tumor more than 5 cm in greatest dimension

T4 Tumor of any size with direct extension to chest wall and/or to skin (ulceration or skin nodules)

Note: Invasion of the dermis alone does not qualify as T4. Chest wall includes ribs, intercostals muscles, and serratus anterior muscle, but not pectoral muscle

- T4a Extension to chest wall (does not include pectoralis muscle invasion only)
- T4b Ulceration, ipsilateral satellite skin nodules, or skin oedema (including peau d'orange)
- T4c Both 4a and 4b, above
- T4d Inflammatory carcinoma

Inflammatory carcinoma of the breast is characterized by diffuse, brawny induration of the skin with an erysipeloid edge, usually with no underlying mass. If the skin biopsy is negative and there is no localized measurable primary cancer, the T category is pTX when pathologically staging a clinical inflammatory carcinoma (T4d). Dimpling of the skin, nipple retraction, or other skin changes, except those in T4b and T4d, may occur in T1, T2, or T3 without affecting the classification.

N – regional lymph nodes

Nx Regional lymph nodes cannot be assessed (e.g. previously removed)

N0 No regional lymph node metastasis

N1 Metastasis in movable ipsilateral Level I, II axillary lymph node(s)

N2 Metastasis in ipsilateral Level I, II axillary lymph node(s) that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary lymph nodes(s) in the absence of clinically evident axillary lymph node metastasis

- N2a Metastasis in axillary lymph node(s) fixed to one another (matted) or to other structures
- N2b Metastasis only in clinically detected* internal mammary lymph nodes(s) and in the absence of clinically detected axillary lymph node metastasis

N3 Metastasis in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident Level I, II axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

- N3a Metastasis in infraclavicular lymph node(s)
- N3b Metastasis in internal mammary and axillary lymph nodes
- N3c Metastasis in supraclavicular lymph node(s)

*clinically detected = detected by clinical examination or by imaging studies (excluding lymphoscintigraphy) 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. Pathological classification (pN) is used for excision or sentinel lymph node only in conjunction with a pathological T assignment.

M – Distant metastasis

M0 No distant metastasis

M1 Distant metastasis

pTNM Pathological Classification

pT- Primary tumour

A case can be classified pT if there is only microscopic tumour in a margin. The pT categories correspond to the T categories.

Note: When classifying pT the tumour size is a measurement of the invasive component. If there is a large in situ component (e.g, 4 cm) and a small invasive component (e.g, 0.5 cm), the tumour is coded pT1a.

pN – Regional Lymph nodes

The pathological classification requires the resection and examination of at least the low axillary lymph nodes (Level I). Such a resection will ordinarily include 6 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

pNx: Regional lymph nodes cannot be assessed (e.g. previously removed, or not removed for pathological study)

pN0: No regional lymph node metastasis*.

*Isolated tumor cell clusters (ITC) are single tumour cells or small clusters of cells not more than 0.2 mm in greatest extent that can be detected by immunohistochemistry or by routine HeE stains. An additional criterion has been proposed to include a cluster of fewer than 200 cells in a single histological cross-section. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification and should be included in the total number of nodes evaluated.

pN1: Micrometastasis; or metastasis in 1-3 axillary ipsilateral lymph nodes; and/or in internal mammary nodes with metastasis detected by sentinel lymph node biopsy but not clinically detected*

- pN1mi micrometastasis (larger than 0.2 mm and/or more than 200 cells, but none larger than 2.0 mm)
- pN1ametastasis in 1-3 axillary lymph node(s), including at least one larger than 2 mm in greatest dimension
- pN1binternal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected*
- pN1c metastasis in 1-3 axillary lymph nodes and internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected*

pN2: Metastasis in 4-9 ipsilateral axillary lymph nodes, or in clinically detected* ipsilateral internal mammary lymph node(s) in the absence of axillary lymph node metastasis

- pN2ametastasis in 4-9 axillary lymph nodes, including at least one larger than 2 mm.
- pN2bmetastasis in clinically detected* internal mammary lymph node(s), in the absence of axillary lymph node metastasis

pN3: Metastasis as described below:

- pN3ametastasis in 10 or more axillary lymph nodes (at least one larger than 2 mm) or metastasis in infraclavicular lymph nodes
- pN3b metastasis in clinically detected* internal ipsilateral mammary lymph node(s) in the presence of positive axillary lymph node(s); or metastasis in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected
- pN3c metastasis in ipsilateral supraclavicular lymph node(s)

*clinically detected is defined as detected by clinical examination or by imaging studies (excluding lymphoscintigraphy) and having characteristics highly suspicious for malignancy or a presumed pathological macrometastasis based on fine-needle aspiration biopsy with cytological examination.

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

pM – Distant Metastasis

pM1 Distant metastasis microscopically confirmed

Note: pM0 and pMx are not valid categories