COLLEGE OF ONCOLOGY

National Clinical Practice Guidelines

Breast Cancer

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Continue

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BREAST CANCER

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BREAST CANCER

General algorithm

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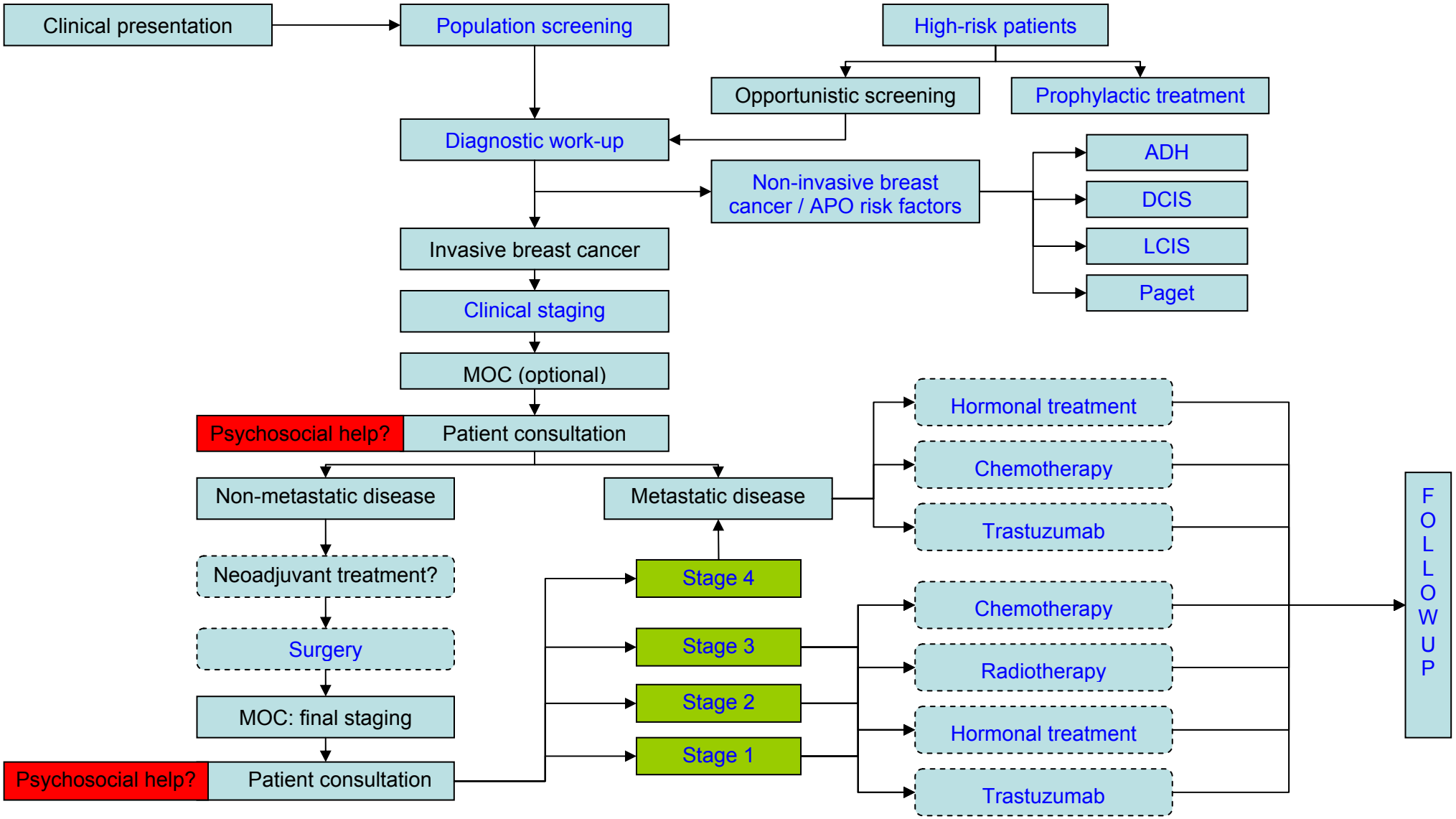

National Guidelines
Breast Cancer

INTRODUCTION

This document provides an overview of the clinical practice guidelines for breast cancer. 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')

The guidelines are based on the best evidence available at the time they are derived (date restriction 2003-2006). The aim of these guidelines is to assist all care providers involved in the care of women with breast cancer.

SEARCH FOR EVIDENCE

Clinical practice guidelines

Sources

A broad search of electronic databases (Medline, Cinahl, EMBASE), specific guideline websites and websites of oncologic organisations (Table 1) was conducted.

In- and exclusion criteria

Both national and international clinical practice guidelines (CPGs) on breast cancer were searched. A language (English, Dutch, French) and date restriction (2003 – 2006) were used. CPGs without references were excluded, as were CPGs without clear recommendations.

Additional evidence

For each clinical question, the evidence – identified through the included CPGs – was updated by searching Medline and the Cochrane Database of Systematic Reviews (CDSR) from the search date of the CPG on.

Grade of recommendation

A grade of recommendation was assigned to each recommendation using the GRADE system (Table 2).

POPULATION SCREENING

The recommendations formulated in the present guideline are in line with the recent European guidelines on breast cancer screening and diagnosis [1], which were not identified through our literature search.

- Based on the literature, the present breast cancer screening programme by mammography for women aged 50-69 years remains

justified ***(2A evidence)*** [2-4].

- There is no hard evidence to recommend other screening methods (e.g. ultrasonography, magnetic resonance imaging (MRI), self-examination) than two-view mammography ***(IC evidence)*** [2,5,6].

MANAGEMENT OF HIGH-RISK WOMEN

Definition of high-risk

A distinction should be made between genetic and familial risk for developing breast cancer:

- Women with a proven mutation of the BRCA1, BRCA2 or TP53 gene are considered to be at genetic risk.
- For the calculation of the familial risk, several models are available. A comparison of four of these models [7] showed that the Tyrer-Cuzick model was the most consistently accurate model for the prediction of breast cancer (rate of expected to observed number of breast cancers = 0.81). This model incorporates the BRCA genes, a low penetrance gene and personal risk factors, such as age at menarche, parity, height, etc [8]. The model has been computerised and an interactive program is available from the authors on request [8]. Women with a lifetime risk of 20% or greater of developing breast cancer are considered to be at high risk.

Breast cancer suspectibility gene testing

- Routine referral for genetic counselling or routine breast cancer suspectibility gene (BRCA) testing for women whose family or personal history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene 1 (BRCA1) or breast cancer susceptibility gene 2 (BRCA2) is not recommended ***(1B evidence)*** [9].
- Women whose family or personal history is associated with an increased risk for:
  - deleterious mutations in BRCA 1 or BRCA 2 gene (early-age-onset breast cancer, two primary breast cancers and/or breast and ovarian cancers in the same individual or close relatives on the same side of the family, known mutation in a family member, Ashkenazi Jewish decent with breast cancer in women < 50 years or ovarian cancer, male breast cancer, more than one ovarian cancer on the same side of the family);
  - Li-Fraumeni and Cowden Syndrome (thyroid cancer, sarcoma, adrenocortical cancer, endometrium cancer, pancreatic cancer, brain tumors, dermatologic manifestations, leukemia/lymphoma)

  Should be referred for genetic counselling ***(1B evidence)*** [9,10].
- All high-risk women should have access to information on genetic tests aimed at mutation finding ***(1C evidence)*** [10].
- Pre-test counselling (preferably two sessions) should be undertaken ***(1A evidence)*** [10].
- Discussion of genetic testing (predictive and mutation finding) should be undertaken by someone with appropriate training ***(1A evidence)*** [10].
- High-risk women and their affected relatives should be informed about the likely informativeness of the test (the meaning of a positive and a negative test) and the likely timescale of being given the results ***(1A evidence)*** [10].
- Women from families with a 20% or greater chance of carrying a

mutation such as BRCA1, BRCA2 or TP53 should have access to testing ***(1C evidence)*** [10].

- The development of a genetic test for a family should usually start with the testing of an affected individual (mutation searching/screening) to try to identify a mutation in the appropriate gene (such as BRCA1, BRCA2 or TP53) ***(1C evidence)*** [10].
- A search/screen for a mutation in a gene (such as BRCA1, BRCA2 or TP53) should aim for as close to 100% sensitivity as possible for detecting coding alterations and the whole gene(s) should be searched ***(1C evidence)*** [10].

Surveillance of high-risk women

- For women from families with BRCA1, BRCA2 or TP53 mutations, or with equivalent high breast cancer risk, individualised screening strategies should be developed ***(1C evidence)*** [10].
- There is a lack of evidence for a high risk population that either clinical breast examination or self-examination is useful as the sole surveillance modality ***(1A evidence)*** [10,11].
- All women with a genetic or familial high risk should be offered mammographic and/or ultrasound and/or MRI surveillance ***(1C evidence)*** [10].
- For women aged 40–49 years at moderate risk or greater, mammographic and ultrasound surveillance should be annual ***(1C evidence)*** [10].
- On the basis of current evidence, MRI should be added to routine surveillance practice of young patients with high genetic risk ***(1C evidence)*** [11,12].

Treatment of high-risk women

Prophylactic mastectomy

- Bilateral risk-reducing mastectomy is appropriate only for a small proportion of women who are from high-risk families and should be managed by a multidisciplinary team ***(1C evidence)*** [10].
- Bilateral mastectomy should be raised as a risk-reducing strategy option with all women at high risk ***(1C evidence)*** [10,11,13].
- High-risk women considering bilateral risk-reducing mastectomy should have genetic counselling in a specialist cancer genetics clinic, before a decision is made ***(1C evidence)*** [10].
- Discussion of individual breast cancer risk and its potential reduction by surgery should take place and take into account individual risk factors, including the woman's current age (especially at extremes of age ranges) ***(1C evidence)*** [10].
- When bilateral mastectomy is considered but no mutation has been identified, family history should be taken into account before a decision is made ***(1C evidence)*** [10].
- Where no family history verification is possible, agreement by a multidisciplinary team (surgeon and genetic specialist) must be sought before proceeding with bilateral risk-reducing mastectomy ***(1C evidence)*** [10].
- Pre-operative counselling about psychosocial and sexual consequences of bilateral risk-reducing mastectomy should be undertaken ***(1C evidence)*** [10].
- The possibility of breast cancer being diagnosed histologically following a risk-reducing mastectomy should be discussed pre-operatively ***(1C evidence)*** [10].
- All women considering bilateral risk-reducing mastectomy should be

able to discuss their breast reconstruction options (immediate and delayed) with a member of a surgical team with specialist oncoplastic or breast reconstructive skills ***(1C evidence)*** [10].

- A surgical team with specialist oncoplastic/breast reconstructive skills should carry out risk-reducing mastectomy and/or reconstruction ***(1C evidence)*** [10].
- Women considering bilateral risk-reducing mastectomy should be offered access to support groups and/or women who have undergone the procedure ***(1C evidence)*** [10].

Prophylactic salpingo-oophorectomy

- Risk-reducing bilateral salpingo-oophorectomy is appropriate only for a small proportion of women who are from high risk families and should be managed by a multidisciplinary team ***(1C evidence)*** [10].
- Information about bilateral salpingo-oophorectomy as a potential risk-reducing strategy should be made available to women who are classified as high risk ***(1C evidence)*** [10,11].
- When bilateral salpingo-oophorectomy is considered but no mutation has been identified, family history should be taken into account before a decision is made ***(1C evidence)*** [10].
- Where no family history verification is possible, agreement by a multidisciplinary team (surgeon and genetic specialist) must be sought before proceeding with bilateral risk-reducing salpingo-oophorectomy ***(1C evidence)*** [10].
- Any discussion of bilateral salpingo-oophorectomy as a risk-reducing strategy should take fully into account factors such as anxiety levels on the part of the woman concerned ***(1C evidence)*** [10].
- Healthcare professionals should be aware that women being offered risk-reducing bilateral salpingo-oophorectomy may not have been aware of their risks of ovarian cancer as well as breast cancer and should be able to discuss this ***(1C evidence)*** [10].
- The effects of early menopause should be discussed with any woman considering risk-reducing bilateral salpingo-oophorectomy ***(1C evidence)*** [10].
- Options for management of early menopause should be discussed with any woman considering risk-reducing bilateral salpingo-oophorectomy, including the advantages, disadvantages and risk impact of hormonal replacement therapy ***(1C evidence)*** [10].
- Women considering risk-reducing bilateral salpingo-oophorectomy should have access to support groups and/or women who have undergone the procedure ***(1C evidence)*** [10].
- Women considering risk-reducing bilateral salpingo-oophorectomy should be informed of possible psychosocial and sexual consequences of the procedure and have the opportunity to discuss these issues ***(1C evidence)*** [10].
- Women not at high risk who raise the possibility of risk-reducing bilateral salpingo-oophorectomy should be offered appropriate information, and if seriously considering this option should be offered referral to the team that deals with women at high risk ***(1C evidence)*** [10].
- Women undergoing bilateral risk-reducing salpingo-oophorectomy should have their fallopian tubes removed as well ***(1C evidence)*** [10].

Chemoprevention with tamoxifen

- Tamoxifen can be considered as a chemoprevention therapy for women with a BRCA2 genetic high risk for developing breast cancer ***(2B evidence)*** [11,14].

DIAGNOSIS

Triple assessment

The diagnosis of breast cancer relies on the so-called triple assessment, including clinical examination, imaging (comprising mammography and ultrasonography) [15,16] and sampling of the lesion with a needle for histological/cytological assessment [17,18]. 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 full clinical examination ***(1C evidence)*** [17,18].
- Where a localised abnormality is present, patients should have mammography and ultrasonography followed by core biopsy and/or fine needle aspirate cytology ***(1C evidence)*** [15-18].
- A lesion considered malignant following clinical examination, imaging or cytology alone should, where possible, have histopathological confirmation of malignancy before any surgical procedure takes place ***(1C evidence)*** [17,18].
- Two-view mammography should be performed as part of triple assessment (clinical assessment, imaging and tissue sampling) in a clinic specialised in breast cancer ***(1C evidence)*** [17,18].
- Also young women presenting with breast symptoms and a strong suspicion of breast cancer should be evaluated by means of the triple test approach to exclude or establish a diagnosis of cancer ***(1C evidence)*** [19].

Magnetic resonance imaging (MRI)

- There is insufficient evidence to use MRI routinely for the diagnosis and staging 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 (invasive lobular carcinoma, suspicion of multicentricity, genetic high-risk patients, T0 N+ patients, patients with breast implants, diagnosis of recurrence, follow-up of neoadjuvant treatment) ***(1C evidence)*** [24,18].

99mTc-MIBI scintimammography (SMM)

- There is insufficient evidence to use 99mTc-MIBI scintimammography routinely 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)*** [20,21].

STAGING

TNM classification and stage grouping see appendix 1.

Routine staging tests

- There is no evidence for pretreatment routine bone scanning, liver ultrasonography and chest radiography for asymptomatic patients with negative clinical findings, unless there is at least clinical stage II disease and/or neoadjuvant treatment is considered ***(2C evidence)*** [22,23].

- In asymptomatic women with ductal carcinoma in situ, routine bone scanning, liver ultrasonography and chest radiography are not indicated as part of baseline staging ***(2C evidence)*** [22,23].

Tumour markers

- There is no good evidence to include tumour markers in the staging workup of breast cancer ***(2C evidence)*** [24-27].

Axillary ultrasonography

- Axillary ultrasonography with fine needle aspiration cytology of axillary lymph nodes suspicious for malignancy can be recommended ***(2C evidence)*** [28,29].

Sentinel lymph node biopsy

- Sentinel lymph node biopsy is not recommended for large T2 (i.e. > 3 cm) or T3-4 invasive breast cancers; inflammatory breast cancer; pregnancy; in the setting of prior non-oncologic breast surgery or axillary surgery; in the presence of suspicious palpable axillary lymph nodes; multiple tumours; and possible disturbed lymph drainage after recent axillary surgery or a large biopsy cave after tumour excision ***(1A evidence)*** [22,30].
- Data are available to support the use of sentinel lymph node biopsy (SLNB) for invasive tumors less than 3 cm. Also for high-grade ductal carcinoma in situ, when mastectomy with or without immediate reconstruction is planned, such data are available ***(1A evidence)*** [22,30]. Age, gender or obesity are no exclusion criteria for SLNB.

Positron emission tomography (PET)

- PET scan is not indicated in the diagnosis of malignancy of breast tumours ***(1B evidence)*** [31,32].
- PET scan is not indicated for axillary staging ***(1C evidence)*** [32].
- PET scan can be useful for the evaluation of metastatic disease of invasive breast cancer ***(1C evidence)*** [31,32].
- PET/CT cannot be recommended for the diagnosis and follow-up of breast cancer ***(2C evidence)*** [33].

TREATMENT OF NON INVASIVE BREAST CANCER

Early precursor and high-risk lesions

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 [22].

- Management of early precursor lesions is preferably discussed in a multidisciplinary setting ***(expert opinion)*** [34,35].
- When atypical lobular hyperplasia, lobular carcinoma in situ, flat epithelial atypia or atypical ductal hyperplasia is present near the margins of an excision specimen, re-excision is not necessary ***(expert opinion)*** [34,35].
- 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 can be recommended ***(expert opinion)*** [34,35].

- When pleomorphic lobular carcinoma in situ or lobular carcinoma in situ with comedonecrosis is found in a core biopsy, complete excision with negative margins can be recommended, and anti-hormonal treatment as well as radiotherapy are an option ***(expert opinion)*** [34,35].
- Annual follow-up mammography after a diagnosis of lobular carcinoma in situ or atypical ductal hyperplasia is indicated ***(2C evidence)*** [22].

Ductal carcinoma in situ

Surgery

These recommendations are completely based on existing guidelines [18,36,37], no additional evidence was identified.

- Women with high-grade and/or palpable and/or large ductal carcinoma in situ of the breast who are candidates for breast conserving surgery should be offered the choice of local wide excision or total mastectomy after the patient is correctly informed. In case of multicentricity local wide excision is not recommended ***(1B evidence)*** [18,36,37].
- In women with ductal carcinoma in situ, mastectomy with or without immediate reconstruction remains an acceptable choice for women preferring to maximize local control or to avoid radiotherapy ***(1B evidence)*** [36,37].
- When local wide excision is performed in women with ductal carcinoma in situ, all evidence of disease should be resected ***(1C evidence)*** [36,37].
- Axillary clearance is not recommended for women with ductal carcinoma in situ, but sentinel lymph node biopsy can be considered for large or grade III ductal carcinoma in situ ***(1C evidence)*** [22].

Radiotherapy

- Radiotherapy is part of the breast-conserving treatment of ductal carcinoma in situ ***(1A evidence)*** [22,36,37].

Hormonal therapy

- Adjuvant homonal therapy can be considered for patients with estrogen-receptor positive ductal carcinoma in situ ***(2A evidence)*** [18,37].

Paget's disease

- Patients with Paget's disease without underlying invasive breast cancer may be treated with a cone excision of the nipple-areola-complex followed by radiotherapy ***(2C evidence)*** [38].

TREATMENT OF INVASIVE NON-METASTATIC BREAST CANCER

- All patients with T3-4 and/or N2-3 breast cancer should be discussed on an individual basis in the multidisciplinary team meeting before any treatment ***(expert opinion)***.

Surgery

- Breast-conserving surgery offers the same survival benefit as modified radical mastectomy in women with stage I or II breast cancer who are

candidates for breast-conserving surgery ***(1A evidence)*** [18,39].

- 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 options ***(1A evidence)*** [18,39].
- In women with primary breast cancer less than 3 cm and with clinically and ultrasonographically negative nodes, a sentinel lymph node biopsy should be performed ***(1A evidence)*** [22,30].
- If the sentinel node is positive (>0.2 mm), axillary lymph node dissection level I and II is indicated ***(1A evidence)*** [22].
- If a sentinel lymph node biopsy is impossible, an axillary lymph node dissection level I and II is indicated ***(1A evidence)*** [22].

Radiotherapy

- In patients with invasive breast cancer, adjuvant irradiation is indicated after breast conserving surgery ***(1A evidence)*** [18,22].
- Radiotherapy of the thoracic wall after mastectomy is indicated for the following conditions ***(1B evidence)*** [17,22]:
  - *pT3*
  - *pN+ (whatever the number of invaded nodes)*
  - *Lymphovascular invasion*
- Internal mammary chain irradiation is to be discussed 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)*** [17,22].
- Axillary radiotherapy should be discussed on an individual basis in the multidisciplinary team meeting ***(1A evidence)*** [22,40,41].
- If adjuvant chemotherapy and radiotherapy are indicated, the chemotherapy should be given first ***(1A evidence)*** [42].

Systemic therapy

The choice of chemotherapy and/or hormonal therapy as adjuvant treatment should be driven by the hormonal sensitivity and risk profile of the tumour, and by the age of the patient [22,43].

Table 4: Risk profiles for local and/or distant recurrence

Low	• ER+ and/or PgR+ and all of the following: N0, pT≤2 cm, G1, ≥35 years, no lymphovascular invasion, no HER2 amplification • pT < 1 cm
Inter-mediate	• ER+ and one of the following characteristics: pT>2 cm, G2-3, N+ 1-3
High	• ER+ and/or PgR+ and: o >3 N+ o Two of the following: pT > 2cm, G3, 1-3 N+ • G3 • 1-3 N+ • ER–, PgR– and pT > 1cm • < 35 years • HER2 amplification • Lymphovascular invasion

ER= oestrogen receptor ; PgR= progesterone receptor ; G= histologic grade ; HER2= human epidermal growth factor receptor 2

Breast tumours are considered to be hormonal sensitive if they are ER+ >10% and hormonal insensitive if they are ER+ <10%. ER+ breast cancer lacking PgR positivity or overexpressing HER2 are less hormonal sensitive. Of course, ER positivity is highly dependent on the used technique.

Tabel 5 summarizes the indications for adjuvant chemotherapy and/or hormonal therapy [44] according to risk profile and hormonal sensitivity. This scheme is similar to that proposed by the Cancer Care Ontario [43].

	Strongly hormonal sensitive	**Intermediate hormonal sensitive**	**Hormonal insensitive**
Low risk	Hormonal therapy	Hormonal therapy	-
Inter-mediate risk	Hormonal therapy Or Chemotherapy followed by hormonal therapy *	Chemotherapy followed by hormonal therapy	Chemotherapy
High risk	Chemotherapy followed by hormonal therapy	Chemotherapy followed by hormonal therapy	Chemotherapy

* to be discussed in the multidisciplinary team meeting

Chemotherapy

- Preferred regimens are standard anthracycline-based regimens with or without a taxane ***(1A evidence)*** [45-48].
- In patients with unifocal operable tumours too large for breast conserving surgery, downstaging with neoadjuvant therapy can be offered ***(1A evidence)*** [17,49].
- High-dose chemotherapy with stem-cell transplantation cannot be recommended ***(1A evidence)*** [50].

Hormonal therapy

- Premenopausal patients with any hormone receptor positive breast cancer should receive adjuvant endocrine treatment with tamoxifen for 5 years with or without an Luteinising-Hormone Releasing Hormone (LHRH) analogue ***(1A evidence)*** [51,52].
- Postmenopausal patients with hormone receptor positive breast cancer should receive adjuvant endocrine treatment with either tamoxifen during 5 years, tamoxifen during 2 - 3 years followed by an aromatase inhibitor during 3 - 2 years, or an aromatase inhibitor ***(1A evidence)*** [51,53,54].
- Postmenopausal women with hormone receptor positive tumours who have completed five years of adjuvant tamoxifen therapy (20mg daily) should be considered for extended treatment with an aromatase inhibitor if node-positive or high-risk node-negative (pT2 or grade III) ***(1A evidence)*** [55].

Trastuzumab

- Based on the criteria from the HERA trial (T > 1cm or node positive), a 1 year treatment with adjuvant trastuzumab is indicated for women with HER2 Fluorescent In Situ Hybridization positive breast cancer, a left ventricular ejection fraction of ≥ 55% and without cardiovascular exclusion criteria ***(1A evidence)*** [56,57].
- During treatment with trastuzumab, cardiac function should be

monitored ***(1A evidence)*** [56].

TREATMENT OF METASTATIC BREAST CANCER

Systemic treatment

Hormonal therapy

- In premenopausal patients with hormone receptor positive or hormone receptor unknown metastatic breast cancer, suppression of ovarian function (e.g. with LHRH analogs, oophorectomy, irradiation of the ovaries) in combination with tamoxifen is the first-line hormonal therapy ***(1A evidence)*** [17,22].
- In postmenopausal patients with hormone receptor positive or hormone receptor unknown metastatic breast cancer, first-line treatment consists of aromatase inhibitors. Tamoxifen remains an acceptable alternative as first-line treatment. As second-line treatment, anastrozole, letrozole or exemestane are recommended ***(1A evidence)*** [17,22,58].

Chemotherapy

- Chemotherapy for patients with metastatic breast cancer is indicated for the following conditions ***(expert opinion)*** [22]:
    - hormone refractory or hormone-receptor negative tumours
    - rapidly progressive disease
    - invasion of vital organs
- The preferred chemotherapy regimen is to be discussed in the multidisciplinary team ***(expert opinion)***.

Trastuzumab

- Trastuzumab should be reserved for those patients whose tumours have HER2 gene amplification ***(1C evidence)*** [18].
- Combination therapy of trastuzumab with a taxane is recommended in women with metastatic breast cancer with HER2 gene amplification ***(1A evidence)*** [18,22].

Treatment of bone metastases

- Bisphosphonates should be routinely used in combination with other systemic therapy in patients with metastatic breast cancer with multiple and lytic bone metastases ***(1A evidence)*** [18,22].
- In patients with painful bone metastases, radiotherapy is a good treatment option ***(1A evidence)*** [18,22].

TREATMENT OF LOCOREGIONAL RELAPSE

- A local recurrence in the thoracic wall should be treated preferentially with surgery and adjuvant radiotherapy whenever possible ***(1C evidence)*** [17,22].
- A recurrence after breast-conserving treatment should be treated by a salvage mastectomy ***(1C evidence)*** [22].
- Systemic treatment for a locoregional recurrence should be discussed in the multidisciplinary team ***(expert opinion)***.

SUPPORTIVE CARE

- Bisphosphonates are not part of the adjuvant treatment of breast cancer ***(1A evidence)*** [59,60].
- Physiotherapy after axillary clearance can be recommended ***(2B evidence)*** [22,61].
- Physical training after treatment for breast cancer can be recommended ***(2A evidence)*** [62].
- Menopausal hormonal replacement therapy is contraindicated in women with breast cancer ***(1C evidence)*** [63].
- Psychological support should be available to all patients diagnosed with breast cancer ***(1A evidence)*** [18,22].
- The possibility of breast reconstruction should be discussed with all patients prior to mastectomy ***(1C evidence)*** [18,22].

SURVEILLANCE

- Yearly mammo/ultrasonography should be used to detect recurrence or second primaries in patients who have undergone previous treatment for breast cancer ***(1C evidence)*** [18].
- Routine diagnostic tests to screen for distant metastases in asymptomatic women should not be performed ***(1C evidence)*** [18].
- Follow-up consultations could be provided every 3 months in the first year after diagnosis, every 6 months until 5 years after diagnosis, and every year after 5 years ***(expert opinion)*** [22].

MULTIDISCIPLINARY APPROACH

- Patients should be seen at a multidisciplinary clinic involving breast clinicians, radiologists and pathologists ***(1C evidence)*** [18,22].
- 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 and treatment ***(1C evidence)*** [18].

BREAST CANCER AND PREGNANCY

- Breast cancer is not a contraindication for a later pregnancy or breastfeeding, but should be individually discussed ***(2C evidence)*** [64].

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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Searched guideline websites and websites of oncologic organisations	
Alberta Heritage Foundation For Medical Research (AHFMR)	http://www.ahfmr.ab.ca/
American Society of Clinical Oncology (ASCO)	http://www.asco.org/
American College of Surgeons (ACS)	http://www.facs.org/cancer/coc/
CMA Infobase	http://mdm.ca/cpgsnew/cpgs/index.asp
Guidelines International Network (GIN)	http://www.g-i-n.net/
National Comprehensive Cancer Network (NCCN)	http://www.nccn.org/
National Guideline Clearinghouse	http://www.guideline.gov/
National Cancer Institute	http://www.cancer.gov/
Haute Autorité de Santé (HAS)	http://bfes.has-sante.fr/HTML/indexBFES_HAS.html
BC Cancer Agency	http://www.bccancer.bc.ca/default.htm
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org/index.asp
National Health and Medical Research Council (NHMRC)	http://www.nhmrc.gov.au/
Scottish Intercollegiate Guidelines Network (SIGN)	http://www.sign.ac.uk/
New Zealand Guidelines Group (NZGG)	http://www.nzgg.org.nz/
Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)	http://www.fnclcc.fr/sor/structure/index-sorspecialistes.html
National Institute for Health and Clinical Excellence (NICE)	http://www.nice.org.uk/

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	Randomized Controlled Trials (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, but may change when higher quality evidence becomes available
2A/ Weak recommendation, high quality evidence	Benefits closely balanced with risks 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 risks 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 risks and burden	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

cT Primary Tumour

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ - DCIS Ductal carcinoma in situ - LCIS Lobular carcinoma in situ - Paget's Paget's disease of the nipple with no tumor (when associated with a tumor, it is classified according to the size of the tumor)
T1	Tumor 2 cm or less in greatest dimension - T1mic Microinvasion 0.1 cm or less 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 size of multiple foci should be noted however as with multiple larger invasive carcinomas. - T1a Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension - T1b Tumor more than 0.5 cm but not more than 1 cm in greatest dimension - T1c Tumor 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 (a) chest wall or (b) skin, only as described below (chest wall includes ribs, intercostals muscles, and serratus anterior muscle, but not pectoralis muscle) - T4a Extension to chest wall, not including pectoralis muscle - T4b Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast - T4c Both T4a and T4b - T4d Inflammatory carcinoma This is characterized by diffuse, brawny induration of the skin with an erysipeloid edge, usually with no underlying mass. 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.

cN Regional Lymph Nodes

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

N0 No regional lymph nodes metastasis.

N1 Metastasis in movable ipsilateral axillary lymph node(s)

N2 Metastasis in fixed ipsilateral axillary lymph node(s) or in clinically apparent* ipsilateral internal mammary lymph node(s) in the absence of clinically evident axillary lymph node metastases
- N2a Metastasis in axillary lymph node(s) fixed to one another or to other structures
- N2b Metastasis only in clinically apparent* ipsilateral internal mammary lymph nodes(s) and in the absence of clinically evident axillary lymph node metastasis

N3 Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement; or in clinically apparent* ipsilateral internal mammary 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 apparent = detected by clinical examination or by imaging studies excluding lymphoscintigraphy

cM Distant Metastasis

Mx Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

pT Corresponds to cT categories, but there may not be gross tumor at the margins of resection. Only the invasive component counts (not in situ).

pN At least level I should have been resected to allow evaluation (generally 6 or more lymph nodes). If classification is based only on sentinel node biopsy without subsequent axillary lymph node dissection, it should be designated with (sn).

Nx Regional lymph nodes cannot be assessed (e.g. previously removed, or not removed for pathologic study).

N0 No regional lymph node metatasis.
Cases with isolated tumor cells in regional lymph nodes are classified as pN0. Isolated tumor cells are single tumor cells or small clusters of cells, not more than 0.2 mm in greatest dimension, that are usually detected by immunohistochemistry or molecular methods but which may be verified on HeE stains. Isolated tumor cells do not typically show evidence of metastatic activity, e.g., proliferation of stromal reaction.

N1
- pN1mi: Micrometastasis (larger than 0.2 mm, but none larger than 2 mm in greatest dimension)
- pN1: Metastasis in 1-3 ipsilateral axillary lymph node(s), and/or in ipsilateral internal mammary nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent*
- pN1a Metastasis in 1-3 axillary lymph node(s), including at least one larger than 2 mm in greatest diameter.
- pN1b Internal mammary nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent*
- pN1c Metastasis in 1-3 axillary lymph node(s) and internal mammary nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent*

*not clinically apparent = not detected by clinical examination or by imaging studies excluding lymphoscintigraphy

N2 Metastasis in 4-9 ipsilateral axillary lymph node(s), or in clinically apparent ipsilateral internal mammary nodes in the absence of axillary lymph node metastasis (clinically apparent = detected by clinical examination or by imaging studies (excl. lymphoscintigraphy) or grossly visible pathologically).
- pN2a Metastasis in 4-9 axillary lymph node(s), including at least one larger than 2 mm.
- pN2b Metastasis in clinically apparent internal mammary nodes, in the absence of axillary lymph node metastasis

N3 Metastasis in 10 or more ipsilateral axillary lymph node(s); or in ipsilateral infraclavicular lymph nodes; or in clinically apparent ipsilateral internal mammary nodes in the presence of one or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative, microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes.
- pN3a Metastasis in 10 or more axillary lymph nodes (at least one larger than 2 mm) or metastasis in infraclavicular lymph nodes
- pN3b Metastasis in clinically apparent ipsilateral internal mammary nodes in the presence of one or more positive axillary lymph nodes; or metastasis in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent.
- pN3c Metastasis in supraclavicular lymph node(s)

Stage 0	Tis	N0	M0
Stage I	T1 *	N0	M0
Stage II A	T0	N1	M0
	T1 *	N1	M0
	T2	N0	M0
Stage II B	T2	N1	M0
	T3	N0	M0
Stage III A	T0	N2	M0
	T1 *	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage III B	T4	N0, N1, N2	M0
Stage III C	Any T	N3	M0
Stage IV	Any T	Any N	M1

Note: * T1 includes T1mic

