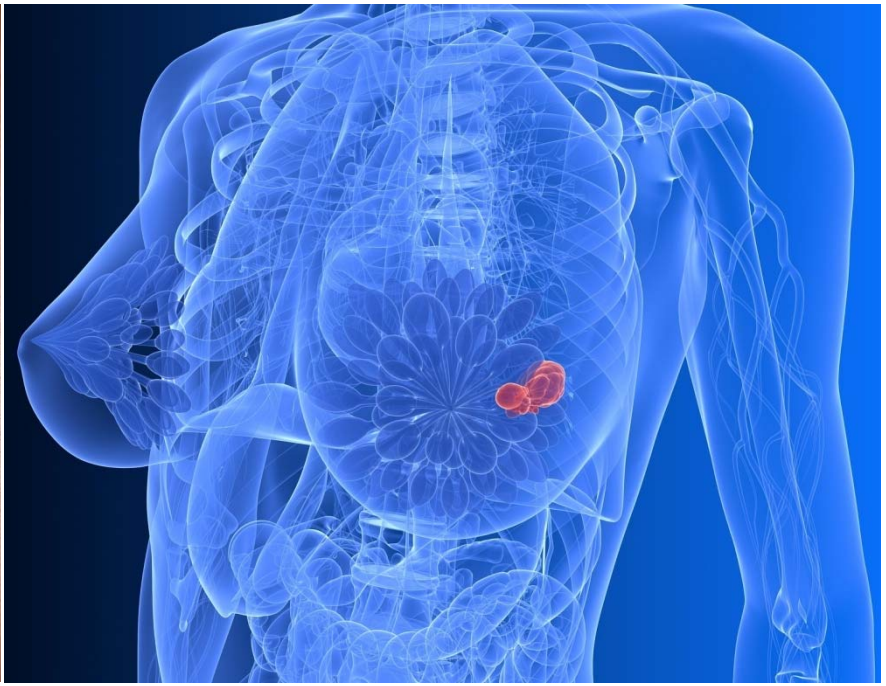
KCE REPORT 143Cs – 3rd EDITION

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

BREAST CANCER IN WOMEN: DIAGNOSIS, TREATMENT AND FOLLOW-UP

SYNTHESIS



Belgian Health Care Knowledge Centre

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KCE REPORT 143Cs – 3rd EDITION
GOOD CLINICAL PRACTICE

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2013 www.kce.fgov.be

COLOPHON

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Disclaimer:	**The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.** **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.** **Finally, this report has been approved by common assent by the Executive Board.** **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

Publication date:	08 July 2013 (3rd edition; 1st edition 9 November 2010; 2nd edition 20 January 2012)
Domain:	Good Clinical Practice (GCP)
MeSH:	Breast Neoplasms; Carcinoma, Ductal, Breast; Neoplasm, Metastasis; Practice Guideline
NLM Classification:	WP 870
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2013/10.273/37

How to refer to this document?

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 –Synthesis. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2013. KCE Reports 143Cs – 3rd EDITION. D/2013/10.273/37.

This document is available on the website of the Belgian Health Care Knowledge Centre.

FOREWORD

As breast cancer remains a priority problem for the female population in Belgium – and in the rest of the Western world – the KCE has devoted a great deal of attention to this illness: its first clinical practice guideline published in 2007 was fully updated in 2010 and once again in 2012. We are glad to present to you yet another update today. Aside from that, the KCE has also conducted four studies on breast cancer screening and one study on the quality indicators for breast cancer patients.

Due to the continuous developments in this particular field, breast cancer will remain a focus of attention. After many years of intensive research it is hardly surprising that today's innovations often only result in minor, at times difficult to demonstrate improvements in the fate of breast cancer patients. The price that often has to be paid in terms of the risk of side effects and the cost to the health insurance or to patients themselves does not make the choice physicians and patients are faced with any easier. Unfortunately, there is no clinical practice guideline that can offer them definitive advice that can be applied across the board. One typical example raised in the present update is whether or not axillary lymph node dissection is indicated in cases where micro-metastases are found in a patient's lymph nodes. It makes for a heartrending choice between either a slightly (lower) chance of relapse, or a lower risk of side effects, like a swollen arm.

In dilemmas such as these, much store is – or ought to be – put by the patient's own point of view. On that account, physicians have a moral duty to ensure that patients are fully and objectively informed about all the implications of the various treatment options. But also the knowledge of how to help people when making this type of decisions is evolving and being professionalised. Aside from the medico-technical elements that came to the fore in our 2010 indicators study, this particular multidisciplinary aspect is just another in favour of more centralisation. It is the only way to ensure that our country is keeping its excellent position in the European breast cancer survival rate tables.

Christian LÉONARD
Deputy general director

Raf MERTENS
General director

SYNTHESIS

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1. INTRODUCTION

Breast cancer is the most common cancer type in Belgian women, accounting for 35.3% of all new cancer cases [1]. In 2010, 9 908 women were diagnosed with breast cancer.

Similar to other European countries, breast cancer is the most frequent cause of cancer deaths and accounts for 20.2% of all cancer deaths within our country [1]. Female breast cancer has a relatively good prognosis, with a 5-year relative survival of 88.0% (Belgium, 2004-2008).

On the one hand, new drug classes, such as targeted therapies, are continuously being developed and tested to improve outcomes in breast cancer. On the other hand, new surgical procedures, such as sentinel lymph node dissection, are increasingly being considered, helping in a number of cases to avoid more invasive interventions, thereby improving the balance between local disease control and procedure-related morbidity.

2. OBJECTIVES AND SCOPE OF THIS GUIDELINE

In 2007, KCE published the first clinical practice guideline (CPG) on the management of breast cancer [2] and completely updated it in 2010 (KCE report 143, first edition) [3]. It covered a broad range of topics: diagnosis, staging, treatment, reconstructive surgery, supportive therapy and follow-up. It primarily concerned women with early invasive or advanced breast cancer.

Furthermore, in 2011, the thresholds adopted for systemic treatment modalities (endocrine therapy, anti-HER2 therapy and chemotherapy) were updated (KCE report 143, second edition).

This 2013 update (third edition) focuses on four therapeutic approaches: 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.

The current guideline replaces the 2nd version of the KCE report 143 [3], and adds the evidence for the four abovementioned therapeutic approaches.

Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences.

This guideline is intended to be used by all care providers involved in the management of breast cancer, including oncologists, surgeons, radiologists, pathologists and nurses. It can also be of interest for patients and their families, for general practitioners, hospital managers and policy makers.

3. METHODS

3.1. Systematic review of the literature (2010)

A search for existing clinical guidelines was carried out in several databases, including the National Guideline Clearinghouse, ASCO, CCO, FNCLCC, NICE, SIGN, GIN. The search for systematic reviews, meta-analyses and primary studies was carried out in Medline, the Cochrane Database of Systematic Reviews and DARE.

Two independent researchers performed the literature selection, the quality appraisal and the data extraction.

3.2. Update (2013)

The literature search and the analysis of the scientific evidence were mainly conducted by the Dutch Cochrane Centre in collaboration with KCE experts. 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

For each of these clinical questions, the literature search focused on new systematic reviews and randomized controlled trials (RCTs). Systematic reviews were searched from January 2010 onwards (the search date of the guideline version 2010) 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 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.

Further information about ongoing research was obtained by contacting study authors and organisations. The EMA website was consulted to find relevant information about authorization for medicines. Members of the Guideline Development Group were also consulted to identify relevant evidence that might have been missed during the search process.

3.3. Elaboration of the recommendations

Based on the evidence retrieved by KCE and Dutch Cochrane Centre experts, recommendations were prepared by a multidisciplinary guideline development group (i.e. the authors of this guideline). These recommendations were subsequently formally reviewed by representatives of professional associations (stakeholders; see colophon). Conflicts of interest were recorded.

A level of evidence and strength of recommendation was assigned to each recommendation using the GRADE system (Table 1 for the 2010 version, Tables 2 and 3 for the 2013 update).

Table 1 - GRADE levels of evidence and strength of recommendation (version applicable to the 2010 KCE guideline).

Grade	Description
1A	Strong recommendation based on high level of evidence
1B	Strong recommendation based on moderate level of evidence
1C	Strong recommendation based on low or very low level of evidence
2A	Weak recommendation based on high level of evidence
2B	Weak recommendation based on moderate level of evidence
2C	Weak recommendation based on low or very low level of evidence

Table 2 - Levels of evidence according to the GRADE system (version applicable to the 2013 KCE guideline update).

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Table 3 - Strength of recommendation according to the GRADE system (version applicable to the 2013 KCE guideline update).

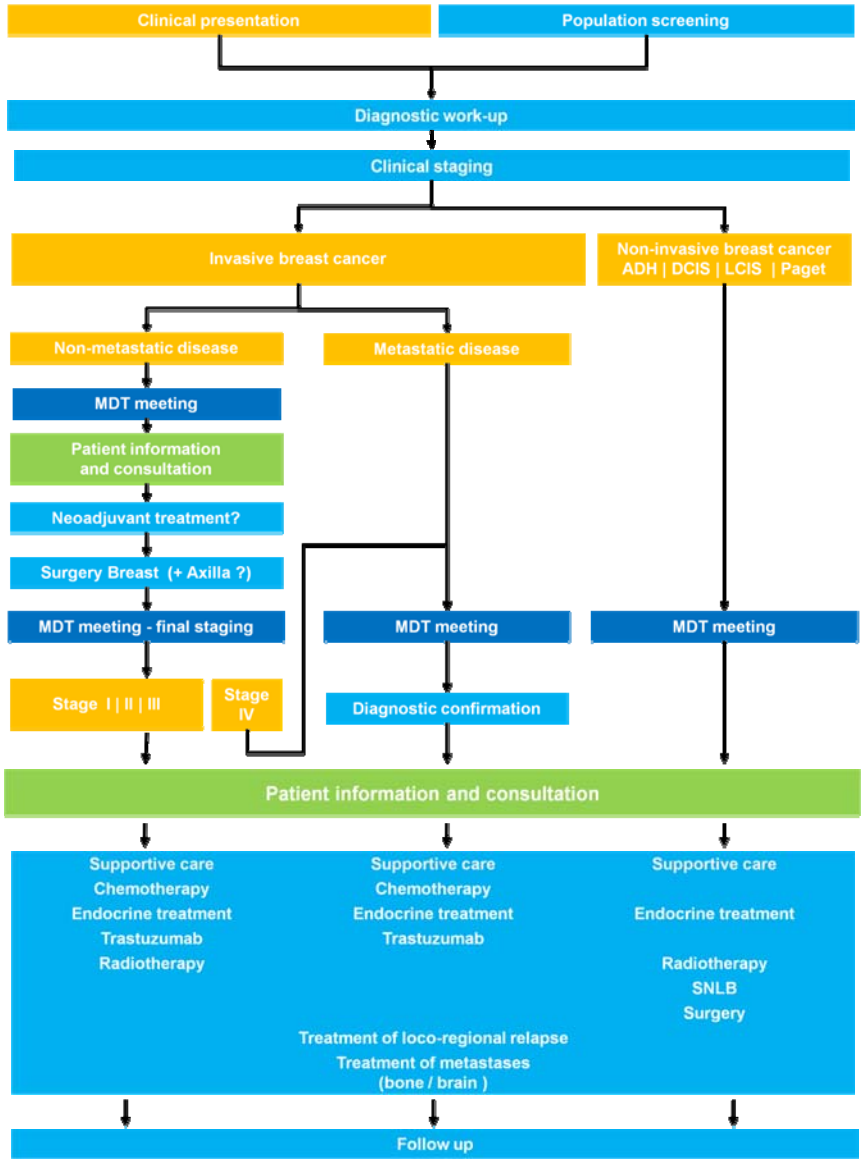
Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice)*, or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice)*
Weak	The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice)*, or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice)*

Three external validators assessed and validated the final draft of this guideline by means of the AGREE II checklist. The validation process was chaired by CEBAM (Belgian Centre for Evidence-Based Medicine).

4. CLINICAL RECOMMENDATIONS

Full details of the evidence underpinning the recommendations below are available in the scientific report and its supplements. The recommendations follow the sequence of the chapters of the scientific report. Below the general algorithm is presented.

4.1. General algorithm



Abbreviations: ADH: atypical ductal hyperplasia; DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ; SLNB: sentinel lymph node biopsy; MDT: multidisciplinary team

4.2. Diagnosis of breast cancer

4.2.1. Triple assessment

Recommendations (2010)	GRADE
All patients should have a clinical examination.	1C
If a localised abnormality is detected, patients should have mammography and/or ultrasonography followed by core biopsy and/or fine needle aspiration cytology.	1C
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
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
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

4.2.2. Magnetic resonance imaging (MRI)

Recommendations (2010)	GRADE
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
For definitive characterization of breast lesions, biopsy cannot yet be replaced by MRI.	1B

4.2.3. 99mTc-MIBI scintimammography (SMM)

Recommendation (2010)	GRADE
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

4.2.4. PET scan

Recommendation (2010)	GRADE
PET scanning is insufficiently accurate to be recommended for diagnosis of breast cancer as an alternative to biopsy.	1B

4.2.5. Hormonal receptor assessment

Recommendations (2010)	GRADE
Estrogen receptors and progesterone receptors (ER/PgR) should be measured on all ductal carcinomas in situ (DCIS) and primary invasive breast cancers.	1B
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

4.2.6. Tumour markers

Recommendation (2010)	GRADE
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

4.3. Staging of breast cancer

4.3.1. Routine staging tests

Recommendations (2010)	GRADE
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
In asymptomatic women with DCIS, the routine use of bone scanning, liver ultrasonography and chest radiography cannot be recommended for baseline staging.	2C

4.3.2. Magnetic resonance imaging (MRI)

Recommendations (2010)	GRADE
Routine MRI of the breast is not recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or DCIS, except in the following situations:	1C
• **if the estimates of the extent of the disease, needed for treatment planning, diverge between clinical examination, mammography and ultrasound;**	2C
• **in invasive lobular cancer;**	1C
• **if, due to high breast density, mammographic assessment does not allow to exclude multicentric or bilateral disease.**	2C
For M-staging (visceral or bone metastases), MRI/CT can be considered.	2C

4.3.3. Axillary ultrasonography

Recommendation (2010)	GRADE
Axillary ultrasonography with fine needle aspiration cytology of axillary lymph nodes with suspected malignancy is recommended.	2C

4.3.4. PET scan

Recommendations (2010)	GRADE
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
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

4.4. Treatment of non-invasive breast tumours

4.4.1. Early precursor and high-risk lesions

Recommendations (2010)	GRADE
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

4.4.2. Ductal carcinoma in situ

4.4.2.1. Surgery

Recommendations (2010)	GRADE
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
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
Cosmetic repair should be offered to patients treated with breast-conserving surgery.	1C
Immediate breast reconstruction should be discussed with all patients being advised to have a mastectomy, except when significant comorbidities preclude this option.	1C
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
Axillary clearance is not recommended for women with DCIS.	1C

4.4.2.2. Sentinel lymph node biopsy

Recommendations (2010)	GRADE
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
Sentinel lymph node biopsy is recommended for high-grade DCIS, when mastectomy with or without immediate reconstruction is planned.	1A

4.4.2.3. Radiotherapy

Recommendation (2010)	GRADE
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

4.4.2.4. Endocrine therapy

Recommendation (2010)	GRADE
Adjuvant hormonal therapy is recommended for patients with ER positive DCIS.	1A

4.4.3. Paget's disease

Recommendations (2010)	GRADE
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
Cosmetic repair should be offered to patients with Paget's disease treated with breast-conserving surgery.	1C

4.4.4. Early invasive breast cancer

Recommendation (2010)	GRADE
All cases of breast cancer should be discussed within a multidisciplinary team before any treatment is initiated.	expert opinion

4.4.4.1. Neoadjuvant treatment

Recommendation (2010)	GRADE
In patients with unifocal operable tumours too large for breast-conserving surgery, downstaging with neoadjuvant systemic therapy can be considered.	1A

4.4.4.2. Surgery to the breast

Recommendations (2010)	GRADE
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
Cosmetic repair should be offered to patients treated with breast conserving surgery.	1C
Immediate breast reconstruction after mastectomy offers the same survival benefits as mastectomy without reconstruction.	1C
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

4.4.4.3. Surgery to the axilla

Recommendations (2010)	GRADE
Sentinel lymph node biopsy is not recommended for: **1. large T2 (i.e. > 3 cm) or T3-4 invasive breast cancers;** **2. inflammatory breast cancer;** **3. patients with suspicious palpable axillary lymph nodes;** **4. multiple tumours; and possibly disturbed lymph drainage after recent axillary surgery or a large biopsy cavity after tumour excision.**	1A
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.	

Recommendations (2013)	Strength of recommendation	Level of evidence
For women with a SLNB that shows isolated tumour cells, completion ALND is not recommended.	Strong	Very low
For women treated with breast-conserving surgery and with one or two positive sentinel lymph nodes with micrometastases, completion ALND is not recommended.	Strong	Very low
For women treated with mastectomy and with one or two positive sentinel lymph nodes with micrometastases, completion ALND is not recommended.	Weak	Very low
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	Very low

Recommendations (2013)	Strength of recommendation	Level of evidence
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	Very low
For women with three or more positive sentinel lymph nodes with micro- or macrometastases, we recommend ALND.	Strong	Very low
Benefits and risks of each procedure have to be discussed with the patient.	Strong	Very low

4.4.4.4. Adjuvant therapy

Recommendations (2010)	GRADE
If adjuvant chemotherapy and radiotherapy are indicated, the chemotherapy should be given first.	1A
It is recommended to start adjuvant chemotherapy or radiotherapy within 8 weeks of completion of surgery.	1C

4.4.4.5. Radiotherapy

Recommendations (2010)	GRADE
In patients with early breast cancer, adjuvant radiotherapy is indicated after breast-conserving surgery.	1A
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
Until data from a large ongoing randomized trial become available, radiotherapy after mastectomy should be offered to patients with 1-3 positive nodes.	1A
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
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
Axillary radiotherapy should be discussed on a case by case basis in the multidisciplinary team meeting.	1A

4.4.4.6. Systemic therapy

Recommendation (2010)	GRADE
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

4.4.4.7. Chemotherapy

Recommendations (2010)	GRADE
For patients with Stage I-III breast cancer, preferred regimens are standard anthracycline-based regimens with or without a taxane.	1A
For patients with lymph node-positive breast cancer, preferred regimens are standard anthracycline and taxane-based regimens.	2A
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.** **- Secondary prophylaxis with CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy.**	1A
In patients with breast cancer, high-dose chemotherapy with stem cell transplantation cannot be recommended.	1A
For women of childbearing age, fertility issues should always be discussed before the induction of breast cancer therapy.	1C
Chemotherapy during pregnancy is not contraindicated after 14 weeks of gestation.	2C

4.4.4.8. Endocrine therapy

Recommendations (2010)	GRADE
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
Premenopausal women with stage I or II breast cancer who cannot take tamoxifen, should receive a LHRH analogue.	1A
Postmenopausal women with hormone receptor-positive breast cancer should receive adjuvant endocrine treatment with either: **- tamoxifen (for 5 years),** **- or 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).**	1A
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

4.4.4.9. Trastuzumab

Recommendations (2013)	Strength of recommendation	Level of evidence
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	Low
Trastuzumab can be combined either with a taxane in an anthracycline-containing regimen or with a non-anthracycline regimen (TCH).	Weak	Low
In patients under trastuzumab, cardiac function should be monitored during treatment (e.g. every 3 months) and during follow-up.	Strong	Low

4.4.4.10. Biphosphonates

Recommendation (2013)	Strength of recommendation	Level of evidence
In women with early non-metastatic breast cancer, bisphosphonates cannot be recommended as an adjuvant breast cancer therapy.	Strong	Low

4.5. Treatment of metastatic breast cancer

4.5.1. Multidisciplinary approach

Recommendation (2010)	GRADE
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

4.5.2. Diagnosis of metastatic breast cancer

4.5.2.1. Tumour markers

Recommendation (2010)	GRADE
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

4.5.2.2. Biopsy of metastatic lesions

Recommendations (2010)	GRADE
Metastatic lesions should be biopsied whenever accessible and ER, PgR and HER2 should be reassessed.	1B
In both pre- and postmenopausal women, HER2 status should be used to identify patients most likely to benefit from Trastuzumab.	1B

4.5.3. Systemic treatment

4.5.3.1. Endocrine therapy and ER antagonists

Recommendations (2010)	GRADE
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
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
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

4.5.3.2. Chemotherapy

Recommendations (2010)	GRADE
Chemotherapy for patients with metastatic breast cancer is indicated for the following conditions : **- hormone-refractory or HR- tumours,** **- rapidly progressive disease or symptomatic disease,** **- life-threatening disease.**	expert opinion
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
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

4.5.3.3. Biological therapy

Recommendation (2010)	GRADE
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

Recommendation (2013)	Strength of recommendation	Level of evidence
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**	Moderate

4.5.4. Treatment of bone metastases

Recommendations (2010)	GRADE
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
In patients with painful or threatening bone metastases, radiotherapy is the treatment of choice, if feasible.	1A

4.5.5. Treatment of brain metastases

Recommendations (2010)	GRADE
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 could be offered to patients for whom surgery or radiosurgery is not appropriate.	2C

4.6. Treatment of locoregional relapse

Recommendations (2010)	GRADE
A local recurrence in the thoracic wall should be treated preferentially with surgery and adjuvant radiotherapy whenever possible.	1C
A local recurrence after breast-conserving treatment should be treated by mastectomy.	1C
Systemic treatment for a completely excised locoregional recurrence should be discussed on a case by case basis in the multidisciplinary team meeting.	expert opinion

4.7. Supportive care for patients with breast cancer

Recommendations (2010)	GRADE
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
Physiotherapy for mobility after axillary clearance should be recommended.	1A
Physical training, including specific exercises for cancer-related fatigue can be considered after treatment for breast cancer.	1A
Menopausal hormonal replacement therapy is contraindicated in women with breast cancer.	1B
Psychological support should be available to all patients diagnosed with breast cancer.	1A
A palliative care team should assess all patients with uncontrolled disease in order to plan a symptom-management strategy.	1C

4.8. Surveillance of patients with breast cancer

Recommendations (2010)	GRADE
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
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
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: **- 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.**	1C
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

4.9. Multidisciplinary approach of patients with breast cancer

Recommendation (2010)	GRADE
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

4.10. Breast cancer and pregnancy

Recommendation (2010)	GRADE
Breast cancer is not a contraindication for later pregnancy or breastfeeding, but should be individually discussed.	2C

Note. A specific KCE report was dedicated to the prevention and treatment of adverse events related to chemotherapy and radiotherapy. This report recommended that all patients of reproductive age should be informed about possible consequences of cancer treatment on fertility and should have access to all possible fertility preservation measures (such as embryo cryopreservation) before the start of cytotoxic treatment. This report can be downloaded on the KCE website (http://kce.fgov.be/publication/report/supportive-treatment-for-cancer-part-2-prevention-and-treatment-of-adverse-events).

4.11. Participation in clinical trials

Recommendation (2010)	GRADE
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

5. IMPLEMENTATION AND UPDATING OF THE GUIDELINE

5.1. Implementation

The implementation of this guideline should be facilitated by the College of Oncology. An online implementation tool similar to the tools accompanying previous guidelines will be developed (www.collegeoncologie.be).

5.2. Monitoring the quality of care

This guideline should be considered as a starting point to develop quality improvement programs that target all caregivers concerned.

The guideline should be viewed as a tool to support health policies to improve the quality of care. A quality indicator set, covering the whole range of diagnostic and therapeutic options, has already been developed in 2011. The set contains 32 quality of care indicators, of which 13, including 2 survival indicators and 11 process indicators, can be measured using national cancer registry and claims data. The publication of this updated guideline should be a good opportunity to reassess the quality of care delivered in Belgium.

The scientific material of this guideline is intended to be disseminated by scientific and professional organisations. They can transform this material into attractive and user-friendly tools tailored to specific groups of caregivers. They could also play a key role in the dissemination, through diverse channels such as websites or continuing medical education.

5.3. Guideline update

In view of the rapidly evolving evidence, this guideline should be updated yearly. If, in the meantime, important new evidence would become available, this will be mentioned on the website of the College of Oncology.

6. REFERENCES

1. Belgian Cancer Registry. Cancer survival in Belgium. Brussels: Belgian Cancer Registry; 2012.
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4. Stordeur S, Vrijens F, Beirens K, Vlayen J, Devriese S, Van Eycken E. Quality indicators in oncology: breast cancer. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2011. KCE Reports 150C (D2010/10.273/101)
5. Stordeur S, Vrijens F, Devriese S, Beirens K, Van Eycken E, Vlayen J. Developing and measuring a set of process and outcome indicators for breast cancer. The Breast. 2012;21(3):253-60.

POLICY RECOMMENDATIONS[a]

To the College of Oncology

- **The implementation of this guideline should be facilitated by the College of Oncology. An online implementation tool similar to the tools accompanying previous guidelines should be developed (www.collegeoncologie.be).**
- **In view of the rapidly evolving evidence, this guideline should be updated yearly. If, in the meantime, important new evidence would become available, this should be mentioned on the website of the College of Oncology (http://www.health.belgium.be/eportal/Healthcare/Consultativebodies/Doctorscolleges/Oncology/Clinicalpracticeguidelines/index.htm).**

To the Belgian Cancer Registry

- **The quality of care delivered to breast cancer women should be reassessed using the set of quality indicators previously elaborated, and the results should be compared with the baseline evaluation (2001-2006 data).**

To the scientific and professional associations in oncology

- **The dissemination of this guideline should be supported by transforming this material into attractive and user-friendly tools tailored to specific groups of caregivers. The associations should also play a key role in the dissemination through diverse channels such as websites or continuing medical education.**

[a] The KCE has sole responsibility for the recommendations.