KCE

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

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
95% CI	95% confidence interval
ADH	Atypical ductal hyperplasia
AHRQ	Agency for Healthcare Research and Quality
ALH	Atypical lobular hyperplasia
ALND	Axillary lymph node dissection
ASCO	American Society of Clinical Oncology
AUS	Axillary ultrasonography
BCS	Breast conserving surgery
BPI	Brachial plexus injuries
BRCA	Breast cancer gene
CBO	Dutch Institute for Healthcare Improvement
CCO	Cancer Care Ontario
CDSR	Cochrane database of systematic reviews
CEA	Carcinoembryonic antigen
CMF	Cyclophosphamide, methotrexate, fluorouracil
CPG	Clinical practice guideline
CT	Computed tomography
DARE	Database of Abstracts of Reviews of Effects
DCIS	Ductal carcinoma in situ
DFS	Disease free survival
ER	Estrogen receptor
FAC	Cyclophosphamide, doxorubicin, fluorouracil
FEA	Flat epithelial atypia
FEC	Cyclophosphamide, epirubicin, fluorouracil
FNAC	Fine needle aspiration cytology
FNCLCC	Fédération Nationale des Centres de Lutte Contre le Cancer
FP	False positive
GDG	Guideline Development Group

GRADE	Grading of Recommendations Assessment, Development and Evaluation
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRT	Hormone replacement therapy
HTA	Health Technology Assessment
IHC	Immuno-histochemistry
IQR	Inter quartile range
ITC	Isolated tumour cells
LCIS	Lobular carcinoma in situ
LHRHa	Luteinising-hormone releasing hormone agonist
LVI	Lymphovascular invasion
MBC	Metastatic breast cancer
MDT	Multidisciplinary team
MeSH	Medical Subject Headings
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Clinical Excellence
NPV	Negative Predictive Value
OR	Odds Ratio
OS	Overall survival
PET	Positron-emission tomography
PFS	Progression free survival
PgR	Progesterone receptor
PLCIS	Pleomorphic lobular carcinoma in situ
PPV	Positive predictive value
PVI	Peritumoral vascular invasion
RCT	Randomised controlled trial
RFS	Recurrence free survival
RR	Risk ratio
SE	Standard error

Se	Sensitivity
SIGN	Scottish Intercollegiate Guidelines Network
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy
SMM	Scintimammography
Sp	Specificity
SR	Systematic review
SUV	Standard Uptake Value
TP	True Positive
TPA	Tissue polypeptide antigen
TPS	Tissue polypeptide specific antigen
US	Ultrasonography
WBS	Whole Body Scan
WLE	Wide Local Excision

■ SCIENTIFIC REPORT

1 INTRODUCTION

1.1 The need for a guideline

In Belgium, breast cancer is the most frequent cancer in women (35.3% of cancer cases), occurring at a mean age of 62 years (incidence year 2008, Belgium) [4]. In 2010, 9 908 new breast cancers were diagnosed, compared to 9 405 new breast cancers diagnosed in 2005. In Belgium as in Europe, breast cancer is the most frequent cause of death by cancer in women (20.2% of all cancer deaths) [4].

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]. This decline can be explained by the combined effect of earlier detection and improved adjuvant treatment.

On the one hand, new drug classes, such as targeted therapies, are continuously being developed and tested to improve outcomes in breast cancer women. On the other hand, the introduction of surgical procedures, such as sentinel lymph node dissection, is more and more considered instead of more extensive interventions to improve the balance between local control of disease progression and procedure-related morbidity.

The clinical evidence evolves, but a lot of questions asked both by cancer patients and by clinicians remained unanswered.

1.2   Remit of the guideline

1.2.1   Overall objectives

A clinical practice guideline (CPG) on the management of breast cancer was firstly published in 2007 [1], and completely updated in 2010 [2]. This guideline was the result of a collaboration between the College of Oncology and the KCE and covered a broad range of topics: diagnosis, staging, treatment, reconstructive surgery, supportive therapy and follow-up. It primarily concerned women with invasive early or advanced breast cancer.

A regular update of the full guideline takes a lot of time and is not cost-effective. The decision was made to regularly update specific parts of the guideline based on alert messages given by the members of the GDG. In 2011, the thresholds adopted for systemic treatment modalities (endocrine therapy, anti-HER2 therapy and chemotherapy) were updated.

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.

This guideline replaces the 2nd version of the KCE report 143 [2], published in 2010. It adds the evidence for the four abovementioned research questions to the main part of the KCE report 143. Updated conclusions and recommendations are added to their respective sections with a special indication.

This guideline provides recommendations based on current scientific evidence both for the diagnosis, treatment, follow-up and supportive care of women with an early, invasive or metastatic breast cancer. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences.

1.2.2   Target users of the guideline

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 could also be of particular interest for patients and their families, for general practitioners, hospital managers and policy makers.

1.3   Statement of intent

Clinical Guidelines are designed to improve the quality of health care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians and researchers for use within the Belgian healthcare context. It provides advice regarding the care and management of breast cancer women.

The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Variations, which take into account individual circumstances, clinical judgement and patient choice, may also be appropriate. The information in this guideline is not a substitute for proper diagnosis, treatment or the provision of advice by an appropriate health professional. It is advised, however, that significant deviations from the national guideline should be fully documented in the patient's file at the time the relevant decision is taken.

1.4   Funding and declaration of interest

The KCE is a federal institution which is financed for the largest part by INAMI/RIZIV, but also by the Federal Public Service of Health, food chain safety and environment, and Federal Public Service of social security. The development of clinical practice guidelines is part of the legal mission of the KCE. Although the development of the guidelines is paid by KCE budget, the sole mission of the KCE is providing scientifically valid information. The KCE has no interest in companies (commercial or not, e.g. hospital, university), associations (e.g. professional association, syndicate), individuals or organisations (e.g. lobby group) on which the guidelines could have a positive or negative impact (financial or other).

All clinicians involved in the GDG or the peer-review process completed a declaration of interest form. The information of possible conflicts of interest is published in the colophon of this report. All members of the KCE Expert Team make yearly declarations of interest and further details of these are available on request.

2 METHODOLOGY

2.1 The Guideline Development Group

2.1.1 Introduction

The KCE guideline is drawn up according to highly codified principles, based on scientific information regularly updated from the international literature. KCE analyses clinical practices in current use on the basis of existing recommendations. This guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes.

2.1.2 The Guideline Development Group

This guideline was developed owing a collaboration between multidisciplinary groups of practising clinicians and KCE experts. The composition of the Guideline Development Group is documented in Appendix 1. Guideline development and literature review expertise, support and facilitation were provided by the KCE Expert Team.

2.2 General approach

The present CPG was developed by adapting (inter)national CPGs to the Belgian context (www.kce.fgov.be). This approach was structured in a formal methodology by the ADAPTE group, an international group of guideline developers and researchers [6]. The ADAPTE methodology generally consists of three major phases (www.adapte.org):

1. **Set-up Phase:** Outlines the necessary tasks to be completed prior to beginning the adaptation process (e.g., identifying necessary skills and resources).
2. **Adaptation Phase**: Assists guideline developers in moving from selection of a topic to identification of specific clinical questions; searching for and retrieving guidelines; assessing the consistency of the evidence therein, their quality, currency, content and applicability; decision making around adaptation; and preparing the draft adapted guideline.

3. **Finalization Phase**: Guides guideline developers through getting feedback on the document from stakeholders who will be impacted by the guideline, consulting with the source developers of guidelines used in the adaptation process, establishing a process for review and updating of the adapted guideline and the process of creating a final document.

2.3 Clinical questions

The CPG addresses the following clinical questions:

1. What diagnostic tests are the most effective to confirm the diagnosis of breast cancer?
- Triple test approach: clinical examination / mammography / pathology
- MRI
- MIBI scintimammography

2. What diagnostic tests are necessary to investigate the extent of the breast cancer?
- Sentinel biopsy
- Chest X-ray
- Ultrasonography of the liver
- Bone scintigraphy
- Biochemical and tumour markers; hormonal receptors
- CT scan of the thorax
- PET scan

3. What is the most effective treatment strategy for:
- Non-invasive breast cancer (ductal carcinoma in situ, Paget's disease)
- Early-stage invasive breast cancer
- Locally-advanced invasive breast cancer
- Metastatic breast cancer
- Locoregional recurrence of breast cancer

4. What is the place of supportive treatment of breast cancer, including erythropoesis stimulating proteins, bisphosphonates, physiotherapy, physical training, psychological support and hormonal substitution?

5. What is the place of reconstructive surgery in the treatment of breast cancer?

6. What is the most effective strategy for the follow-up of patients with breast cancer?

2.4 Clinical practice guidelines

2.4.1 Search for evidence

2.4.1.1 Sources

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

Table 1 - Searched guideline websites and websites of organisations in oncology.

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/
Cancer Care Ontario	http://www.cancercare.on.ca/english/home/
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/

2.4.1.2 Search terms

For Medline (OVID) the following MeSH terms were used in combination: breast, breast diseases, neoplasms, breast neoplasms, breast tumour, breast carcinoma, breast malignant, breast metastases. These MeSH

terms were combined with a standardised search strategy to identify CPGs (Table 2).

Table 2 - Standardised search strategy for CPGs.

Database	Search strategy
Medline	guideline [pt] OR practice guideline [pt] OR recommendation* [ti] OR standard* [ti] OR guideline* [ti]

2.4.1.3 In- and exclusion criteria

Both national and international CPGs on breast cancer were searched. A language (English, Dutch, French) and date restriction (2006 – 2009) were used. CPGs without references were excluded, as were CPGs without clear recommendations.

2.4.2   Quality appraisal

In total, 47 CPGs were identified. All were quality appraised by two independent reviewers (S. Stordeur, J. Vlayen) using the AGREE instrument (www.agreecollaboration.org). Disagreement was discussed face-to-face. At the end, agreement was reached for all CPGs, and 20 CPGs were included. In Appendix 2, an overview is provided of all aggregated dimension scores of the identified CPGs.

2.5   Additional evidence from original studies (2010)

2.5.1   Search for evidence

2.5.1.1   Source

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

2.5.1.2   Search terms

A combination of appropriate MeSH terms and free text words was used (Appendix 3).

2.5.1.3   In- and exclusion criteria

An iterative approach was followed. 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. Inclusion criteria for the diagnostic studies were: prospective cohort study design (or RCT), ability to construct a 2x2 table, no partial verification, description of reference standard.

All searches were run between March and December 2009, and updated in January 2010.

The identified studies were selected based on title and abstract. For all eligible studies, the full-text was retrieved. In case no full-text was available, the study was not taken into account for the final recommendations.

2.5.2   Quality appraisal

The methodological quality of the diagnostic accuracy studies was assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist, which is a standardised instrument endorsed by the Cochrane Collaboration [7].

The quality of the retrieved systematic reviews and RCTs was assessed using the checklists of the Dutch Cochrane Centre (www.cochrane.nl).

2.6   Guideline update (2013)

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.

2.6.1 Search for evidence

2.6.1.1 Source

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.

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

2.6.1.2 Search terms

The search strategies were based on the strategies reported in the KCE guideline 143 [1, 2] or on the strategies applied in the included reviews.

The PICOs and the search strategy that correspond to these four updated therapeutic approaches are documented in Appendix 4 (Appendices 4.1. and 4.2.).

2.6.1.3 In- and exclusion criteria

Studies were selected by two researchers independently (F. van de Wetering and R. Scholten). In case of doubt the content experts were consulted. First, the titles and abstracts of the identified studies were checked and irrelevant studies were withheld. Of the remaining studies the full-text was assessed.

To be included a systematic review had to have:

- addressed any of the research questions;

- evaluated at least one of the selected critical and important outcomes;
- included RCTs;
- searched MEDLINE and at least one other electronic database;
- included an assessment of risk of bias of each primary study which included at least the three following main items: concealment of allocation, blinded outcome assessment and completeness of follow-up (preferably summarised in a table);
- been published in English, French, or Dutch.

If more than one systematic review was identified for a particular research question, the focus was on the most complete systematic review.

To be included a primary study had to:

- be an RCT or an observational study for RQ1, an RCT for RQ2-4;
- address any of the research questions;
- evaluated at least one of the selected critical and important outcomes;
- have been published in English, French or Dutch.

Studies presented as conference abstract only were excluded. In case no full-text was available, the study was not taken into account for the final recommendations.

The whole process of the studies selection is detailed in Appendix 4 (section 4.3.) by research question.

2.6.2 Quality appraisal

The methodological quality of included studies was assessed by two researchers independently (F. van de Wetering and R. Scholten for RCT; S. Stordeur and J. Vlayen for observational studies). Any disagreements were resolved by discussion or with consultation of a third researcher (GJ van Tienhoven) in case of persisting disagreement. Content experts were involved to judge any other flaws that could have been overlooked by non-content experts (e.g. comparing a new drug with a too low dose of an existing competitor drug). The risk of bias of identified RCTs was assessed by the Cochrane Collaboration's tool for assessing risk of bias [8]. Judgement of each item includes three categories: 'low risk of bias', 'high

risk of bias', and 'unclear risk of bias'. For each criterion the definitions as described in the Cochrane Handbook were used. If applicable, risk of bias for the items regarding detection bias and attrition bias were assessed per class of outcomes (e.g. subjective and objective outcomes). At the end, each study was labelled as low risk of bias, unclear risk of bias or high risk of bias according to the criteria described in the Cochrane Handbook. The CoCanCPG checklist for cohort studies was used to assess the validity of the observational studies. Risk of bias of included systematic reviews and RCTs are summarized for each research question in Appendix 4 (section 4.3).

2.7   Analysis (guideline update 2013)

For each comparison (intervention vs. comparator) separate analyses were done. If a recent systematic review with low risk of bias was available, the results of the review were used and presented in Summary of Findings Tables (Appendix 6). If new RCTs were identified, the existing systematic review was updated as was the meta-analysis of the review. This was only feasible if the required data in the review were readily available (i.e. the review reports the 2 by 2 Tables of the included studies). If this was not feasible, the results of the newly identified RCTs were summarized and presented in Summary of Findings Tables (Appendix 6). If the RCTs served for a new systematic review, meta-analyses were performed and the results were presented in Summary of Findings Tables.

Meta-analyses were performed according to the statistical guidelines described in the Cochrane Handbook (http://www.cochrane.org/training/cochrane-handbook) and by the use of Review Manager Software (Review Manager 2011). Results of studies that were sufficiently clinically homogeneous, i.e. sufficiently similar with respect to the patients, interventions, outcomes and timing of the follow-up measurements (to be judged by the content experts) were combined by the use of a fixed-effect model. If the studies were statistically heterogeneous a random-effects model was used and – if sufficient studies were available – heterogeneity was explored by subgroup analyses. Statistical heterogeneity was assessed by a combination of visual inspection of the forest plots, the Chi-square test for homogeneity (p-value set at 0.1 to increase the power of this test) and the I^2 statistic. For dichotomous outcomes the relative risk was used as the measure of

treatment effect and for continuous outcomes the mean difference or – if applicable – the standardized mean difference. If possible, all analyses were performed according to the intention-to-treat principle.

Studies that were clinically heterogeneous or did not present the data in sufficient detail to enable statistical pooling were summarized qualitatively.

2.8   Data extraction

For each included CPG the following data were extracted: searched databases and search terms, search date, publication year, in- and exclusion criteria, quality appraisal, availability of evidence tables, the consistency between the evidence and its interpretation, and the consistency between the interpretation of the evidence and the recommendations.

For each systematic review, the search date, publication year, included studies and main results were extracted. For RCTs and longitudinal studies, the following data were extracted: publication year, study population, study intervention, and outcomes. All evidence tables are reported in Appendix 5.

The seventh edition of the TNM Classification of Malignant Tumours (Appendix 8) was used to describe and categorize cancer stages and progression [9].

Data extraction was performed by two researchers independently and entered in evidence tables using standard KCE templates. Any disagreements were resolved by discussion or, if required, by a third party.

2.9   Grading of evidence

For each recommendation, we provided its strength and the quality of the supporting evidence [10]. According to GRADE, we classified the quality of evidence into 4 categories: high, moderate, low, and very low (Table 3). The quality of evidence reflects the extent to which a guideline panel's confidence in an estimate of the effect was adequate to support a particular recommendation.

For RCTs, quality rating was initially considered to be of high level (Table 3). The rating was then downgraded if needed based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down -1 or -2 points

respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain [11].

Observational studies were by default considered low level of evidence (Table 3). However, the level of evidence of observational studies with no threats to validity can be upgraded for a number of reasons:

1. Large magnitude of effects: The larger the magnitude of effect, the stronger becomes the evidence. As a rule of thumb, the following criteria were proposed by GRADE:
   a. Large, i.e. RR >2 or <0.5 (based on consistent evidence from at least 2 studies, with no plausible confounders): upgrade 1 level
   b. Very large, i.e. RR >5 or <0.2 (based on direct evidence with no major threats to validity): upgrade 2 levels
2. All plausible confounders: all plausible confounding from observational studies or randomized trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed
3. Dose-response gradient: The presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the quality of evidence.

The general principles used to downgrade the quality rating are summarized in Table 5. Decisions on downgrading with -1 or -2 points were based on the judgement of the assessors. Reasons for (no) downgrading were summarized in the GRADE profiles in Table 5.

For each clinical question, conclusions were formulated at the level of individual treatment outcomes using standardized language (Table 6).

Table 3 – A summary of the GRADE approach to grading the quality of evidence for each outcome.[12]

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖)
Observational studies	Low		3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)

Table 4 - Levels of evidence according to the GRADE system.

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 5 - Downgrading the quality rating of evidence using GRADE.

Quality element	Reasons for downgrading
Limitations	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of unvalidated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down. If the body of evidence included only a single study, rating was downgraded with -1 point as consistency of results cannot be judged and there is no proof that results are reproducible. The only exception was the availability of one large multicentre trial without heterogeneity across sites.
Indirectness	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision	Evaluation of the imprecision of results was primarily based on <u>examination of the 95%CI</u>. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention. Even if 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the <u>optimal information size (OIS)</u>. If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

Table 6 - Standardized language used for formulating scientific conclusions.

Evidence base	Conclusion	Recommendation
High level of evidence	It is demonstrated that …	… is (not) recommended / needed / indicated / standard / should be ….
Moderate level of evidence	It is plausible that …	
One study of high or moderate quality	There are indications that	… can(not) be considered / is (not) an option.
Low or very low level of evidence		
Inconsistent evidence	There is conflicting evidence that …	
Limited evidence	There is limited evidence that …	

2.10 Formulation of recommendations

Based on the retrieved evidence, the first draft of recommendations was prepared by a small working group (S. Stordeur, J. Vlayen and H. Wildiers). This first draft together with the evidence tables was circulated to the guideline development group 2 weeks prior to the face-to-face meetings (March 24ᵗʰ 2009, November 10ᵗʰ 2009, November 26ᵗʰ 2009, January 12ᵗʰ 2010, February 7ᵗʰ 2013 and February 25ᵗʰ 2013). Recommendations were changed if important evidence supported this change. Based on the discussion meetings a second draft of recommendations was prepared and once more circulated to the guideline development group for final approval.

A level of evidence and strength of recommendation was assigned to each recommendation using the GRADE system (Table 7 for the original version, Table 8 and Table 9 for the update 2013).

The strength of recommendations depends on a balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), quality of available evidence, values and preferences, and cost (resource utilization). In general, the higher the quality of the supporting evidence, the more likely it is for the recommendation to be strong. Strong recommendations based on low or very low quality evidence are rare, but possible. Factors that influence the strength of a recommendation are reported in Table 9.

Table 7 - GRADE levels of evidence quality and strength of recommendations (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 8 - Strength of recommendations 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)*

Table 9 - Factors that influence the strength of a recommendation.

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted

A strong recommendation implies that most patients would want the recommended course of action. A weak recommendation implies that the majority of informed patients would want the intervention, but many would not [12]. Specifically, a strong negative recommendation means the harms of the recommended approach clearly exceed the benefits whereas a weak negative recommendation implies that the majority of patients would not want the intervention, but many would. In the case of a weak recommendation, clinicians are especially required to spend adequate time with patients to discuss patients' values and preferences. Such an in-depth discussion is necessary for the patient to make the best decision. This may lead a significant proportion of patients to choose an alternative approach. Fully informed patients are in the best position to make decisions that are consistent with the best evidence and patients' values and preferences.

For policy-makers, a strong recommendation implies that variability in clinical practice between individuals or regions would likely be inappropriate whereas a weak recommendation implies that variability between individuals or regions may be appropriate, and use as a quality of care criterion is inappropriate[12].

We offer the suggested interpretation of "strong" and "weak" recommendations in Table 10 [13, 14].

Table 10 - Interpretation of strong and conditional (weak)* recommendations.[13, 14]

Implications	Strong recommendation	Weak recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

* the terms "conditional" and "weak" can be used synonymously

2.11 Consultation and peer review

2.11.1 Healthcare professionals

The recommendations prepared by the guideline development group were circulated to the Professional Associations (Table 11). Each association was asked to assign one or two key representatives to discuss the recommendations during an open meeting. All expert referees made declarations of interest.

Globally, 20 clinical experts and representatives of professional associations were involved in the evaluation of the clinical recommendations, through a Delphi survey. The Delphi survey aimed to achieve consensus or define positions among experts panellists, through iterations of anonymous opinions and of proposed compromise statements from the group moderator. It corresponds to a systematic collection and aggregation tool of informed judgment from a group of experts on specific questions and issues.

All invited panellists received the scientific reports for all research questions and 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 panellists were also able to answer 'not applicable' in case they were not familiar with the underlying evidence). In case a panellist 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. In Appendix 9, an overview is provided of how the comments of the stakeholders were taken into account.

Table 11 - List of Professional Associations to which the recommendations were communicated.

- Belgian Society of Medical Oncology (BSMO)
- Belgian Society of Surgical Oncology (BSSO)
- Vlaamse Vereniging voor Obstetrie en Gynecologie (VVOG)
- Groupement de Gynécologues et Obstétriciens de la Langue Française de Belgique (GGOLFB)
- Royal Belgian Society for Surgery
- Belgian Section for Breast Surgery
- Belgische Vereniging Senologie - Société Belge de Sénologie
- Belgian Society for Pathology (BSP) - Belgische Vereniging voor Pathologie (BVP) - Société Belge de Pathologie (SBP)

2.11.2 Patient representatives

Europa Donna Belgium, the Belgian branch of Europa Donna Europe (the European Breast Cancer Coalition, i.e. an independent non-profit organisation that represents the interests of women regarding breast cancer to local and national authorities as well as to institutions of the EU), 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.

The two patient representatives were asked the following questions:

- Are there considerations from the patients' perspective that we missed in formulating our recommendations?
- Do we need to add information that allows to make clear choices when doctors discuss treatment options with patients?
- Are all recommendations relevant, or can we omit some of them?

2.12 Final validation

As part of the standard KCE procedures, an external scientific validation of the report was conducted prior to its publication. Such validation process were done in September 2010 (first edition), in December 2011 (second edition), and in April 2013 (current edition). The current guideline was reviewed prior to its publication by 3 independent validators (cf. names in the colophon), 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.

3 CLINICAL RECOMMENDATIONS

3.1 General algorithm

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

3.2 Diagnosis of breast cancer

3.2.1 Triple assessment

The diagnosis of breast cancer relies on the so-called triple assessment, including clinical examination, imaging (comprising mammography and/or ultrasonography [US]) [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 (FNAC) depends on the clinician's, radiologist's and pathologist's experience [19-21].

In the SIGN guideline two-view mammography (cranio-caudal and oblique projections) was recommended as part of the triple assessment [18]. However, additional views (rolled views, magnifications, extra incidence views, etc.) can be left at the radiologist's discretion. Indeed, a supplementary latero-lateral view (three-view mammography) is not needed in all circumstances.

Younger age (i.e. < 40 years) has been associated with delay in referral for investigation of breast symptoms. Therefore, if a young woman presents with breast symptoms, she should also be evaluated with the triple assessment approach [22].

Recommendations

- **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).**

3.2.2 Magnetic resonance imaging (MRI)

Prospective cohort studies showed that MRI is a sensitive procedure for the diagnosis of breast cancer, with sensitivities ranging from 86–98% [23-25]. In a recent meta-analysis including 44 diagnostic studies, Peters et al. [26] reported pooled weighted estimates of sensitivity and specificity of 90% (95%CI 88% - 92%) and 72% (95%CI 67% - 77%), respectively (Table 22, Appendix 5.1.2.). However, the performance of breast MRI was influenced by the prevalence of cancer in the studied population and by the number of criteria used to differentiate benign from malignant lesions. Breast MRI also demonstrated a higher sensitivity to diagnose early BRCA-associated breast cancer than mammography (86% vs. 48%, p=0.02), albeit without an association with an improved survival [27]. Similar results were obtained in two other studies with higher sensitivies and specificities for MRI compared to mammography [28, 29] and US [29].

Nevertheless, for definitive characterization of breast lesions, biopsy cannot yet be replaced by MRI. In some specific cases, such as clinically palpable and mammographically occult breast cancer, patients with positive lymph nodes without an obvious tumour or diagnosis of recurrence, MRI can be useful [30].

Recommendations

- **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).**

3.2.3   99mTc-MIBI scintimammography (SMM)

Numerous observational studies have shown that SMM is a procedure with a moderate sensitivity (ranging from 58 – 93%) and specificity (71 – 91%) for the diagnosis of breast cancer [23, 24, 31-36]. In 2007, the Medical Advisory Secretariat (Ontario Ministry of Health and Long-Term Care) [37] published a meta-analysis of 49 studies reporting higher diagnostic performance results (Se: 84%, Sp: 81%, PPV: 84% and NPV: 76%), indicating a moderate effectiveness of SMM in differentiating benign and malignant breast lesions (Table 23, Appendix 5.1.3.). However, this evidence does not permit to advocate the routine use of SMM for the diagnosis of breast cancer. SMM may play a role as a third-line adjunctive technique in the evaluation of breast abnormalities, in particular when other imaging modalities are not reliable or were inconclusive. Overall, the same specific indications for MRI can also be applied to SSM (clinically palpable and mammographically occult breast cancer, cT0N+ patients, diagnosis of recurrence).

Two prospective cohort studies directly compared MRI and SSM for the diagnosis of breast cancer [23, 24], showing that MRI is a slightly more sensitive procedure.

Recommendation

- **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).**

3.2.4   PET Scan

The KCE recently published a Health Technology Assessment report on the use of PET scan [38]. This report was in part based on a high-quality HTA report published by the NCCHTA [39] assessing the clinical effectiveness of PET (Table 24, Appendix 5.1.4.). Management decisions relating to diagnosis, staging/restaging, recurrence and treatment response were evaluated. The NCCHTA 2007 report included one systematic review conducted by AHRQ in 2001 [40], and further updated by the AHRQ in 2006 [41]. This systematic review was of high quality, but the quality of the included studies was moderate. The objective of the systematic review was to determine if the available non-invasive diagnostic tests (PET, MRI, US, SMM) are sufficiently accurate to exclude malignancy, avoiding women with an abnormal mammogram to undergo biopsy. Ninety-six publications were included: 9 on PET (8 WBS, 1 gamma camera), 45 on SMM, 19 on MRI and 8 on US. Some publications reported data for more than one test. The reference standard was histopathology obtained after biopsy for all studies. Patients considered were those who had suspicious breast lesions (abnormal mammogram and/or physical examination and/or US examination). For suspicious lesions, sensitivity of diagnostic tests was higher for MRI (92%) than for US (86%) or PET (82%) [41]. On the other hand, specificity was higher for PET (78%) than for MRI (72%) or US (66%). For non-palpable lesions, only scintimammography was studied, yielding a sensitivity of 68% and a specificity of 85%.

The authors concluded that MRI is a more valuable tool than PET for the diagnosis of breast cancer. However, if a <2% risk of having breast cancer with a negative diagnostic test is considered, an acceptable level of risk for a diagnostic test to reliably preclude biopsy, none of these tests was sufficiently accurate to replace biopsy for women at average risk of breast cancer.

For non-palpable lesions, data were insufficient to estimate the accuracy of PET, MRI or US. SMM was not sufficiently accurate to avoid biopsy. For palpable lesions, data were insufficient to estimate the accuracy of PET, MRI, US and SMM.

The additional primary study retrieved by the NCCHTA 2007 [39] compared PET and MRI in 36 women with suspicious lesions on mammography or clinical examination. In this study, PET yielded lower sensitivity than MRI (76%, 95%CI 52-91% vs. 95%, 95%CI 74-99%) and a similar specificity (73%, 95%CI 45-91%). PET was less accurate to detect smaller lesions (< 10 mm).

The systematic review conducted by Bourguet et al. (2006) [42] reported that PET is not indicated in the diagnosis of breast cancer.

Recommendation

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

3.2.5   *Hormonal receptor assessment*

In 2007, the American Society of Clinical Oncology [43] updated its 1996 recommendations for the use of tumour markers in breast cancer. This update also encompassed assessment of oestrogen receptors (ER) and progesterone receptors (PgR) (Table 25, Appendix 5.1.5. and Table 26, Appendix 5.1.6.). Recommendations related to ER and PgR assessment are supported by data from The Early Breast Cancer Trialists' Collaborative Group [EBCTCG] 2005 [44] and other clinical studies [45-47]. In 2010, a guideline jointly produced by the American Society of Clinical Oncology and College of American Pathologists was published that confirmed the utility of ER and PgR status assessment in all invasive breast cancer women [48]. However, the authors reported that up to 20% of the current determinations of ER and PgR testing worldwide were potentially inaccurate, due to false positive and false negative results [48]. They developed recommendations for optimal immunohistochemical (IHC) ER/PgR testing performance (available on http://www.asco.org/guidelines/erpr; accessed on September 28th 2010).

Breast cancer patients with tumours that are ER-positive and/or PR-positive have lower risks of mortality after their diagnosis compared to women with ER- and/or PR-negative disease [49]. More importantly, ER and PgR status are predictive of benefit from endocrine treatment (tamoxifen, chemical ovarian ablation, aromatase inhibitors and fulvestrant) in both the adjuvant and metastatic settings [50]. An emerging topic is the potential role of hormone receptor determination in the management of DCIS. The addition of tamoxifen to the lumpectomy followed by breast radiation therapy is supported by the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial [51, 52] which showed a significant decrease in the recurrence of both in situ and invasive breast cancer in the tamoxifen group, with no impact on overall survival. However, another large randomized trial of adjuvant tamoxifen in DCIS, the United Kingdom Coordinating Committee on Cancer Research trial [53], failed to show an advantage for the tamoxifen-treated group in either the recurrence of breast cancer or overall survival.

The treatment of patients with advanced breast cancer is also guided by a number of factors including the hormone receptor (ER and PR) status and the expression of HER2 of the primary tumour or the metastases. If the receptor status of the primary tumour is unknown and further analysis is not possible, it may be necessary to biopsy the metastatic disease, particularly if the results would influence treatment planning [43, 54].

HER2 is a member of the epidermal growth factor receptor (EGFR) family. The amplification of the HER2 gene or the overexpression of its protein is observed in 20% to 30% of human breast cancers and is associated with a poor prognosis in patients with primary breast cancer [55]. Amplification and/or overexpression of HER2 in breast cancer is associated with a number of adverse prognostic factors. HER2 status is of great clinical value in breast tumours for the identification of those patients who are eligible for trastuzumab or lapatinib therapy. Moreover, level II evidence suggests that overexpression of HER2 identifies patients who have greater benefit from anthracycline-based adjuvant therapy [43].

Recommendations

- **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).**

3.2.6   *Tumour markers*

There is no good evidence (only from very low quality observational studies) to support the routine use of biochemical tests for the diagnosis of breast cancer, including tumour markers such as circulating tumour cells (CTC), CA 15-3, CA 27.29, CEA and Cathepsin D [56-59] (Table 26, Appendix 5.1.6.).

CA 15-3 and CA 27.29 are well-characterized assays that allow the detection of circulating MUC-1 antigen in peripheral blood. Several studies

supported the prognostic relevance of this circulating marker in early-stage breast cancer [60-63]. However, its role in the management of early-stage breast cancer is unclear [64, 65]. It has yet to be determined that MUC-1–based serum markers are helpful in making treatment decisions in this setting.

Recommendation

- **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).**

3.3   Staging of breast cancer

3.3.1   *Routine staging tests*

There is no good evidence to support the pre-treatment routine screening for metastatic disease in asymptomatic women with early operable breast cancer (i.e. cT1-2, N0-1) [18, 66, 67].

Imaging investigations including chest X-ray, bone scan, liver US, and chest and liver CT have a low diagnostic yield and are not indicated in asymptomatic women with ductal carcinoma in situ and pathological stage I disease. They should be used only when clinically indicated (e.g. symptoms of lung disease, a palpable liver, abnormal liver function tests, bone pain or bony tenderness). Serological tests for cancer-specific antigens, such as CEA and CA 15-3, are non-specific and unreliable as indices of active disease [56-59, 64, 65].

However, observational data have shown that specific subsets of patients (e.g. triple negative patients, young patients) harbour a higher risk of distant metastases [68,69], and should therefore be staged more aggressively.

The conclusions above are confirmed by the results of a recent observational study that reported an overall detection rate of 6.3% for skeletal metastases by bone scintigraphy, 0.7% for liver metastases by liver US, and 0.9% for lung metastases by chest X-ray [70].

Of course, these results should be interpreted with caution because of the retrospective study design.

Recommendations

- **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).**

3.3.2   *Magnetic resonance imaging (MRI)*

There is insufficient evidence to recommend the routine use of preoperative MRI in invasive breast cancer and no evidence that detection with MRI makes a difference to outcomes. There is also little evidence on which to base any recommendation on the use of MRI in the assessment of the breast in patients with a diagnosis of pure DCIS (Table 27, Appendix 5.2.1.).

Breast MRI demonstrated moderate to high sensitivity (75-100%) and specificity (82-100%) in detecting multicentric tumour foci in fibroglandular or dense breasts [71, 72]. MRI will detect additional mammogram-occult foci greater than 2 cm from the index cancer in +/- 10% of women [73, 74]. Contrast-enhanced MRI has the lowest false negative rate in detecting invasive lobular carcinoma and has the highest accuracy in measuring the size of the invasive lobular carcinoma [75]. MRI has been shown to detect occult invasive breast cancers with a sensitivity of 97%-100%.

Combined mammography, clinical examination and MRI were more sensitive than any other individual test or routine triad [76]. However, all these results need to be interpreted with caution because of the methodological limitations of the studies and the small sample sizes.

Nevertheless, the increased use of breast MRI at the time of diagnosis and staging is one potential reason for the increased rate of mastectomy [77]. Breast MRI is increasingly being used to exclude the presence of multifocal or multicentric breast cancer in the ipsilateral breast, but also to identify mammographically occult contralateral breast cancers in women who present with unilateral invasive breast cancer. MRI can improve the detection of cancer in the contralateral breast when added to a thorough clinical breast examination and mammographic evaluation at the time of

the initial diagnosis of breast cancer. The increased cancer detection rate is associated with a false positive rate of 10.9% and a relatively low risk of detecting benign disease on biopsy (9.4%) [78]. In a recent meta-analysis [79], MRI identified additional tumour foci in 16% (95%CI 6-34%) of patients newly diagnosed with breast cancer and led to a change in surgical therapy in 8% to 33% of patients, most commonly resulting in mastectomy that would not have been performed otherwise. MRI detected contralateral lesions in a substantial proportion of women, but did not reliably distinguish benign from malignant findings. Relatively high incremental cancer detection rates may be due to selection bias and/or overdetection.

Houssami et al. [80] identified 19 studies (n=2 610) in a meta-analysis to determine the accuracy and impact of breast MRI in the context of local staging, with a focus on detection of multifocal and/or multicentric cancer not identified on conventional imaging. MRI detected additional disease in 16% of women with breast cancer. The accuracy differed according to the reference standard (p=0.16), from 99% to 86% as the quality of the reference standard increased. The overall summary estimate for positive predictive value (PPV) was 66% (95%CI 52-77%). True positive to false positive ratio was 1.91 (95%CI 1.09–3.34). Due to MRI-detected lesions, conversion from wide local excision (WLE) to mastectomy was 1.1% (95% CI 0.3–3.6%), while conversion from WLE to more extensive surgery was 5.5% (95%CI 3.1–18.3%). The authors concluded that MRI staging causes more extensive breast surgery in an important proportion of women by identifying additional cancer. There is a need to reduce the false positive rate in MRI detection.

The COMICE trial (Comparative Effectiveness of Magnetic Resonance Imaging in Breast Cancer) [81] evaluated whether adding a MRI scan to conventional triple assessment (mammogram, US and biopsy) assisted loco-regional staging, and thereby reduced re-operation rates, for patients with primary breast cancer scheduled for wide local excision. In this trial, the MRI group of women was more likely to proceed to mastectomy instead of the previously planned wide local excision (7% vs. 1%), with no difference in re-operation rates (19% in both groups, OR 0.96, 95% CI 0.75–1.24) within 6 months after randomization. The results of the COMICE trial suggest no significant benefit in terms of reduction in re-operation rates by the addition of MRI to conventional triple assessment for this patient group.

MRI is also able to detect previously unidentified metastases, including those that were non-skeletal [54]. When the field was extended to include the pelvis, CT had a higher diagnostic accuracy in detecting bone metastases than scintigraphy [54].

Recommendations

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).

3.3.3 Axillary ultrasonography

For patients with early invasive breast cancer, staging of the ipsilateral axilla is essential for deciding what local and systemic treatments are subsequently required [82].

Two prospective cohort studies showed that axillary ultrasonography (AUS) is a specific procedure for the detection of axillary lymph nodes [83, 84]. Altinyollar et al. performed US of the axillary, infraclavicular and supraclavicular region in 100 consecutive patients with breast cancer [83]. Specificity and sensitivity for detecting metastatic lymph nodes were 92% and 79% respectively. In the study of Podkrajsek et al., 165 patients with breast cancer and clinically negative axilla underwent AUS (and US-guided fine-needle aspiration biopsy if suspicious lymph nodes) [84]. A specificity and sensitivity of 89% and 58% were found.

NICE [82] included 8 case series and one meta-analysis [85] with pooled estimates based on 16 case series (Table 28, Appendix 5.2.2.). The staging performance of US-guided FNAC showed a mean sensitivity of

43% and a mean specificity of 100%, a PPV of 99% and a negative predictive value (NPV) of 72%. The meta-analysis included only patients in whom it was possible to obtain biopsy material by US; the pooled sensitivity was 75.0% and the pooled specificity was 98.3%.

Recommendation

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

3.3.4   PET scan

In the KCE report on the use of PET scan [38], one systematic review and four additional primary studies evaluated PET for staging axillary lymph nodes (Table 29, Appendix 5.2.3.). Two studies used axillary lymph node dissection (ALND) with sentinel lymph node biopsy (SLNB) as reference standard, one study used only ALND and the fourth study used ALND or SLNB plus ALND. When ALND was used as reference, PET yielded a sensitivity that ranged between 40% and 93%, with a specificity that ranged between 87% and 100%. When ALND + SLNB were used as reference standard, sensitivity decreased to 20-50%, while specificity did not change (82-100%). Since prevalence of node-positive disease approximated 33-64%, 36-67% patients with negative PET would have undetected axillary disease if further tests were not undertaken.

The systematic review conducted by Sloka et al. [86] included 19 studies for staging axillary lymph nodes in patients with breast cancer. Due to the high heterogeneity between studies, planned meta-analysis was not performed. Particularly, reference standards were quite different between studies (histology via ALND, SLNB, histology + ALND, SLNB + histology via ALND). In 3 high-quality studies, i.e. studies with broad generalisability and no significant flaws in research methods, sensitivity ranged between 61% and 94%, while specificity ranged between 80% and 98%.

Four additional primary studies [87-90] were retrieved by our own literature search. Ueda et al. [89] included 183 patients with primary operable breast cancer that underwent PET/CT and AUS followed by SLNB and/or ALND for axillary staging. Using visual assessment of PET/CT images, PET/CT yielded a sensitivity of 58% (95%CI 44-70%) and a specificity of 95% (95%CI 89-98%). When a cut-off of SUV was set at 1.8, sensitivity and

specificity were 36% (95%CI 24-49%) and 100% (95%CI 96-100%), respectively. On the other hand, the diagnostic performance of AUS was not so different, with a sensitivity of 54% (95%CI 31-55%) and a specificity of 99% (95%CI 95-100%). With the combination of PET/CT (visual assessment) and AUS, sensitivity and specificity changed to 64% (95%CI 51-76%) and 94% (95%CI 88-97%) respectively.

Veronesi et al. [90] enrolled 236 patients with breast cancer and clinically negative axilla undergoing PET/CT before surgery. In all patients, SLNB was carried out after identification through lymphoscintigraphy. Patients also underwent ALND in cases of positive FDG-PET or positive SLNB. The results of PET scan were compared with histopathology of SLNB and ALND. In all, 103 out of the 236 patients (44%) had metastases in axillary nodes. Sensitivity of PET/CT was low (37%, 95%CI 28-47%), but specificity was acceptable (96%, 95%CI 91-99%). Comparatively, sensitivity and specificity of SLNB were 96% (95%CI 90-99%) and 100% (95%CI 96-100%), respectively.

Gil-Rendo et al. [87] conducted a prospective study including 275 women with breast cancer. In a first group (150 women), ALND was performed regardless of PET results. In a second group (125 women), the axillary examination was complemented by SLNB only in women without pathological axillary uptake on PET scan. In the first group, the sensitivity and specificity of PET for detecting axillary lymph nodes were 90% (95%CI 83-97%) and 98% (95%CI 93-99%) respectively. PET detected axillary involvement in 64 of 71 patients (7 false negatives) and correctly diagnosed 78 of 79 patients without axillary metastases.

Finally, Kumar et al. [88] conducted a prospective study in 80 women with a histological diagnosis of breast cancer and clinically negative axillary lymph nodes, in order to assess the diagnostic efficacy of PET in detecting axillary lymph nodes. Overall, 36 out of the 80 patients (45%) had metastases in axillary lymph nodes. Sensitivity of PET was very low (44%, 95%CI 28-62%), whereas specificity was good (95%, 95%CI 83-99%).

Shie et al. [91] conducted a systematic review comparing PET and bone scintigraphy for the detection of bone metastases from breast cancer. Three studies presented patient-based data, whereas the other 3 studies reported lesion-based data. Reference standards were CT, MRI or bone biopsy with clinical follow-up longer than 6 months. The pooled patient-based sensitivity and specificity of PET were 81% (95%CI 70-89%) and

93% (95%CI 84-97%), respectively. For bone scan, the pooled sensitivity was 78% (95%CI 67-86%), while specificity was 79% (95%CI 40-95%).

In addition to this high-quality review, 15 small comparative studies or case series were identified. These were generally of poor to medium quality and many were retrospective studies.

One prospective [92] and one retrospective cohort study [93] were identified that studied the role of PET scan in the evaluation of metastatic breast cancer. Nakai et al. [93] compared the diagnostic efficacy of PET and bone scintigraphy for the evaluation of osteoblastic bone metastases in patients with breast cancer. The sensitivity and specificity of bone scintigraphy were 78% (95%CI 64-88%) and 82% (95%CI 65-92%) respectively, and those of PET were 80% (95%CI 66-89%) and 88% (95%CI 71-96%) respectively. Uematsu et al. [92] compared PET scan to bone scanning with SPECT for the evaluation of bone metastases. In the lesion-by-lesion analysis (n = 900), the sensitivity and specificity were 85% and 99% respectively for SPECT, and those of PET were 17% and 100% respectively (95% CI were not provided). However, both studies suffered from methodological flaws. In the study of Nakai et al., the reference standard was not applied to all included patients [93], whereas the study of Uematsu et al. only included 15 patients [92].

MRI and FDG-PET were equal to or better than scintigraphy in visualising bone metastases, other than osteoblastic lesions, but whole body MRI was better than FDG-PET in detecting distant metastases, particularly in abdominal organs, brain and bone.

Recommendations

- **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).**

3.4 Treatment of non-invasive breast cancer

3.4.1 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 [66]. Therefore, when ALH/LCIS is found within or near the margins of a wide excision specimen, re-excision is not necessary [94, 95]. On the other hand, clear margins do not exclude the presence of residual ALH/LCIS elsewhere in the breast.

The presence of ALH/LCIS in a core biopsy has a totally different meaning. Since only a minority of ALH/LCIS is associated with microcalcifications, these lesions are not visible on imaging, and hence are not the targeted lesion, but merely a coincidental finding.

Multidisciplinary discussion is essential as the abnormality identified radiologically may not be represented in the core biopsy [95]. Furthermore, at present it is not yet known whether ALH/LCIS diagnosed via a targeted core biopsy of a mammographic abnormality carries the same (low) risk as ALH/LCIS encountered serendipitously in an excision specimen. Therefore, these cases must be managed cautiously, and a surgical diagnostic excision might be considered. Following a diagnosis of ALH/LCIS – even if completely excised – careful follow-up is indicated [66]. As these lesions are only recognized to constitute a separate entity for about a decade, no large follow-up studies are available. Indeed, such lesions were until recently considered as DCIS and treated accordingly. Many authorities advise to continue to do so. This means that when these lesions are encountered in a core biopsy, complete excision is advocated.

If margins are not free, re-excision may be considered. Following surgical excision, radiotherapy and hormonal therapy may be administered.

Recommendations

- **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).**

3.4.2 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.

3.4.2.1 Surgery

1. Different well-established surgical procedures for the treatment of early breast cancer are available to eradicate the primary tumour and any local extension [96]: wide local excision (excision of a tumour with a margin free of both invasive and in situ disease), segmental excision or sector resection (as above, but the excision incorporates tissue from the nipple right out to the periphery of the breast in a segmental shape), quadrantectomy (involves a similar excision to segmental excision but a whole quadrant of the breast is removed), and mastectomy (refers to removal of the entire breast). Wide local excision, partial mastectomy, quadrantectomy and segmentectomy are usually referred to as breast conserving surgery (BCS).

2. Our recommendations are completely based on existing guidelines [82] (Table 30, Appendix 5.3.1.). One additional meta-analysis of clinical trials that examined BCS with RT for the treatment of DCIS was identified [97]. However, due to the absence of a quality appraisal of the included studies, this meta-analysis was not considered here.

3. The choice of BCS versus total mastectomy (with the option for reconstruction) is based on a sub-analysis of a RCT and a meta-analysis of observational studies [18], that showed similar mortality rates at 5 years for both procedures.

4. Multicentricity and residual disease (positive margins) are contraindications for local wide excision [66]. Complete resection of the lesion should be achieved. Indeed, studies have shown that positive or indeterminate resection margins increase the risk of local recurrence [98].

5. The best available evidence for the optimal surgical resection margin was drawn from 32 observational studies described in the NICE guideline [82]. There was no consistency whether to use wide tumour-free resection margins or smaller margins together with radiotherapy. Most studies agree that margins containing tumour cells are associated with local recurrence or bear the risk of residual cancer. There is agreement that the risk of local recurrence is reduced with very wide margins, e.g. more than 10 mm of tumour-free tissue. Nevertheless, the wider the margin, the more breast tissue is removed and the greater the detrimental effect on cosmesis. When margins of 2 mm or more are achieved, local recurrence rates of 2% (with radiotherapy) to 11% (without radiotherapy) are reported [82].

6. Immediate breast reconstruction is an acceptable procedure that does not disadvantage patients compared to delayed reconstruction. With respect to psychological outcomes, one systematic review of observational studies suggested that better psychological outcomes are achieved in patients treated with immediate reconstruction compared to delayed reconstruction [99]. Further observational studies reported similar findings [100, 101]. High rates of acceptable cosmetic results were also reported by observational studies. Two systematic

reviews of observational studies [99, 102] suggested that immediate reconstruction may be associated with a higher rate of complications compared to delayed reconstruction. In the same way, no reliable evidence was identified to suggest that recurrence or survival differs in patients treated with immediate reconstruction compared to those receiving delayed reconstruction.

7. By definition, DCIS is pre-invasive and does not have the potential to spread to regional lymph nodes [103]. However, a significant proportion of patients with larger volume and higher grade DCIS diagnosed on imaging and core needle biopsy will be found to have invasive disease. Therefore, these women will need an assessment of regional lymph nodes status. Axillary clearance can be considered only for large or stage III DCIS [66, 98, 104].

Recommendations

- **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).**

3.4.2.2 Sentinel lymph node biopsy

SLNB is a targeted technique to identify and remove the sentinel lymph node(s) (SLN), causing minimal disruption to the axilla. SLNB is a less invasive axillary staging technique than ALND and has been shown to reduce the complication rate [82] (Table 30, Appendix 5.3.1.)

Currently, there is insufficient evidence to support the routine use of SLNB in patients with DCIS. Ansari et al. [103] conducted a meta-analysis (of observational studies) of the incidence of SLN metastases in patients with DCIS. This analysis showed that the frequency of SLN positivity in patients with a preoperative diagnosis of DCIS ranged from 0 to 16.7%. The estimate for the incidence of SLN metastases in patients with a preoperative diagnosis of DCIS was 7.4% (95% CI 6.2- 8.9%) compared with 3.7% (95% CI 2.8-4.8%) in patients with a definitive (postoperative) diagnosis of DCIS alone. This was a significant difference with an odds ratio of 2.11 (95%CI 1.15-2.93).

There was no evidence to suggest a correlation between the rate of positive SLN and DCIS grade or DCIS size. It was not possible to reliably estimate from the studies identified the proportion of patients with DCIS and positive SLN who had further axillary nodal involvement, because of the small numbers of patients in the series. None of the selected studies (all retrospective) reported changes to treatment plans as a result of staging by SLNB.

Evidence on a subset of patients with a biopsy diagnosis of DCIS who were at high risk of an invasive component was reviewed and suggested that a palpable mass, a mammographic mass, a high-grade DCIS and a large size were associated with a significant risk of invasive disease in the final resection specimen [103]. SLNB can be considered for high-grade DCIS, when mastectomy with or without immediate reconstruction is planned [105, 106].

Recommendations

- **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).**

3.4.2.3 Radiotherapy

In a Cochrane systematic review, Goodwin et al. evaluated the addition of RT to BCS for the treatment of DCIS [107] (Table 31, Appendix 5.3.2.). Four RCTs involving 3 925 women were reviewed. Meta-analysis confirmed a statistically significant benefit from the addition of RT on all ipsilateral breast events (hazard ratio [HR] 0.49; 95%CI 0.41-0.58, p<0.00001), ipsilateral invasive recurrence (HR 0.50; 95%CI 0.32-0.76, p=0.001) and ipsilateral DCIS recurrence (HR 0.61; 95%CI 0.39-0.95, p=0.03). All analyzed subgroups benefited from addition of RT, including women having small DCIS lesion (less than 10 mm). Nine women require treatment with RT to prevent one ipsilateral breast recurrence.

However, no difference in 8-year and in 10-year overall survival was found in 2 RCTs (NSAPB and EORTC respectively) between patients treated for DCIS with local excision alone or local excision plus radiotherapy (95% in both groups).

Recommendation

- **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).**

3.4.2.4 Endocrine therapy

The systematic literature review conducted by CCO [108] retrieved two randomized trials that investigated the use of tamoxifen in patients with DCIS who had undergone BCS and adjuvant radiotherapy (Table 32, Appendix 5.3.3.). The NSABP B-24 trial compared tamoxifen versus placebo in 1 804 women [51, 52] while the UKCCCR trial included 1 576 patients [53].

The NSABP B-24 trial [51, 52] randomized women with DCIS after surgery to 5 years of tamoxifen or placebo. The cumulative 7-year incidence of ipsilateral or contralateral breast malignancy was lower for patients in the tamoxifen group versus those in the placebo group (10% vs. 17%, p=0.0003). The overall 7-year survival rate was 95% for both groups. The recurrence rate in those with negative margins (74% of all patients) was lower and the effect of tamoxifen less substantial. A subgroup analysis on ER-positive DCIS (77% of all patients) was done. The risk ratio (RR) of recurrent or new breast pathology with tamoxifen was 0.41 (95%CI 0.25-0.65).

Results also indicated that adjuvant tamoxifen is optimally given for a period of about 5 years, the majority of patients being disease-free at the time they discontinue tamoxifen.

In the UKCCCR trial [53], 1 576 patients were included, with 794 patients receiving tamoxifen and 782 not. Only 34% of the tamoxifen group and 32% of the no-tamoxifen group received radiation. Of the 794 patients randomized to receive tamoxifen, 11% stopped taking the drug prematurely. After a median follow-up of 52.6 months, there was no statistically significant difference in the occurrence of ipsilateral (6% vs. 4%, p=0.23) or contralateral (1% vs. 2%, p=0.30) invasive carcinoma or DCIS, but there was a difference in the overall incidence of DCIS (ipsilateral and contralateral combined) (HR 0.68; 95%CI 0.49-0.96) favouring the tamoxifen group.

The benefits and harms of endocrine therapy should be discussed with women with DCIS, and treatment decisions should be based on individual circumstances.

Recommendation

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

3.4.3 Paget's disease

Paget's disease of the breast is an eczema-like change in the skin of the nipple, almost always caused by an underlying breast cancer (either DCIS or invasive cancer) [82].

The NICE guideline (2009) [82] reviewed 11 observational studies providing data on breast cancer recurrence in patients treated with mastectomy or BCS for Paget's disease (Table 33, Appendix 5.4.1.). In a prospective study, 61 patients with Paget's disease without associated invasive

disease were treated with a cone excision and radiotherapy [109]. At a median follow-up of 6.4 years, 4 patients developed a local recurrence. One patient with an invasive local recurrence died of disseminated breast carcinoma. The 5-year local recurrence rate was 5.2% (95%CI 1.8 – 14.1%). In rare and selected cases, such as Paget's disease limited to the nipple or surrounding skin, radiotherapy alone may be sufficient [110]. In these cases, surgery could be avoided.

In 3 out of 4 studies in which survival data were reported for both mastectomy and BCS, post-mastectomy breast cancer-specific survival was superior [111-114]. A single study statistically compared survival following mastectomy or BCS and found no statistical difference in breast cancer-specific survival at 15 years following treatment [115].

However, these cases should first be discussed in the multidisciplinary team (MDT).

Patients with Paget's disease and underlying DCIS or invasive breast cancer should be treated according to the respective recommendations (see above).

Recommendations

- **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).**

3.5   Treatment of early invasive breast cancer

For all women with early invasive breast cancer, treatment may consist of the following components [82]:

- neoadjuvant systemic therapy
- surgery to the breast and surgery to the axilla
- locoregional radiotherapy
- adjuvant chemotherapy
- adjuvant endocrine treatment if hormone receptor positive.

However, this treatment is multidisciplinary and should therefore be discussed on an individual basis in the multidisciplinary team.

Recommendation

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

3.5.1   Neoadjuvant treatment

A Cochrane review [116] aimed to assess the effectiveness of preoperative chemotherapy in women with operable breast cancer (Table 34, Appendix 5.5.1.). This review, identifying 14 RCTs involving 5 500 women, revealed no difference in overall survival and disease-free survival for women receiving either preoperative or postoperative chemotherapy (HR 0.98; 95%CI 0.87-1.09; p=0.67; no heterogeneity). Preoperative treatment increases the possibility for BCS because of shrinkage of the tumour before surgical intervention (RR 0.82; 95%CI 0.76-0.89), yet at the associated cost of slightly increased locoregional recurrence rates (HR 1.12; 95%CI 0.92-1.37; p=0.25; no heterogeneity). Pathological complete response was associated with better survival than residual disease (HR 0.48; 95%CI 0.33-0.69; p < 0.0001). This review suggests safe application of preoperative chemotherapy for downstaging in the treatment of women with early stage breast cancer [116].

Recommendation

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

3.5.2   Surgery to the breast

Several RCTs compared BCS (followed by loco-regional radiation therapy) with total mastectomy and found no difference in survival between the two procedures [18, 117-120] (Table 35, Appendix 5.5.2.). Yang et al. [120] carried out a meta-analysis to determine the effectiveness of BCS or mastectomy for stage I or stage II breast cancer. Globally, 18 RCTs of moderate quality including a total of 9 388 patients were analysed. The meta-analysis

showed that the overall survival at 3, 5, 10, 15 and 20 years and the locoregional recurrence rate at 3, 5, 15 and 20 years were not significantly different between the two groups, but 10-year locoregional recurrence rate increased in the group with BCS. The sensitivity analysis indicated that both overall survival and locoregional recurrence rate were not statistically different between the BCS group and the mastectomy group. Blichert-Toft et al. [117] reported similar results from the 20-year follow-up of the Danish randomized DBCG-82TM protocol. The main analyses were conducted on a subgroup of 793 correctly randomized patients. The 10-year recurrence free survival and 20-year overall survival based on the intention-to-treat principle did not reveal significant differences in outcome between BCS vs. mastectomy (p=0.95 and p=0.10, respectively). In conclusion, long-term data indicate that BCS (followed by loco-regional radiation therapy) in eligible patients proves as effective as mastectomy both regarding local tumour control, recurrence free survival and overall survival.

Breast reconstruction involves the use of a prosthesis or tissue from elsewhere in the body to rebuild a breast shape following mastectomy. Immediate breast reconstruction occurring at the time of initial surgery results in less surgical interventions. Delayed reconstruction requires a subsequent surgical procedure once a woman has recovered from initial surgery and any other adjuvant treatment. This may be a better choice for some women who need radiation to the chest area after mastectomy [96]. Our literature review did not identify any studies comparing the effectiveness of immediate compared with delayed breast reconstruction. Some evidence regarding local recurrence and surgery was available in the SIGN guideline (2003) [18], whereas the NICE guideline (2009) [82] retrieved one systematic review of observational studies [99] suggesting that better psychological outcomes are associated with immediate reconstruction compared to delayed reconstruction. Subsequently published observational studies [100, 101] suggested that psychological outcomes are generally good following immediate reconstruction. No reliable evidence was identified to suggest that recurrence or survival differs in patients treated with immediate reconstruction compared to those who receive delayed reconstruction [82].

All patients eligible for BCS should be fully informed about both options before the choice of surgery is made.

Recommendations

- **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).**

3.5.3 Surgery to the axilla

Axillary surgery is currently required for adequate staging and treatment of early invasive breast cancer. The aims of axillary surgery are to eradicate local disease thereby minimising local recurrence and possibly influencing survival, and to determine prognosis in order to guide adjuvant therapy. Axillary surgery includes techniques, such as sentinel lymph node biopsy (SLNB), axillary lymph node dissection (ALND) or axillary sampling [82, 96].

A large amount of evidence is available on the use of SLNB in breast cancer [66, 82, 106] (Table 36, Appendix 5.5.3.). In 2004, ASCO identified 1 RCT, 4 meta-analyses and 60 controlled trials [106]. A well-conducted systematic review and meta-analysis of 69 studies was further undertaken by Kim et al. [105] with data from over 8 000 patients. The overall SLN localisation rate was 96.4%, the pooled estimate of the false negative rate was 7.0% (95%CI 5.2%-8.8%), the mean proportion of patients with positive SLNs was 42% and the post-test probability negative was 4.6%.

SLNB is indicated in women with primary breast cancer less than 3 cm and clinically and ultrasonographically negative nodes [66, 105, 106]. Appropriately identified patients with negative results from SLNB, when done by an experienced surgeon, do not need completion ALND [106].

The sentinel node is positive if any tumour deposit in the node or in the afferent or efferent lymph vessels is found. Tumour deposits are

categorized as isolated tumour cells (<0.2 mm), micrometastases (0.2–2 mm), or macrometastases (>2 mm) [121].

Isolated cancer cells detected by pathologic examination of the SLN with use of specialized techniques are currently of unknown clinical significance and are not a required part of SLN evaluation for breast cancer at this time. This recommendation is based on a large body of mainly observational evidence [106].

Recommendations

- **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

3.5.3.1 Clinical evidence from RCTs

One RCT published in three papers (American College of Surgeons Oncology Group Z0011 [ACOSOG Z0011] trial)[122-124] compared axillary lymph node dissection (ALND) versus no ALND in women with invasive breast cancer and sentinel lymph node (SLN) metastasis. The aim of the ACOSOG Z0011 study was to examine the impact of ALND on regional control and survival in women with early-stage breast cancer undergoing breast-conserving therapy. The goal was to identify whether ALND can be safely omitted in women with early-stage disease. Evidence from this study is presented in the clinical GRADE Summary of Findings table (Table 60, Appendix 6.1.) and in the clinical evidence table (Table 37, Appendix 5.5.3.).

The trial was a phase 3 non-inferiority trial conducted at 115 sites and enrolled patients from May 1999 to December 2004. The limit for non-inferiority was set at 1.3 for the upper limit of the confidence interval (CI) for the hazard ratio (HR). Patients were women with clinical T1-T2 invasive breast cancer, no palpable adenopathy and *one or two* SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section. No discrimination was made between isolated tumor cells, micrometastasis or macrometastasis in the SLN. All patients underwent lumpectomy and tangential whole-breast irradiation. Patients with SLN metastases identified by SLN dissection (SLND) were randomized to undergo ALND or no further axillary treatment. Those randomized to ALND underwent dissection of ten or more nodes. Systemic therapy was at the discretion of the treating physician. Targeted enrollment was 1 900 women with final analysis after 500 deaths, but the trial closed early as the mortality rate was much lower than expected (94 events in 856 patients). The authors explicitly mentioned that no interim analyses had been performed. Due to the inevitable lack of blinding, the risk of bias of this trial was considered as high for all outcomes, except for survival outcomes.

At a median follow-up of 6.3 years the HR for overall survival was 0.79 (90% CI 0.56 to 1.10), which was in favour of the SLND-alone group and did not cross the pre-specified boundary of 1.3. Five-year overall survival was 92.5% (95% CI 90.0% to 95.1%) with SLND alone and 91.8% (95% CI 89.1% to 94.5%) with ALND and the HR (adjusted for adjuvant therapy [chemotherapy, endocrine therapy, and/or radiation therapy] and age) was 0.87 (90% CI 0.62 to 1.23). Disease-free survival did not differ significantly between the treatment groups. The 5-year disease-free survival was 83.9% (95% CI, 80.2% to 87.9%) for the SLND-alone group and 82.2% (95% CI, 78.3% to 86.3%) for the ALND group (p=0.14). The unadjusted HR for disease-free survival was 0.82 (95% CI 0.58 to 1.17) and the adjusted HR was 0.88 (95% CI 0.62 to 1.25). As for local recurrence and regional recurrence, no statistically significant differences in local recurrence or regional recurrence between the two groups were found at a median follow up time of 6.3 years (local recurrence: RR= 0.51, 95% CI 0.22 to 1.20; regional recurrence in ipsilateral axilla: RR= 1.93, 95% CI 0.35 to 10.46). As for arm morbidities, significant differences were found for wound infections (RR= 0.36; 95% CI 0.18 to 0.70) and axillary seromas

(RR= 0.40; 95% CI 0.25 to 0.65) at 30 days and for axillary paresthesias on various time points (30 days: RR= 0.25 (95% CI 0.18 to 0.34); 6 months: RR=0.28 (95% CI 0.20 to 0.39) and 12 months: RR= 0.23 (95% CI 0.15 to 0.34)), all in favour of the SLND alone group. Lymphedema by subjective report was significantly more common in the ALND group (at 12 months: RR= 0.46 (95% CI 0.26 to 0.82); after 12 months: RR= 0.29 (95% CI 0.16 to 0.51)). By objective assessment of arm measurements, no significant differences on any of the time points were found (30 days: RR= 0.69 (95% CI 0.38 to 1.27); 6 months: RR= 0.72 (95% CI 0.42 to 1.23) and 12 months: RR = 0.58 (95% CI 0.31 to 1.08)). The authors reported 18 brachial plexus injuries (BPI), of which after re-evaluation 10 were classified as axillary paresthesias. Three BPIs occurred after SLND alone, but all of these had resolved at last follow-up, as had 88% of all BPIs. Quality of life was not addressed in this study.

Numerous critics on the ACOSOG Z0011 trial have been formulated[125]:

- the smaller than anticipated sample size (891 patients were enrolled instead of the planned target of 1 900 patients);

- the low event rate (94 deaths were recorded at a median follow-up length of 6.3 years compared to the 500 deaths required to have 90% power to confirm non-inferiority of SLNB alone compared with ALND);

- the older (> 50 years) study population (raising the question of applicability to younger women);

- the largely ER+ study population (raising the question of applicability to women with ER– or HER2+ tumours);

- the applicability to invasive lobular carcinoma, which comprised a minority of the study cohort;

- the length of follow-up;

- the lack of stratification based on the size of SLN metastasis (a higher percentage of the SLN-only cohort had micrometastasis).

Moreover, it is not clear whether these results would apply to patients with larger tumours, more extensive nodal involvement or when whole breast irradiation is omitted.

3.5.3.2   *Clinical evidence from observational studies*

Since patient characteristics in the ACOSOG Z0011 trial did not represent the spectrum of patients who present with breast cancer, an additional search for observational studies was conducted, focusing on the three critical outcomes: 5-year overall survival, 5-year disease free survival and axillary recurrence.

Five-year overall survival

Five observational studies were included that evaluated differences in 5-year overall survival for SLND alone versus completion ALND (Table 38, Appendix 5.5.3. and Table 61, Appendix 6.1.). All these studies were retrospective cohort studies that included a large population of breast cancer women with different characteristics in terms of tumour size (T1-T3), tumour type (including infiltrating ductal carcinoma and infiltrating lobular carcinoma of the breast), type of surgery (BCS or mastectomy) and type of adjuvant treatment (hormonal therapy, chemotherapy, radiotherapy),

Four studies reported outcomes for micrometastases only, one study for macrometastases only and two studies for women who had sentinel lymph nodes involved with micro- or macrometastases (without stratification as did ACOSOG Z0011 trial). As the results from these studies were reported in an inconsistent way (adjusted hazard ratio, 5-year survival estimated by Kaplan-Meier method, number of deaths after 5 years), pooling of treatment effects was not feasible.

The results of the RCT were already described above. From the results of the three observational studies that attempted to adjust for some confounding factors (Yi 2010, Yi 2013, Bilimoria 2009) no conclusion can be drawn in favour of SLND or ALND on 5-year survival.

No conclusions can be drawn either from the observational studies that did not adjust for confounding factors, as the differences in 5-year survival could be due to differences in prognostic factors in the two groups of women.

Five-year disease-free survival

Only one retrospective cohort study (n=861) evaluated 5-year disease free survival in T1/T2, N0 patients with 1 or 2 positive SLNs with

micrometastases or macrometastases (Table 38, Appendix 5.5.3. and Table 62, Appendix 6.1.). Disease-free survival rates did not differ significantly between patients undergoing SLND alone vs. ALND when all patients were evaluated regardless of surgical approach or when evaluating just those undergoing breast conserving surgery (BCS). For patients who underwent BCS, the 5-year DFS rate was 94.3% (95% CI 91.1% to 98.0%) for the SLND-alone group and 93.8% (95% CI 91.4% to 95.5%) for the ALND group. The hazard ratio adjusted for clinical T stage, age, and adjuvant treatment was 0.3 (95% CI 0.1 to 1.1, p=0.06). Multivariate analysis showed that lack of chemotherapy and larger tumours were significantly associated with worse DFS. Such results can be explained by the more favourable clinicopathologic characteristics of patients for whom ALND was omitted.

Axillary recurrence

Eight observational studies were included that evaluated differences in axillary recurrence for SLND alone versus completion ALND (Table 38, Appendix 5.5.3. and Table 63, Appendix 6.1.). Six of these studies were retrospective cohort studies whereas two were prospective. They included either a large population of breast cancer women or very small sample sizes. Patients presented with different characteristics in terms of tumour size (T1-T3), tumour type (including infiltrating ductal carcinoma and infiltrating lobular carcinoma of the breast), type of surgery (BCS or mastectomy) and type of adjuvant treatment (hormonal therapy, chemotherapy, radiotherapy).

Three studies reported outcomes for isolated tumour cells, five studies for micrometastases only, and three studies for macrometastases only.

Axillary recurrence is a rare event in these populations. In some small studies, no participant in either the intervention or the control group, or both, experienced an axillary recurrence. Treatment comparisons are expressed using the risk difference, which allowed all studies to be included, even the small ones[126]. Treatment effects were pooled in a meta-analysis, under the assumption that a difference in prognostic factors between the groups would have no (or a small) impact on the risk of recurrence.

The meta-analysis of the 3 observational studies that assessed axillary recurrence when macrometastases were present in the sentinel lymph

node showed a risk difference of 0.14% (95%CI -0.12% to 0.41%) between patients who underwent SLND alone (range from 0% to 1.2%) and those who underwent ALND (range 0.8% to 10.3% (Figure 17, Appendix 7).

Meta-analyzing the five observational studies that assessed axillary recurrence when micrometastases were present in the sentinel lymph node showed a risk difference of 1.51% (95%CI -0.1.59% to 4.62%) between patients who underwent SLND alone (range from 0% to 5.7%) and those who underwent ALND (range from 0% to 1%) (Figure 17, Appendix 7).

Finally, the meta-analysis of the 3 observational studies that assessed axillary recurrence when isolated tumour cells were present in the sentinel lymph node showed a risk difference of 0.94% (95%CI -0.77% to 2.66%) between patients who underwent SLND alone (range 0% to 2%) and those who underwent ALND (range 0% to 1%) (Figure 17, Appendix 7).

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).

Other considerations

Predictive models for additional positive lymph nodes

Systematic reviews have investigated the probability of non-sentinel lymph node involvement when sentinel node was positive. In a meta-analysis of 25 studies of patients with SLN micrometastases, the pooled overall risk of non–sentinel lymph node involvement was as high as 20%, falling to 9% when the SLN involvement was detected by IHC[127]. The overall risk of non–sentinel lymph node involvement was 12% among patients with isolated tumour cells in the sentinel lymph nodes[128].

Because most patients with SLNB metastases will not have additional positive nodes on completion ALND, several predictive nomograms for estimating the risk of additional positive nodes have been developed in an effort to spare women from unnecessary and potentially morbid surgery: the Memorial Sloan-Kettering Cancer Center (MSKCC)[129] (https://www.mskcc.org/mskcc/html/15938.cfm), Mayo[130] (http://www.mayoclinic.org/breast-cancer/sentinelbiopsy.html), Cambridge[131] and Stanford[132] (https://www3-hrpdcc.stanford.edu/nsln-calculator/). These nomograms include both clinical and pathologic features, such as the size and/or number of the SLN metastases, extranodal extension, the size and/or presence of lymphovascular invasion in the primary tumor, and the size of the metastatic disease in the SLN.

r example, The Memorial Sloan-Kettering Cancer Centre (MSKCC) has developed a nomogram, based on its own data, to estimate the risk of non-SLN metastases after a positive SLNB for individual patients. The nodal metastasis nomogram, designed for patients with primary invasive breast cancer that has already spread to the sentinel lymph nodes, can be used to predict whether cancer has spread to other non-sentinel lymph nodes under the arm. To provide an accurate prediction, this model uses nine variables: frozen section performed, tumour size, tumour type and grade, number of positive sentinel lymph nodes, method of detection in sentinel lymph nodes, number of negative sentinel lymph nodes, lymphovascular invasion, multifocality and oestrogen receptor status[129, 133].

What is the current position of international practice guidelines?

- The NCCN has not changed their guidelines and continues to recommend completion ALND for all women with positive sentinel nodes until additional randomized trial results are available, but mentions specific situations[134].
  - For women with three or more positive SLNs, performing ALND is recommended.
  - For women with one or two positive sentinel nodes, who will be treated with whole breast radiation, ALND is suggested. However, for women with T1, hormone receptor positive tumours, who are comfortable with some level of uncertainty about long-term outcomes, avoidance of completion ALND is an option.
  - A distinction can be made between isolated tumour cells, micrometastases, and macrometastases, in terms of clinical management. Omission of the ALND can be considered if the tumour burden appears low (e.g., in cases with isolated tumour cells or micrometastases) when whole breast radiation with high axillary tangents is planned. ALND can also be considered as optional for elderly women or patients with serious co-morbid conditions. Women who are having mastectomy rather than breast conserving therapy should be counselled that they will need completion ALND if the SLNB is positive, in order to determine the need for post-mastectomy radiation. In addition, patients having a mastectomy and those who underwent neoadjuvant chemotherapy were excluded from the Z-011 trial, and therefore results of this trial could not be extrapolated to these patients.

  - When completion ALND is omitted in patients with a positive SLNB, whole breast radiotherapy is indicated. If partial breast irradiation is planned, completion ALND should be performed.
- The 12th St Gallen International Breast Cancer Conference supported that isolated tumour cells, and even metastases up to 2 mm (micrometastases) in a single sentinel node, were not considered an indication for axillary dissection regardless of the type of breast surgery carried out. The Panel accepted the option of omitting axillary dissection for macrometastases in the context of lumpectomy and radiation therapy for patients with clinically node negative disease and 1–2 positive sentinel lymph nodes as reported from ACOSOG trial Z0011. The Panel, however, was very clear that this practice, based on a specific clinical trial setting, should not be extended more generally, such as to patients undergoing mastectomy, those who will not receive whole-breast tangential field radiation therapy, those with involvement of more than two sentinel nodes, and patients receiving neoadjuvant therapy.

New evidence from publication found after the search date (IBCSG trial 23–01)[135]

In this multicentre, randomised, non-inferiority, phase 3 trial, patients were eligible if they had clinically non-palpable axillary lymph node(s) and a primary tumour of 5 cm or less and who, after sentinel-node biopsy, had one or more micrometastatic (≤2 mm) sentinel lymph nodes with no extracapsular extension. The primary endpoint was disease-free survival. Non-inferiority was defined as a hazard ratio (HR) of less than 1.25 for no axillary dissection versus axillary dissection. Accrual started on April 1, 2001, and closed on Feb 28, 2010, after 934 patients had been randomised. The intention-to-treat population included 931 patients (464 patients were in the axillary dissection group and 467 patients were in the no axillary dissection group). After a median follow-up of 5.0 (IQR 3.6–7.3) years, 5-year disease-free survival was 87.8% (95% CI 84.4–91.2) in the group without axillary dissection and 84.4% (95% CI 80.7–88.1) in the group with axillary dissection (log-rank p=0.16. Disease-free survival in the group without axillary dissection was non inferior to the axillary dissection group (HR for no axillary dissection vs. axillary dissection was 0.78, 95% CI 0.55–1.11, non-inferiority p=0.0042). Five-year overall survival was 97.6% (95% CI 96.0−99.2) in the group with axillary dissection and 97.5%

(95.8−99.1) in the group without axillary dissection (HR 0.89, 90% CI 0.52–1.54; log-rank p=0.73). Patients with reported long-term surgical events (grade 3–4) included one sensory neuropathy (grade 3), three lymphoedema (two grade 3 and one grade 4), and three motor neuropathy (grade 3), all in the group that underwent axillary dissection, and one grade 3 motor neuropathy in the group without axillary dissection. One serious adverse event was reported, a postoperative infection in the axilla in the group with axillary dissection.

Authors concluded that axillary dissection could be avoided in patients with early breast cancer and limited sentinel-node involvement with no adverse effect on survival. Most patients (92%) in this study had tumours smaller than 3 cm, received breast conserving surgery (91%), and had adjuvant systemic therapy (96%), and thus these results are most directly applicable to these patient subpopulations. However, 9% of the patients in this trial received mastectomy. Although numbers are small, subgroup analysis suggested that no axillary dissection might be acceptable for patients undergoing mastectomy provided the invasive component of the breast lesion is small.

Potential alternative to a completion of ALND in patients with a positive SLN: primary regional radiotherapy

Results are awaited from the EORTC 10981-22023 AMAROS trial, which is evaluating the use of axillary radiotherapy as an alternative to axillary dissection in women with involved sentinel lymph nodes. In this trial patients with positive sentinel lymph nodes (any number and any tumour size), including those undergoing conservation surgery or mastectomy, are being randomised to have either axillary clearance or radiotherapy.

Recommendations 2013

- **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).**

3.5.4 Adjuvant therapy

3.5.4.1 Sequencing of adjuvant therapy

In a recent Cochrane review of RCTs evaluating different sequencing of chemotherapy and radiotherapy, no significant differences were found between the various methods of sequencing adjuvant therapy in terms of survival, distant metastases or local recurrence [136]. However, radiotherapy before chemotherapy was associated with a significantly increased risk of neutropenic sepsis (OR 2.96, 95%CI 1.26-6.98) compared with chemotherapy before radiotherapy. Therefore, if both adjuvant chemotherapy and radiotherapy are indicated, the chemotherapy should be given first (Table 39, Appendix 5.5.4.).

Evidence from a meta-analysis of 8 observational studies suggests that locoregional recurrence is more likely if radiotherapy is delayed more than 8 weeks following surgery (OR [interval>8 weeks : interval ≤8 weeks] 1.62; 95%CI, 1.21-2.16) corresponding to an increase in the 5-year loco-regional

recurrence rate from 5.8% in those patients treated within 8 weeks to 9.1% in those patients treated between 9 and 16 weeks after surgery [137].

Similar results were obtained in a retrospective analysis of 2 594 patients receiving adjuvant chemotherapy for stage I and II breast cancer. Five-year overall survival rates were 84%, 85%, 89%, and 78%, (log-rank p=0.013); Relapse-free survival rates were 74%, 79%, 82%, and 69% (log-rank p=0.004) for patients starting chemotherapy 4 weeks or fewer, more than 4 to 8 weeks, more than 8 to 12 weeks, and more than 12 to 24 weeks after surgery, respectively. Lohrisch et al. [138] concluded that 5 year-relapse-free survival and 5 year-overall survival seem to be compromised by delaying chemotherapy more than 12 weeks after definitive surgery.

However, there is conflicting evidence about the higher impact of delaying chemotherapy according to the hormonal receptor status (ER negative or ER positive) [138-141].

Recommendations

- **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).**

3.5.4.2 Radiotherapy

The recommendation to give adjuvant radiotherapy to patients treated with BCS is based on the systematic review of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) and subsequent RCTs [18, 66, 142] (Table 40, Appendix 5.5.5.). Ten trials reported a substantial and significant reduction in local recurrence (mainly in the conserved breast) after adjuvant radiotherapy (p<0.00001). The recurrence rate ratio, comparing those allocated radiotherapy with those not, was about 0.3 in every trial, corresponding to a proportional reduction of 70% [142]. The proportional risk reduction for breast cancer mortality is much less extreme, but highly significant (breast cancer death rate ratio 0.83, SE 0.05, 95%CI 0.75–0.91, 2p=0.0002), indicating a reduction of about one-sixth in the annual breast cancer mortality rate [142].

However, the effect on mortality of radiotherapy of the thoracic wall following mastectomy is less clear [18]. In a systematic review of the EBCTCG of 34 RCTs involving approximately 20 000 women, no reduction of all-cause mortality or breast cancer mortality was found with radiotherapy after mastectomy alone or mastectomy plus axillary clearance [18]. However, radiotherapy did reduce all-cause mortality and breast cancer mortality after mastectomy plus axillary sampling. A recent RCT showed a clear survival benefit of radiotherapy in premenopausal women with node-positive breast cancer treated with modified radical mastectomy and adjuvant chemotherapy [143].

In their large overview of all EBCTCG trials conducted since 1995, Clarke et al. [45] reported that for women with mastectomy, axillary clearance, and node-positive disease, the 5-year local recurrence risks, irradiated versus control, were 4% versus 16% for women with 1-3 involved nodes (reduction 12%, SE 2) and 12% versus 26% for women with 4+ involved nodes (reduction 14%, SE 2). The 15-year local recurrence risk reduction differed more substantially, however, and was 14% and 20% for women with 1-3 and for those with 4+ involved nodes, respectively. The paper published by Overgaard et al. [144] on a subgroup of the DBCG 82 b&c trials confirmed the effectiveness of radiotherapy for women with less than 4 involved nodes. Radiotherapy reduced the 15-year loco-regional failure rate from 51% to 10% (p<0.001) in 4+ positive node patients and from 27% to 4% (p<0.001) in patients with 1-3 positive nodes. Similarly, the 15-year survival benefit after radiotherapy was significantly improved in both patients with 1-3 positive nodes (57% vs. 48%, p=0.03) and in patients with 4+ positive nodes (21% vs. 12%, p=0.03). However, in women having at least two out of three unfavourable criteria (>3 positive nodes, tumour size >5 cm, Grade 3 malignancy), a large absolute reduction in 5-year local recurrence probability (36%) did not translate into any reduction in 15-year breast cancer mortality (0%) [145].

As no RCT evaluated the harm/benefit ratio obtained with post-mastectomy irradiation for only one positive node, this treatment has to be discussed with the patient, taking into account prognostic characteristics of the tumour, the positive node's size, woman's age, her desire to have a breast reconstruction and cardiotoxicity of RT. Altogether, these issues may be clarified in the prospective randomized international SUPREMO trial including patients with 1–3 positive lymph nodes (ISRCTN61145589).

The role of internal mammary chain irradiation is unclear at the moment [146] and is currently being investigated in the EORTC 22922/10925 trial [147]. Patients eligible for internal mammary chain irradiation are to be discussed in the MDT.

For breast cancer patients having primary BCS or mastectomy, the commonest schedule used internationally involves 25 fractions of 2 Gy to a total dose of 50 Gy [82]. The aim of conventional fractionation at 2 Gy per fraction is to minimise late tissue damage whilst maximising tumour control. However, some trials are testing the delivery of an effective dose of radiation in a shorter period in order to increase patient throughput and convenience for rural patients [148, 149]. Two high-quality RCTs [148, 150] were evaluated in a systematic review [151]. Whelan et al. compared two different fractionation regimes (42.5 Gy in 16 fractions and 50 Gy in 25 fractions) while Owen et al. [148] compared three fractionation regimens (39 Gy in 13 fractions, 42.9 Gy in 13 fractions, and 50 Gy in 25 fractions). Hypofractioned radiotherapy did not appear to affect local recurrence free survival (absolute difference 0.4%, 95%CI -1.5% to 2.4%), breast appearance (RR 1.01, 95%CI 0.88 to 1.17), survival at five years (RR 0.97, 95%CI 0.78 to 1.19), late skin toxicity at five years (RR 0.99, 95%CI 0.44 to 2.22), and late radiation toxicity in sub-cutaneous tissue (RR 1.0, 95%CI 0.78 to 1.28). The START Trialists' Group also conducted a RCT comparing two radiotherapy schedules in women with early breast cancer (pT1-3a pN0-1 M0): 50 Gy in 25 fractions of 2.0 Gy over 5 weeks (n=1 105 women) or 40 Gy in 15 fractions of 2.67 Gy over 3 weeks (n=1 110 women) [149]. After a median follow up of 6.0 years (IQR 5.0–6.2) the rate of local-regional tumour relapse at 5 years was 2.2% (95% CI 1.3–3.1%) in the 40 Gy group and 3.3% (95%CI 2.2 to 4.5%) in the 50 Gy group. The authors concluded that fewer, larger fractions are at least as safe and as effective as the 'standard' schedule of 50 Gy in 25 fractions. However, a median follow-up of 5 years is too short to allow assessment of all potential late normal tissue effects such as cardiac damage [149]. The length of follow-up and the evidence are currently insufficient to identify one optimal fractionation schedule.

To reduce the risk of local recurrence after radiotherapy, an additional boost dose of radiation to the tumour bed can be considered. NICE [82] reported results from the European Organisation for Research and Treatment of Cancer trial EORTC 22881–10882, in which participants,

younger than 70 years old, were randomised to a boost radiotherapy dose of 16 Gy to the original tumour bed or no boost. RCT data were consistent in the finding that a boost dose to the tumour bed reduced local recurrence (4.3% in 'boost' arm vs. 7.3% in 'no boost' arm), but had little effect on overall survival. Nevertheless, fibrosis and teleangiectasia tended to be worse in the boost group [152].

Veronesi et al. assessed the role of axillary radiotherapy in the treatment of node negative early breast cancer [153]. No significant differences were found between the axillary radiotherapy group and group receiving no axillary treatment in terms of local recurrence and disease-free survival. In a RCT of Louis-Sylvestre et al., no difference in long-term survival was found after axillary radiotherapy vs. axillary dissection in patients with clinically node-negative invasive breast cancer [154]. Based on these data, axillary radiotherapy cannot be considered routine practice and should be discussed in the MDT on an individual basis.

Recommendations

- **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).**

3.5.4.3 Systemic therapy

Classification of patients for therapeutic purposes

The 12th St Gallen International Breast Cancer Conference (2011) Expert Panel adopted a new approach for the classification of patients for therapeutic purposes based on the recognition of intrinsic biological subtypes within the breast cancer spectrum [155]. For systemic therapy, recommendations were formulated for each of the biological subtypes, since these already incorporate many of the risk factors and response predictors previously considered separately. However, gene expression array information is not always simple to obtain. Consequently, a simplified classification has been adopted. Subtypes defined by clinicopathological criteria are similar to but not identical to intrinsic subtypes and represent a convenient approximation. This approach, summarized in Table 12, uses an immunohistochemical definition of oestrogen and progesterone receptors, the detection of over-expression and/or amplification of the human epidermal growth factor receptor 2 (HER2) oncogene, and the Ki-67 labelling index [156], a marker of cell proliferation, as the means of identifying tumour subtypes [155].

The classification of breast tumours according to the intrinsic subtypes is helpful for estimating the prognosis of breast cancer patients [157]. Nevertheless, there are no data from phase III trials on their role as predictive tools for chemotherapy benefit.

The systemic treatment recommendations summarized in Table 13 mainly recommend endocrine therapy alone for patients with clinicopathologically classified 'Luminal A' disease (except in defined high-risk cases), chemoendocrine therapy for 'Luminal B', the addition of anti-HER2 therapy in the presence of 'HER2 positivity', and a reliance on chemotherapy for most patients with 'Triple negative' disease (e.g. those with invasive ductal carcinoma) [155].

Recommendation

- **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 12 - Surrogate definitions of intrinsic subtypes of breast cancer.[157, 158]

Intrinsic Subtype	Clinico-pathologic definition	Notes
Luminal A	**'Luminal A'** ER and/or PgR positive [48] HER2 negative [159] Ki-67 low (<14%)*	This cut-off point for Ki-67 labelling index was established by comparison with PAM50 intrinsic subtyping [158]. Local quality control of Ki-67 staining 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 [160]. 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 overexpression	**'HER2 positive (non luminal)'** 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 [161] although shown to aid selection of true basal-like tumours, is considered insufficiently reproducible for general use.

Note. This table is based on Goldhirsch et al. (2011) [155], adapted by our GDG
*This cut-off point is derived from comparison with gene array data as a prognostic factor [158]. 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 [162].

Table 13 - 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'*		
Endocrine responsive	Endocrine therapy	
Endocrine nonresponsive	Cytotoxics	Medullary** and adenoid cystic carcinomas may not require any adjuvant cytotoxics (if node negative).

Note. This table is based on Goldhirsch et al. (2011) [155], adapted by our GDG
*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 [163].
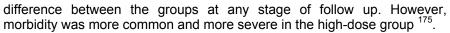
Chemotherapy

In a combined analysis of 2 RCTs, Arriagada et al. found a better 10-year disease-free survival in early breast cancer patients (stage I – III) treated with adjuvant anthracycline-based chemotherapy compared to patients not treated with chemotherapy (65% vs. 60%, p=0.01) [164]. Also, the 10-year distant metastasis rates were significantly better in the active treatment group (23% vs. 28%, p=0.02). However, the 10-year local recurrence rate did not differ significantly between the two treatment groups [164].

Hutchins et al. found a slightly better 10-year overall survival rate in node-negative breast cancer patients treated with adjuvant FAC (cyclophosphamide, doxorubicin, fluorouracil) compared to those treated with adjuvant CMF (cyclophosphamide, methotrexate, fluorouracil) (85% vs. 82%, p=0.03) [165]. However, disease-free survival did not differ significantly, and FAC was associated with greater toxicity. In node-positive breast cancer patients, adjuvant FEC (cyclophosphamide, epirubicin, fluorouracil) was associated with a better 10-year relapse-free survival (52% vs. 45%, p=0.007) compared to adjuvant CMF (cyclophosphamide, methotrexate, fluorouracil) [166]. Toxicity associated with FEC was acceptable.

High level evidence concluded to the superiority of anthracyclines-based chemotherapy on CMF in moderate or high risk breast cancer patients. The EBCTCG 2005 systematic review reported the superiority of anthracycline-based regimens to standard CMF regimens, in reducing breath cancer death rate by about 38% (SE 5) for women younger than 50 years of age and by about 20% (SE 4) for those of age 50–69 years, largely irrespective of the use of tamoxifen and of oestrogen receptor (ER) status, nodal status, or other tumour characteristics [44] (Table 41, Appendix 5.5.6.). Eljertsen et al. [167] concluded that anthracycline-based therapy also resulted in an improvement in both disease free survival (HR 0.84; 95%CI 0.71–0.99) and overall survival (HR 0.79; 95%CI 0.66–0.94) at the 10-year follow-up. Toxicity associated with anthracyclines-based chemotherapy was considered acceptable with adverse events including nausea and vomiting, alopecia, mucositis. The risk of secondary leukaemia and congestive heart failure was similar in both chemotherapy regimens.

However, for patients with HER2 positive breast cancer who receive anti-HER2 therapy, the risk of cardiotoxicity is greatest when trastuzumab is used concurrently with anthracyclines (doxorubicin or epirubicin) [168]. Huybrechts et al. concluded that trastuzumab and anthracyclines should not be used currently in combination except in a well-controlled clinical trial setting with cardiac monitoring [168]. The pooled efficacy data of one year of trastuzumab was stronger when trastuzumab was administered concurrently with a taxane after anthracycline chemotherapy. Disease-free survival was significantly improved with a RR 0.49 (95%CI 0.41 – 0.57) [168].

In a pooled analysis of 9 RCTs, Bria et al. found significant differences in favour of taxanes in terms of disease-free survival in the overall (RR 0.86; 95%CI 0.81 – 0.90) and lymph node-positive population (RR 0.84; 95%CI 0.79 – 0.89), and in terms of overall survival in the overall (RR 0.87; 95%CI 0.81 – 0.83) and lymph node-positive population (RR 0.84; 95%CI 0.77 – 0.92) [169] (Table 41, Appendix 5.5.6.). Further studies which reported overall survival also showed improved overall survival with use of the taxanes [170, 171]. A meta-analysis including 12 studies (N=22 379 participants, N=3 329 deaths) also showed a significant reduction in the risk of death for taxane-based treatment (HR 0.85, 95%CI 0.79 - 0.91, p<0.00001) [172]. The inclusion of a taxane in an anthracycline-based regimen should be considered [82, 173]. However, neutropenia and febrile neutropenia were identified as occurring more frequently in patients in the taxane groups than in the control groups. Primary prophylaxis is recommended for the prevention of febrile neutropenia in patients who have a high risk of febrile neutropenia based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. Clinical trial data support the use of CSF when the risk of febrile neutropenia is in the range of 20% or higher [174]. Secondary prophylaxis with CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome [174].

In a recent systematic review of Farquhar et al. – based on the results of 13 RCTs – no evidence was found to support the routine use of high-dose chemotherapy with autologous stem-cell transplantation in women with early poor-prognosis breast cancer [175]. At six years there was no statistically significant difference between the groups in event-free survival. With respect to overall survival, there was no statistically significant

difference between the groups at any stage of follow up. However, morbidity was more common and more severe in the high-dose group [175].

Fertility may be transiently or permanently affected by cancer treatment or only become manifest later on through premature ovarian failure. Before the induction of the cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists [176].

For pregnant women with breast cancer, neoadjuvant or adjuvant anthracycline-based chemotherapy (FAC) can be given with minimal risks (premature labour and foetal wastage) to the foetus during the second or third trimester [177-179]. Anthracyclines need to be fractionated. Data on the immediate and long-term effects of chemotherapy on the child remain limited [177]. However, two year data did not demonstrate adverse events on the children [180, 181]. Until now, the use of newer therapeutic agents, such as docetaxel and paclitaxel, in pregnant patients is limited to case reports [179, 182, 183]. Given the potential foetal toxicity of methotrexate, CMF should not be used during pregnancy.

Recommendations

- **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.**
- o **Primary prophylactic G-CSF (granulocyte colony-stimulating factor) is recommended if risk of febrile neutropenia is 20% or higher (1A evidence).**

- o **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

Adjuvant treatment with tamoxifen substantially improves the 15-year survival of premenopausal women with ER-positive tumours and of women whose tumours are of unknown ER status [44] (Tables 42 and 43, Appendix 5.5.7.). For ER-positive disease only, 5 years of adjuvant tamoxifen reduces the mortality rate by 31%, largely irrespective of the use of chemotherapy and of age (<50, 50-69, ≥ 70 years), progesterone receptor status, or other tumour characteristics. Five years of treatment is significantly more effective than 1-2 years of tamoxifen [44]. For women with ER-negative and PR-negative tumours, adjuvant tamoxifen must not be given.

In a recent systematic review of Sharma et al., 4 RCTs were identified that studied the addition of LHRH agonists (mainly goserelin) to adjuvant hormonal therapy in premenopausal women with early breast cancer [184]. Overall, these studies demonstrated the efficacy of adjuvant goserelin with or without tamoxifen, in reducing the risk of recurrence and delaying the death. The evidence is insufficient to support LHRH agonists over chemotherapy, or vice versa, regarding recurrence-free survival and overall survival, but LHRH agonists have fewer or less severe adverse effects.

The authors concluded that combined tamoxifen and LHRH agonists may be regarded as a treatment option for premenopausal women with endocrine-responsive disease.

Hackshaw et al. [185] published 12 years follow-up data of 2 700 premenopausal women with operable stage I or II breast cancer, recruited for the ZIPP trial (Zoladex In Premenopausal Patients), evaluating the LHRH agonist goserelin and tamoxifen, given for 2 years. They concluded that 2 years of goserelin treatment was as effective as 2 years of tamoxifen treatment until 15 years after starting therapy. In women who did not take tamoxifen, there was a large benefit of goserelin treatment on survival and recurrence (8.5 fewer breast cancer deaths vs. no goserelin). In women who did take tamoxifen, there was a marginal benefit when goserelin was added (possibly 2.6 fewer deaths). This confirmed previous results, indicating that the addition of tamoxifen and goserelin to adjuvant chemotherapy significantly improved disease-free survival (HR=0.74; 95%CI 0.56 – 0.99; p=0.04) [186].

Aromatase inhibitors (anastrozole, exemestane and letrozole) are alternative options to tamoxifen for ER-positive invasive breast cancer in postmenopausal women [82, 187]. Switching to adjuvant anastrozole from adjuvant tamoxifen showed a statistically significant improvement in disease-free survival (HR 0.66; 95%CI 0.44-1.00; p=0.049), and improved overall survival (HR 0.53; 95%CI 0.28-0.99; p=0.045) compared with continuing on tamoxifen [188]. A meta-analysis of the ABCSG-8 (The Austrian Breast and Colorectal Cancer Study Group), ARNO-95 (German Adjuvant Breast Cancer Group Arimidex/Nolvadex), and ITA (The Italian Tamoxifen Arimidex) trials found improvements in disease-free survival (HR 0.59; 95%CI 0.48-0.74; p<0.0001), distant recurrence-free survival (HR 0.61, 95%CI 0.45-0.83, p=0.002), and overall survival (HR 0.71; 95%CI 0.52-0.98; p=0.04) for women who switched to anastrozole [189]. However, consistent advantage in overall survival has not been observed, particularly for other aromatase inhibitors and in other treatment settings. Moreover, evidence indicates that patients treated with aromatase inhibitors experience a higher incidence of fractures and an increased loss of lumbar spine and hip bone mineral density [82].

The Intergroup Exemestane Study (IES) (n=4 742) compared two to three years of tamoxifen followed by exemestane with two to three years of tamoxifen followed by further tamoxifen, each to a total of five years of adjuvant hormone therapy [190, 191]. At a median follow-up of 55.7 months, disease-free survival was significantly improved in the exemestane arm (HR 0.76; 95%CI 0.6-0.88), but overall survival did not. Overall survival was only significantly improved in ER-positive women (HR 0.83, 95% CI 0.69-1.00 in favour of switching to exemestane).

The Breast International Group (BIG) 1-98 trial compared letrozole versus tamoxifen in 8 028 women. After a median follow-up of 51 months, patients treated with letrozole had significantly better disease-free survival versus those treated with tamoxifen (HR 0.82; 95%CI 0.71-0.95). There was also significant benefit as to time-to-recurrence and time-to-distant-recurrence with letrozole. Overall survival was not significantly different. The Breast International Group (BIG) 1-98 trial also compared 2 years of treatment with one agent followed by 3 years of treatment with the other [192]. At a median follow-up of 71 months after randomization, disease-free survival was not significantly improved with either sequential treatment as compared with letrozole alone (HR for tamoxifen followed by letrozole, 1.05; 99%CI 0.84-1.32; HR for letrozole followed by tamoxifen, 0.96; 99%CI 0.76-1.21). The updated analysis of monotherapy showed that there was a non-significant difference in overall survival between women assigned to treatment with letrozole and those assigned to treatment with tamoxifen (HR for letrozole, 0.87; 95%CI 0.75-1.02; p = 0.08).

Patients who started tamoxifen at baseline should consider a switch to an oral aromatase inhibitor after 2-3 years of tamoxifen therapy, especially if they are at high-risk for recurrence (node positive, grade 3, HER2 positive, LVI or large tumour size).

The MA-17 trial showed that extended adjuvant treatment with letrozole (after 5 years of standard tamoxifen treatment) significantly reduces the risk of recurrent breast cancer regardless of the patient's nodal status or receipt of prior chemotherapy [187, 193]. Above this, letrozole was associated with a significant improvement in overall survival in women with node-positive disease.

In the absence of good clinical data, but as a matter of precaution, it is current practice to give adjuvant hormonal treatment after chemotherapy and not concomitantly [194]. Albain et al. [195] supported this recommendation, reporting that chemotherapy with CAF (cyclophosphamide, doxorubicin, and fluorouracil) plus tamoxifen given sequentially was more effective adjuvant therapy for disease free survival and overall survival in postmenopausal patients with endocrine-responsive, node-positive breast cancer than is tamoxifen alone (Table 44, Appendix 5.5.7.).

Recommendations

- **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):**

  o **tamoxifen (for 5 years),**

  o **anastrozole (for 5 years) or letrozole (for 5 years),**

  o **or tamoxifen (for 2 - 3 years) followed by an aromatase inhibitor (up to a total of five years of hormone therapy),**

  o **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

The humanised monoclonal antibody trastuzumab targets the extracellular domain of HER2. Its use in the adjuvant therapy of HER2-positive breast cancer reduces the risk of relapse by about 50% and the risk of death by about 30% [82]. Dahabreh et al. [196] conducted a systematic review and meta-analysis to compare treatment outcomes for HER2–positive breast cancer patients receiving adjuvant chemotherapy with or without trastuzumab (Table 45, Appendix 5.5.7). The authors identified five trials reporting outcomes on 13 493 women. Fixed-effects analysis showed higher disease-free survival for trastuzumab treated patients (RR 0.62; 95%CI 0.56–0.68), lower mortality (RR 0.66; 95%CI 0.57–0.77), lower locoregional recurrence (RR 0.58; 95% CI 0.43–0.77), and lower distant recurrence (RR 0.60; 95%CI 0.52–0.68). However, in the trastuzumab arm, patients had a higher risk for congestive heart failure (RR, 7.60; 95%CI, 4.07–14.18) and for left ventricular ejection fraction decline (RR, 2.09; 95%CI, 1.84–2.37). A higher risk for central nervous system metastasis as the first recurrence event (RR, 1.60; 95%CI, 1.06–2.40) was also reported in this group.

KCE published a report on the use of trastuzumab as an adjuvant treatment in women with early-stage breast cancer [168]. According to the identified evidence, the authors concluded that – based on the criteria from the HERA trial (T > 1cm and/or previously chemotherapy) [197, 198] – a 1 year treatment with adjuvant trastuzumab is usually effective in women with early-stage HER2 FISH-positive breast cancer, a left ventricular ejection fraction of ≥ 55% and without cardiovascular exclusion criteria [168]. However, this treatment was not found to be cost-effective in all cases (stage I patients over 60 years, stage II patients over 70 years, and stage III patients over 80 years). A nine weeks treatment with adjuvant trastuzumab according to the criteria from the FinHer trial was found to be cost-saving [168]. It should be stressed, however, that the optimal treatment regimen and duration is unknown at present.

A safety and efficacy meta-analysis identified an increased risk of grade III-IV congestive heart failure, asymptomatic left ventricular ejection fraction and brain metastases with trastuzumab compared with controls, along with prolonged disease-free survival, prolonged distant disease-free survival and prolonged overall survival with trastuzumab [199]. In view of the safety profile of trastuzumab, cardiac function should be monitored during treatment with trastuzumab [168].

ASCO and the College of American Pathologists recently published a guideline on HER2-testing in invasive breast cancer [159]. Besides a practical testing algorithm, this guideline also contains an interesting discussion on HER2-testing variation and tissue handling requirement. An analogue discussion can be found in the European guidelines [200].

It is important to note that, based on the phase III multicenter study BCIRG006, in 2008 the US Food and Drug Administration approved a new treatment consisting of the chemotherapeutic agents Taxotere® (docetaxel) and carboplatin combined with Herceptin® (trastuzumab) (TCH) for the adjuvant treatment of HER2-positive early breast cancer.

This regimen is not currently approved by the European Medicines Agency (EMA).

Update 2013

Previous studies showed that Trastuzumab improves survival in the adjuvant treatment of HER-positive breast cancer, although combined therapy with anthracycline-based regimens has been associated with cardiac toxicity. This update reports the scientific evidence about the efficacy and safety of a new nonanthracycline regimen with trastuzumab.

One RCT [201] was identified that compared trastuzumab with adjuvant non-anthracycline chemotherapy versus trastuzumab with adjuvant anthracycline–taxane chemotherapy among breast cancer patients with HER-2 positive invasive (non metastatic) breast cancer (Table 46, Appendix 5.5.8). The trial randomly assigned 3 222 women with HER2-positive early-stage breast cancer to receive doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T: Group 1), the same regimen plus 52 weeks of trastuzumab (AC-T plus trastuzumab: Group 2), or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH: Group 3). As the research question solely concerns the comparison between the TCH group (Group 3) and the AC-T plus trastuzumab group (Group 2), only the results of these comparisons will be discussed. The trial was considered low risk of bias for survival outcomes (overall survival and disease free survival) and high risk of bias for adverse events. The Summary of Findings table is reported in Appendix 6.2. (Table 64).

At a median follow up of 65 months, no significant differences in efficacy (disease-free or overall survival) were found between the two trastuzumab regimens (overall survival of group 3 versus group 2: RR=1.20; 95%CI 0.93-1.56; disease-free survival: RR=1.16; 95%CI 0.97-1.38). The same applies to the overall and disease-free survival rates. The authors mention, however, that their study was not powered to detect equivalence between these two regimens. The occurrence of congestive heart failure (New York Heart Association grade 3 or 4) and cardiac dysfunction (defined as >10% relative reduction in left ventricular ejection fraction) was significantly lower in the group receiving TCH plus trastuzumab than in the group receiving AC-T plus trastuzumab (RR=0.19; 95%CI 0.07-0.55, and RR=0.50; 95%CI 0.40-0.63, respectively). With respect to other adverse effects a significant difference favouring TCH (Group 3) compared with AC-T plus trastuzumab

(Group 2) for arthralgias, myalgias, the hand–foot syndrome, stomatitis, and vomiting. Significant differences in sensory and motor neuropathies, nail changes, and myalgias also favored the TCH group (Group 3). The incidences of neutropenia and leukopenia were significantly lower in the TCH group (Group 3) than in the group receiving AC-T plus trastuzumab (Group 2), whereas the incidences of anemia and thrombocytopenia were significantly lower in the group receiving AC-T plus trastuzumab (Group 2) than in the TCH group (Group 3).

The authors concluded that the addition of 1 year of adjuvant trastuzumab significantly improved disease-free and overall survival among women with HER2-positive breast cancer. The risk–benefit ratio favored the non-anthracycline TCH regimen over AC-T plus trastuzumab, given its similar efficacy, fewer acute toxic effects, and lower risks of cardiotoxicity and leukemia.

Conclusions

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).

Other considerations

On February 2012, the EMA gave the authorization for an extension of the indication to include the use of Herceptin as part of a treatment regimen in combination with docetaxel and carboplatin (EMA, Herceptin - EMEA/H/C/000278 -II/0059). Following the introduction of this dossier to the EMA, the package leaflet has been updated. The main changes agreed in the product information focused on:
- the extension of the indication (Herceptin is indicated for the treatment of patients with HER2 positive early breast cancer in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin),
- the cardiotoxicity of the product (that is higher when Herceptin was administered after anthracycline-containing chemotherapy),
- the need for cardiac assessment (for early breast cancer patients, cardiac assessment, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration. In patients who receive anthracycline containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administration, or longer if a continuous decrease of LVEF is observed),
- the risk of neutropenia (that may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy).

Uncertainty remains on the necessity to include anthracyclines in adjuvant chemotherapy regimens in HER2 positive invasive non metastatic breast cancer. Until more solid and confirmatory data become available, both antracycline-taxane regimens, and non-anthracycline chemotherapy (TCH) combined with trastuzumab, remain valid options.

A matter of debate is the timing of trastuzumab initiation with respect to chemotherapy. Some studies have used trastuzumab sequentially after adjuvant chemotherapy was finished. Other studies initiated trastuzumab after anthrayicline, but together with taxanes. A randomized phase III trial, the N9831 study, has compared concurrent and sequential use of trastuzumab. The updated results showed a higher benefit in DFS from concomitant trastuzumab rather than from sequential schedule [202].

Patients representatives emphasized the need to obtain an in-depth information about the benefits and the risks of each therapeutic alternative.

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

A recent systematic review identified 3 RCTs examining the use of bisphosphonates in the treatment of women with breast cancer but without clinically evident bone metastases. No risk reduction for the development of skeletal metastases was found, but a significant heterogeneity was found among the 3 studies [203]. In terms of survival, the combined results indicated that adjuvant clodronate may improve survival, again with significant heterogeneity among the three studies [203]. There are insufficient data to support the use of bisphosphonates in women without metastatic bone involvement or without tumour-induced hypercalcemia [204, 205]. However, different results can be expected in the near future, potentially leading us to reconsider this conclusion.

Update 2013

Three systematic reviews comparing bisphosphonates versus no bisphosphonates in women with early non-metastatic breast cancer were found. As the most recent and complete review of Wong 2012 [206] includes all RCTs that were included in Mauri 2010 [207] and Huang 2012 [208], only the results of the latter will be discussed (Table 47, Appendix 5.5.9).

The review of Wong (2012) [206] assessed the effect of bisphosphonates on skeletal-related events (SREs), bone pain, quality of life (QoL), recurrence and survival in women with breast cancer with bone metastases (BCBM), advanced breast cancer (ABC) without clinical evidence of bone metastases and early breast cancer (EBC). As the study question of the guideline group concerned bisphosphonates solely in women with early non-metastatic breast cancer, only these results are discussed. The search date of the review was April 2011 and the overall risk of bias of this review was considered as low. Three outcomes of interest were discussed: overall survival; disease free survival and adverse events.
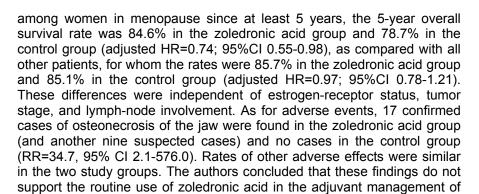
The review included twelve RCTs examining the effect of bisphosphonates in 10 124 patients with EBC. No significant differences were found for overall survival (any bisphosphonate) (RR 0.84; 95%CI 0.68-1.04). One study included in the review found a significant difference for disease-free survival (HR 0.64; P=0.0094). As for adverse events, the authors stated that reported toxicity was generally mild and similar between intervention and control groups. Renal toxicity and osteonecrosis of the jaw (ONJ) have been identified as potential problems with bisphosphonate use. There were great disparities between EBC studies. A large number of the included studies were bone mineral density trials that were not powered to detect differences in recurrence or survival between treatment and control arms. Studies also varied greatly in design, methodology and study sample. Furthermore, there was a wide range of follow up time for these studies (one to ten years) so that event rates can be vastly different between studies. All these contributed to the large statistical heterogeneity that was especially apparent in the survival meta-analysis. The authors concluded that currently, there is insufficient evidence to support the routine use of bisphosphonates as adjuvant treatment for patients with EBC.

The update of the search resulted in the inclusion of six **additional RCTs**, of which two were already included in the review of Wong 2012. The

Summary of Findings table is reported in Appendix 6.3 (Table 65). The forest plots are reported in Appendix 7 (Figures 18-20).

In the first RCT [209] (Table 48, Appendix 5.5.9), 119 women with stage II/III breast cancer were randomised to intravenous zoledronic acid (4 mg every 3 weeks for 1 year) or no zoledronic acid (ZOL) starting with the first chemotherapy cycle. The trial was of high risk of bias for adverse events and low risk of bias for survival outcomes. At 61.9 months' median follow-up, there was no significant difference in recurrence (P=0.92) or survival (P=0.92) between study arms. HRs for DFS and OS were significantly less among patients with ER-negative tumours who received ZOL vs no ZOL (DFS: HR=0.36, 95%CI 0.14-0.88; OS: HR= 0.37, 95%CI 0.14-0.98). Concerning adverse events, ZOL was generally well tolerated; toxicities were similar in the two treatment groups, with no observed cases of nephrotoxicity resulting in dose modifications. One of the 60 patients (1.7%) developed osteonecrosis of the jaw after receiving 11 infusions of ZOL (RR=2.95, 95%CI 0.12-71.01). The authors concluded that zoledronic acid administered with chemotherapy may improve DFS and OS in a subset of breast cancer patients with ER-negative tumours, although they report that this study was not powered to compare subgroups of patients and, thus, that these findings should be considered hypothesis generating.

The second RCT [210] reported the long-term results of the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trial (Table 48, Appendix 5.5.9). Zoledronic acid in addition to standard adjuvant therapy was compared with no zoledronic acid in patients with early-stage breast cancer. In this open-label phase 3 study, 3 360 patients were randomly assigned to receive standard adjuvant systemic therapy either with or without zoledronic acid. The zoledronic acid was administered every 3 to 4 weeks for 6 doses and then every 3 to 6 months to complete 5 years of treatment. The trial was considered of high risk of bias for adverse events and low risk of bias for survival outcomes. At a median follow-up of 59 months, no significant differences in overall survival were found between the zoledronic acid group and the control group (adjusted HR=0.85; 95%CI 0.72-1.01). Also, no significant difference in disease-free survival was found (adjusted HR=0.98, 95%CI 0.85-1.13). At 5 years, rates of invasive-disease–free survival differed significantly among both postmenopausal patients (adjusted HR with zoledronic acid, 0.75; 95%CI 0.59-0.96) and among all other patients (adjusted HR=1.15; 95%CI 0.97-1.36). In addition,

among women in menopause since at least 5 years, the 5-year overall survival rate was 84.6% in the zoledronic acid group and 78.7% in the control group (adjusted HR=0.74; 95%CI 0.55-0.98), as compared with all other patients, for whom the rates were 85.7% in the zoledronic acid group and 85.1% in the control group (adjusted HR=0.97; 95%CI 0.78-1.21). These differences were independent of estrogen-receptor status, tumor stage, and lymph-node involvement. As for adverse events, 17 confirmed cases of osteonecrosis of the jaw were found in the zoledronic acid group (and another nine suspected cases) and no cases in the control group (RR=34.7, 95% CI 2.1-576.0). Rates of other adverse effects were similar in the two study groups. The authors concluded that these findings do not support the routine use of zoledronic acid in the adjuvant management of breast cancer.
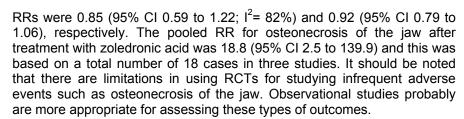
The third RCT [211] described the long-term results of the Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12) (Table 48, Appendix 5.5.9). The ABSCG-12 was a randomised, controlled, open-label, two-by-two factorial, multicentre trial in 1 803 premenopausal women with endocrine-receptor positive early-stage (stage I–II) breast cancer. All patients received goserelin (3.6 mg every 28 days). The efficacy and safety of anastrozole (1 mg per day) or tamoxifen (20 mg per day) with or without zoledronic acid (4 mg every 6 months) for 3 years were compared. The trial was considered at high risk of bias for adverse events and low risk of bias for survival outcomes. Analysis was done by intention to treat. At a median follow-up of 62 months (range 0 to 114.4 months), more than 2 years after treatment completion, zoledronic acid did not significantly affect overall survival (HR=0.67, 95%CI 0.41-1.07). A significant difference was found for disease-free survival (HR=0.68, 95%CI 0.51-0.91). When analysed within the respective hormonal groups similar HRs were found for DFS (HR=0.67, 95%CI 0.44-1.03 in the tamoxifen group and HR=0.68, 95%CI 0.45-1.02 in the anastrozole group). Furthermore, zoledronic acid improved disease-free survival, i.e. reducing the relative risk of recurrence to a similar extent in both node-positive (HR=0.67, 95%CI 0.45-0.99) and node-negative disease (HR=0.66, 95%CI 0.43-1.03). Also overall survival did not differ significantly between treatment groups in patients with node-positive (HR=0.62, 95%CI 0.34-1.15) and node-negative disease (HR=0.70, 95%CI 0.33-1.52). As for adverse events, the authors reported that treatments were generally well tolerated. There were no reports of

renal toxic effects or osteonecrosis of the jaw after 62 months follow-up. Patients in the zoledronic acid groups had a higher incidence of bone pain (RR=1.39, 95%CI 1.22-1.59), arthralgia (RR=1.20, 95%CI 0.96-1.50), and pyrexia (RR=4.06, 95%CI 2.54-6.49). As for other adverse events, no significant differences were found. The authors concluded that the addition of zoledronic acid improved disease-free survival in the patients taking anastrozole or tamoxifen, that these data showed persistent benefits with zoledronic acid and supported its addition to adjuvant endocrine therapy in premenopausal patients with early-stage breast cancer.

The last RCT [212] described the National Surgical Adjuvant Breast and Bowel Project protocol B-34 (NSABP B-34) trial which was a multicentre, randomised, double-blind, placebo-controlled study in 3 323 women with stage I–III breast cancer (Table 48, Appendix 5.5.9). After surgery to remove the tumour, patients were stratified by age, axillary nodes, and oestrogen and progesterone receptor status and randomly assigned to either oral clodronate 1600 mg daily for 3 years or placebo. The trial was considered having a low risk of bias. After a median follow-up of 90.7 months no significant differences were found for overall survival (HR=0.84, 95%CI 0.67-1.05) and disease-free survival (HR=0.91, 95%CI 0.78-1.07). In addition, reported side-effects (diarrhoea, alanine / aspartate aminotransferase, hypocalcaemia, creatinine, thrombosis or embolism, pancreatitis) were low in both arms and were similar between treatments. One possible case of osteonecrosis of the jaw arose in a woman assigned clodronate who had a 1 mm area of exposed bone on the maxillary taurus, which has since healed. A slightly higher frequency of grade 3 diarrhoea was noted in the clodronate arm.

The results of the identified recent RCTs were added to the meta-analyses of the systematic review. The pooled RR for overall survival of any bisphosphonate vs. no bisphosphonate was 0.85 (95%CI 0.72-1.00). There was, however, vast heterogeneity (I^2= 73%) and the follow-up ranged from 59 to 120 months. For intravenous zoledronic acid, oral clodronate and oral pamidronate these RRs were 0.86 (95% CI 0.74 to 1.00; I^2= 0%), 0.80 (95% CI 0.60 to 1.08; I^2= 79%) and 1.02 (95% CI 0.91 to 1.14), respectively. The pooled RR for disease-free survival of any bisphosphonate vs. no bisphosphonate was 0.90 (95% CI 0.76 to 1.06) with vast heterogeneity (I^2= 65%) and wide range of follow-up duration (59 to 120 months). For intravenous zoledronic acid and oral clodronate these

RRs were 0.85 (95% CI 0.59 to 1.22; I^2= 82%) and 0.92 (95% CI 0.79 to 1.06), respectively. The pooled RR for osteonecrosis of the jaw after treatment with zoledronic acid was 18.8 (95% CI 2.5 to 139.9) and this was based on a total number of 18 cases in three studies. It should be noted that there are limitations in using RCTs for studying infrequent adverse events such as osteonecrosis of the jaw. Observational studies probably are more appropriate for assessing these types of outcomes.

Conclusions

- 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).

Other considerations

On the one hand, the Cochrane review lacks to show a clear benefit of bisphosphonates as agents that may potentially lower the risk of breast cancer recurrence or improve the overall survival in the adjuvant setting. Nevertheless, a possible benefit of zoledronic acid in patients who had undergone menopause more than 5 years before study entry was suggested by Coleman et al. [210]. Further investigation into the possible interaction between zoledronic acid efficacy and estrogen environment is needed.

On the other hand, Cancer Australia (2011) [213] conducted a meta-analysis of the effect of bisphosphonates on the incidence of osteoporosis in women with early breast cancer (bisphosphonates: N=378 vs. control: N=381). Four studies were included evaluating 4 bisphosphonates. Zoledronic acid significantly reduced the incidence of osteoporosis compared with control (RR [95% CI] 0.03 [0.00, 0.46]). No significant differences in osteoporosis incidence were reported between treatment arms for clodronate (RR [95% CI] 0.30 [0.09, 1.01]), ibandronate (RR [95% CI] 0.20 [0.03, 1.59]), or risedronate (RR [95% CI] 0.20 [0.01, 4.12]) compared with control. Differences in length of follow-up (≤ 2 years to 15 years) were considered as a potential source of heterogeneity in this meta-analysis.

Recommendation 2013

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

3.6   Treatment of metastatic breast cancer

3.6.1   Multidisciplinary approach

The management of women with metastatic breast cancer is complex and can include endocrine therapy, chemotherapy and biological therapy. Above this, supportive and palliative care will also be needed for these patients [54]. Treatment choices are made according to patients' expectations and preferences, the risks of toxicity and the probable benefits in terms of improving symptoms, quality of life or survival [54].

However, the treatment is multidisciplinary and should therefore be discussed on an individual basis in the multidisciplinary team.

Recommendation

- **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).**

3.6.2 Diagnosis of metastatic breast cancer

3.6.2.1 Tumour markers

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. Present data are insufficient to recommend the use of CA 15-3, CA 27.29 or CEA alone for monitoring response to treatment. However, in the absence of readily measurable disease, an increasing CA 15-3, CA 27.29 or CEA may indicate treatment failure. Caution should be used when interpreting a rising CA 27.29, CA 15-3 or CEA level during the first 4-6 weeks of a new therapy, since spurious early rises may occur [43], specially with endocrine therapy.

Recommendation

- **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).**

3.6.2.2 Biopsy of metastatic lesions

Histological or cytological verification of metastatic disease should be done whenever possible. The biopsy of metastatic lesions allows to confirm the presence of a metastatic tumour (in cases of doubt), to characterize the biological markers associated with tumour recurrence and to define the treatment planning. In such cases, a reassessment of the ER and PgR status by standardized immunohistochemistry (IHC) and of Her-2/neu status by IHC or fluorescence in situ hybridization (FISH) have to be included in the diagnostic work-up [204,34].

Recommendations

- **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).**

3.6.3 Systemic treatment

3.6.3.1 Endocrine therapy and ER antagonists

In premenopausal patients with HR+ or HR-unknown metastatic breast cancer, suppression of ovarian function in combination with tamoxifen is the first-line hormonal therapy [17, 66]. This recommendation is based on a meta-analysis of 4 RCTs, in which a significant survival benefit (HR 0.78, p=0.02) and progression-free survival benefit (HR 0.70, p=0.0003) was found in favour of the combined treatment [214] (Table 49, Appendix 5.6.1).

In a recent systematic review including 6 RCTs, aromatase inhibitors were found to have a clear advantage in overall response rate, clinical benefit, and time to progression over tamoxifen as first-line hormonal treatment in postmenopausal patients with metastatic breast cancer [215]. Overall survival did not differ significantly. These results confirm the recommendations of CBO [66], the German Cancer Society [17], Cancer Care Ontario [216] and the Central European Cooperative Oncology Group [204] (Table 50, Appendix 5.6.1.). However, tamoxifen remains an acceptable alternative as first-line treatment. Based on data from RCTs, following tamoxifen failure, the use of a third generation aromatase inhibitor (anastrozole, letrozole, exemestane) or fulvestrant are recommended for second-line treatment for post-menopausal patients with HR-positive metastatic breast cancer based upon the more favourable side-effect profile [204, 216].

Flemming et al. [217, 218] reported results from two phase III, multicentre RCTs comparing fulvestrant versus anastrozole in patients with prior metastatic or adjuvant endocrine therapy (Table 51, Appendix 5.6.1.). No significant differences were observed between fulvestrant and anastrozole therapy arms for time-to-progression (primary endpoint), objective response rate, time-to-treatment failure, clinical benefit, and overall survival (median follow-up ranging from 15.1 to 27.0 months). No

significant differences in tolerability measures were identified between therapy arms with the exception of a higher incidence of joint disorders (including arthralgia, arthrosis, and arthritis) for patients treated with anastrozole (12.8% vs. 8.3%, p = 0.0234).

Flemming et al. [217, 218] also reported the results of the Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) (n = 693) [219] comparing fulvestrant with exemestane in women with HR-positive breast cancer recurring after prior adjuvant non-steroidal aromatase inhibitor (NSAI) therapy (during or within 6 months of discontinuation) or progressing during prior NSAI therapy for advanced disease. At a median follow-up of 13 months, there were no significant differences for median time-to-progression (primary endpoint), objective response rate, clinical benefit rate, or duration of response. Fulvestrant and exemestane were both well tolerated, with no significant differences noted across any adverse events.

Recommendations

- **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).**

3.6.3.2   *Chemotherapy*

Chemotherapy is indicated for women with hormone refractory or HR-negative metastatic breast cancer, rapidly progressive disease or symptomatic disease, or with life-threatening disease (e.g. diffuse lung or liver metastases, massive bone marrow metastases with pancytopenia) [66]. Multiple systematic reviews exist evaluating different chemotherapy regimens for women with metastatic breast cancer [175, 220-222] (Table 52, Appendix 5.6.2).

A systematic review of 43 randomized trials (n = 9 742 women) suggests that polychemotherapy is associated with higher response rates and longer progression-free survival and a modest improvement in overall survival compared to single-agent treatment, but produces more adverse events including a decrease in white blood cell count, increased hair loss and nausea and vomiting [220]. On the other hand, the only major RCT [223] comparing sequential monotherapies with combined anthracyclines and taxanes did not demonstrate improved survival or quality of life with the latter approach, despite increased response rates [204]. In the absence of rapid clinical progression, life-threatening visceral metastases, or the need for rapid symptom and/or disease control [224], sequential use of single cytotoxic agents is preferred to combination chemotherapy in metastatic disease. Patient- and disease related factors should be considered to choose between combination and sequential single-agent chemotherapy for MBC [224].

Anthracycline- and/or taxane-based regimens are to be preferred as first-line treatment in symptomatic patients and/or those with rapidly progressive disease [204]. The combined use of anthracyclines and taxanes increased objective response rate and time-to-progression in some trials. Moreover, overall survival was improved in two RCTs [225, 226]. A higher treatment-related toxicity was reported.

Polychemotherapy compared to single-agent therapy obtained slightly superior results in overall survival in metastatic breast cancer women pretreated with anthracycline. In one phase III trial [227], the combination of capecitabine plus docetaxel resulted in significantly superior efficacy in time-to-disease progression (HR 0.65; 95%CI 0.54-0.78; median, 6.1 vs. 4.2 months), overall survival (HR 0.77; 95%CI 0.63-0.94; median, 14.5 vs. 11.5 months), and objective tumour response rate (42% vs. 30%, p=0.006)

compared with docetaxel. The combination resulted in significantly increased hematologic and non-hematologic toxicity. Another randomized phase III trial compared paclitaxel plus gemcitabine with paclitaxel [228]. The combination regimen was associated with an improved overall survival (18.6 months versus 15.8 months; log-rank p = 0.0489, with an adjusted Cox hazard ratio of 0.78 [95% CI 0.64-0.96; p = 0.0187]), a longer time-to-progression (6.14 vs. 3.98 months; log-rank p = 0.0002) and a better response rate (41.4% vs. 26.2%; p = 0.0002). The gemcitabine/paclitaxel arm was also associated with increased pain relief and better quality of life. However, there was more grade 3 to 4 neutropenia on combined therapy and grade 2 to 4 fatigue and neuropathy were slightly more prevalent. Data from these two RCTs demonstrated that the combination of a taxane with capecitabine or gemcitabine is superior to taxane alone in increasing overall survival in patients with metastatic breast cancer [204].

A randomized phase III trial compared docetaxel plus gemcitabine (DG) with docetaxel plus capecitabine (DC) and showed similar efficacy in terms of progression-free survival (median PFS was 8.05 months [95% CI, 6.60 to 8.71] for DG and 7.98 [95% CI, 6.93 to 8.77] for DC), tumour response rate (32% in both arms) and overall survival. Time-to-failure was longer and non-hematologic toxicity was significantly lower in the DG arm [229]. However, severe hematologic toxicity rates (grades 3 to 4 leukopenia) were higher in DG group (78% vs. 66%; p=0.025), as was the transfusion rate (DG, 17%; CD, 7%; p=0.0051).

Very few randomized phase III trials have addressed optimal selection of treatment after failure of taxanes and/or anthracyclines. Chan et al. [230] conducted a large non-systematic review evaluating the relative efficacy of capecitabine and vinorelbine alone or in combination in metastatic breast cancer. They identified 6 capecitabine and 2 vinorelbine phase III trials, numerous phase II monotherapy studies and 35 phase I/II studies exploring capecitabine–vinorelbine combination therapy (1 with trastuzumab in HER2-positive MBC). For the majority of patients, capecitabine monotherapy appeared to be the more effective agent for metastatic breast cancer women with prior taxane exposure or who are unsuitable for taxane therapy. Treatment options should take into account prior therapy, comorbidities, tolerability and patient preferences. Combination regimens of capecitabine and vinorelbine potentially improve efficacy compared with monotherapy, but at the cost of increased toxicity.

Such regimens need further evaluation against effective sequential, monotherapy strategies before they can be recommended for routine use [230].

Recommendations

- **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).**

3.6.3.3 Biological therapy

Trastuzumab

Trastuzumab is only used in patients whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated test [54].

In a pivotal, randomized phase III trial performed in patients with HER-2/neu overexpressing metastatic breast cancer, first-line treatment with the combination of trastuzumab plus chemotherapy has been shown to result in a significantly higher tumour response rate and significantly prolonged overall survival as compared with chemotherapy alone [204] (Table 53, Appendix 5.6.3). Numerous RCTs have shown the advantage of adding

trastuzumab to chemotherapy with taxanes [204]. This was confirmed by a RCT that showed that the combination of trastuzumab and docetaxel is superior to docetaxel alone as first-line treatment of patients with HER2-positive metastatic breast cancer in terms of overall survival, response rate, response duration, time to progression, and time-to-treatment failure, although combination treatment was complicated by a higher risk of cardiotoxicity [231]. In this trial, survival was longest for the group who received trastuzumab and docetaxel concomitantly from the start of treatment (median OS, 31.2 months), indicating that that earlier treatment with trastuzumab could lead to the improvement in survival. Patients have to undergo baseline measurement of cardiac function prior to trastuzumab–based therapy and continue cardiac surveillance while continuing treatment [204].

An important phase III trial investigated if trastuzumab treatment should be continued beyond progression [232]. Patients with HER2-positive breast cancer progressing during treatment with trastuzumab with a taxane were randomly assigned to receive capecitabine alone or in combination with trastuzumab. Continuation of trastuzumab plus capecitabine showed a significant improvement in overall response (OR 2.50; p=0.0115) and time-to-progression (HR 0.69; 95%CI 0.48 - 0.97; two-sided log-rank p=0.0338) and a trend to improved survival (25.5 months vs. 20.4 months; HR 0.76; p=0.13) compared with capecitabine alone. Continuation of trastuzumab beyond progression was not associated with increased toxicity. In another phase III trial, women with HER2-positive, locally advanced or metastatic breast cancer previously treated with anthracycline-, taxane-, and trastuzumab-containing regimens were randomized to lapatinib plus capecitabine or capecitabine alone [233]. The addition of lapatinib to capecitabine prolonged time-to-progression (HR 0.57; 95% CI 0.43-0.77; p < 0.001) and was associated with a trend towards improved overall survival (HR 0.78; 95% CI 0.55-1.12; p = 0.177).

It is striking to note that the optimal sequencing of anti-HER2 agents is currently unknown.

Recommendation

- **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).**
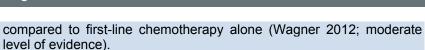
Bevacizumab

A meta-analyse of RCTs was published (after our literature search), examining the benefits of bevacizumab in HER2-negative metastatic breast cancer patients [234]. Combination of bevacizumab and chemotherapy resulted in a small but statistically significant improvement in progression-free survival and tumour response rate compared with chemotherapy alone. The pooled HR for overall survival did not show significant advantages for the use of bevacizumab compared to placebo. Meta-analyses suggested benefits of a carefully managed bevacizumab-containing treatment for patients with histologically or cytologically confirmed HER2-negative metastatic breast cancer not received previously receiving cytotoxic therapy.

Update 2013

Six relevant systematic reviews were identified [234-239]. As the most recent and complete review of Wagner includes all RCTs (and outcomes) that were included in the other reviews, only the results of the latter will be discussed.

The review of Wagner (2012) [239] evaluated overall survival, progression-free survival and harms of VEGF-targeting therapies in patients with hormone-refractory or hormone-receptor negative metastatic breast cancer (Table 54, Appendix 5.6.4). The search date of the electronic databases was September 8, 2011. The overall risk of bias of this review was considered as low.

The review included a total number of seven RCTs, data from one register, and five ongoing trials examining the effect of bevacizumab in combination with chemotherapy. Five of the included RCTs addressed (predominantly) HER-2 negative patients (with a maximum of 4% HER-2 positive patients). As the guideline group decided to focus only on bevacizumab in women with HER-2 negative metastatic breast cancer, only the results of this subgroup (HER-2 negative patients) are reported (Table 66, Appendix 6.4).

Overall survival did not differ significantly between the groups with and without bevacizumab, neither in first-line chemotherapy (HR=0.93; 95%CI 0.84-1.04), nor in second-line chemotherapy (HR=0.90; 95%CI 0.71-1.14) in HER-2 negative patients. Progression-free-survival was significantly better after treatment with bevacizumab in both first-line (HR=0.67; 95%CI 0.61-0.73) and second-line chemotherapy (HR=0.78 ; 95%CI 0.64-0.93). Significantly higher rates of grade 3/4 adverse events (OR=1.77; 95%CI 1.44-2.18) and serious adverse events (OR=1.41; 95%CI 1.13-1.75) were observed in patients treated with bevacizumab. They include increased frequencies of high blood pressure, blood clots in arteries, haemorrhages and bowel perforations. Rates of treatment-related deaths were lower in patients treated with bevacizumab (OR=0.63; 95%CI 0.38-1.06).

The authors concluded that overall, the clinical value of bevacizumab in metastatic breast cancer can at best be considered as modest and this benefit has to be weighed up against an increased risk of serious adverse events. Treatment related deaths, however, were lower in patients treated with bevacizumab. Therefore, the clinical relevance of bevacizumab in metastatic breast cancer remains controversial, as reflected by the different attitudes of health authorities in Europe and the United States.

Conclusions

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)

Other considerations

Bevacizumab fails to demonstrate a benefit on overall survival, in spite of the consistent increase in progression-free survival. At the contrary, adverse effects of bevacizumab may be occasionally serious including blood clots in arteries, bowel perforations, cardiac failure, and treatment related mortality. Consequently, the benefits of bevacizumab in combination with first-line or second-line chemotherapy in terms of increased PFS need to be balanced against potential harms and costs.

Health authorities in Europe and the United States have different views regarding the use of bevacizumab. On November 18, 2011 the Department of Health and Human Services Food and Drug Administration decided to withdraw approval for Avastin® (bevacizumab) for use with paclitaxel in the treatment of metastatic breast cancer due to lack of sufficiently relevant clinical benefit based on the results of the AVADO trial and the RIBBON-1 trial. Available data do not support continued accelerated approval of this drug for this indication. After accelerated approval had been granted in 2008, updated data of these two trials did not confirm the expected 5.5 months increase in median PFS. Moreover, the FDA evaluated the toxicity profile as not tolerable for a drug, for which no overall survival benefit has

been demonstrated. However, if new data are submitted they will be considered by the Commissioner of Food and Drugs (http://www.fda.gov/downloads/NewsEvents/Newsroom/UCM280546.pdf). In Europe, bevacizumab is approved in combination with paclitaxel for first-line treatment of patients with metastatic breast cancer and bevacizumab in combination with capecitabine is approved for the first-line treatment of patients with metastatic breast cancer who are not eligible for treatment with taxanes or anthracyclines; patients who have received taxane- and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with bevacizumab in combination with capecitabine (http://www.ema.europa.eu/docs/en˙GB/document˙library/Summary˙of˙opinion/human/000582/WC500112811.pdf).

Bevacizumab in combination with chemotherapy has currently no market approval as a second-line therapy for metastatic breast cancer, neither in the US nor in Europe.

In Belgium, bevacizumab (Avastin®) is only reimbursed if administered in association with paclitaxel in the first-line treatment of triple-negative metastatic breast cancer women (ER-, PR- and HER2-).The patient has to meet specific criteria at the beginning of the treatment based on histopathological evaluation of hormonal receptors, the absence of arterial thromboembolic history or an uncontrolled arterial hypertension.

The lack of overall survival benefit, the high cost, and the increased risk of (occasional) severe side effects does not allow recommending bevacizumab in routine clinical practice. However, for individual patients, the PFS improvement might be clinically meaningful. Future studies should focus on better identification of patients that benefit significantly from bevacizumab.

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).**

3.6.4   Treatment of bone metastases

Extensive evidence has shown the effectiveness of bisphosphonates in patients with breast cancer and multiple lytic bone metastases in terms of pain reduction, reduction of skeletal events, improvement of the quality of life, and time-to-progression [18, 54, 66] (Table 55, Appendix 5.6.5). Although most trials evaluated treatment given for about 2 years, no data are available on optimal duration of bisphosphonate treatment [204]. These findings were confirmed by a recent systematic review of Pavlakis et al. including 21 RCTs [203]. In patients with painful or threatening bone metastases, radiotherapy remains the treatment of choice [18, 54, 66].

Recommendations

- **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).**

3.6.5   Treatment of brain metastases

Some patients with metastatic breast cancer will develop symptomatic brain metastases, usually at multiple sites. The main treatment options include surgery and radiotherapy (Table 55, Appendix 5.6.5). Surgery is only considered for patients who have a solitary metastasis or a limited number of brain metastases; this applies to the minority of patients. Most patients will subsequently be treated with whole brain radiotherapy (WBRT) which may improve their symptoms and function. More recently, treatment with stereotactic radiosurgery was considered as an acceptable alternative to resection or to radiotherapy alone for patients with brain metastases. Retrospective studies suggest clinical effectiveness in younger patients and those with good performance status [54].

Recommendation

- **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).**

3.7 Treatment of locoregional relapse

In case of a local recurrence in the thoracic wall, a complete excision of the tumour should be aimed for [17, 66]. Small recurrences in the scar can be removed by wide excision in healthy tissue. Large chest-wall recurrences can be treated by chest wall resection. If no radiotherapy has been performed as part of the primary therapy, radiotherapy should be performed postoperatively [17, 66]. However, in the presence of unfavourable risk factors, an additional course of (small-volume) radiotherapy may be given postoperatively even in patients who have received prior adjuvant radiotherapy. This should first be discussed in the MDT. In patients with a local recurrence after breast conserving treatment, salvage mastectomy is recommended [66]. However, for some cases BCS may be an option. Few trials exist on the use of systemic treatment for a locoregional recurrence that has been completely excised [66]. Therefore, this should be discussed in the MDT for each individual patient.

Recommendations

- **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).**

3.8 Supportive care for patients with breast cancer

Patients with metastatic breast cancer may develop lymphoedema following surgery or radiotherapy, or due to the pathological changes associated with progressive localised disease [54] (Table 56, Appendix 5.7). Early identification and management of the swelling is important, but there are no agreed diagnostic tests and assessment methods [54]. A Cochrane review of Badger et al. identified 3 RCTs examining the use of physical therapies for the reduction and control of lymphoedema of the limbs [240].

Only one of these RCTs (a crossover study of manual lymph drainage followed by self-administered massage versus no treatment) exclusively included women with unilateral lymphoedema of the upper limb following treatment for breast cancer. No extra benefit of manual lymph drainage was found [240].

One meta-analysis was identified on the use of physical exercise in breast cancer patients [241] (Table 56, Appendix 5.7). The authors identified 14 RCTs with important heterogeneity and small sample sizes. Physical exercise was found to be associated with statistically significant improvements in quality of life and physical functioning [241]. Meta-analysis of data from 28 RCTs [242] showed a highly significant effect of exercise compared with controls on fatigue reduction both in cancer patients in general (n = 2 083 participants), and in a large sub-group of patients with breast cancer (n = 1 172 participants). Since the review included all forms of exercise, a specific regime, intensity or duration cannot be recommended [54].

There are no clear and uniform data as to whether the use of conventional hormonal replacement therapy (HRT) alleviates menopausal symptoms or alters outcomes in women with breast cancer treated with endocrine agents [18, 66, 243] (Table 57, Appendix 5.8). In the HABITS trial, a clinically and statistically significant increased risk of a new breast cancer event was reported in patients receiving menopausal HRT after a median follow-up of 4 years [244]. Therefore, this treatment cannot be recommended after treatment for breast cancer [244].

A systematic review of Edwards et al. identified 5 RCTs examining the use of psychological interventions for women with metastatic breast cancer [245]. The authors concluded that there was insufficient evidence to advocate group therapy for all women diagnosed with metastatic breast cancer.

Numerous additional RCTs on group interventions [246-251], individual interventions [252-259], couple and family interventions [260-262], and computer- and telephone-based interventions [263-265] were identified (Table 58, Appendix 5.9). The psychological interventions included strategies to reduce stress, improve mood, alter health behaviours, and maintain adherence to cancer treatment and care. These interventions were reported to have positive impact on different outcomes such as stress and depression, dietary and smoking habits, breast cancer recurrence and overall survival. However, many of these trials were hampered by methodological limitations and small sample sizes, and reporting on outcomes was heterogeneous. Nevertheless, psychological support should be available to all patients diagnosed with breast cancer [18, 54].

For symptomatic anaemia (haemoglobin <11 g/dl), erythropoietin and erythrocyte transfusions are reasonable options. For acute symptoms and in case of non-responsiveness to erythropoesis-stimulating proteins, erythrocyte transfusions can be administered [204].

The management of uncontrolled disease needs to be individualised and will usually involve a combination of treatments. A team approach is therefore very important and will include nurses, surgeons, oncologists and psychologists. A palliative care team should assess all patients with uncontrolled disease in order to plan a symptom management strategy [54].

Recommendations

- **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).**

3.9   Surveillance of patients with breast cancer

Local recurrences or second primaries in the treated breast can be detected clinically or mammographically [18, 54, 64, 66]. Mammography is the gold standard method of imaging for cancer detection, but no evidence was identified to suggest the optimal frequency of this procedure. In current practice, mammography is offered once yearly after treatment for breast cancer. Since there is no evidence that performing diagnostic tests such as X-rays and scans to screen for distant metastases improves survival, these tests should not be performed in asymptomatic women [18, 64, 66] (Table 59, Appendix 5.10).

There is no evidence that breast MRI improves outcome when used as a breast cancer surveillance tool during routine follow-up in asymptomatic patients. The decision to use breast MRI in high-risk patients should be made on an individual basis depending on the complexity of the clinical scenario [64].

The frequency of follow-up consultations is not extensively studied, and therefore mainly based on expert opinion. 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 [66].

Studies are currently comparing different forms of follow-up such as traditional hospital follow-up with telephone follow-up by specialist nurses [266]. Such studies highlight the importance to consider who will organise and execute the follow-up (specialists in a breast clinic, general practitioner, breast care nurse specialist,…), if it is possible to transfer the surveillance of breast cancer patients from the hospital to the community and which training and resources are needed in the future.

Recommendations

- **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):**
  o   **Lobular invasive cancer**
  o   **Very young patients (< 35 years)**
  o   **BRCA associated cancers**
  o   **If initial tumour was not seen at mammography/ultrasound**
  o   **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).**

3.10 Multidisciplinary approach of patients with breast cancer

There is evidence that a multidisciplinary breast clinic provides an accurate and effective means of establishing a correct diagnosis in women referred with breast symptoms [18]. A multidisciplinary clinic will usually involve breast clinicians, radiologists and cytologists. Above this, 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 [18]. One RCT reported that telephone follow-up by specialist nurses (consultation with structured intervention and mammography according to hospital policy) can be suitable for women at low to moderate risk of recurrence and those with long travelling distances

or mobility problems, and decreases the burden on busy hospital clinics, with no physical or psychological disadvantage [266].

Recommendation

- **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).**

3.11 Breast cancer and pregnancy

In a recent population-based descriptive study, women aged <45 with a diagnosis of breast cancer who subsequently conceived were identified [267]. Subsequent pregnancy was associated with improved overall survival. However, due to the observational nature of the study, these results should be interpreted with caution. Nevertheless, breast cancer is not considered a contraindication for a later pregnancy or breastfeeding [268]. This should be individually discussed.

Chemotherapy and radiotherapy can have serious adverse effects on fertility. As an increasing number of patients who are diagnosed with cancer in the reproductive age can be cured, fertility preservation has become an important issue in cancer treatment. 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).

Recommendation

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

3.12 Participation in clinical trials

The inclusion of breast cancer women in research protocols should always be considered, particularly when the curative options are poor, i.e. in the metastatic setting.

Recommendation

- **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).**

4 IMPLEMENTATION AND UPDATING OF THE BREAST CANCER GUIDELINE

4.1 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).

4.2 Monitoring the quality of care

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

On one hand the guideline should be viewed as a tool to support health policies to improve the quality of care: support of actions to increase caregivers' awareness and to improve their practice, development (or revision) of sets of process and outcome quality indicators. KCE previously recommended to set up an integrative quality system in oncology, covering the development and implementation of clinical practice guidelines, the monitoring of the quality of care with quality indicators, feedback to health care providers and organisations and targeted actions to improve the quality if needed [269].

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. Cancer registry data of 50 039 women with invasive breast cancer could be linked to the claims data for the period 2001-2006 [3, 270]. The set of quality indicators is reported on Appendix 10. The whole KCE report can be downloaded on the KCE website (http://kce.fgov.be/publication/report/quality-indicators-in-oncology-breast-cancer-0).

The KCE report on breast cancer was picked up by the Flemish government, and led to the development of an adapted quality indicator set which is currently undergoing evaluation at the Belgian Cancer Registry. The updated guidelines should be a good opportunity to reassess the quality of care delivered in Belgium.

On the other hand 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 caregivers groups. They will also play a key role by a dissemination that makes use of diverse channels such as websites or sessions of continuing education.

4.3   Guideline update

In view of the changing 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.

■ REFERENCES

1. Christiaens M-R, Vlayen J, Gailly J, Neven P, Carly B, Schobbens J-C, et al. Support scientifique du Collège d'Oncologie: un guideline pour la prise en charge du cancer du sein. Brussels: Centre fédéral d'expertise des soins de santé; 2007. Good Clinical Practices (GCP) 63B

2. Cardoso F, Stordeur S, Vlayen J, Bourgain C, Carly B, Christiaens M-R, et al. Soutien scientifique au Collège d'Oncologie: mise à jour des recommandations de bonne pratique pour la prise en charge du cancer du sein. Brussels: Centre Fédéral d'expertise des Soins de santé; 2010. Good Clinical Practices (GCP) KCE report 143

3. 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)

4. Belgian Cancer Registry. Cancer survival in Belgium. Brussels: Belgian Cancer Registry; 2012.

5. Levi F, Bosettic C, Lucchinib F, Negric E, La Vecchiab C. Monitoring the decrease in breast cancer mortality in Europe. European Journal of Cancer Prevention. 2005;14:497-502.

6. Fervers B, Burgers JS, Haugh MC, Latreille J, Mlika-Cabanne N, Paquet L, et al. Adaptation of clinical guidelines: literature review and proposition for a framework and procedure. Int J Qual Health Care. 2006;18(3):167-76.

7. Whiting P, Rutjes A, Reitsma J, Bossuyt P, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Medical Research Methodology. 2003;3(1):25.

8. Higgins JPT, Altman DG. Assessing risk of bias in included studies. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions: Wiley 2008. p. 187-241.

9. Sobin L, Gospodarowicz M, Wittekind C. TNM - Classification of Malignant Tumours. Seventh edition ed. Oxford: Blackwell Publishing Ltd; 2009.

10. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

11. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol. 2013;66(2):151-7.

12. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 15. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013.

13. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126(3):466-76.

14. Fiocchi A, Schunemann HJ, Brozek J, Restani P, Beyer K, Troncone R, et al. Diagnosis and Rationale for Action Against Cow's Milk Allergy (DRACMA): a summary report. J Allergy Clin Immunol. 2010;126(6):1119-28 e12.

15. Park JM, Yoon GS, Kim SM, Ahn SH. Sonographic detection of multifocality in breast carcinoma. J Clin Ultrasound. 2003;31(6):293-8.

16. Shoma A, Moutamed A, Ameen M, Abdelwahab A. Ultrasound for accurate measurement of invasive breast cancer tumor size. Breast J. 2006;12(3):252-6.

17. Kreienberg R, Kopp I, Lorenz W, Budach W, Dunst J, Lebeau A, et al. Interdisciplinary S3 Guidelines for the Diagnosis and Treatment of Breast Cancer in Women. Frankfurt: German Cancer Society; 2003.

18. Scottish Intercollegiate Guidelines Network (SIGN). Management of breast cancer in women. A national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN); 2003.

19. Feoli F, Paesmans M, Van Eeckhout P. Fine Needle Aspiration Cytology of the Breast : Impact of Experience on Accuracy, Using Standardized Cytologic Criteria. Acta Cytologica. 2008;52(2):145-51.

20. Kaur G, S S. Comparison of unsatisfactory aspirates in fine needle aspiration performed by surgical medical officers and pathologists. J Cytol. 2007;24:82-4.

21. Klijanienko J, Coté JF, Thibault F, Zafrani B, Meunier M, Clough K, et al. Ultrasound-guided fine needle aspiration cytology of nonpalpable breast lesions. Institut Curie's experience with198 histologically correlated cases. Cancer. 1998;84:36-41.

22. National Breast Cancer Centre. Clinical practice guidelines for the management and support of younger women with breast cancer. Camperdown: NSW; 2004.

23. Bagni B, Franceschetto A, Casolo A, De Santis M, Bagni I, Pansini F, et al. Scintimammography with 99mTc-MIBI and magnetic resonance imaging in the evaluation of breast cancer. Eur J Nucl Med Mol Imaging. 2003;30(10):1383-8.

24. Howarth D, Slater S, Lau P, Booker J, Clark D, Sillar R. Complementary role of adjunctive breast magnetic resonance imaging and scintimammography in patients of all ages undergoing breast cancer surgery. Australas Radiol. 2005;49(4):289-97.

25. Van Goethem M, Schelfout K, Dijckmans L, Van Der Auwera JC, Weyler J, Verslegers I, et al. MR mammography in the pre-operative staging of breast cancer in patients with dense breast tissue: comparison with mammography and ultrasound. Eur Radiol. 2004;14(5):809-16.

26. Peters NH, Borel Rinkes IH, Zuithoff NP, Mali WP, Moons KG, PH. P. Meta-analysis of MR imaging in the diagnosis of breast lesions. Radiology. 2008;246(1):116-24.

27. Hagen AI, Kvistad KA, Maehle L, Holmen MM, Aase H, Styr B, et al. Sensitivity of MRI versus conventional screening in the diagnosis of BRCA-associated breast cancer in a national prospective series. Breast. 2007;16(4):367-74.

28. Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging,

ultrasound, mammography, and clinical breast examination. JAMA. 2004;292:1317-25.

29. Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med. 2004;351:427-37.

30. Demaerel P, Hermans R, Verstraete K, Bogaert J, Van Goethem M, Deblaere K, et al. Magnetische Resonantie Beeldvorming. Health Technology Assessment (HTA). Brussel: Federaal Kenniscentrum voor de gezondheidszorg (KCE); 2006. KCE reports 37A (D/2006/10.273/32)

31. Bekis R, Derebek E, Balci P, Kocdor MA, Degirmenci B, Canda T, et al. 99mTc sestamibi scintimammography. Screening mammographic non-palpable suspicious breast lesions: preliminary results. Nuklearmedizin. 2004;43(1):16-20.

32. Chen J, Wu H, Zhou J, Hu J. Using Tc-99m MIBI scintimammography to differentiate nodular lesions in breast and detect axillary lymph node metastases from breast cancer. Chinese Medical Journal. 2003;116(4):620-4.

33. Fondrinier E, Muratet JP, Anglade E, Fauvet R, Berger V, Lorimier G, et al. Clinical experience with 99mTc-MIBI scintimammography in patients with breast microcalcifications. Breast. 2004;13(4):316-20.

34. Krishnaiah G, Sher-Ahmed A, Ugwu-Dike M, Regan P, Singer J, Totoonchie A, et al. Technetium-99m sestamibi scintimammography complements mammography in the detection of breast cancer. Breast J. 2003;9(4):288-94.

35. Sampalis FS, Denis R, Picard D, Fleiszer D, Martin G, Nassif E, et al. International prospective evaluation of scintimammography with (99m)technetium sestamibi. Am J Surg. 2003;185(6):544-9.

36. Tiling R, Kessler M, Untch M, Sommer H, Linke R, Hahn K. Initial evaluation of breast cancer using Tc-99m sestamibi scintimammography. European Journal of Radiology. 2005;53(2):206-12.

37. Medical Advisory Secretariat of Ontario Ministry of Health and Long-Term Care. Scintimammography as an Adjunctive Breast Imaging Technology - Integrated Health Technology Literature Review. Toronto: 2007.

38. Vlayen J, Stordeur S, Van Den Bruel A, Mambourg M, Eyssen M. La tomographie par émission de positrons en Belgique: une mise à jour. Brussels: Belgian Health Care Knowledge Centre (KCE); 2009. KCE Reports 110B

39. Facey K, Bradbury I, Laking G, Payne E. Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. Health Technology Assessment. 2007;11(44):iii-iv, xi-267.

40. Agency for Healthcare Research and Quality. FDG positron emission tomography for evaluating breast cancer - systematic review. Rockville: Agency for Healthcare Research and Quality; 2001.

41. Agency for Healthcare Research and Quality. Effectiveness of Noninvasive Diagnostic Tests for Breast Abnormalities. Rockville: AHRQ; 2006.

42. Bourguet P, Hitzel A, Houvenaeghel G, Vinatier D, Bosquet L, Bonichon F, et al. [Synthesis bulletin of 2005 surveillance. Clinical practice recommendations: the use of PET-FDG in cancers of the breast, ovary and uterus]. Bulletin du Cancer. 2006;93(4):385-90.

43. Harris L, Fritsche H, Mennel R, Norton L, Ravdin P, Taube S, et al. American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer. Journal of Clinical Oncology. 2007;25(33).

44. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet. 2005;365:1687-717.

45. Clark GM, McGuire WL, Hubay CA, et al. The importance of estrogen and progesterone receptor in primary breast cancer. Prog Clin Biol Res 1983;132E:183-90.

46. Diaz LK, Sneige N. Estrogen receptor analysis for breast cancer: Current issues and keys to increasing testing accuracy. Adv Anat Pathol. 2005;12:10-9.

47. Ravdin PM, Green S, Dorr TM, et al. Prognostic significance of progesterone receptor levels in estrogen receptor-positive patients with metastatic breast cancer treated with tamoxifen: Results of a prospective Southwest Oncology Group study. J Clin Oncol. 1992;10:1284-91.

48. Hammond MEH, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). Arch Pathol Lab Med. 2010;134(7):e48-72.

49. Dunnwald L, Rossing M, Li C. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Research. 2007;9(1R6).

50. Fisher B, Jeong JH, Bryant J, Anderson S, Dignam J, Fisher ER, et al. Treatment of lymph-node-negative, oestrogen receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. Lancet. 2004;364:858-68.

51. Fisher B, Dignam J, Wolmark N, al. e. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet. 1999;353:1993-2000.

52. Fisher B, Land S, Mamounas E, et al. Prevention of invasive breast cancer in women with ductal carcinoma in situ: An update of the national surgical adjuvant breast and bowel project experience. Semin Oncol. 2001;28:400-18.

53. Houghton J, George WD, Cuzick J, al. e. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: Randomised controlled trial. Lancet. 2003;362:95-102.

54. National Institute for Health and Clinical Excellence. Advanced breast cancer - Diagnosis and treatment. London: NICE; 2009. NICE Clinical guideline 81

55. Dhesy-Thind B, Pritchard K, Messersmith H, O'Malley F, Elavathil L, Trudeau M, et al. The Role of HER2/neu in Systemic and Radiation Therapy for Women with Breast Cancer: A Clinical Practice Guideline. Toronto: 2006. Evidence-based Series #1-17: Section 1

56. Frenette PS, Thirlwell MP, Trudeau M, Thomson DM, Joseph L, Shuster JS. The diagnostic value of CA 27-29, CA 15-3, mucin-like carcinoma antigen, carcinoembryonic antigen and CA 19-9 in breast and gastrointestinal malignancies. Tumour Biology. 1994;15(5):247-54.

57. Kopczynski Z, Thielemann A. The value of tissue polypeptide specific antigen TPS determination in serum of women with breast cancer comparison to mucin-like associated antigen MCA and CA 15-3 antigen. European Journal of Gynaecological Oncology. 1998;19(5):503-7.

58. Seth LRK, Kharb S, Kharb DP. Serum biochemical markers in carcinoma breast. Indian Journal of Medical Sciences. 2003;57(8):350-4.

59. Sliwowska I, Kopczynski Z, Grodecka-Gazdecka S. Diagnostic value of measuring serum CA 15-3, TPA, and TPS in women with breast cancer. Postepy Higieny i Medycyny do Swiadczalnej. 2006;60:295-9.

60. Ebeling FG, Stieber P, Untch M, et al. Serum CEA and CA 15-3 as prognostic factors in primary breast cancer. Br J Cancer. 2002;86:1217-22.

61. Kumpulainen EJ, Keskikuru RJ, Johansson RT. Serum tumor marker CA 15.3 and stage are the two most powerful predictors of survival in primary breast cancer. Breast Cancer Res Treat 2002;76:95-102.

62. Martín A, Corte MD, Alvarez AM, et al. Prognostic value of pre-operative serum CA 15.3 levels in breast cancer. Anticancer Res. 2006;26:3965-71.

63. Molina R, Filella X, Alicarte J, et al. Prospective evaluation of CEA and CA 15.3 in patients with locoregional breast cancer. Anticancer Res. 2003;23:1035-41.

64. Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, et al. American Society of Clinical Oncology 2006

update of the breast cancer follow-up and management guidelines in the adjuvant setting. Journal of Clinical Oncology. 2006;24(31):5091-7.

65. Molina R, Barak V, van Dalen A, et al. Tumor markers in breast cancer: European Group on Tumor Markers recommendations. Tumour Biology. 2005;26:281-98.

66. Kwaliteitsinstituut voor de Gezondheidszorg (CBO) en Vereniging van Integrale Kankercentra (VIKC), V. Zuiden (Eds). Richtlijn Behandeling van het mammacarcinoom 2005. Alphen aan den Rijn: 2005.

67. Myers RE, Johnston M, Pritchard K, Levine M, Oliver T, and the Breast Cancer Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative. Baseline staging tests in primary breast cancer: a practice guideline. Toronto: Cancer Care Ontario; 2003.

68. Haffty BG, Yang Q, Reiss M, Kearney T, Higgins SA, Weidhaas J, et al. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J Clin Oncol. 2006;24(36):5652-7.

69. Zhou P, Gautam S, Recht A. Factors affecting outcome for young women with early stage invasive breast cancer treated with breast-conserving therapy. Breast Cancer Res Treat. 2007;101(1):51-7.

70. Puglisi F, Follador A, Minisini AM, Cardellino GG, Russo S, Andreetta C, et al. Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications. Annals of Oncology. 2005;16(2):263-6.

71. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Breast MRI for detection or diagnosis of primary or recurrent breast cancer. Chicago: 2004. TEC Assessment Program Available from: http://www.bcbs.com/tec/vol19/19_1

72. Del FC, Borghese L, Cedolini C, Bestagno A, Puglisi F, Isola M, et al. Role of pre-surgical breast MRI in the management of invasive breast carcinoma. Breast. 2007;16:469-81.

73. Deurloo EE, Klein Zeggelink WF, Teertstra HJ, Peterse JL, Rutgers EJ, Muller SH, et al. Contrast-enhanced MRI in breast cancer patients eligible for breast-conserving therapy: complementary value for subgroups of patients. Eur Radiol. 2006;16(3):692-701.

74. Schnall MD, Blume J, Bluemke DA, Deangelis GA, Debruhl N, Harms S, et al. MRI detection of distinct incidental cancer in women with primary breast cancer studied in IBMC 6883. Journal of Surgical Oncology. 2005;92:32-8.

75. Boetes C, Veltman J, Van Die L, Bult P, Wobbes T, Barentsz JO. The role of MRI in invasive lobular carcinoma. Breast Cancer Research and Treatment. 2004;86(1):31-7.

76. Chung A, Saouaf R, Scharre K, Phillips E. The impact of MRI on the treatment of DCIS. The American Surgeon. 2005;71(9):705-10.

77. Morrow M, Harris J. More mastectomies: is this what patients really want? J Clin Oncol. 2009;27(25):4038-40.

78. Lehman C, Gatsonis C, Kuhl C, et al. MRI Evaluation of the Contralateral Breast in Women with Recently Diagnosed Breast Cancer. NEJM. 2007;356:1295-303.

79. Brennan ME, Houssami N, Lord S, Macaskill P, Irwig L, Dixon JM, et al. Magnetic Resonance Imaging Screening of the Contralateral Breast in Women With Newly Diagnosed Breast Cancer: Systematic Review and Meta-Analysis of Incremental Cancer Detection and Impact on Surgical Management. J Clin Oncol. 2009;27(33):5640-9.

80. Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol. 2008;29(16):3248-57.

81. Turnbull L, Brown S, Harvey I, Olivier C, Drew P, Napp V, et al. Comparative eff ectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. Lancet. 2010;375(9714):563-71.

82. National Institute for Health and Clinical Excellence. Early and locally advanced breast cancer: diagnosis and treatment London: NICE; 2009. NICE clinical guideline 80

83. Altinyollar H, Dingil G, Berberoglu U. Detection of infraclavicular lymph node metastases using ultrasonography in breast cancer. Journal of Surgical Oncology. 2005;92(4):299-303.

84. Podkrajsek M, Music MM, Kadivec M, Zgajnar J, Besic N, Pogacnik A, et al. Role of ultrasound in the preoperative staging of patients with breast cancer. European Radiology. 2005;15(5):1044-50.

85. Alvarez S, Anorbe E, Alcorta P, Lopez F, Alonso I, Cortes J. Role of sonography in the diagnosis of axillary lymph node metastases in breast cancer: a systematic review. American Journal of Roentgenology. 2006;186(5):1342-8.

86. Sloka JS, Hollett PD, Mathews M. A quantitative review of the use of FDG-PET in the axillary staging of breast cancer. Medical Science Monitor. 2007;13(3):RA37-46.

87. Gil-Rendo A, Zornoza G, Garcia-Velloso MJ, Regueira FM, Beorlegui C, Cervera M. Fluorodeoxyglucose positron emission tomography with sentinel lymph node biopsy for evaluation of axillary involvement in breast cancer. British Journal of Surgery. 2006;93(6):707-12.

88. Kumar R, Zhuang H, Schnall M, Conant E, Damia S, Weinstein S, et al. FDG PET positive lymph nodes are highly predictive of metastasis in breast cancer. Nuclear Medicine Communications. 2006;27(3):231-6.

89. Ueda S, Tsuda H, Asakawa H, Omata J, Fukatsu K, Kondo N, et al. Utility of 18F-fluoro-deoxyglucose emission tomography/computed tomography fusion imaging (18F-FDG PET/CT) in combination with ultrasonography for axillary staging in primary breast cancer. BMC Cancer. 2008;8:165.

90. Veronesi U, De Cicco C, Galimberti VE, Fernandez JR, Rotmensz N, Viale G, et al. A comparative study on the value of FDG-PET and sentinel node biopsy to identify occult axillary metastases. Annals of Oncology. 2007;18(3):473-8.

91. Shie P, Cardarelli R, Brandon D, Erdman W, Rahim NA. Meta-analysis: comparison of F-18 fluorodeoxyglucose-positron emission tomography and bone scintigraphy in the detection of bone metastases in patients with breast cancer. Clinical Nuclear Medicine. 2008;33(2):97-101.

92. Uematsu T, Yuen S, Yukisawa S, Aramaki T, Morimoto N, Endo M, et al. Comparison of FDG PET and SPECT for detection of bone metastases in breast cancer.[see comment]. AJR. 2005;American Journal of Roentgenology. 184(4):1266-73.

93. Nakai T, Okuyama C, Kubota T, Yamada K, Ushijima Y, Taniike K, et al. Pitfalls of FDG-PET for the diagnosis of osteoblastic bone metastases in patients with breast cancer.[see comment]. European Journal of Nuclear Medicine & Molecular Imaging. 2005;32(11):1253-8.

94. Pinder SE, Reis-Filho JS. Non Operative Breast Pathology: columnar cell lesions. J Clin Pathol. 2006.

95. Reis-Filho JS, Pinder SE. Non Operative Breast Pathology: lobular neoplasia. J Clin Pathol. 2006.

96. New Zealand Guidelines Group. Management of early breast cancer. Wellington: New Zealand Guidelines Group; 2009.

97. Dunne C, Burke JP, Morrow M, Kell MR. Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ. Journal of Clinical Oncology. 2009;27(10):1615-20.

98. Wright JR, Whelan TJ, McCready DR, O'Malley FP. Management of Ductal Carcinoma In Situ of the Breast. Toronto: Cancer Care Ontario; 2003.

99. Fischbacher C. Immediate versus delayed breast reconstruction. STEER. 2002;2(17):4-18.

100. Drucker-Zertuche M, Robles-Vidal C. A 7 year experience with immediate breast reconstruction after skin sparing mastectomy for cancer. Eur J Surg Oncol. 2007;33:140-6.

101. Gendy RK, Able JA, Rainsbury RM. Impact of skin-sparing mastectomy with immediate reconstruction and breast-sparing reconstruction with miniflaps on the outcomes of oncoplastic breast surgery. Br J Surg. 2003;90:433-9.

102. Javaid M, Song F, Leinster S, Dickson MG, James NK. Radiation effects on the cosmetic outcomes of immediate and delayed

autologous breast reconstruction: an argument about timing. Journal of Plastic, Reconstructive & Aesthetic Surgery. 2006;59:16-26.

103. Ansari B, Ogston SA, Purdie CA, Adamson DJ, Brown DC, Thompson AM. Meta-analysis of sentinel node biopsy in ductal carcinoma in situ of the breast. British Journal of Surgery. 2008;95(5):547-54.

104. FNCLCC. Recommandations pour la pratique clinique : Standards, Options et Recommandations 2004 pour la prise en charge des carcinomes canalaires in situ du sein. Paris: FNCLCC; 2004 September 2004.

105. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a meta-analysis. Cancer. 2006;106(1):4-16.

106. Lyman GH, Giuliano AE, Somerfield MR, Benson AB, 3rd, Bodurka DC, Burstein HJ, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. Journal of Clinical Oncology. 2005;23(30):7703-20.

107. Goodwin A, Parker S, Ghersi D, Wilcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast. Cochrane Database of Systematic Reviews; 2009. Issue 4. Art.No.: CD000563. DOI: 10.1002/14651858.CD000563.pub6

108. Shelley W, McCready D, Holloway C, Trudeau M, Sinclair S, and the Breast Cancer Disease Site Group. Management of Ductal Carcinoma in Situ of the Breast: A Clinical Practice Guideline. Cancer Care Ontario (CCO); 2006. Evidence-based Series #1-10 Version 2.2006: Section 1

109. Bijker N, Rutgers EJ, Duchateau L, Peterse JL, Julien JP, Cataliotti L. Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. Cancer. 2001;91(3):472-7.

110. Bulens P, Vanuytsel L, Rijnders A, van der Schueren E. Breast conserving treatment of Paget's disease. Radiother Oncol. 1990;17(4):305-9.

111. Dixon AR, Galea MH, Ellis IO, Elston CW, Blamey RW. Paget's disease of the nipple. Br J Surg. 1991;78:722-3.

112. Howard PW, Locker AP, Dowle CS, Ellis IO, Elston CW, Blamey RW. In situ carcinoma of the breast. Eur J Surg Oncol. 1989;15:328-32.

113. Polgár C, Orosz Z, Kovács T, Fodor J. Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. Cancer. 2002;94:1904-5.

114. Sutton RJ, Singh A, Baker CB, Sacks NPM. Is mastectomy overtreatment for Paget's disease of the nipple? Breast. 1999;8:191-4.

115. Chen CY, Sun LM, Anderson BO. Paget disease of the breast: Changing patterns of incidence, clinical presentation, and treatment in the U.S. Cancer. 2006;107:1448-58.

116. Mieog JSD, van der Hage JA, van de Velde CJH. Preoperative chemotherapy for women with operable breast cancer. Cochrane Database of Systematic Reviews; 2007. Issue 2. Art. No.: CD005002

117. Blichert-Toft M, Nielsen M, During M, Moller S, Rank F, Overgaard M, et al. Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. Acta Oncologica. 2008;47(4):672-81.

118. Jatoi I, Proschan MA. Randomized trials of breast-conserving therapy versus mastectomy for primary breast cancer: a pooled analysis of updated results. American Journal of Clinical Oncology. 2005;28(3):289-94.

119. McCready D, Holloway C, Shelley W, Down N, Robinson P, Sinclair S, et al. Surgical management of early stage invasive breast cancer: a practice guideline. Canadian Journal of Surgery. 2005;48(3):185-94.

120. Yang SH, Yang KH, Li YP, Zhang YC, He XD, Song AL, et al. Breast conservation therapy for stage I or stage II breast cancer: a

meta-analysis of randomized controlled trials. Annals of Oncology. 2008;19:1039-44.

121. Straver ME, Meijnen P, van Tienhoven G, van de Velde CJH, Mansel RE, Bogaerts J, et al. Sentinel node identification rate and nodal involvement in the EORTC 10981-22023 AMAROS trial. Ann Surg Oncol. 2010;17(7):1854-61.

122. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. Jama. 2011;305:(6):569-75.

123. Giuliano AE, McCall LM, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, et al. Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases. Annals of Surgery. 2010;252:426-33.

124. Lucci A, McCall LM, Beitsch PD, Whitworth PW, Reintgen DS, Blumencranz PW, et al. Surgical Complications Associated With Sentinel Lymph Node Dissection (SLND) Plus Axillary Lymph Node Dissection Compared With SLND Alone in the American College of Surgeons Oncology Group Trial Z0011. J Clin Oncol. 2007;25:3657-63.

125. Shah-Khan M, Boughey JC. Evolution of axillary nodal staging in breast cancer: clinical implications of the ACOSOG Z0011 trial. Cancer Control. 2012;19(4):267-76.

126. Friedrich JO, Adhikari NK, Beyene J. Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. BMC Med Res Methodol. 2007;7:5.

127. Cserni G, Gregori D, Merletti F, Sapino A, Mano MP, Ponti A, et al. Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer. Br J Surg. 2004;91(10):1245-52.

128. van Deurzen CHM, de Boer M, Monninkhof EM, Bult P, van der Wall E, Tjan-Heijnen VCG, et al. Non-sentinel lymph node metastases associated with isolated breast cancer cells in the sentinel node. Journal of the National Cancer Institute. 2008;100(22):1574-80.

129. Van Zee KJ, Manasseh DM, Bevilacqua JL, Boolbol SK, Fey JV, Tan LK, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. Ann Surg Oncol. 2003;10(10):1140-51.

130. Degnim AC, Reynolds C, Pantvaidya G, Zakaria S, Hoskin T, Barnes S, et al. Nonsentinel node metastasis in breast cancer patients: assessment of an existing and a new predictive nomogram. Am J Surg. 2005;190(4):543-50.

131. Pal A, Provenzano E, Duffy SW, Pinder SE, Purushotham AD. A model for predicting non-sentinel lymph node metastatic disease when the sentinel lymph node is positive. Br J Surg. 2008;95(3):302-9.

132. Kohrt HE, Olshen RA, Bermas HR, Goodson WH, Wood DJ, Henry S, et al. New models and online calculator for predicting non-sentinel lymph node status in sentinel lymph node positive breast cancer patients. BMC Cancer. 2008;8:66.

133. Specht MC, Kattan MW, Gonen M, Fey J, Van Zee KJ. Predicting nonsentinel node status after positive sentinel lymph biopsy for breast cancer: clinicians versus nomogram. Ann Surg Oncol. 2005;12(8):654-9.

134. National Comprehensive Cancer Network. Breast Cancer. 2012. NCCN Clinical Practice Guidelines in Oncology Version 3.2012

135. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet oncol. 2013.

136. Hickey BE, Francis D, Lehman MH. Sequencing of chemotherapy and radiation therapy for early breast cancer. Cochrane Database of Systematic Reviews. 2006;4:4.

137. Huang J, Barbera L, Brouwers M, Browman G, Mackillop W. Does delay in starting treatment affect the outcomes of radiotherapy: a systematic review. Journal of Clinical Oncology. 2003;21:555-63.

138. Lohrisch C, Paltiel C, Gelmon K, Speers C, Taylor S, Barnett J, et al. Impact on survival of time from definitive surgery to initiation of

adjuvant chemotherapy for early-stage breast cancer. J Clin Oncol. 2006;24(30):4888-94.

139. Cold S, During M, Ewertz M, Knoop A, Moller S. Does timing of adjuvant chemotherapy influence the prognosis after early breast cancer? Results of the Danish Breast Cancer Cooperative Group (DBCG). Br J Cancer. 2005;93(6):627-32.

140. Colleoni M, Bonetti M, Coates AS, Castiglione-Gertsch M, Gelber RD, Price K, et al. Early start of adjuvant chemotherapy may improve treatment outcome for premenopausal breast cancer patients with tumors not expressing estrogen receptors. The International Breast Cancer Study Group. J Clin Oncol. 2000;18(3):584-90.

141. Shannon C, Ashley S, Smith IE. Does timing of adjuvant chemotherapy for early breast cancer influence survival? J Clin Oncol. 2003;21(20):3792-7.

142. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366(9503):2087-106.

143. Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial.[see comment]. Journal of the National Cancer Institute. 2005;97(2):116-26.

144. Overgaard M, Nielsen HM, J O. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiother Oncol. 2007;82(3):247-53.

145. Kyndi M, Overgaard M, Nielsen HM, Sørensen FB, Knudsen H, Overgaard J. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. Radiother Oncol. 2009;90(1):74-9.

146. Kaija H, Maunu P. Tangential breast irradiation with or without internal mammary chain irradiation: results of a randomized trial. Radiother Oncol. 1995;36(3):172-6.

147. Musat E, Poortmans P, Van den Bogaert W, Struikmans H, Fourquet A, Bartelink H, et al. Quality assurance in breast cancer: EORTC experiences in the phase III trial on irradiation of the internal mammary nodes. Eur J Cancer. 2007;43(4):718-24.

148. Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet oncol. 2006;7(6):467-71.

149. START Trialists Group. The UK standardisation of breast radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet. 2008;371(9618):1098-107.

150. Whelan T, Mackenzie R, Julian J, LevineM, ShelleyW, Grimard L, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. Journal of the National Cancer Institute. 2002;94(15):1143-50.

151. James ML, Lehman M, Hider PN, Jeffery M, Francis DP, Hickey BE. Fraction size in radiation treatment for breast conservation in early breast cancer. Cochrane Database of Systematic Reviews. 2008(3).

152. Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol. 2007;25(22):3259-65.

153. Veronesi U, Orecchia R, Zurrida S, Galimberti V, Luini A, Veronesi P, et al. Avoiding axillary dissection in breast cancer surgery: a randomized trial to assess the role of axillary radiotherapy. Annals of Oncology. 2005;16(3):383-8.

154. Louis-Sylvestre C, Clough K, Asselain B, Vilcoq JR, Salmon RJ, Campana F, et al. Axillary treatment in conservative management of operable breast cancer: dissection or radiotherapy? Results of a

randomized study with 15 years of follow-up. Journal of Clinical Oncology. 2004;22(1):97-101.

155. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B, Senn HJ. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol. 2011;22(8):1736-47.

156. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J, et al. Assessment of Ki67 in Breast Cancer: Recommendations from the International Ki67 in Breast Cancer Working Group. J Natl Cancer Inst. 2011;103:1656-64.

157. Nielsen TO, Parker JS, Leung S, Voduc D, Ebbert M, Vickery T, et al. A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor-positive breast cancer. Clin Cancer Res. 2010;16(21):5222-32.

158. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst. 2009;101(10):736-50.

159. Wolff AC, Hammond MEH, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Journal of Clinical Oncology. 2007;25(1):118-45.

160. Wirapati P, Sotiriou C, Kunkel S, Farmer P, Pradervand S, Haibe-Kains B, et al. Meta-analysis of gene expression profiles in breast cancer: toward a unified understanding of breast cancer subtyping and prognosis signatures. Breast Cancer Res. 2008;10(4):R65.

161. Cheang MC, Voduc D, Bajdik C, Leung S, McKinney S, Chia SK, et al. Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clin Cancer Res. 2008;14(5):1368-76.

162. Colleoni M. Adjuvant therapies for special types of breast cancer. Breast. 2011;20 Suppl 1:S15.

163. Rakha EA, Aleskandarany M, El-Sayed ME, Blamey RW, Elston CW, Ellis IO, et al. The prognostic significance of inflammation and medullary histological type in invasive carcinoma of the breast. Eur J Cancer. 2009;45(10):1780-7.

164. Arriagada R, Spielmann M, Koscielny S, Le Chevalier T, Delozier T, Reme-Saumon M, et al. Results of two randomized trials evaluating adjuvant anthracycline-based chemotherapy in 1146 patients with early breast cancer. Acta Oncologica. 2005;44(5):458-66.

165. Hutchins LF, Green SJ, Ravdin PM, Lew D, Martino S, Abeloff M, et al. Randomized, controlled trial of cyclophosphamide, methotrexate, and fluorouracil versus cyclophosphamide, doxorubicin, and fluorouracil with and without tamoxifen for high-risk, node-negative breast cancer: treatment results of Intergroup Protocol INT-0102. Journal of Clinical Oncology. 2005;23(33):8313-21.

166. Levine MN, Pritchard KI, Bramwell VHC, Shepherd LE, Tu D, Paul N, et al. Randomized trial comparing cyclophosphamide, epirubicin, and fluorouracil with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer: update of National Cancer Institute of Canada Clinical Trials Group Trial MA5. Journal of Clinical Oncology. 2005;23(22):5166-70.

167. Ejlertsen B, Mouridsen HT, Jensen M-B, Andersen J, Cold S, Edlund P, et al. Improved outcome from substituting methotrexate with epirubicin: results from a randomised comparison of CMF versus CEF in patients with primary breast cancer. Eur J Cancer. 2007;43(5):877-84.

168. Huybrechts M, Hulstaert F, Neyt M, Vrijens F, Ramaekers D. Trastuzumab pour les stades précoces du cancer du sein. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre(KCE); 2006. KCE reports 34B (D/2006/10.273/23)

169. Bria E, Ciccarese M, Giannarelli D, Cuppone F, Nistico C, Nuzzo C, et al. Early switch with aromatase inhibitors as adjuvant hormonal therapy for postmenopausal breast cancer: pooled-

analysis of 8794 patients. Cancer Treatment Reviews. 2006;32(5):325-32.

170. Ferguson T, Wilcken N, Vagg R, Ghersi D, Nowak AK. Taxanes for adjuvant treatment of early breast cancer. 2007. Issue 4 (No.: CD004421.)

171. Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A. Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation. Health Technol Assess. 2007;11:1-144.

172. De Laurentiis M, Cancello G, D'Agostino D, Giuliano M, Giordano A, Montagna E, et al. Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. J Clin Oncol. 2008;26:44-53.

173. Trudeau M, Eisen A, Messersmith H, Pritchard K, and the Breast Cancer Disease Site Group. Adjuvant Taxane Therapy for Women with Early-stage, Invasive Breast Cancer: A Clinical Practice Guideline. Cancer Care Ontario; 2006. Evidence-based Series #1-7: Section 1

174. American Society of Clinical Oncology. 2006 Update of ASCO Practice Guideline Recommendations for the Use of White Blood Cell Growth Factors: Guideline Summary. J Oncol Pract. 2006;2(4):196-201.

175. Farquhar C, Marjoribanks J, Basser R, Hetrick S, Lethaby A. High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer. Cochrane Database Syst Rev. 2005(3):CD003142.

176. Lee S, Schover L, Partridge A, Patrizio P, Wallace W, Hagerty K, et al. American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients. J Clin Oncol. 2006;24(18).

177. Berry DL, Theriault RL, Holmes FA, et al. Management of breast cancer during pregnancy using a standardized protocol. J Clin Oncol. 1999;17:855-61.

178. Keleher AJ, Theriault RL, Gwyn KM, Hunt KK, Stelling CB, Singletary SE, et al. Multidisciplinary management of breast cancer concurrent with pregnancy. J Am Coll Surg. 2002;194(1):54-64.

179. Loibl S, von Minckwitz G, Gwyn K, Ellis P, Blohmer JU, Schlegelberger B, et al. Breast carcinoma during pregnancy. International recommendations from an expert meeting. Cancer. 2006;106(2):237-46.

180. Hahn KME, Johnson PH, Gordon N, Kuerer H, Middleton L, Ramirez M, et al. Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. Cancer. 2006;107(6):1219-26.

181. Peccatori FA, Azim HA, Jr., Scarfone G, Gadducci A, Bonazzi C, Gentilini O, et al. Weekly epirubicin in the treatment of gestational breast cancer (GBC). Breast Cancer Res Treat. 2009;115(3):591-4.

182. Gadducci A, Cosio S, Fanucchi A, et al. Chemotherapy with epirubicin and paclitaxel for breast cancer during pregnancy: case report and review of the literature. Anticancer Res. 2003;23:5225-9.

183. Gonzalez-Angulo AM, Walters RS, Carpenter RJ, et al. Paclitaxel chemotherapy in a pregnant patient with bilateral breast cancer. Clin Breast Cancer. 2004;5:317-9.

184. Sharma R, Hamilton A, Beith J. LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. Cochrane Database of Systematic Reviews. 2008;Issue 4 Art. No.: CD004562. DOI: 10.1002/14651858.CD004562.pub3.

185. Hackshaw A, Baum M, Fornander T, Nordenskjold B, Nicolucci A, Monson K, et al. Long-term effectiveness of adjuvant goserelin in premenopausal women with early breast cancer. Journal of the National Cancer Institute. 2009;101(5):341-9.

186. De Placido S, De Laurentiis M, De Lena M, Lorusso V, Paradiso A, D'Aprile M, et al. A randomised factorial trial of sequential doxorubicin and CMF vs CMF and chemotherapy alone vs chemotherapy followed by goserelin plus tamoxifen as adjuvant

treatment of node-positive breast cancer. British Journal of Cancer. 2005;92(3):467-74.

187. Eisen A, Trudeau M, Shelley W, Sinclair S, and the Breast Cancer Disease Site Group. The Role of Aromatase Inhibitors in Adjuvant Therapy for Postmenopausal Women with Hormone Receptor-positive Breast Cancer: Guideline Recommendations. Toronto: Cancer Care Ontario; 2008. Evidence-based Series #1-18: Section 1

188. Kaufmann M JW, Hilfrich J, Eidtmann H, Gademann G, Zuna I, et al. Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 Study. J Clin Oncol. 2007;25:2664-70.

189. Jonat W GM, Boccardo F, Kaufmann M, Rubagotti A, Zuna I, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. Lancet Oncol. 2006;7:991-6.

190. Coombes RC HE, Gibson LJ, Paridaens R, Jassem J, Delozier T, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med. 2004;350(11):1081-92.

191. Coombes RC KL, Snowdon CF, Paridaens R, Coleman RE, Jones SE, et a. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet. 2007;369:559-70.

192. The BIG 1-98 Collaborative Group. Letrozole Therapy Alone or in Sequence with Tamoxifen in Women with Breast Cancer. N Engl J Med. 2009;361:766-76.

193. Goss PE. Preventing relapse beyond 5 years: the MA.17 extended adjuvant trial. Seminars in Oncology. 2006;33(2 Suppl 7):S8-12.

194. Kim R, Tanabe K, Emi M, Uchida Y, Osaki A, Toge T. Rationale for sequential tamoxifen and anticancer drugs in adjuvant setting for patients with node- and receptor-positive breast cancer. Int J Oncol. 2005;26(4):1025-31.

195. Albain KS, Barlow WE, Ravdin PM, Farrar WB, Burton GV, Ketchel SJ, et al. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. Lancet. 2009;374(9707):2055-63.

196. Dahabreh I, Linardou H, Siannis F, Fountzilas G, Murray S. Trastuzumab in the Adjuvant Treatment of Early-Stage Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. The Oncologist. 2008;13:620-30.

197. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet. 2007;369(9555):29-36.

198. Suter TM PM, van Veldhuisen DJ, Muscholl M, Bergh J, Carlomagno C, et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. J Clin Oncol. 2007;25:3859-65.

199. Bria EC, Cuppone F, Fornier M, Nisticò C, Carlini P, Milella M, et al. Cardiotoxicity and incidence of brain metastases after adjuvant trastuzumab for early breast cancer: The dark side of the moon? A meta-analysis of the randomized trials. Breast Cancer Res Treat. 2008;109:231-9.

200. Perry N, Broeders M, de Wolf C, Tornberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. Annals of Oncology. 2008;19(4):614-22.

201. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273-83.

202. Perez E, Suman V, Davidson N, Gralow J, Kaufman P, et al. Results of Chemotherapy Alone, with Sequential or Concurrent Addition of 52 Weeks of Trastuzumab in the NCCTG N9831 HER2-Positive Adjuvant Breast Cancer Trial. In: CTRC-AACR, editor. 32rd San Antonio Breast Cancer Symposium; 2009.

203. Pavlakis N, Schmidt R, Stockler M. Bisphosphonates for breast cancer. Cochrane Database Syst Rev. 2005(3):CD003474.

204. Beslija S, Bonneterre J, Burstein H, Cocquyt V, Gnant M, Goodwin P, et al. Second consensus on medical treatment of metastatic breast cancer. Annals of Oncology. 2007;18(2):215-25.

205. Warr D, Johnston M, Breast Cancer Disease Site Group. Use of Bisphosphonates in Women with Breast Cancer. Practice Guideline Report #1-11. Toronto: Cancer Care Ontario; 2004.

206. Wong MH, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. Cochrane database of systematic reviews (Online). 2012;2:CD003474.

207. Mauri D, Valachis A, Polyzos NP, Tsali L, Mavroudis D, Georgoulias V, et al. Does adjuvant bisphosphonate in early breast cancer modify the natural course of the disease? A meta-analysis of randomized controlled trials. JNCCN Journal of the National Comprehensive Cancer Network. 2010;8:279-86.

208. Huang WW, Huang C, Liu J, Zheng HY, Lin L. Zoledronic acid as an adjuvant therapy in patients with breast cancer: A systematic review and meta-analysis. PLoS ONE. 2012;7.

209. Aft RL, Naughton M, Trinkaus K, Weilbaecher K. Effect of (Neo)adjuvant zoledronic acid on disease-free and overall survival in clinical stage II/III breast cancer. British Journal of Cancer. 2012;107(1):26.

210. Coleman RE, Marshall H, Cameron D, Dodwell D, Burkinshaw R, Keane M, et al. Breast-cancer adjuvant therapy with zoledronic acid. The New England journal of medicine. 2011;365:1396-405.

211. Gnant M, Mlineritsch B, Stoeger H, Luschin-Ebengreuth G, Heck D, Menzel C, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. Lancet Oncology. 2011;12(7):631-41.

212. Paterson AHG, Anderson SJ, Lembersky BC, Fehrenbacher L, Falkson CI, King KM, et al. Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel Project protocol B-34): A multicentre, placebo-controlled, randomised trial. The lancet oncology. 2012;13(7):July.

213. Cancer Australia. Bisphosphonates in early breast cancer: a systematic literature review. Surry Hills, NSW: Cancer Australia; 2011.

214. Klijn JG, Blamey RW, Boccardo F, Tominaga T, Duchateau L, Sylvester R. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol. 2001;19(2):343-53.

215. Ferretti G, Bria E, Giannarelli D, Felici A, Papaldo P, Fabi A, et al. Second- and third-generation aromatase inhibitors as first-line endocrine therapy in postmenopausal metastatic breast cancer patients: a pooled analysis of the randomised trials. Br J Cancer. 2006;94(12):1789-96.

216. Eisen A, Prichard K, Johnston M, Oliver T, Breast Cancer Disease Site Group. Role of aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer. Toronto: Cancer Care Ontario; 2003.

217. Flemming J, Madarnas Y, Franek JA. Fulvestrant for Systemic Therapy of Locally Advanced or Metastatic Breast Cancer in Postmenopausal Women: Guideline Recommendations. Toronto: Cancer Care Ontario; 2008. Evidence-based Series #1-13: Section 1

218. Flemming J, Madarnas Y, Franek JA. Fulvestrant for systemic therapy of locally advanced or metastatic breast cancer in postmenopausal women: a systematic review. Breast Cancer Research & Treatment. 2009;115(2):255-68.

219. Chia S, Gradishar W. Fulvestrant vs exemestane following non-steroidal aromatase inhibitor failure: first overall survival data from the EFECT trial. Breast Cancer Res Treat. 2007;106(Suppl 1):S115, A2091.

220. Carrick S, Parker S, Thornton CE, Ghersi D, Simes J, Wilcken N. Single agent versus combination chemotherapy for metastatic breast cancer (Review). 2009. Cochrane Database of Systematic Reviews Issue 2. Art. No.: CD003372. DOI: 10.1002/14651858.CD003372.pub3.

221. Carrick S, Ghersi D, Wilcken N, Simes J. Platinum containing regimens for metastatic breast cancer. Cochrane Database Syst Rev. 2004(3):CD003374.

222. Carrick S, Parker S, Wilcken N, Ghersi D, Marzo M, Simes J. Single agent versus combination chemotherapy for metastatic breast cancer. Cochrane Database of Systematic Reviews. 2005(2):CD003372.

223. Sledge GW ND, Bernardo P et al Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol. 2003;21:588-92.

224. Cardoso F, Bedard PL, Winer EP, Pagani O, Senkus-Konefka E, Fallowfield LJ, et al. International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. J Natl Cancer Inst. 2009;101(17):1174-81.

225. Bonneterre J, Dieras V, Tubiana-Hulin M, et al. Phase II multicentre randomised study of docetaxel plus epirubicin vs 5-fluorouracil plus epirubicin and cyclophosphamide in metastatic breast cancer. Br J Cancer. 2004;91:1466-71.

226. Jassem J, Pienkowski T, Pluzanska A, et al. Doxorubicin and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized phase III multicenter trial. J Clin Oncol. 2001;19:1707-15.

227. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 2002;20:2812-23.

228. Albain KS, Nag SM, Calderillo-Ruiz G, Jordaan JP, Llombart AC, Pluzanska A, et al. Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol. 2008;26(24):3950-7.

229. Chan S, Romieu G, Huober J, et al. Phase III study of gemcitabine plus docetaxel compared with capecitabine plus docetaxel for anthracycline-pretreated patients with metastatic breast cancer. J Clin Oncol. 2009;27(11):1753-60.

230. Chan A, Verrill M. Capecitabine and vinorelbine in metastatic breast cancer. Eur J Cancer. 2009;45(13):2253-65.

231. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group.[see comment]. Journal of Clinical Oncology. 2005;23(19):4265-74.

232. von Minckwitz G, du Bois A, Schmidt M, Maass N, Cufer T, de Jongh FE, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study.[see comment]. Journal of Clinical Oncology. 2009;27(12):1999-2006.

233. Cameron D, Casey M, Press M, Lindquist D, Pienkowski T, Romieu CG, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Research & Treatment. 2008;112(3):533-43.

234. Valachis A, Polyzos NP, Patsopoulos NA, Georgoulias V, Mavroudis D, Mauri D. Bevacizumab in metastatic breast cancer: a meta-analysis of randomized controlled trials. Review. Breast Cancer Res.Treat. 2010;122:(1):1-7.

235. An MM, Zou Z, Shen H, Liu P, Chen ML, Cao YB, et al. Incidence and risk of significantly raised blood pressure in cancer patients treated with bevacizumab: an updated meta-analysis. Eur.J.Clin.Pharmacol. 2010;66:(8):813-21.

236. Mackey JR, Kerbel RS, Gelmon KA, McLeod DM, Chia SK, Rayson D, et al. Controlling angiogenesis in breast cancer: a systematic review of anti-angiogenic trials. Review. Cancer Treat.Rev. 2012;38:(6):673-88.

237. Ranpura V, Hapani S, Wu S. Treatment-related mortality with bevacizumab in cancer patients: a meta-analysis (Structured abstract). JAMA. 2011;305:487-94.

238. Ranpura V, Pulipati B, Chu D, Zhu X, Wu S. Increased risk of high-grade hypertension with bevacizumab in cancer patients: a meta-analysis. Review 52 refs. Am.J.Hypertens. 2010;23:(5):460-8.

239. Wagner AD, Thomssen C, Haerting J, Unverzagt S. Vascular-endothelial-growth-factor (VEGF) targeting therapies for endocrine refractory or resistant metastatic breast cancer. Cochrane Database Syst Rev. 2012;7:CD008941.

240. Badger C, Preston N, Seers K, Mortimer P. Physical therapies for reducing and controlling lymphoedema of the limbs. Cochrane Database Syst Rev. 2004(4):CD003141.

241. McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. Cmaj. 2006;175(1):34-41.

242. Cramp F, Daniel J. Exercise for the management of cancer-related fatigue in adults. Cochrane Database of Systematic Reviews; 2008. Issue 2. Art. No.: CD006145. DOI: 10.1002/14651858.CD006145.pub2.

243. von Schoultz E, Rutqvist LE. Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. J Natl Cancer Inst. 2005;97(7):533-5.

244. Holmberg L, Iversen OE, Rudenstam CM, Hammar M, Kumpulainen E, Jaskiewicz J, et al. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. J Natl Cancer Inst. 2008;100(7):475-82.

245. Edwards AG, Hailey S, Maxwell M. Psychological interventions for women with metastatic breast cancer. Cochrane Database Syst Rev. 2004(2):CD004253.

246. Andersen BL, Yang H-C, Farrar WB, Golden-Kreutz DM, Emery CF, Thornton LM, et al. Psychologic intervention improves survival for breast cancer patients: a randomized clinical trial. Cancer. 2008;113(12):3450-8.

247. Lane LG, Viney LL. The effects of personal construct group therapy on breast cancer survivors. Journal of Consulting & Clinical Psychology. 2005;73(2):284-92.

248. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part II: Immunologic effects. Journal of Clinical Oncology. 2005;23(25):6097-106.

249. Taylor KL, Lamdan RM, Siegel JE, Shelby R, Moran-Klimi K, Hrywna M. Psychological adjustment among African American breast cancer patients: one-year follow-up results of a randomized psychoeducational group intervention. Health Psychology. 2003;22(3):316-23.

250. Antoni MH, Wimberly SR, Lechner SC, Kazi A, Sifre T, Urcuyo KR, et al. Reduction of cancer-specific thought intrusions and anxiety symptoms with a stress management intervention among women undergoing treatment for breast cancer. American Journal of Psychiatry. 2006;163(10):1791-7.

251. Vos PJ, Visser AP, Garssen B, Duivenvoorden HJ, de Haes HCJM. Effects of delayed psychosocial interventions versus early psychosocial interventions for women with early stage breast cancer. Patient Education & Counseling. 2006;60(2):212-9.

252. Andersen BL, Farrar WB, Golden-Kreutz DM, Glaser R, Emery CF, Crespin TR, et al. Psychological, behavioral, and immune changes after a psychological intervention: a clinical trial. Journal of Clinical Oncology. 2004;22(17):3570-80.

253. Lee V, Robin Cohen S, Edgar L, Laizner AM, Gagnon AJ. Meaning-making intervention during breast or colorectal cancer treatment improves self-esteem, optimism, and self-efficacy. Social Science & Medicine. 2006;62(12):3133-45.

254. Hack TF, Pickles T, Bultz BD, Ruether JD, Weir LM, Degner LF, et al. Impact of providing audiotapes of primary adjuvant treatment consultations to women with breast cancer: a multisite, randomized, controlled trial. Journal of Clinical Oncology. 2003;21(22):4138-44.

255. McGregor BA, Antoni MH, Boyers A, Alferi SM, Blomberg BB, Carver CS. Cognitive-behavioral stress management increases benefit finding and immune function among women with early-stage breast cancer. Journal of Psychosomatic Research. 2004;56(1):1-8.

256. Scheier MF, Helgeson VS, Schulz R, Colvin S, Berga S, Bridges MW, et al. Interventions to enhance physical and psychological functioning among younger women who are ending nonhormonal adjuvant treatment for early-stage breast cancer. Journal of Clinical Oncology. 2005;23(19):4298-311.

257. Stanton AL, Ganz PA, Kwan L, Meyerowitz BE, Bower JE, Krupnick JL, et al. Outcomes from the Moving Beyond Cancer psychoeducational, randomized, controlled trial with breast cancer patients. Journal of Clinical Oncology. 2005;23(25):6009-18.

258. Shapiro SL, Bootzin RR, Figueredo AJ, Lopez AM, Schwartz GE. The efficacy of mindfulness-based stress reduction in the treatment of sleep disturbance in women with breast cancer: an exploratory study. Journal of Psychosomatic Research. 2003;54(1):85-91.

259. Tatrow K, Montgomery GH. Cognitive behavioral therapy techniques for distress and pain in breast cancer patients: a meta-analysis. Journal of Behavioral Medicine. 2006;29(1):17-27.

260. Manne SL, Ostroff JS, Winkel G, Fox K, Grana G, Miller E, et al. Couple-focused group intervention for women with early stage breast cancer. Journal of Consulting & Clinical Psychology. 2005;73(4):634-46.

261. Northouse L, Kershaw T, Mood D, Schafenacker A. Effects of a family intervention on the quality of life of women with recurrent breast cancer and their family caregivers. Psycho-Oncology. 2005;14(6):478-91.

262. Scott JL, Halford WK, Ward BG. United we stand? The effects of a couple-coping intervention on adjustment to early stage breast or gynecological cancer. Journal of Consulting & Clinical Psychology. 2004;72(6):1122-35.

263. Owen JE, Klapow JC, Roth DL, Shuster JL, Jr., Bellis J, Meredith R, et al. Randomized pilot of a self-guided internet coping group for women with early-stage breast cancer. Annals of Behavioral Medicine. 2005;30(1):54-64.

264. Sandgren AK, McCaul KD. Short-term effects of telephone therapy for breast cancer patients. Health Psychology. 2003;22(3):310-5.

265. Winzelberg AJ, Classen C, Alpers GW, Roberts H, Koopman C, Adams RE, et al. Evaluation of an internet support group for women with primary breast cancer. Cancer. 2003;97(5):1164-73.

266. Beaver K, Tysver-Robinson D, Campbell M, Twomey M, Williamson S, Hindley A, et al. Comparing hospital and telephone follow-up after treatment for breast cancer: randomised equivalence trial. BMJ. 2009;338(a3147).

267. Ives A, Saunders C, Bulsara M, Semmens J. Pregnancy after breast cancer: population based study. BMJ. 2007;334(7586):194.

268. MacLean AB, Sauven P, for the Royal College of Obstetricians and Gynaecologists. Pregnancy and breast cancer. London: Royal College of Obstetricians and Gynaecologists; 2004.

269. Vlayen J, Stordeur S, Vrijens F, Van Eycken E. Quality indicators in oncology: prerequisites for the set–up of a quality system. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2011. KCE Reports 152 (D/2011/10.273/01)

270. 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.