integraal kankercentrum Nederland

NABON

Nationaal Borstkanker Overleg Nederland

Breast cancer

Dutch Guideline, version 2.0

Authorized: 2012

Methodology: Evidence based

Accountability: NABON

oncoline

Contents

INTRODUCTION

Approximately 14,000 women (and 100 men) are diagnosed with invasive breast cancer each year in the Netherlands, and about 1,900 have an in situ carcinoma. A woman's risk of having breast cancer over the course of her life is 12-13%. This means that breast cancer is the most common form of cancer in women in the Netherlands. Early detection, particularly via national breast cancer screening, combined with adjuvant therapy followed by locoregional treatment, improves the prognosis in women with breast cancer

The guideline on Breast Cancer Screening and Diagnostics, published in 2000, was updated in 2007. In 2002, the first multidisciplinary National Breast Cancer Guideline was published, it was revised in 2004, 2005 and 2006. In 2008 both guidelines were combined to Breast Cancer Guideline, which 2012 revision is now effected.

Objectives

This guideline is a document with recommendations and instructions to support daily practice. The guideline is based on the results of scientific research and expert opinion, with the aim of establishing good medical practice. It specifies the best general care for women with (suspected) breast cancer and for those who are eligible for screening. The guideline aims to serve as a guide for the daily practice of breast cancer screening, diagnostics, treatment and aftercare. This guideline is also used in the creation of informational materials for patients, in cooperation with the KWF (Dutch Cancer Society).

User guideline

This guideline is written for all the members of the professional groups that have contributed to its development. They are listed in the Imprint.

Guideline development group members

A core group consisting of a radiologist, surgeon, pathologist, medical oncologist and radiation therapist began preparing for the revision of the breast cancer practice guidelines in 2009. A multidisciplinary guideline development group was formed in early 2010 to implement the revision. This group consisted of mandated representatives from all of the relevant specialisations concerned with breast cancer, plus two delegates from the BVN (Dutch Breast Cancer Society) (see list of guideline development group members). The benefits of such a multidisciplinary approach are obvious: not only does it best reflect the care, but it offers the greatest possible expertise for the guideline. In composing the development group, geographic distribution of the members, balanced representation of the various organisations and agencies concerned, and a fair distribution in academic background were taken into account as much as possible.

The guideline development group received procedural and administrative support from IKNL (Comprehensive Cancer Centre for the Netherlands) and support on methodology from Bureau ME-TA. Partial funding was obtained from SKMS (Quality Funds Foundation of Dutch Medical Specialists). This subsidy would not have been possible without the extensive assistance provided by the NVvR (Radiological Society of the Netherlands).

Methods used by the guideline development group

In developing this guideline, four clinical questions were formulated. These questions emerge from an inventory of clinical problems collected in the field from professionals, patients and patient representatives.

1. What is the sensitivity, specificity, positive predictive value, negative predictive value and feasibility of MRI in addition to mammography, rather than mammography alone, for women with an increased risk of breast cancer due to family history?
2. For patients who have undergone breast-conserving therapy (BCT), what are the differences in local control, cosmetics and survival between hypofractionated radiation therapy regimens and the current (long-term) radiation therapy regimens?
3. For patients with (sub-) micrometastasis in the axillary sentinel lymph node, what are the differences in locoregional control and survival when adjuvant systemic therapy or regional treatment of the axillary region is used versus when it is not used?
4. For patients with an invasive breast tumour (5-30 mm) and at most 3 lymph node metastases, what new forms of risk profiling – as opposed to the traditional prognostic factors such as tumour size, lymph node status and grade of tumour differentiation – influence the choice of whether or not to start adjuvant therapy, and does this differ in patients under age 50, between ages 50 and 70, and over age 70?

With the help of the ME-TA information specialist, the guideline development group searched the medical literature for answers to these clinical questions, using established selection criteria. A description of the literature searches is given in the appendices at www.oncoline.nl/breastcancer. The guideline development group members selected the literature they found for relevance, and evaluated the quality and contents. The results of individual searches were compiled and summarised in evidence tables.
Aside from answering the clinical questions, subgroups have updated the guideline by subject, based on current evidence. The experts from the guideline developmental group were consulted regularly in this process.

The guideline development group formulated the final version of the guideline taking into consideration the results of discussions and comments gathered from a widely disseminated, nationwide written request for comments on the draft guideline.

How this guideline is organised

A revision of an existing guideline consists of revised and updated text. *Revised text* is new text based on an evidence-based review of the medical literature; *updated text* is the old guideline text which has been edited by the experts without performing a review of medical literature. Each section of the guideline states what type of revision has taken place. Each chapter of the guideline is structured according to a set format, given below. The purpose of this is to make the guideline transparent, so that each user can see on what literature and considerations the recommendations are based on.

Description of the literature

To the greatest extent possible, the answers to the fundamental questions (and therefore the recommendations in this guideline) were based on published scientific research. The articles selected were evaluated by an expert in methodology for their research quality, and graded in proportion to evidence using the following classification system:

Classification of research results based on level of evidence

A1	Research on the effects of diagnostics on clinical outcomes in a prospectively monitored, well-defined patient group, with a predefined policy based on the test outcomes to be investigated, or decision analysis research into the effects of diagnostics on clinical outcomes based on results of a study of A2-level and sufficient consideration is given to the interdependency of diagnostic tests.
A2	Research relative to a reference test, where criteria for the test to be investigated and for a reference test are predefined, with a good description of the test and the clinical population to be investigated; this must involve a large enough series of consecutive patients; predefined upper limits must be used, and the results of the test and the "gold standard" must be assessed independently. Interdependence is normally a feature of situations involving multiple diagnostic tests, and their analysis must be adjusted accordingly, for example using logistic regression.
B	Comparison with a reference test, description of the test and population researched, but without the other features mentioned in level A.
C	Non-comparative trials
D	Opinions of experts, such as guideline development group members

Conclusions

Based on the medical literature, one or more relevant conclusions are made for each section. The most important literature is listed according to the level of evidential strength, allowing conclusions to be drawn based on the level of evidence. All the medical literature included in the conclusion is described in the bibliography.

Classification of conclusions based on literature analysis

1	Based on 1 systematic review (A1) or at least 2 independent A2 reviews.
2	Based on at least 2 independent B reviews
3	Based on 1 level A2 of B research, or any level C research
4	Opinions of experts, such as guideline development group members

Other considerations
Based on the conclusion(s), recommendations are made. However, there are other considerations that contribute to formulation of the recommendation besides literature evidence, such as safety, the patients' preferences, professional expertise, cost-effectiveness, organisational aspects and social consequences. The other considerations are mentioned separately. In this manner, it is clear how the guideline development group arrived at a particular recommendation.

Recommendation
The final wording of the recommendation is the result of the scientific conclusion, taking into account the other considerations. The purpose of following this procedure and drawing up the guidelines in this format is to increase transparency.

References
An alphabetical list of literature references can be found at the end of the guideline.

All draft texts have been discussed by the guideline development group.

Implementation
Feasibility has been taken into account in developing the guideline. This included attention to factors that could promote or hinder putting the advice into practice. Examples include the implementation of an analysis of problems, the multidisciplinary composition of the guideline development group, and making active use of support from the guideline development group members. Presenting the draft guideline to the field and communicating what, if anything, is being done with the responses, also promotes implementation. In this manner, a guideline has been developed that answers current questions in the field.
The guideline is distributed widely and is available in digital form on the Oncoline web site (www.oncoline.nl/breastcancer). The guideline may also be brought to the attention of a wider audience in other periodicals or continuing education sessions, for example. To promote use of the guideline, we recommend that the regional tumour working groups and group practices, as well as scientific and professional organisations, repeatedly bring the guideline to the attention of their members. Any problems that may arise in using the guidelines can then be discussed and, when appropriate, submitted to the national guideline development group, as it is a "living" guideline. If desirable, parts of the guideline can be made more explicit by formulating regional additions or translation to the local situation in departmental and/or hospital protocols.
In principle, indicators are determined during development of the guideline that can be used to monitor implementation of the recommendations. Via a documentation project, these indicators can then be used to determine the extent of compliance with the guideline. The information from the documentation project becomes input for the revision of the guideline.

Conflicts of interest
Partial funding for the guideline revision was obtained from the Society of Dutch Medical Specialists in the framework of the SKMS. IKNL sponsored some of the cost. On two occasions, as well as at the beginning and end of the process, all of the members of the guideline development group were asked to fill out a statement of potential conflicts of interest, in which they stated their relationship with the pharmaceutical industry. A list of these statements of interest can be found in the appendices.

Updating/living guideline
The national Breast Cancer guideline 2012 is a living guideline, in other words there is no standard term of revision. NABON continually watches at new developments and clinical problems in the areas of screening, diagnostics, treatment and aftercare, and whether this requires an update.

Members and tasks

Chairmen

Prof. dr. J.W.R. Nortier, oncologist
Nederlandse Internisten Vereniging / Nederlandse Vereniging voor Medische Oncologie, LUMC
Prof. dr. E.J.T. Rutgers, surgeon
Nederlandse Vereniging voor Heelkunde / Nederlandse Vereniging voor Chirurgische Oncologie, NKI-AVL
Drs. M.J.C. van der Sangen, radiotherapist
Namens het Nationaal Borstkanker Overleg Nederland (NABON), Catharina Ziekenhuis
Dr. G. van Tienhoven, radiotherapist
Nederlandse Vereniging voor Radiotherapie en Oncologie, AMC
Drs. T. van Vegchel, project leader
Integraal Kankercentrum Nederland
Dr. J. Wesseling, pathologist
Nederlandse Vereniging voor Pathologie, NKI-AVL
Dr. H.M. Zonderland, radiologist
Nederlandse Vereniging voor Radiologie, AMC

Guideline working group

Dr. C.J. van Asperen, clinical geneticist
Vereniging Klinische Genetica Nederland, LUMC
Prof. dr. G.H. de Bock, epidemiologist
Nederlands Huisartsen Genootschap, UMCG
Dr. L.J. Boersma, radiotherapist
Nederlandse Vereniging voor Radiotherapie en Oncologie, Maastro Clinic
Dr. M. Bontenbal, oncologist
Nederlandse Internisten Vereniging / Nederlandse Vereniging voor Medische Oncologie, Erasmus MC, loc. Daniel den Hoed
Drs. M.C. Corsten, general practitioner
Nederlands Huisartsen Genootschap
Prof. dr. P.J. van Diest, pathologist
Nederlandse Vereniging voor Pathologie, UMCU
Dr. P.H.M. Elkhuizen, radiotherapist
Nederlandse Vereniging voor Radiotherapie en Oncologie, NKI-AVL
Dr. H.R. Franke, gynaecologist
Nederlandse Vereniging voor Obstetrie en Gynaecologie, MST
Prof. dr. G.J. den Heeten, radiologist
Nederlandse Vereniging voor Radiologie, Landelijk Referentiecentrum voor Bevolkingsonderzoek op Borstkanker
G. van der Heide-Schoon, patient
BorstkankerVereniging Nederland
J. Hidding, MSc. PT, physiotherapist
Koninklijk Nederlands Genootschap Fysiotherapie
Drs. M.G.G. Hobbelink, nucleair medicine specialist
Nederlandse Vereniging voor Nucleaire Geneeskunde, UMCU
Dr. J. Hoekstra-Weebers, psychologist
Nederlandse Vereniging voor Psychosociale Oncologie, Integraal Kankercentrum Nederland
Dr. Y. Jonasse, plastic surgeon
Nederlandse Vereniging voor Plastische Chirurgie, UMCU
Dr. C.M. Kets, clinical geneticist
Vereniging Klinische Genetica Nederland, UMCN
Prof. dr. H.J. de Koning, epidemiologist
Vereniging voor Epidemiologie, Erasmus Medisch Centrum
Dr. E.J.T. Krul, radiologist
Nederlandse Vereniging voor Radiologie, OLVG
Dr. Y.M. van der Linden, radiotherapist
Nederlandse Vereniging voor Radiotherapie en Oncologie, LUMC
Dr. M.B.E. Menke-Pluymers, surgeon
Nederlandse Vereniging voor Heelkunde / Nederlandse Vereniging voor Chirurgische Oncologie, Erasmus MC, loc. Daniel den Hoed
Dr. J.W.S. Merkus, surgeon
Nederlandse Vereniging voor Heelkunde / Nederlandse Vereniging voor Chirurgische Oncologie, Haga Ziekenhuis, locatie Rode Kruis Ziekenhuis

Prof. dr. M.F. von Meyenfeldt, surgeon
Nederlandse Vereniging voor Heelkunde / Nederlandse Vereniging voor Chirurgische Oncologie, MUMC
Drs. A.I.M. Obdeijn, radiologist
Nederlandse Vereniging voor Radiologie, Erasmus MC, loc. Daniel den Hoed
G.M. Smit-Hoeksma, MaNP, nurse specialist
Verpleegkundigen & Verzorgenden Nederland Oncologie, Waterlandziekenhuis
Dr. C.H. Smorenburg, oncologist
Nederlandse Internisten Vereniging / Nederlandse Vereniging voor Medische Oncologie, MCA
L.K. Tang-Liu, secretary
Integraal Kankercentrum Nederland
Prof. dr. V.C.G. Tjan-Heijnen, oncologist
Nederlandse Internisten Vereniging / Nederlandse Vereniging voor Medische Oncologie, MUMC
H.P.M. Verdonk, fysiotherapist
Koninklijk Nederlands Genootschap Fysiotherapie
Dr. P.J. Westenend, pathologist
Nederlandse Vereniging voor Pathologie, Laboratorium voor Pathologie
J. Witkamp-van der Veen, patient
BorstkankerVereniging Nederland
Dr. L.A.E. Woerdeman, plastic surgeon
Nederlandse Vereniging voor Plastische Chirurgie, NKI-AVL

Responsibility per chapter
Chapter 1: screening
Dr. H.M. Zonderland, dr. C.J. van Asperen, prof. dr. G.H. de Bock, drs. M.C. Corsten, prof. dr. G.J. den Heeten, dr. C.M. Kets, dr. M.B.E. Menke-Pluymers, drs. A.I.M. Obdeijn
Chapter 2: diagnostics
Dr. H.M. Zonderland, prof. dr. G.H. de Bock, drs. M.C. Corsten, prof. dr. P.J. van Diest, drs. A.I.M. Obdeijn, prof. dr. E.J.T. Rutgers
Chapter 3: loc(oregion)al treatment
Prof. dr. E.J.T. Rutgers, dr. P.H.M. Elkhuizen, dr. P.J. Westenend, dr. L.A.E. Woerdeman, dr. H.M. Zonderland
Chapter 4: pathology
Dr. J. Wesseling, dr. M. Bontenbal, prof. dr. P.J. van Diest, dr. P.J. Westenend,
Chapter 5: risk profiling
Dr. C.H. Smorenburg, dr. P.H.M. Elkhuizen, dr. J.W.S. Merkus
Chapter 6: adjuvant systemic therapy
Dr. M. Bontenbal, dr. L.J. Boersma, prof. dr. J.W.R. Nortier
Chapter 7: neoadjuvant systemic therapy
Dr. G. van Tienhoven, prof. dr. V.C.G. Tjan-Heijnen, dr. P.H.M. Elkhuizen, dr. E.J.T. Krul, dr. J.W.S. Merkus
Chapter 8: locoregional recurrence
Dr. G. van Tienhoven, prof. dr. V.C.G. Tjan-Heijnen, prof. dr. E.J.T. Rutgers
Chapter 9: metastatic breast cancer
Prof. dr. J.W.R. Nortier, dr. Y.M. van der Linden, dr. C.H. Smorenburg
Chapter 10: male breast cancer
Dr. H.M. Zonderland, dr. Y.M. van der Linden, dr. C.H. Smorenburg
Chapter 11: pregnancy and fertility
Dr. G. van Tienhoven, dr. M. Bontenbal, dr. H.R. Franke, G. van der Heide-Schoon
Chapter 12: aftercare and follow-up
Dr. L.J. Boersma, prof. dr. G.H. de Bock, drs. M.C. Corsten, G. van der Heide-Schoon, J. Hidding, MSc. PT, dr. J. Hoekstra-Weebers, dr. E.J.T. Krul, prof. dr. M.F. von Meyenfeldt, G.M. Smit-Hoeksma, MaNP, H.P.M. Verdonk, J. Witkamp-van der Veen, dr. H.M. Zonderland
Chapter 13: organisation of care
G.M. Smit-Hoeksma, MaNP, dr. L.J. Boersma, dr. H.M. Zonderland

Responsibility per clinical question
What is the sensitivity, specificity, positive predictive value, negative predictive value and feasibility of MRI in addition to mammography, rather than mammography alone, for women with an increased risk of breast cancer due to family history?
dr. H.M. Zonderland, drs. A.I.M. Obdeijn

For patients who have undergone breast-conserving therapy (BCT), what are the differences in local control, cosmetics and survival between hypofractionated radiation therapy regimens and the current (long-term) radiation therapy regimens?
drs. M.J.C. van der Sangen, dr. G. van Tienhoven

For patients with (sub-)micrometastasis in the axillary sentinel lymph node, what are the differences in locoregional control and survival when adjuvant systemic therapy or regional treatment of the axillary region is used versus when it is not used?

dr. G. van Tienhoven, prof. dr. V.C.G. Tjan-Heijnen, dr. J. Wesseling

In patients with an invasive breast tumour (5-30 mm) and at most 3 lymph node metastases, what new forms of risk profiling – as opposed to the traditional prognostic factors such as tumour size, lymph node status and grade of tumour differentiation – influence the choice of whether or not to start adjuvant therapy, and does this differ in patients under age 50, between ages 50 and 70, and over age 70?

dr. P.H.M. Elkhuizen, dr. J.W.S. Merkus, dr. C.H. Smorenburg

Editors

Dr. H.M. Zonderland, drs. T. van Vegchel

Responsibilty for translation

Dr. H.M. Zonderland, prof. dr. J.W.R. Nortier, prof. dr. E.J.T. Rutgers, drs. M.J.C. van der Sangen, dr. G. van Tienhoven, drs. T. van Vegchel, dr. J. Wesseling

Several components are co-created with the support of the NVMO breast cancer group, the Dutch Radiotherapy Platform for Breast Cancer (LPRM) and the Breast Cancer Care Special Interest Group (SIG) Oncology Nursing Society.

Screening

Screening may be done using breast self-examination, clinical breast examination, mammography, ultrasound or MRI. If screening is to be effective, at a minimum the following conditions must be met:

- The cancer must occur often enough in the population being screened.
- The chance of detecting cancer using the screening method must be great enough (high enough prevalence). The number of false-positive and false-negative results must be limited as much as possible (high sensitivity and specificity).
- There must be a great enough chance of improving the prognosis by treating the cancer that was detected by screening.

1.1 Screening methods

1.1.1 Regular breast self-examination as a screening method

Four systematic reviews have evaluated screening by means of regular breast self-exam [Kösters, 2003; Weiss, 2003; Elmore, 2005; Nelson, 2009]. In addition, there are both prospective and retrospective cohort studies comparing regular breast self-exams as a screening method with not performing them, and comparing cancers that are found by women themselves with those that are not.
Women can detect pre-symptomatic breast cancer by performing regular breast self-exams. This does not lead to a reduction in mortality, however. After analyzing the results of two large RCTs from St. Petersburg, Russia and Shanghai, comparing one group of women who were given extensive training in how to perform regular breast self-exams with another group of women who were not advised to, the Cochrane review by Kösters (2003) found that the average tumour size was the same, as was the rate of death from breast cancer. Women who perform regular breast self-exams have a greater chance of having unnecessary breast surgery for a benign condition. This has been confirmed by other comparative studies. [Elmore, 2005; Weiss, 2003; Humphrey, 2002; Nelson, 2009]. This is one reason that the US Preventive Services Task Force no longer recommends instructing patients to perform regular breast self-exams [USPSTF, 2009].
On the other hand, the percentage of cancers detected because they are palpable is still significant. In a retrospective study of 41,427 diagnostic mammograms, Barlow (2002) found that when a breast lump was felt by the woman herself, the sensitivity of the mammogram increased. The percentage of cancers was larger in this group than when there was no self-detected lump: 72.2% versus 48.4%. In other words, an abnormality felt by the woman herself is positively associated with an actual mass being present. This has been confirmed in multiple studies and applies in particular to the palpable abnormality, not to other symptoms such as nipple discharge, local pain, etc. [Kavanagh, 2000; Lumachi, 2002; Aiello, 2004]. The specificity is adversely impacted, however, especially in the young age groups, due to a relatively small chance of breast cancer compared with a much greater chance of benign abnormalities [Thomas, 2002].
Furthermore, Barlow's test results (2002), cannot be traced back exclusively to mammography, because additional ultrasound was performed when indicated, which is also daily practice in the Netherlands.
Women who have undergone breast-conserving therapy (BCT) for breast cancer form a separate group. The locoregional recurrences that develop are found just as often by the woman herself as they are by clinical breast exams and mammograms [Orel, 1992; Elkhuizen, 1998].

Conclusions

Level 1	Breast cancers detected through regular breast self-examination have no better prognosis than breast cancers detected by other means. A1 Kösters 2003, Elmore 2005, Weiss 2003, Nelson 2009

Level 1	A self reported lump by the woman is positively associated with an actual mass being present. A2 Barlow 2002, Lumachi 2002, Aiello 2004

Level 1	The sensitivity of the mammogram increases for a self reported lump by the woman, but the specificity decreases, especially in very young women.

	A2 Barlow 2002, Kavanagh 2000, Thomas 2002

Other considerations
The finding that regular breast self-exams have no value as a screening method has caused confusion. In general, knowledge of one's own body is seen as positive (breast awareness)and can be propagated. Questions, women ask their doctors, the breast cancer team, and patient organisations, etc., about how and why to do breast self-examination should be answered likewise .
Regular breast self-examination is not recommended, but that does not mean that palpable abnormalities and any other symptoms found by a woman at any given moment should not be taken seriously. The potential presence of a palpable abnormality causes worry, so it should be investigated regardless of the woman's age or risk profile. If the finding is not clearly benign, additional imaging should be done and low threshold referral to a breast outpatient clinic is recommended.
Women at screening age should be told that a lump is a reason for further imaging and that screening is not suited to this. What must be avoided is having the symptomatic woman feel unjustifiably reassured by screening.

Recommendations
Regular breast self-exams are not recommended as a method for reducing mortality from breast cancer.

A woman's request for information and explanations with regard to breast self-exams and with regard to self reported lumps should always be honored; it is very important to reassure young women who are worried.

In each case it must be decided whether a palpable abnormality found by the woman herself qualifies for imaging or referral to a breast cancer clinic.

1.1.2 Clinical breast examination as a screening method
The same four systematic reviews that evaluated screening by periodic breast self-exam also assessed screening by clinical breast exams [Kösters, 2003; Weiss, 2003; Elmore, 2005; Nelson, 2009]. Barton conducted a meta-analysis of clinical breast examinations in 1999. Besides these, there are cohort studies comparing clinical breast examination to imaging techniques, in particular mammography, as screening methods. The CNBSS-2 study [Miller, 2000] is an RCT with clinical breast examination as one of the study arms. Especially in the large studies, clinical breast examination is performed by trained health care staff. One of the differences between breast self-examination and clinical breast examination is the quality standards that can be placed on clinical breast examination. Studies indicate that a good clinical breast examination requires training and takes time, at least several minutes. When these conditions are met, no difference in quality is reported between the results from doctors and from other health care staff [Coleman, 2001]. Kösters (2003) is less clear with respect to clinical breast examination than breast self-examination.
In studies, the sensitivity and positive predictive value are limited. Feigin (2006) describes a retrospective study on the role and costs of clinical breast examination by nurse practitioners compared with mammography in 60,027 asymptomatic women. Without clinical breast examinations, 3% of cancers would have been missed. The costs were over $122,000 per cancer found.
The results are highly dependent on the composition of the population. In the prospective study conducted by Oestreicher (2005) in 61,688 asymptomatic women of age 40 and older, the mean sensitivity was 4% and was highest in women between the ages of 50-59 with dense breasts (6.8%) and lowest in women between the ages of 50 and 59 with adipose breasts (1.8%).
In an observational study, Chiarelli (2009) compared screening units where only mammography was performed with screening units in which mammography and clinical breast examination were conducted. In the latter group, 4 more cancers were found in 10,000 women, compared to 219 false-positive findings.
Similarly, very few additional cancers are found when women at high or very high risk are screened using clinical breast examination in combination with mammography and MRI [Warner, 2004]. These studies contain relatively small populations. In the MRISC screening study [Rijnsburger, 2010] the sensitivity is 20.6%. Out of 98 breast cancers, 3 were exclusively detected using clinical breast examination. At 10.3%, the positive predictive value is slightly better than that of mammography (8.5%) and MRI (7.7%).

Conclusions

Level 1	Clinical breast examination combined with mammography for breast cancer screening has a low sensitivity and a high percentage of false-positive findings, and is therefore not cost-effective. A1 Nelson 2009 A2 Oestreicher 2005, Chiarelli 2009 B Feigin 2006, Elmore 1998, Bobo 2000, Elmore 2005, Pisani 2006

Level 3	In women with an increased risk of breast cancer, the number of false-positive palpation findings is slightly more favorable than with mammography and MRI. A2 Rijnsberger 2010

Other considerations
Clinical breast examination, which can detect presymptomatic cancers, is an integral part of every consultation for women with breast pathology. This method can be used as a screening method in areas of the world where screening mammography is unavailable. However, regular clinical breast examination in addition to imaging as a selected screening method is not cost-effective in the general population of the Netherlands.

Recommendations
Clinical breast examination is part of the consultation.

Clinical breast examination is indicated when there are symptoms and when palpable abnormalities are found by the woman herself during a self-exam.

For women in the general population without a history of breast cancer, clinical breast examination as a screening method in addition to imaging has very limited added value for finding a primary breast carcinoma, and is therefore not recommended.

Clinical breast examination in women who are screened outside the national breast screening programme has limited added value.

1.1.3 Screening by mammography
Mammography is the only screening method with a proven cost-effective reduction in mortality, particularly in women between the ages of 50 and 75 [de Koning 2003, Otto 2003, Groenewoud 2007]. In a review of the results of long-term screening programs in 10 countries, a 16-36% reduction in mortality was found in women who were invited and a 24-48% reduction in mortality in women who had participated at least once in the screening. Correcting for selection bias, the trend in mortality reduction remained consistent. There are as yet no screening programs with a follow-up duration of 25 years or more, as would be required to make a definitive statement on the impact of screening.
Not all the reduction in mortality can be attributed to screening; one third of the reduction may be attributable to adjuvant systemic therapy [Schopper, 2009]. Evaluation of case control studies also show a consistent decrease in mortality from participation in mammography screening, with the difference between screened and non-screened women varying between 38% and 70%. The large variation seems to be due to differences in organisational structure and level of participation [Paap, 2010].

Both the US Preventive Task Force and the national breast screening programme recommend women between the ages of 50 and 74 [USPST, 2009] or women between 50 and 75 [RIVM, 2008] undergo screening by mammogram once every 2 years. Screening women under the age of 50 is advised only in individual high risk cases, and should be done annually. The number of interval cancers would otherwise be disproportionately high because of the higher rate at which some of the cancers grow in this group [Tabar, 1995]. The disadvantages of screening increase even more with age, due to various factors. There are indications that the sojourn time (the period during which the tumour is asymptomatic, but can be detected by testing) increases with age [Fracheboud, 2006]; apart from this, additional comorbidity plays a role. This means that the negative effects of screening become increasingly relevant in older women [Mandelblatt 2009]. The number of years of life gained also decreases relatively [Kerlikowske, 1999]. This is seen as support for the decision to stop screening women in the national breast screening programme when they reach the age of 75.

Dosimetry

Digital mammography is used in the screening practice in the Netherlands. The mean tissue dose per mammogram is highly dependent on the thickness of the breast and is about 1.66 mGy for a standard exposure of 6 cm (mGy = milliGray = common unit for radiation exposure dose). The average dose per test is about 3 times 1.66 mGy. This number varies greatly per individual; the dose can be as high as 2.12 mGy per test in women who have very thick breasts and a lot of glandular tissue. The glandular doses are monitored continuously by the LRCB (National Expert and Training Centre for Breast Cancer Screening) [LRCB, 2008]. They are below the acceptable dose limits set by the EUREF (European Reference Organisation for Quality Assured Breast Screening and Diagnostic Services) (2006).
In comparison: each resident of the Netherlands absorbs approximately 2.5 mGy annually from natural background radiation coming from space and the earth [RIVM, 2003].

Risk estimation and risk figures

The chance of radiation-induced cancer is very small and cannot be calculated; it can only be estimated based on epidemiological risk models from retrospective studies. Such cancers cannot be distinguished from "ordinary" cancers, so it is very difficult to estimate the risk accurately. Furthermore, the latency period can be very long: up to 20 years. An analysis by Preston, combining data from eight cohorts, found a linear relationship between the extra risk of breast cancer and the radiation dose [Preston, 2002].

The lifetime risk of getting radiation-induced breast cancer depends on the age at which exposure began. It is very low in women aged 50 to 65: 1 per million per mGy dose. The lifetime risk for a woman between the age of 25 and 30 is almost twice as high (1.8) [NHSBSP, 2003; Berrington de Gonzalez, 2005].
A British screening study estimates the ratio of the number of detected cancers to the number of induced cancers at 170:1. This ratio worsens where there is more glandular tissue [NHSBSP, 2003]. A Dutch study on risk models assuming a dose of 1.3 mGy per exposure found the ratio between the number of detected and the number of induced lethal cancers to be 684:1 [de Gelder, 2011].

BEIR VII (2006) provides with a model for tumour induction resulting from ionizing radiation. In this model, the additional risk of tumours resulting from ionizing radiation increases quadratically with decreasing age. Therefore, the younger a woman is when exposed to ionizing radiation and the higher the dose, the greater the chance of tumour induction.
BRCA1 and BRCA2 genes contribute to DNA repair processes. Theoretically, mutation carriers will therefore be less able to repair any damage after their exposure to ionizing radiation. On this basis it must be assumed that the chance of a radiation-induced breast cancer in this population is greater than in non-carriers. To get a sense of these risks, a systematic search was done of the medical literature over the period 1989-2009, aimed at finding studies on exposure to low-dose radiation and risk of breast cancer in women who had a higher breast cancer risk due to a family history or gene mutation [Jansen-van der Weide, 2010]. This search found 7 studies [Andrieu, 2006; Bernstein, 2006; Goldfrank, 2006; John, 2007; Ma, 2008; Millikan, 2005; Narod, 2006]. Since none of the studies provided precise information on the radiation doses to which the patients were exposed, the cumulative dose was estimated.
The odds ratios from the various studies were pooled. Low-dose radiation exposure was found to increase the risk of breast cancer by 1.3 (95% CI 0.9-1.8) in the group of women with an increased risk of breast cancer. Exposure before the age of 20 gave a higher risk of radiation-induced breast cancer (OR 2.0; 95% CI 1.3-3.1), as did an average of more than 5 screenings (OR 1.8 95% CI 1.1-3.0). Exposure between the ages of 20 and 40 also gave a higher risk, albeit not significant (OR 1.3; 95% CI 0.96-1.7).

Conclusions

Level 1	Screening of the general population by mammography starting at age 50 reduces mortality. There is a difference in mortality between women who do participate in screening and women who do not. One third of the proven reduction in mortality might be attributable to adjuvant systemic therapy. A1 Schopper 2009, Paap 2010

Level 1	For a woman between the ages of 50 and 75 who participates in the national breast screening programme, the lifetime risk of getting a lethal radiation-induced breast cancer is estimated at 1.6 per 100,000 women. The lifetime risk for a woman between 25 and 30 years of age is almost twice as high. A1 NHSBSP 2003, de Gelder 2010

Level 3	Exposure to low-dose ionizing radiation elevates the risk of tumour induction 1.3 times in women with a BRCA1 or 2 gene mutation, compared to non-exposed women with a BRCA1 or 2 gene mutation. B Jansen-van der Weide 2010

Other considerations
Radiation-induced cancers cannot be distinguished from breast cancers from other causes. The risk of their occurrence is very small, and they occur only after a latency period of at least 10-20 years. Nevertheless, extra caution is advised, since this is a matter of annual radiation exams in healthy women. The LRCB therefore provides continuous monitoring and quality control.

Recommendations
Screening by mammography is indicated for women in the general population between the ages of 50 and 75, with a screening interval of 2 years.

Because of the elevated risk of interval carcinoma in women between ages 30 and 50, a screening interval of one year is recommended for this group.

Because of the elevated risk of radiation-induced tumours in young women, specifically gene mutation carriers, a starting age of 30 is advised for this group.

Breast cancer screening is not advised for women over age 75.

1.1.4 Screening by ultrasound
Results of the 14-centre study [ACRIN 6666 trial; Berg, 2008] were published in 2008, comparing cancer detection by means of screening mammography with that of screening mammography plus screening by ultrasound. The study population consisted of 2,809 women who had heterogeneously dense glandular tissue in at least one quadrant. Almost all the women had an elevated risk of breast cancer with an RR of 2.5 or more. Using mammography, cancer detection was 7.6 per 1,000. By adding ultrasound to the screening, this figure rose by 4.2, reaching 11.8 per 1,000 (95% CI 1.1-7.2). The average size of the tumours detected by ultrasound was 10 mm, 92% were invasive, 89% were lymph node negative. The positive predictive value (PPV) of the mammography was 22.6%; after adding ultrasound this fell to 11.2%. The average duration of the ultrasound examination was 19 minutes, not including time for comparison with earlier examinations, contact and discussions with the patients, or reporting time. A follow-up study into the cost-effectiveness is in progress. In a single-centre study, 6 cancers were found in 1,862 women who underwent an ultrasound screening performed by radiology technicians.
The results may be compared with 6 previously published single-centre studies. In these studies a total of 42,838 ultrasound screening exams were performed, from which a total of 150 cancers were found in 126 women. Ninety-four percent (94%) were invasive and 70% were less than 1 cm [Kolb, 2002; Buchberger, 2000; Crystal, 2003; Gordon, 1995; Kaplan, 2001; Leconte 2003]. In these studies, as well, there were women with an elevated risk and dense glandular tissue. In 5 studies, women with an elevated risk underwent mammography, ultrasound, and MRI. The combined sensitivity of mammography and ultrasound was 52%, the combined sensitivity of mammography and MRI was 92.7%. The percentage of false positives was higher than with MRI [Kuhl, 2005; Lehman, 2007; Sardanelli, 2007; Warner, 2004; Berg, 2009].

Conclusions

Level 1	The added cancer detection yield from screening with ultrasound added to mammography is on average 4.2 cancers for every 1,000 women with an elevated breast cancer risk and dense glandular tissue, but also leads to a substantial increase in false positives.

	A2 Berg 2008, Berg 2009

Level 3	If mammography screening is combined with MRI screening, ultrasound screening has no added value. A2 Berg 2009

Level 3	Ultrasound screening in women with a lifetime risk of <15% who do not have dense glandular tissue has no added value. A2 Berg 2009

Other considerations
Just as in the 14-centre trial, in the Netherlands a radiologist performs the ultrasound examination of the breast, preferably the same radiologist who supervises and interprets the mammogram. Screening by a medical specialist, including the increase in the number of biopsies, is probably not cost-effective. There are developments in progress, for example in the area of automated ultrasound systems, to handle the practical application problems, but the image resolution with these systems is not yet state of the art. Training of special staff can also be considered. It must also be realised that the results of studies always give a somewhat flattering picture compared to daily practice, in which there is no controlled or standardised way of working. The study population consisted only of women with an elevated risk of breast cancer and dense glandular tissue in at least one quadrant. Nevertheless, based on this study ultrasound screening could be considered in individual cases, if other imaging techniques are not possible.
Digitisation has increased the interpretability of dense glandular tissue, and its sensitivity is also increased by the presence of earlier images [Barlow, 2002]. The results of the cost-effectiveness study that will comprise the final part of the 14-centre trial are important in helping to define the subgroup of patients who are eligible for this form of screening, for lack of better modalities.

Recommendations
Screening by ultrasound is not recommended in the general population.

Screening by ultrasound for women with an elevated risk is only recommended when other forms of screening cannot be used.

1.1.5 Screening by MRI
Clinical question: What is the sensitivity, specificity, positive predictive value, negative predictive value and feasibility of MRI in addition to mammography, rather than mammography alone, for women with an increased risk of breast cancer due to family history?

Diagnostic accuracy
Sensitivity / specificity
Lord's systematic review (2007) is qualitatively the best implemented and therefore provides the most reliable estimate of the diagnostic accuracy of MRI for this indication. It shows that, based on 5 studies, the sensitivity increases when MRI is added to mammography, namely 58% (95% CI 47-70) incremental sensitivity. In absolute terms, the sensitivity of MRI in combination with mammography is 94% (95% CI 86-98).
The specificity was too heterogeneous to be able to pool in a meta-analysis; for MRI combined with conventional tests it varied from 77-96%. The authors estimate that for every 1,000 screens, 10-24 additional cancers are detected by adding MRI.
Two studies published after this systematic review confirm these results for sensitivity and specificity [Bigenwald, 2008; Kuhl 2010]. But Hoogerbrugge (2008) reports a much lower sensitivity of 71% for MRI combined with mammography and 60% for just MRI. The reason for this lower sensitivity is not clear. Weinstein (2009) found a sensitivity of 71% for MRI and a specificity of 79%.

Cut-off values
In Warner's systematic review (2008) the sensitivity of MRI for BI-RADS 3 is not significantly different from that for BI-RADS 4; the specificity is, however, significantly lower for BI-RADS 3 than for BI-

RADS 4 (86% vs. 96%). Bigenwald (2008) also reports the sensitivity according to the BI-RADS score, with an apparent trend of decreasing sensitivity as the BI-RADS score increases, but with greater inaccuracy due to the small sample size. This study does not give specificity statistics.

Subgroups

Bigenwald (2008) reports the sensitivity of MRI vs. mammography based on the density of the breast tissue. Unfortunately, this study is small, so the estimates are imprecise. Their results show a possible trend of sensitivity decreasing as breast tissue density increases, but the confidence intervals are very wide, so the trend is not significant.

Some studies included a few women with a BRCA1/2 mutation [Hoogerbrugge, 2008], others included women with an elevated risk based on a mutation or family history [Bigenwald, 2008; Kriege, 2006; Kriege, 2007], or breast cancer in their own previous medical history [Kuhl, 2010; Weinstein, 2009]. There is no clear difference in sensitivity and specificity between these different groups. The heterogeneity within each group is at least as significant as the heterogeneity between the groups: for MRIs, Hoogerbrugge reports a sensitivity of 60% and Weinstein 71%, whereas the other studies report sensitivity ranging from 57-100%.

Effect of the screening round

All the studies included women with an elevated risk, who in many cases had already had a mammogram before the study began, but had never had an MRI. This distorts the comparison between MRI and mammography, because in the case of MRI scans, prevalent tumours are found in the first round, while in the case of mammograms it is no longer the first round.

Two studies evaluated a possible effect based on screening round [Hoogerbrugge, 2008; Kriege, 2006]. The first study found a decrease in the number of positive MRI scans, namely 18% after the first round and 9% in subsequent rounds. Kriege (2006) found a significant trend ($p<0.001$) for the number of positive MRI scans over the various rounds: 12.9% in the first round, 11.3% in the second round, 12.7% in the third round, 9.3% in the fourth round and 6.9% in the fifth and subsequent rounds. This study also evaluated the effect of undergoing a mammogram for inclusion in the study, and found 14.9% positive MRI scans in women who had had a mammogram previously, and 8.3% positive MRI scans in women without previous mammograms ($p<0.001$). Notably, for MRI scanning in women who had not had any previous mammograms, a sensitivity of 57% was found for invasive breast cancer. Even for mammography a significant difference was found: there were more abnormal mammograms (7.6%) in women who were receiving mammography for the first time than in women who had already had a mammogram (5.6%, $p=0.09$).

Predictive values

The predictive values are directly dependent on the prevalence of the outcome in the study population. The prevalence varied from 2.6 to 9.5%. This prevalence is of course dependent on the follow-up time, since most of the studies used follow-up to verify negative tests. The study with the lowest prevalence [Kriege, 2007] had a follow-up of 2.9 years; the study with the highest prevalence [Bigenwald, 2008] reported no follow-up duration, only the study duration, which was 9 years.

Two systematic reviews [Granader; 2008; Warner, 2008] also reported wide ranges in positive predictive values: 3-79% for MRIs, 6-100% for mammograms. The combination MRI and mammogram has a PPV between 3 and 79%.

Hoogerbrugge reports a positive predictive value of 17% for MRI; a different study [Kuhl, 2010] found a PPV of 48% for MRI, compared to 39% for mammography and 40% for the combination of MRI and mammography.

Kriege (2006) reports a PPV of 3.7-10.8% for MRI, depending on the round but without a significant trend. For invasive carcinomas, the same study did find a significantly higher PPV for mammography when it was the woman's first mammogram (22%) than when she had had a previous mammogram (3.8%, $p=0.003$). No significant difference was found for MRI: PPV 16% for a previous mammogram compared to 6.6% without a previous mammogram ($p=0.18$).

The negative predictive values are not reported in the two systematic reviews [Granader, 2008; Warner, 2008], due to the difficulty in verifying negative tests.

Only one study reports the negative predictive value [Kuhl, 2010]: MRI 99.9%, mammography 98.9%, MRI + mammography 100%.

Effect on quality of life

We found a study that evaluated the effect of screening on quality of life in this high risk group

[Rijnsburger, 2004]. The authors reported that the screening modality had no effect on quality of life, but they did find a significant effect from additional diagnostic testing, which changed over time.
Also, an apparently greater proportion of women reported pain and inconvenience with mammography than with MRI, and an apparently greater proportion of women reported distress/anxiety with MRI than with mammography (no statistical hypothesis testing).

Effect on morbidity, including treatments for breast cancer

One study found no significant difference between cancers detected by MRI and cancers detected by a different method, in terms of the size, grade of tumour differentiation, estrogen/progesterone receptor and tumour type [Kriege, 2007]. The tumours that were found using MRI were significantly less node positive (6% vs. 44%, p=0.02). Compared with mammography, MRI is significantly more sensitive for T_1 tumours, N_0, non-ductal tumours and estrogen receptor positive tumours. Another study did find a significant difference in size of the invasive tumour when screening by MRI in comparison with screening without MRI: 6 mm vs. 22 mm, p<0.0001 [Chereau, 2010].

A systematic review found that the risk of having to be re-tested because of false-positive results increases by a factor 3 (RR 3.43-4.86), which is equal to 71-74 additional call-backs for false-positive results per 1,000 screens. This involves 7-46 additional benign percutaneous biopsies (RR 1.22-9.50), and 2 additional benign surgical biopsies (RR 2.0; 95% CI 0.5-8.0) [Lord 2007]. A later study also found an increase in the number of biopsies, but without statistical hypothesis testing [Weinstein, 2009].

As far as treatments are concerned, there were fewer axillary node dissections (43% vs. 68%, p=0.03), less adjuvant chemotherapy (43% vs. 86%, p=0.0001), and less radiotherapy (62% vs. 81%, p=0.05) [Chereau, 2010] using MRI screening compared to screening without MRI.

A false-positive result from MRI plus mammography has no effect on the woman's preference for having a prophylactic mastectomy or surveillance [Hoogerbrugge, 2008].

Effects on mortality

There are no randomised studies on the effect of adding MRI to the screening program. It is therefore unknown whether the higher sensitivity of MRI for diagnosing breast cancer also translates into a lower mortality: either breast cancer-related mortality or general mortality.
MRI was already included in various screening programs, which complicates conducting an RCT, hence an RCT may never be conducted. Because of this, it may never be possible to quantify the risk of overdiagnosis and overtreatment in this high-risk group.

Chereau (2010) found no significant difference in three-year disease-free survival, metastasis-free survival and total survival using MRI screening compared to screening without MRI. It should be noted that with screening, survival (as opposed to mortality) is a poor measure of outcome, because it is distorted by lead-time bias. MRI scans can accelerate the time of diagnosis but do not change the ultimate mortality rate.

Conclusions

Level 1	Adding MRI to mammography for the screening of high-risk women results in a higher sensitivity for breast cancer. A2 Lord 2007, Bigenwald 2008, Kuhl 2010, Hoogerbrugge 2008, Weinstein 2009

Level 1	The diagnostic accuracy of MRI as a screening method varies according to the cut-off value used. A2 Warner 2008, Bigenwald 2008

Level 3	The diagnostic accuracy of MRI as a screening method decreases as breast tissue density increases. A2 Bigenwald 2008

Level 1	No obvious differences have been observed among the various groups in the diagnostic accuracy of MRI as a screening method. The heterogeneity within each group is just as

	significant as the heterogeneity between the groups. A2 Bigenwald 2008, Kriege 2007, Hoogerbrugge 2008, Weinstein 2009

Level 1	It is likely that the comparison between mammograms and MRI in a first round is distorted by the fact that prior to the study mammograms had already been performed. The sensitivity of MRI is lower in women who have not had a prior mammogram; the numer of positive MRI scans decreases in subsequent rounds. A2 Kriege 2007, Hoogerbrugge 2008

Level 1	It is likely that with MRI screening there is a higher risk of being called back and of having more biopsies, fewer lymphadenectomies, less adjuvant chemotherapy and less radiation therapy. A2 Chereau 2010, Lord 2007

MRISC follow-up study

After the clinical question appeared, the long-term results of the MRISC (MRI Screening in women with familial or genetic predisposition for breast cancer) study were published [Rijnsburger, 2010]. This study found that MRI has a sensitivity of 71%, a specificity of 90% and a PPV of 7.7%. Mammography has a sensitivity of 41%, a specificity of 95% and a PPV of 8.5%. The percentage of tumours of 1 cm or less is 40.5%, the percentage of node-negative tumours is 70%. The overall five-year survival of 93% is higher than the 74% survival of historic cohorts who were not screened by MRI.
The detection rate in the gene mutation carriers was 62/1,000 screens, in very high-risk women 24/1,000 screens, and in moderately high-risk women 31/1,000 screens.
The study shows that breast cancers in the BRCA1 gene mutation carriers form a separate group. In almost all cases these were invasive (93.5%), high-grade (grade 3, 78%) cancers, occurring at a young age (58% under age 40). The sensitivity of mammography was very low, at 25%, and the sensitivity of MRI was higher, at 67%. The percentage of interval cancers was 32%. This indicates a higher rate of growth, as described previously by Tilanus-Linthorst (2007).

Level 3	It is likely that screening by both MRI and mammography improves the five-year survival rate of women at high risk due to a family history of the disease. A2 Rijnsburger 2010

Level 1	The characteristics of tumours in BRCA1 gene mutation carriers differ from the tumours in BRCA2 gene mutation carriers and other high-risk groups; the tumours in BRCA1 carriers have poorer prognostic features and higher rates of growth. A2 Rijnsburger 2010, Tilanus-Linthorst 2007

Other considerations

MRI screening requires radiological expertise, especially because of its low specificity. This expertise is best guaranteed in hospitals with a clinical geneticist, because surveillance of mutation carriers is concentrated there.
It is gradually becoming clear that cancers that occur with BRCA1 have characteristics associated with a poorer prognosis than cancers in other women with elevated risk due to family history. There is discussion of changing the screening schedule, with the idea of alternating screening by mammography or MRI respectively with an interval of 6 months. Another concept is increasing the frequency of MRI: every 6 months until age 40. However, insight inthe consequences for the women (long-term effects of additional use of Gadolineum and false-positive findings) is lacking. Detection of cancers in very high risk groups and moderately high risk groups lags behind detection in mutation carriers. An RCT was started in November 2010 at Erasmus Medical Centre to obtain more insight into the relationships between breast tissue density, cancer risk and diagnostic accuracy of MRI in these women. This is the FaMRISC study, to be conducted at 9 centres. The intent is to include 2,000 women with a lifetime risk (LTR) of more than 20%, with the goal of detecting 50 cancers in 4 years. In one arm women undergo annual clinical breast examination and mammography. In the other arm women undergo annual clinical breast examination and MRI. Every two years, an additional

mammogram will be done, because of the lower sensitivity of MRI for DCIS.

Recommendation

Screening by MRI should be reserved for women at very high risk, specifically the BRCA1/2 mutation carriers.

1.2 Screening by way of the national breast cancer screening programme

The national breast cancer screening programme is generally accepted in the Netherlands. The turnout in the period from 2004 to 2007 was 81.7% [LETB XII, 2009]. The number of false-negative and false-positive referrals to assessment centres is subject to continuous quality control by the LETB (National Evaluation Team for Breast Cancer Screening) and the LRCB (National Expert and Training Centre for Breast Cancer Screening). Now the entire population is screened using digital mammography machines. This has led to higher referral rates. In the period from 2002 to 2004, 23.2 out of every 1,000 screens were referred in the first round. This increased from 2005 to 2007, both for the exams conducted conventionally and for those conducted digitally: 30 of 1,000 screens were conventional and 45.6 of 1,000 screens were digital.
In the period from 2002 to 2004, 11.1 out of every 1,000 screens were referred in follow-up rounds. This increased in the period from 2005 to 2007 for both conventional and digital exams: 13.3 of 1,000 screens were conventional and 18.2 of 1,000 screens were digital.
The positive predictive value of a referral decreased gradually from 41.3% in 2002 to 34.5% in 2007 [LETB XII, 2009].
Digital mammography mainly led to an increase in the number of referrals for microcalcifications. This resulted in a significant increase in the detection of DCIS, but also a significant increase in the detection of IDC, of which the microcalcifications were the only sign [Karssemeijer, 2009]. Additional benefits are more options for processing the image digitally, and that data can be shared more easily [Karssemeijer, 2009; Bluekens, 2010].

For Dutch women between the ages of 35 and 84, the rate of death from breast cancer was rising until 1994, and began falling thereafter. A marked decrease of 2.3-2.8% per year took place for the age groups 55-64 and 65-74, starting in 1994. In the older age group this kind of trend was observed only after 2001, and in women from 45-54 after 1992. Although improved treatments and changes in the population do play a role, the age-specific trends observed are clearly associated with the different implementation phases of the national breast screening programme [Otten, 2008].

1.2.1 Lowering the screening age to 40-50 years: what are the pros and cons?

Screening women between age 40 and 50 is controversial. In 2002 the USPSTF stated that there was sufficient evidence to recommend annual mammograms [Qaseem, 2007], but in their 2009 publication [USPSTF, 2009] they no longer recommended it. This change was in response to the results of a study on risk models by Mandelblatt (2009) reporting just 3% more mortality reduction in this group (range 1% to 6%) than screening in the age category from 50 to 75 years. The harm (high costs and high percentage of false-positive results) exceeds the benefits. They state that the decision to move to annual screening should be made on an individual basis, weighing up the benefits against the potential harm.
In 2006 the results were published from a randomised study on screening in ages 40 to 49 (basic assumption: reduction in mortality) which had a convincing design and adequate power; the study was initiated in 1991 in the United Kingdom [Moss, 2006]. The statistics appear to be consistent with previous studies [Moss, 2005]: in women between ages 40 and 49 invited for screening, the breast cancer diagnosis was made earlier than in women who were not invited [Moss, 2006]. In Moss's study, a 17% reduction was reached after an average follow-up of 10.7 years. This number did not turn out to be statistically significant, however. When corrected for non-compliance (entirely or partly refraining from participation) a 24% reduction in mortality was calculated. The turnout was 68% in the first round and 70% in the follow-up rounds; in total 81% had at least one screening mammogram.
In the accompanying editorial it was suggested that the trend toward reduced mortality was confirmed, but that there is still too much uncertainty about the adverse effects, such as unjustified reassurance, false-positive exams and cancer induction from radiation [Djulbegovic, 2006].

Conclusion

Level 3	Mammography screening in women between the age of 40 and 50 showed a 15-17% reduction in mortality in the intervention arm compared to the control arm. This difference was not statistically significant.

	A 24% reduction was calculated for the women who participated fully in the program. A2 Moss 2006

Other considerations
In the Netherlands, women between 50 and 75 years of age are currently screened through the national breast cancer screening programme. The upper age limit recommended by the Netherlands Health Council is partly based on the fact that the disease occurs in 75% of women above 50 years of age. The question is whether screening should be expanded to include younger age groups. According to the National breast cancer screening Act, before the screening can be expanded the Dutch Ministry of Health would need to issue a permit based on the recommendation of the Health Council (http://www.rijksoverheid.nl/onderwerpen/bevolkingsonderzoek). However, the Centre for Population Screening of the RIVM (National Institute for Public Health and the Environment) is giving priority to other screening activities at the moment.

Gradual change in diagnostics in the later stages
The advent of screening involves a considerable number of non-palpable abnormalities. Developments in hospitals have mainly focused on rapid diagnosis (breast clinics) and on obtaining a definitive preoperative diagnosis using minimally invasive ultrasound-guided or stereotactic-guided procedures, partly through participation in projects such as the Breakthrough Project. The ultimate percentage of patients who undergo unnecessary surgery as a result of screening is much lower now compared to the approach used in the period the foundation for the screening was laid. Based on the quality criteria currently being used (NABON note: Manual for the Organisation of Breast Cancer Care, www.NABON.nl), it can be inferred that a preoperative diagnosis should be possible in 90% of the cases.

Experience and policy elsewhere
Of the 19 members of the International Breast Cancer Screening Network, only Iceland, Uruguay, Sweden and the United States start screening at age 40, and in fact in the US they are now debating whether to raise this starting age again [USPSTF, 2009; Mandelblatt, 2009]. Uruguay and the United States screen annually, the United Kingdom once every 3 years, and the other member states once every 2 years.

1.2.2 National Breast Cancer Screening programme: what conditions must be met for the transfer of information to the clinic?

Everyone involved in the screening and follow-up process must fully realise that screening is a way of reducing breast cancer mortality and is not a perfect and comprehensive way to protect women against breast cancer. Only a small proportion of participants have breast cancer, and false-negative and false-positive results are unavoidable but constantly cause debate.
Jørgensen (2006) states that this can at least partly be traced back to the educational information given to women who are invited. The picture sketched is often too rosy and creates unrealistic expectations. Possibly because this information serves a double purpose: national breast cancer screening greatly benefits from a large turnout and makes an effort to do so in an inviting manner, influencing the balance between benefit and harm. It is of utmost importance that attention is paid to providing this information in an objective manner [BVN, 2003]. Specifically, it should be pointed out that women who have a palpable abnormality or other symptom do not belong in the screening program. The nationwide coordination is the job of the RIVM, which is responsible for distribution of information in the Netherlands. The invitation brochure and the standard invitation letter is updated annually, to enable women to make their dicisions on current information.
In addition, the national breast cancer screening programme must strive for the highest level of communication with the follow-up care path, for planning purposes as well as to mitigate negative effects of screening, in particular extra tests due to false-positive findings.

The screening mammogram: Is it still necessary to repeat the digital mammogram?
The screening radiologist's annotations are saved digitally using the Dutch IT/DigiBOB software. At present, the key information (the abnormality on the mammogram) with the data transfer information from the screening radiologist, as described below, is usually delivered on a CD. There are various reasons to send the screening mammogram to the breast clinic in the hospital to which the woman is being referred:

1. The quality of images on a CD is often not diagnostic; differences between image processing

systems complicate the interpretation and processing.

2. Repeating the test is of practical value for additional magnification views or tomosynthesis. But it also increases the final sensitivity (up to 30%) by repeat imaging of the same pathology [Bick, 2006].
3. It can also be considered the system's own quality control: abnormalities that are cause for referral are sometimes not detectable on the mammogram made in the clinic. That is especially true of abnormalities that are small, found at the edge of the image, or based on incidental overprojection of normal structures. The radiation exposure is negligible.

Creation of a broadband connection between screening organisations and hospitals is in progress.
When the hospital has the same image processing system as the screening organisation, so that the image quality is equivalent, or if the hospital has access to the images via broadband technology, repeating the image is not necessary.

The screening radiologist

A large cohort study of the performance of 120 screening radiologists in the United States found that it is mainly radiologists doing both diagnostic breast radiology and screening who achieve the best results. The sensitivity in this study was 85.2% (95% CI 83.7-86.6%). There were no significant differences between large and small volume screens; the relationship between the number of screens and performance proved to be complex [Buist, 2011]. A minimum of 3,000 screens per years was set; in the Netherlands the average volume handled by a screening radiologist is 7,000. This and the other standards that must be met by screening radiologists in the Netherlands are described in the Quality Registry of the LRCB: www.lrcb.nl/hoofdmenu/kwaliteitsregister.aspx. It also states the requirement that screening radiologists must be involved in diagnostic breast radiology. The LRCB registers the licensed screening radiologists in the Quality Registry.
Screening radiologists provide the patient's general practitioner with all the information necessary for referral. At a minimum this information must include: the side, localisation, nature and size of the abnormality and the number of abnormalities. This must be recorded in a standard sketch annotated on the mammogram.
The following BI-RADS categories may be assigned to a screening mammogram used for referral (a "positive screening result") (see section 2.22) [ACR, 2003]:

- BI-RADS 0, incomplete exam; need additional imaging evaluation and/or prior mammograms for comparison
- BI-RADS 4, probably malignant, suspicious laesion
- BI-RADS 5, highly suggestive of malignancy

For instance, BI-RADS 0 may imply there is reason to take a magnification view or do an ultrasound, or to compare the mammogram with previous mammograms that are not available at the national breast cancer screening centre, in order to differentiate between a real laesion and a composition image. If the final assessment category assigned is BI-RADS 4 or 5, the emphasis is on the degree to which the laesion is suspected of malignancy; whether needle biopsy is needed will be determined in the hospital. BI-RADS final assessment category 3 (probably benign) does not belong in a routine screening setting. This category can be assigned only after the necessary additional imaging has taken place, thus in the hospital. This is because in the follow-up rounds the Dutch screening programme confines to MLO (mediolateral oblique) views The remaining categories (BI-RADS 1 and 2) are considered negative screening results, and therefore meet the criteria for routine screening, not for referral.
Applying the BI-RADS categories with some explanatory text helps general practitioners, giving them more understanding of the level of suspicion. If the woman has been referred with a BI-RADS 0, her general practitioner can explain to her that an irregularity was indeed seen on the mammogram, but that more imaging is needed for confirmation. The chance of cancer is about 10%. Also within the breast clinicthe BI-RADS final assessment category will influence the referral routine. ZonMw (The Netherlands Organisation for Health Research and Development) has subsidised a prospective, epidemiological study by the University Medical Centre Sint Radboud and the LRCB, investigating various different scenarios including the possibility of whether BI-RADS 0 referrals can be held entirely outside the breast clinic and can be evaluated within the screening setting.
(http://www.lrcb.nl/Hoofdmenu/watwijdoen/Onderzoek_en_innovatie/http_www_lrcb_nl_mass.aspx)

The screening organisation

The five regional screening organisations are responsible for the screening programme. Job descriptions and responsibilities of screening technicians can be viewed at www.lrcb.nl. The organisations must ensure that all women who participate in national breast cancer screening are

notified of their results by mail as soon as the organisation can do so – preferably within 10 workdays [Harmonisatie Kwaliteitsbeoordeling in de Zorgsector, 2006]. Mailing of results should not be timed so that the message arrives on a Friday or right before holidays. If the results are positive, the woman's general practitioner will be notified before the woman herself. The woman will then receive a letter advising her to contact her general practitioner. She will also receive the folder "When Further Testing is Needed." Often general practitioners contact the woman before she receives the letter. This is preferable.
The screening organisation is in charge of sending a letter of referral and for making the digital images available. The screening organisation communicates promptly with hospitals in the area about the local screening schedule, so that the hospitals can adjust their breast clinic's capacity accordingly.

The general practitioner

If a woman is referred for further diagnostic testing, her general practitioner is responsible for:

- giving her information on the procedure of referral, to add to the information in the results letter the woman received.
- referring the patient to a breast clinic or breast care team, taking into account the woman's preference. In most areas referral is done using a set of forms. In this set, the form for the specialist contains the same information and has a space for the primary care physician to provide additional information, such as relevant patient history. These forms must be given to the woman.
- contacting the woman herself, if she does not contact her doctor.
- reporting the referral (which specialist, which hospital) to the screening organisation. In many regions a "return mail form" in the set of forms can be used for this purpose.

The breast care team

The specialists (the breast care team) involved in the process of further diagnostic testing of the referred woman are responsible for ensuring that:

- diagnostics and treatment take place within a recognisable organisational structure (see Chapter 13);
- the general practitioner is notified promptly of follow-up diagnostic findings, the treatment plan and its results;
- the screening organisation is notified (preferably within three months) of the results of diagnostic tests.

The woman brings the records (forms and CD) she received to her breast clinic appointment. The surgeon or breast care nurse specialist sees to it that the radiologist has access to the mammograms and the additional information. The pathologist must also have access to this information.

Relaying information to the patient

Well-informed patients are more able to process stress. The further diagnostic test results must be relayed to the patient at each moment in the diagnostic process, though she will mainly receive this information at the breast clinic directly from the attending surgeon and nurse specialist.

Mammograms that are difficult to perform

Under the terms of the Equal Treatment Act, in 2008 the RIVM established that every woman in the Netherlands must have access to one of the national breast cancer screening centres. For women with a physical disability, each screening unit has an elevator. In exceptional cases they can rely on the radiological department of an associated hospital.
Another group is made up of women for whom mammograms may not be technically feasible, such as women who have had breast-conserving therapy (see also 12.4) or have silicone breast implants (see also 2.2.5). If both the first and second radiologists reading the mammogram find it hard to interpret, they advise the individual women to have their screening examination performed in the radiology department of a hospital, because there more options for imaging are available. The decision to give the woman this advice must be based on the RIVM protocol. Given the improved contrast ratios in digital mammography, these would be exceptions to the rule: the vast majority will be able to be screened normally.

Conclusion

Level 3	The screening radiologist's performance improves with a good balance between screening radiology and diagnostic radiology.

	The relationship between performance and the volume of exams to be screened is complex; there is no straightforward correlation. A2 Buist 2011

Recommendations

The national guideline development group is of the opinion that:

- objective information should be available to women to help them in their decision to participate in the national breast cancer screening programme;
- the screening organisation should notify area hospitals promptly of scheduling, so that the hospitals can adjust their breast clinic's capacity accordingly;
- the application of BI-RADS in screening aids communication between the screening radiologist, the primary care physician and the breast care team;
- the general practitioner should refer the referred woman to a breast clinic or breast care team;
- the mammogram should be repeated if the screening mammogram she brings is not of diagnostic quality;
- if a screening mammogram is not feasible, the woman should be advised to have the test conducted in the radiology unit of a hospital;
- if, after evaluation by the breast care team, there seems to be a false-positive referral, the woman should be referred back actively to the national breast cancer screening programme.

1.3 Screening outside the national breast cancer screening programme

1.3.1 Risk factors

There are various known risk factors that play a role in breast cancer. For a summary of the literature search, based on reviews, see appendices on Oncoline. The table below gives a global overview of the risk factors named in these reviews. The decision was made to state the risks in terms of relative risks (RR). It is not always possible to convert RR to lifetime risk (LTR), since the information required for populations is not always known. For the Netherlands, an RR of 1 corresponds to an LTR of 10%.

Risk factors for developing breast cancer

Factor	*Relative risk*	*Reference*
Older age (over age 45 versus under age 25)	< 10	Dumitrescu 2005 McPherson 2000
Mutations in BRCA1/2	6 – 8	Dumitrescu 2005 McPherson 2000
Geographic region (North American and Northern Europe versus the Far East, Africa and South America)	5 - 10	Dumitrescu 2005
High density mammogram	4 - 6	Boyd 2010
Atypical benign breast laesions: Atypical (ductal or lobular) hyperplasia, flat epithelial atypia, lobular carcinoma in situ, papillary laesions and complex sclerosing laesions (radial scars)	4 - 5	Dumitrescu 2005 McPherson 2000 Morrow 1999 Santen 2005
Prior history of radiation; chest and/or axillary radiation, e.g. due to Hodgkin's lymphoma before age 40	3 - 20	De Bruin 2009 Van Leeuwen 2003 Aleman 2003
Breast carcinoma or DCIS in medical history	2 - 4	Morrow 1999
Late age at the time of first child, over age 35 vs. before age 20	2	Dumitrescu 2005 McPherson 2000
High postmenopausal bone density	2 - 3.5	Dumitrescu 2005
Diethylstillbestrol (DES) use during pregnancy	2	McPherson 2000
Late menopause, after age 54	≤ 2	Dumitrescu 2005 McPherson 2000 Morrow 1999
Nulliparity	< 2	Dumitrescu 2005 McPherson 2000 Morrow 1999
Hormone replacement therapy (HRT) use for over 10 years	1.4 - 3	Dumitrescu 2005
Alcohol intake, risk is dose-dependent, 2-5 units per day vs. no alcohol intake	1.2 - 1.5	Brennan SF 2010 Key 2006 Li 2010

Oral contraception Recent use Past use	1.2 -2.4 1.0-1.2	Dumitrescu 2005 Cibula 2010
Mutations in other highly penetrant genes; p53, PTEN	1 - 6	Dumitrescu 2005
Early menarche, before age 11	1 - 3	Dumitrescu 2005 McPherson 2000 Morrow 1999
Physical exercise 5x per week vs. inactivity	0.85	Patterson 2010 Bernstein 2009
In vitro fertilisation	Not clearly elevated	Salhab 2005 Dor 2002 Zreik 2010
Obesity Premenopausal, body mass index > 35 Postmenopausal, body mass index > 35	 0.7 2	McPherson 2000

General population

People with two risk factors – age over 50 and of the female sex – are screened under the national screening for breast cancer. Regarding geographic region, note that for people from low-risk areas (such as Asia), the difference decreases the longer they live in a high risk area (such as North America).

Genetic risk factors

The gene mutations in the BRCA1 and 2 genes are the most significant genetic risk factors, with an RR of 6-8. In addition, there are several rare tumour syndromes caused by highly penetrant genes including breast cancer. The most significant are Li Fraumeni (P53), Cowden syndrome (PTEN), Peutz-Jeghers (STK11) and hereditary diffuse gastric cancer (CDH1). For more information on these syndromes, go to http://www.vkgn.org.

If one has a first-degree relative with breast cancer, the RR is 1 to 4, depending on one's age and other family history. In women with breast cancer in the family, the RR depends greatly on the number of relatives, whether it is first- or second-degree kinship, and at what age the breast cancer occurred. If there is only third-degree kinship with breast cancer, the RR is not elevated enough to justify screening outside the national breast cancer screening programme. See the decision tree after section 1.3.4.

Hormonal risk factors

Risk factors with an RR of 2 or higher are present when the woman is over age 35 at the time of having her first child, and in postmenopausal women with high bone density. Since estrogen can contribute to high bone density, estrogen use as a part of hormone replacement therapy can have a direct relationship as a risk factor in developing breast cancer. As a result, it may not be the high bone density, but estrogen use that may be the risk factor that gives an RR of 2 or higher.

DES use during pregnancy gives an RR of 2, as does postmenopausal overweight.

An RR of up to 2 has been published for menopause after age 54. Menarche before the age of 11 gives an RR of 1-3. Long-term hormone replacement therapy gives an RR of 1.4 to 3. Use of oral contraceptives gives an RR of less than 2 in most studies. It is notable that there is currently no obvious evidence that in vitro fertilisation increases the risk of breast cancer.

Many other risk factors are indeed associated with a statistically significant increase in risk in large populations, but have little practical significance for an individual woman.

An exception are women who underwent chest or axillary radiation before the age of 40, usually as part of treatment for Hodgkin's Lymphoma.

There are no prospective studies on this group. In a retrospective study of 91 patients with an average age of 42, treated for Hodgkin's, 10 cancers were found in a period of 10 years; 4 by MRI only, 3 with mammography in addition to MRI, and 3 only with mammography (based on microcalcifications) [Sung, 2011].

Based on a risk estimate, beginning 8 years after the radiation therapy these women are offered the same screening program as gene mutation carriers. See section 1.3.2, Table 2.

Another exception is women who receive radiation in the breast region for other forms of childhood cancer, including Wilms tumour, sarcoma, neuroblastoma or non-Hodgkin lymphoma. For information on the definition of risk groups and the associated screening policy for breast cancer after treating childhood cancer, see the guideline "Follow-up after childhood cancer," sections 1, 2 en 3 (www.skion.nl).

For women who underwent chest radiation therapy after the age of 40, screening may be started 10

years after radiation therapy. This means that the national breast cancer screening programme is adequate for these women.

Conclusion

Level 2	It has been shown that the following risk factors give an RR ≥ 4 for developing breast cancer: • carrier of mutations in genes with high penetrance, including BRCA1 or 2; • very high risk due to family history, without a proven mutation in BRCA1 or 2; • chest radiation therapy before the age of 40; • atypical benign breast laesions consisting of atypical (ductal or lobular) hyperplasia, flat epithelial atypia, lobular carcinoma in situ, papillary laesions and complex sclerosing laesions (radial scars); • history of ductal carcinoma in situ; • history of breast cancer; • high density mammogram at advanced age. B Dumitrescu 2005, Morrow 1999, McPherson 2000, Santen 2005

Other considerations

In the texts below, a very high risk is roughly equivalent to RR 6-8, a high risk RR 3-4, a moderately increased risk RR 2-3 and a slightly increased risk RR <2.

There is no consensus on how to define the degree of increased risk. Different risk factors are usually studied in different populations, so adding them together is not possible. However, there are models that combine some risk factors, such as menarche, age at the time of first child, and first-degree relative with breast cancer [Gail, 1989; Tyrer, 2004].

The epidemiologically proven relationship between density of glandular tissue and an increased risk of breast cancer applies to both premenopausal and postmenopausal populations [MacCormack, 2006]. It seems paradoxical that the percentage of glandular tissue reduces with age, while the cancer incidence increases. But this paradox can be explained: it is mainly a question of exposure to hormones, growth factors and effects of menarche, pregnancy and menopause on glandular tissue. Dense glandular tissue is also associated with atypical benign breast laesions. The density of the breast tissue has a hereditary component.

Since evidence of the relationship between dense glandular tissue and breast cancer has mainly been found in screening populations, no recommendations can be made for other screening modalities [Boyd, 2010].

The increased incidence of breast cancer in general and the high frequency of mild risk factors, such as low number of pregnancies and late age at first child, increase the demand for screening outside the national breast cancer screening programme. This calls for a good information campaign. If all women with mild risk factors would go to a hospital radiology department outside the national breast cancer screening centre, this would heavily overcrowd these departments. Furthermore, it is questionable whether those departments are adequately equipped for this screening role, and whether this could be in conflict with the national breast cancer screening Act [Wet op het bevolkingsonderzoek (WBO)]

The following points are important in the information for women who are worried about their risk of breast cancer: most women will not get breast cancer. Most of those who do get breast cancer have no family history of it. For most women older age is the main risk factor for getting breast cancer.

1.3.2 Indications for urgent DNA testing

Urgent diagnostic testing for a DNA defect causing breast cancer could be meaningful when there is concern that the presence of a hereditary diseasemight influence the choice for local treatment with consequences for survival. A woman with breast cancer due to a BRCA1 or 2 mutation is not only has a risk of recurrence, but also at increased risk of a second primary tumour, usually contralateral. This risk is also affected by other factors: her age at the time the primary breast cancer was diagnosed, adjuvant therapy of the primary breast cancer (radiation therapy, chemotherapy and/or hormone therapy) and prophylactic adenectomy.

When urgent DNA testing is indicated, it is important to know:

a. If a mutation is diagnosed, is a particular primary treatment preferred, in view of the chance of recurrence?
b. Could a simultaneous prophylactic contralateral mastectomy (PCM) have a clear survival

benefit?

Regarding a: Risk of ipsilateral recurrence
In a systematic review, BRCA mutation carriers in 5 of the 17 studies had an elevated risk of an ipsilateral recurrence, and in 4 of the 14 studies poorer survival rates [Liebens, 2007]. In a study published later, 223 breast cancer patients with a BRCA1 mutation, 103 breast cancer patients with a BRCA2 mutation, 311 breast cancer patients with a high familial risk but without gene mutation, and 759 breast cancer patients with no family history, the risk of an ipsilateral recurrence did not differ between these 4 groups. The incidence after 10 years in each of these groups was 16%, 17%, 15% and 21%, respectively [Brekelmans, 2007]. In a comparison of 54 breast cancer patients with a BRCA1/2 mutation who were matched with 162 patients with sporadic breast cancer, Garcia-Etienne (2009) reports a 10-year cumulative incidence of ipsilateral recurrence of 27% for the mutation carriers and 4% for the sporadic controls.
The studies done by Pierce (2010) and Kirova (2010) also report a slightly greater chance of ipsilateral recurrence, but it did not affect survival. Metcalfe (2011) followed 396 mutation carriers who had BCT; the risk of ipsilateral recurrence was 1.2% per year. The risk was lower in women who were treated with radiation therapy, chemotherapy or oophorectomy. Currently there are no strong arguments for treating diagnosed breast cancer in BRCA mutation carriers differently from non-mutation carriers.

Regarding b: Risk of contralateral breast cancer
Various large studies have shown that there is a markedly increased risk of a second diagnosis of breast cancer in BRCA gene mutation carriers. Liebens found this in 14 of the 16 studies [Liebens, 2006]. The 10-year risk of contralateral breast cancer varied from 25-31% for BRCA mutation carriers compared to 4-8% for sporadic breast cancer. More recent studies confirmed the strongly increased risk of a contralateral tumour. Graeser (2009) found that over 47% of the BRCA breast cancer patients had developed a contralateral tumour after 25 years. A younger age at the time of the first tumour meant a significantly higher risk: 63% of the patients with a BRCA1 mutation who were under age 40 at the time of the first breast cancer had developed contralateral breast cancer 25 years later, compared to 20% of those over age 50 at the time of the first breast cancer . The studies of van der Kolk (2010) and Malone (2010) are also consistent with these results.

The study of Domchek (2010), a multicentre cohort of 2,482 women with a BRCA1/2 mutation, describes the effects of risk-reducing surgery. Risk-reducing mastectomy was associated with a significantly lower risk of breast cancer. No breast cancers were found in a group of 247 women who had undergone risk-reducing mastectomy. There was no clear survival benefit after risk-reducing mastectomy. After correcting for stage and therapy, Brekelmans (2007) found that a contralateral carcinoma did not affect survival. Van Sprundel (2005) showed survival benefit from PCM in 145 BRCA1/2 mutation carriers in univariate analysis, but not in multivariate analysis. In this study it was found that survival was determined by the characteristics of the primary carcinoma. In a small study, Peralta (2000) did find better disease-free survival after PCM, but no difference in survival. Heron (2000) showed, studying 1,465 patients, that survival was no worse after contralateral breast cancer.

In Domchek's (2010) study, risk-reducing (preventive) bilateral salpingo-oophorectomy (pBSO) was associated with a significantly lower risk of ovarian cancer in both BRCA1 and BRCA 2 mutation carriers and in those with and without a history of breast cancer. After pBSO in both BRCA1 and BRCA2 mutation carriers, there is a significantly lower risk of breast cancer, a decrease in mortality from all causes but also from breast cancer- and ovarian cancer-induced mortality.

Conclusions

Level 2	There is no clear contraindication for breast-conserving therapy in the presence of an identified BRCA1/2 gene mutation. B Liebens 2007, Brekelmans 2007, Garcia-Etienne 2009.

Level 2	There is a markedly increased risk of contralateral breast cancer in BRCA1/2 gene mutation carriers. Risk-reducing mastectomy significantly reduces the risk of a second diagnosis of breast cancer. B Liebens 2007, Domchek 2010

Level 2	Risk-reducing contralateral mastectomy has been found to have no clear survival

	benefit. The survival is primarily determined by the prognosis and therapy of the primary breast carcinoma. B Brekelmans 2007, van Sprundel 2005

Level 3	After risk-reducing salpingo-oophorectomy in BRCA1/2 mutation carriers, there is a significantly lower risk of breast cancer, a decrease in mortality from all causes but also from breast cancer- and ovarian cancer-induced mortality. B Domchek 2010

Recommendations

Tumour treatment must be the priority in diagnosing breast cancer.

Urgent DNA testing for a mutation in the BRCA1/2 gene can be considered if it might influence the woman's choice for local treatment of the primary cancers with consequences for survival.
Women who might be eligible for this are:

- those with a high risk of a BRCA1 or 2 mutation
- young women (under age 40) with very early stage breast cancer

Since advice on whether to initiate urgent DNA testing for BRCA1/2 mutations is highly complex, at a minimum the decision should be shared by the clinical geneticist, the medical oncologist and the surgical oncologist, and referral to a centre with expertise is advisable.
The women must be told that prophylactic contralateral mastectomy (PCM) will barely affect survival, but will strongly reduce their risk of contralateral breast cancer.

1.3.3 Screening for ovarian cancer

Studies have investigated whether ovarian cancer is cost-effective screening in women who have a family history of breast/ovarian (or tubal) cancer. The most recent Dutch study included a group of 888 BRCA1/2 carriers who had annual screening by ultrasound and CA 125 measurement. Five of the 10 ovarian cancers found in this group were interval cancers, diagnosed between 3 and 10 months after a normal screening, and eight of them were stage III/IV [Hermsen 2007]. Up to the present there has been no evidence that routine screening for ovarian cancer results in diagnosing early stage ovarian cancer or in reducing mortality. Other authors have also come to the conclusion that screening for ovarian cancer in women with a mutation or hereditary risk of breast and/or ovarian cancer is not cost-effective [Stirling, 2005; Oei, 2006; Vasen, 2005; Meeuwissen, 2005].

Conclusion

Level 2	Screening for ovarian cancer in women with a BRCA1/2 mutation or family history of breast and/or ovarian cancer is not cost-effective. B Oei 2006, Vasen 2005, Meeuwissen 2005, Stirling 2005, Hermsen 2007

Other considerations

Ovarian cancer has no detectable preliminary stage that is detectable with current diagnostic tests, and therefore does not meet the criteria for screening. An alternative to screening for ovarian cancer at present is a preventive bilateral salpingo-oophorectomy (pBSO). A meta-analysis of 10 studies on the effects of a pBSO found an 80% reduction in ovarian cancer and 50% reduction in breast cancer in BRCA1/2 mutation carriers, with consistent results in the different studies [Rebbeck 2009]. Bilateral pBSO before the age of 45 is associated with higher mortality, especially if no hormone replacement therapy is given [Rivera, 2009]. Other drawbacks are menopausal symptoms and poorer sexual function [Madalinska, 2005; Madalinska, 2006].
The reported effects of early menopause include a higher risk of cardiovascular disease, neurological disease, osteoporosis and mood disorders, which can be partially mitigated by hormone replacement therapy [Sushter, 2010]. It is unknown whether and to what degree this is also true for women with a BRCA1/2 mutation who undergo a pBSO premenopausally. It is important to monitor these women in order to learn about the delayed effects of premenopausal pBSO. In a study conducted by Rebbeck (2005) in BRCA1/2 mutation carriers, the reduced risk of breast cancer did not change substantially with short-term hormone replacement therapy after pBSO.
From the age of 35, women with BRCA1/2 mutations are referred to the gynaecologist, becoming

eligible for a pBSO starting at age 35-40 if they have BRCA1 and starting at age 40-45 if they have BRCA2. There is no consensus on the policy before pBSO. There are gynaecologists who do annual screening until the patient has a pBSO. The disadvantage of such an approach is the risk of false-positive results and the associated unnecessary additional diagnostic testing, which adds to the woman's distress. Other gynaecologists support BRCA mutation carriers to decide for themselves what the best time is for a pBSO and do not offer any screening. We therefore recommend informing women about the pros and cons of screening and pBSO.

Recommendation

The guideline development group recommends telling women with an elevated risk of ovarian cancer due to BRCA1/2 gene mutations about the pros and cons of screening and preventive bilateral salpingo-oophorectomy (pBSO), and asking them to consider a pBSO starting at age 35 or 40.

The group recommends considering pBSO starting at age 35 for BRCA1 and starting at 40 for BRCA2.

1.3.4 Screening outside national breast cancer screening, and referral to a clinical geneticist

Basic principle

In formulating these referral criteria, we drew upon the findings in sections 1.3.1 and 1.3.2. We have decided to present the risks in terms of RRs. For the Netherlands, an RR of 1 roughly equals an LTR of 10%.

Section 1.3.1 contains the recommendations drafted for RR ≥ 4, which require clinicians to consider whether screening outside the national breast cancer screening programme is feasible. For the risk factors with an RR between 2 and 4: Up to now, screening has been offered outside the national breast cancer screening programme when there is a moderate increased risk due to family history. The lower limit for screening outside the national breast cancer screening programme due to a family history is therefore an RR of 2. This limit is not based on scientific evidence, however, nor do we have data on the results of this approach. These limits do comply with guidelines used both in the Netherlands and internationally [STOET/VKGN, 2010; NICE, 2006].
Important points include the starting and ending ages of screening outside the national breast cancer screening programme, the value of clinical breast examinations and regular breast self-exams, and referral criteria for diagnostic DNA testing. Also see flowcharts 1 and 2 for this.

Considerations regarding the starting age of mammography screening outside the national breast cancer screening programme

Increased risk due to family history

Based on cost-effectiveness and on radiation exposure, there must be an RR of at least 3 in women under 40 to justify screening outside the national breast cancer screening programme.

Moderate increased risk due to family history

An acceptable starting age for screening outside the national breast cancer screening programme for women with a moderate increased risk due to family history (RR 2-3) and negative DNA-testing is no longer age 35, but age 40.

High risk due to family history

For women with a high risk and negative DNA testing (RR 3-4), the starting age for screening outside the national breast cancer screening programme is 35. We do not advise a starting age younger than 35 when familial breast cancer occurs at under age 35 in this group. Neither is MRI screening advisable (except as part of a study. See section 1.1.5).

Very high risk: Gene mutation carriers and other highly penetrant genes

For BRCA1/2 mutation carriers with an RR of 6-8, we do not advise starting mammography before age 30. At age 25 they can start MRI screening. Screening should take place annually [Rijnsburger, 2010; van der Kolk, 2010].
Patients with rare hereditary conditions such as Li-Fraumeni syndrome (p53), Cowden syndrome (PTEN), Peutz-Jeghers syndrome (STK11) and hereditary diffuse gastric cancer (CDH1) have an LTR of developing breast cancer ranging from 25% to over 50%. For screening regimens see http://www.vkgn.org. No data is available on the effectiveness in this small group of women.

Approximately 75% of women with Cowden syndrome have extensive benign breast disease, hamartomas, fibroadenomas and fibrocystic changes, which complicate the sensitivity for detecting breast cancer in both mammography and MRI [Farooq, 2010; Thull, 2004].

Other information:

Regular breast self-exams

With regard to regular breast self-exams it is concluded that this technique cannot be recommended as a method to reduce breast cancer mortality. Knowledge of one's own body may well play a significant role in recognizing breast abnormalities, though.

Clinical breast examinations

Clinical breast examinations as a screening method in the general population is not cost-effective. Be aware of the limited value of clinical breast examinations as a screening method, even for women screened outside the national breast cancer screening programme, although it may play a greater role in young women at high and very high risk [Chiarelli, 2009; Barton, 2009].

Clinical Genetics

The Clinical Genetics departments usually coordinate the multidisciplinary outpatient clinics for hereditary (or familial) tumours, and are located in teaching hospitals and unaffiliated cancer hospitals; see appendices for addresses. A more detailed risk assessment can take place here, based upon which recommendations for screening are given to those requesting advice and to their family members. If technically possible, DNA testing may be a part of the testing. Psychosocial support can also be given in this context.

DNA Testing

DNA testing is offered when there is a detection chance of approximately 10% or higher of having a mutation in the BRCA1 and 2 genes. Triple negative tumours are more common in BRCA1 gene mutation carriers [Kwon, 2010]. DNA testing for a hereditary predisposition to tumours should be requested by the clinical geneticist. The reason for this policy is the clinical and genetic heterogeneity of many tumour syndromes and the psychological and social stress. Advice may also be given if preventive bilateral mastectomy is being considered. See also section 1.1.2.

Recommendations

Who is eligible for screening outside the national breast cancer screening programme?

In the Netherlands, a relative risk (RR) of 1 approximately equals an LTR of 10%.

RR 6-8 = very high risk, usually due to gene mutation BRCA 1/2
RR 3-4 = high risk
RR 2-3 = moderately increased risk
RR <2 and >1 = slightly increased risk

Screening is definitely indicated in cases of:

- Mutation carriership of BRCA1 or 2 and other high penetrance genes
- History of therapeutic radiation to the upper torso before age 40
- Atypical benign breast laesions: atypical (ductal or lobular) hyperplasia, flat epithelial atypia, lobular carcinoma in situ, papillary laesions or complex sclerosing laesions (radial scars)
- Breast cancer or DCIS in the personal medical history

Screening is recommended in case of:

- RR between 2 and 4 with a (moderate or strong) family history
- HRT use for more than 10 years

Screening is not advised in case of:

- dense or very dense breast tissue

Screening can be discontinued:

- after age 75

How to screen?

Screening schedules for women with no history of breast cancer but at increased risk.

Screening in case of a moderately increased risk (RR 2-3) due to family history and HRT longer than 10 years:

- From 40-50 years of age, annual mammography to be requested by the general practitioner
- From 50-75 years, participation in the national breast screening programme

Screening in case of a high risk (RR 3-4) due to family history:

- From 35-60 years, annual mammogram and clinical breast screening, performed by a specialist in this area
- From 60-75 years, participation in the national breast screening programme

Screening of BRCA1 or 2 mutation carriers or those who have a 50% chance (RR 6-8):

- Screening to be performed by the breast clinic Annual MRI from 25-60 years
- Annual clinical breast screening from 25-60 years
- Annual mammography from 30-75 years
- Depending on the breast density on mammography biannual mammography from 60-75 years is sufficient, in the hospital where the woman is being screened or via the national breast screening programme.
- There is no indication for screening after prophylactic (bilateral) mastectomy

Screening for other high penetration genes: see http://www.vkgn.org

- Depending on the breast density on mammography biannual mammography from 60-75 years is sufficient, in the hospital where the woman is being screened or via the national breast screening programme.

Screening if there is a medical history of chest irradiation:

- In the case of radiotherapy prior to the age of 40: *see www.skion.nl;*
- In the case of radiotherapy after the age of 40: inclusion in the national breast screening programme
- Depending on the breast density on mammography biannual mammography from 60-75 years is sufficient, in the hospital where the woman is being screened or via the national breast screening programme.

Screening with atypical benign breast laesions:

- Annual mammogram from the 1st year after diagnosis
- Depending on the breast density on mammography biannual mammography from 60-75 years is sufficient, in the hospital where the woman is being screened.

Screening if the patient has had DCIS or breast cancer

- Annual mammogram from the 1st year after diagnosis
- Screening with MRI is not recommended (irrespective of the detection method of the primary tumour)
- See chapter 12 (Aftercare and follow-up) for a complete screening schedule after DCIS or breast cancer.

The table below and both flow charts have been created as a tool to be used for patient management in the case of increased risk due to family history. If applicable: read the table and flow charts in their entirety.

Table 1. Information required for the family medical history

When collecting information about the family history, it is important to gather information about at least first- and second-degree relatives in the paternal and maternal branch. The physician should enquire about the occurrence of breast cancer, possible bilateral tumours, and other tumours in the same branch of the family, especially ovarian carcinoma, tubal carcinoma and prostate carcinoma. The extent of the risk is estimated using the number of first-degree, second-degree or third-degree family members with breast cancer and the age of diagnosis. The management plan for the healthy woman requesting screening is determined by her age and the life risk for breast cancer on the basis of family history (see flow chart 1). All affected relatives should be on the same side of the family and are family of the person requesting advice.

First-degree relatives:	father, mother, daughter, son, brother, sister.
Second-degree relatives:	grandparents, grandchildren, uncles and aunts, children of brothers and sisters, half-brothers and half-sisters.
Third-degree relatives:	great-grandparents, great-grandchildren, great-uncles and great-aunts, cousins (children of uncles and aunts).

Watch for the combination breast cancer in a family with Jewish/Azhkenazi ancestors. Women with Jewish/Ashkenazi ancestors have a 5-10 times greater chance of carrying a BRCA 1/2 mutation.

Flow charts 1 and 2: indications for screening outside the national breast screening programme and reason for referral to a clinical geneticist.

HEALTHY WOMEN WITH RELATIVES WITH BREAST CANCER AND/OR OVARIAN/TUBAL CARCINOMA

Is there an indication for screening outside the national breast cancer screening programme or referral to a clinical geneticist?

Follow the decision tree with data from her own medical history and family history. Also see widget on www.erfelijkekanker.nl

BC = Breast cancer in the family

One of the following situations:

- 1st degree with BC < 40
- 1st degree with bilateral or multiple tumours in 1 breast with 1st tumour < 50
- Father or brother with BC
- BC < 50 and prostate cancer < 60 in the same branch of family
- 2 or more 1st degree with BC < 50
- 3 or more 1st and/or 2nd degree with BC, of which at least 1 < 50
- 1st grade with BC and OC/TC

no

One of the following situations:

- BC in 1st and/or 2nd degree with average age at diagnosis < 50
- BC in 2 1st degree with age at diagnosis < 60
- 3 or more 1st and/or 2nd degree with BC

yes

Indication for screening outside national screening programme from 40 years

yes

no

OC/TC = Epithelial Ovarian /Tubal carcinoma in the family

1st degree with OC

Or

1st degree with TC

yes

Indication for referral to clinical geneticist. Screening is determined there

no

No referral or screening necessary other than the national screening programme

WOMEN with BREAST CANCER and/or OVARIAN/TUBAL CARCINOMA
Is there an indication for referral to a clinical geneticist?

Follow the below decision tree with data from her own medical history and family history.
Also see widget on www.erfelijkekanker.nl

BC = Breast cancer in the family

OC/TC = Epithelial Ovarian/Tubal carcinoma in the family

One of the following situations:

- BC < 40
- bilateral BC or multiple tumours in 1 breast with 1st tumour < 50
- father or brother with BC
- BC < 50 and prostate cancer < 60 in the same branch of family
- BC < 50 and 1 or more 1st degree with BC < 50
- BC and 2 or more 1st and/or 2nd degree with BC, of which at least 1 < 50
- BC and OC/TC in 1 person

OC

or

TC

no

- BC and 1st and/or 2nd degree with an average age at diagnosis < 50
- BC and 1st degree with BC with age at diagnosis < 60
- BC and 2 or more 1st and/or 2nd degree with BC

yes

no

yes

no

Indication for referral to clinical geneticist, possibly DNA analysis.

Screening for her and her relatives is determined there

No reason for referral to clinical geneticist

Diagnostics

Diagnostics must focus on describing the nature, size and localisation of the laesion as precisely as possible, determining the the range of suspicion for malignancy is suspected and indicating the possibilities for further diagnostics and treatment.
If the diagnosis breast cancer has been determined based on pre-operative pathology, staging should be performed in relation to local extent, complemented by pre-operative staging of the axilla and distant metastases (where necessary).

2.1 Clinical aspects

2.1.1 Criteria for referral of symptomatic patients by the general practitioner to the second-line

The guideline development group has decided to adopt the referral criteria from the NHG Standard 2008 [de Bock NHG, 2008].

In first instance, women with breast complaints turn to the general practitioner. He/she should pay attention to each complaint with a focused medical history and clinical breast examination. Given the frequent occurrence of a familial history in the case of breast cancer, each woman should be asked for possible occurrence of breast cancer in the maternal or paternal branch (see 1.3.2, Table 1). The nature of complaints as well as the age of the woman plays a role in determining further steps to be taken. The urgency for additional examination and referral is therefore greater with older women than younger women. Classification in one of the following categories can be made on the basis of the nature of the complaints, from which further actions can be undertaken:

Local complaints or abnormalities

- If there are signs of malignancy (irregular or poorly defined tumour margins, tumour that is stuck to the skin/and or sublayer, scaling or eczema of the nipple (and not only the areola), skin and/or nipple withdrawal, regional lymph node swelling, non puerperal mastitis that does not heal rapidly): refer directly to the breast clinic.
- If there is a local palpable abnormality without indications of malignancy and an age of 30 years or older: perform a mammogram. In young women an ultrasound is sufficient, unless the abnormality has disappeared in another phase of the cycle.
    - If the result is suspect: refer to the breast clinic
    - If the result is benign: follow-up after 3 months. If the palpable abnormality remains or increases in size: refer to the breast clinic
- The woman feels a lump, the general practitioner does not: check after 2 weeks. If the woman continues to feel something: perform a mammogram (an ultrasound in women younger than 30). If complaints persist: refer to the breast clinic
- If there is local pain or sensitiveness in one breast: check after 2 weeks and, if complaints persist, after 3 months; if complaints persist: perform a mammogram. If pain persist 3 months after a negative result in mammogram: refer to the breast clinic

Diffuse complaints or abnormalities

- Diffuse lumpy breast tissue (often there are also complaints of pain) usually indicates mastopathy. Dense, firm, lumpy breast tissue may mask a carcinoma and is therefore an indication for a mammogram. Watch for women with dense breast tissue on a mammogram and repeat the mammogram if there are new complaints.
- Diffuse sensitiveness or painful breasts without abnormalities on physical examination are not an indication for a mammogram.

Nipple discharge

- A malignancy should be suspected if there is brown or bloody nipple discharge. Another cause could be a milk duct fistula with a fistula opening on the edge of the areola. Refer to a breast clinic if there is nipple discharge because a mammogram is insufficient.
- One-sided or bilateral, milky or clear nipple discharge is not suspicious for breast cancer and is not an indication for mammography or referral.

If a woman presents with new complaints, a recent mammogram without abnormalities (e.g.national breast screening programme) is not a reason to deviate from the formulated guidelines.
If additional imaging is indicated for women older than 30 years, this should consist of a mammogram, supplemented with an ultrasound if required. In women younger than 30 years, ultrasound is the

method of choice due to the low positive predictive value of mammography in this group. Obviously, evaluation on the basis of mammography is indicated if the ultrasound provides insufficient information. When requesting imaging, the general practitioner provides adequate information to the radiologist about the indication (in line with the above classification), the side(s) involved, nature and localisation of abnormalities found during the clinical breast examination, and important information from the medical history (familial history, mastitis, any prior breast surgery etc).

Remaining considerations

Mastopathy is a collective term for various complaints and disorders of one or both breasts in both men and women. The definition used here is: dense, granular and lumpy breast tissue, sensitive on palpation and sometimes spontaneously painful, especially during the premenstrual phase. In addition, there may be non-cyclical complaints or pain in the chest wall. This definition includes both palpation findings and patient complaints. Terms such as mastalgia, mastodynia and fibrocystic disease are sometimes used, but only cover part of the problem [Knuistingh Neven, 2007].

The following histological changes can be seen in mastopathy: fibrocystic changes, adenosis, sclerosing adenosis and epithelial proliferation. Mammography shows that there is not always dense breast tissue, but that there may be micro- or marcocysts, a granular or more irregular glandular structure, either in or not in combination with dense tissue, microcalcifications and milk of calcium. Ultrasound is a good supplement if there are cysts. Regarding the sensitivity of MRI results of the still limited study results vary, partly because there is a correlation in the various studies with density but not with the clinical presentation [Boyd, 2006; Kriege, 2006; Warren 2002].

Patients with mastopathic complaints and breasts that can be easily examined with low density breast tissue on the mammogram may be reassured. Caution is advised with patients who present with recurring complaints, persistent lumpiness and dense breast tissue (see above), partly given the extra risk of breast cancer in the case of dense breast tissue [McCormack, 2006; Boyd, 2010].

A pitfall is the palpable, but not very alarming abnormality that is diagnosed to be malignant after all in second instance. There is a risk that follow-up is not organised well enough. The appointment to return 3 months later is the joint responsibility of the patient and physician. The physician must explicitly instruct the patient to do so.

Recommendations

The general practitioner refers the patient to a breast care team or breast clinic if clinical breast examination yields the following symptoms:

- Signs of malignancy
- Local palpable abnormality with a suspicious mammogram
- Persistent complaints (3 months) with a non-suspicious mammogram:
    - Local palpable abnormality
    - A lump felt by the patient
    - Local pain or sensitiveness in one breast
- Brown or bloody nipple discharge

It is sufficient for the general practitioner to refer the patient to a radiology department:

- Localised palpable abnormality without signs of malignancy
- A lump felt by the patient without signs of malignancy
- Localised pain or sensitiveness in one breast without signs of malignancy
- Diffuse lumpy breast tissue with complaints of mastopathy

If no abnormalities are found on clinical breast examination, then nipple discharge that is not brown or bloody and diffuse pain in both breasts is not an indication for imaging.

Mastopathy is not a radiological diagnosis.

2.2 Imaging

2.2.1 Mammography and ultrasound

The prevalence of breast cancer in a patient with a palpable abnormality lies between 9-11%. It varies strongly with age: less than 1% in women younger than 40 years, 9% in women between 41 and 55 years and 37% in women of 55 years and older [Kerlikowske, 2003].

Mammography is the basis of imaging in symptomatic women. Supplemental examination with

ultrasound is indicated if thesymptoms are not adequately clarified (i.e. a negative mammogram). In a large retrospective study containing more than 40,000 mammograms, the average sensitivity of diagnostic mammography was 85.5% with a specificity of 87.7% [Barlow, 2002]. The sensitivity was higher as the breast tissue reduced in density and if there was a previous mammogram available for comparison. The sensitivity increased if the patients had reported the palpable abnormality themselves; however, the specificity decreased. A high age was associated with a higher positive predictive value, while supplemental ultrasound was found to be indicated more often in younger age groups. It was not possible to determine the sensitivity of the mammogram separately from the ultrasound in this study. In a number of smaller studies, in which this was possible, the contribution of ultrasound to a malignant diagnosis was found to be 6.5–14% [Zonderland, 1999; Flobbe, 2003; Moss, 1999]. The Sydney Breast Imaging Accuracy Study shows that knowledge of the mammogram performed prior to the ultrasound improves diagnosis [Irwig, 2006]. While the relationship between sensitivity and specificity between a mammogram, ultrasound and age is not linear in this study, the ultrasound is clearly more beneficial for women under 45 years of age.

A small indication area for mammography is the presence of metastases of an unknown primary tumour. The lack of a large series means there is no evidence regarding the right choice of diagnostic method. In the Guideline *Primary Tumour Unknown* [NVVP, 2011] and in the NICE Guideline 104 (2010), the recommendation is made that imaging of separate organ systems need to be requested on the basis of pathology results (and immunohistochemistry) and if there are clinical indications to do so. This is certainly the case with axillary lymph node metastases of an adenocarcinoma. Supplemental MRI must be considered if the resulting mammogram is negative.

Triple diagnostics is still the cornerstone in the diagnosis *malignancy* [Houssami, 2003; Houssami, 2005; Chuo, 2003], but this is changing in the case of palpable abnormalities in which malignancy is not suspected. There are an increasing number of studies in which the negative predictive value of a negative mammogram and a negative ultrasound is so high that supplemental punction is not indicated (anymore).
In four studies, with a follow-up period of at least 2 years, the negative predictive value varied from 97.3-100% [Dennis, 2001; Moy, 2002; Shetty, 2002; Soo, 2003]. Ultrasound also has a high negative predictive value as exclusive supplemental diagnostic method with palpable abnormalities not suspicious for malignancy [Cid, 2004; Whitehouse, 2001]. Authors of the abovementioned studies, even where a positive predictive value of 100% was achieved, nonetheless remain aware of the danger of delay in the diagnosis of an unjustly missed carcinoma and almost all studies also recommend clinical follow-up.
Improvement in the image quality of high resolution ultrasound has lead to a number of studies on the value of ultrasound with microcalcifications. Despite the fact that especially polymorphic, malignant microcalcification can be recognised, this does not have added value in the diagnostic process [Gufler, 2000; Yang, 2004].

Conclusions

Level 1	The prevalence of malignancy in patients with palpable abnormalities is high, on average 9-11%. This prevalence is dependent on age. The sensitivity of the mammogram increases with age and availability of previous imaging. A1 Kerlikowske 2003 A2 Barlow 2002

Level 1	The negative predictive value of a normal mammogram and ultrasound in patients with a palpable abnormality that is not clinically suspect is high: 97.3–100%. A1 Kerlikowske 2003 A2 Dennis 2001, Moy 2002, Shetty 2002, Soo 2003

Remaining considerations

Mammography in symptomatic patients must at least consist of images of two views, craniocaudal and mediolateral-oblique, supplemented with local compression images or magnification views of the symptomatic area where required. Identification of the abnormality may be facilitated by use of (lead) markers. The indications for this be made by the radiologist.

Additional ultrasound should be performed directly after the mammogram. This should be performed by a radiologist that also has knowledge of the mammography findings. Images of the symptomatic area should be taken in two views. In the area around the mamilla, the scan plane radial to the nipple often provides additional information. The transducer position must be indicated on the image.
Ultrasound is the method of choice in women under 30 years of age, but also with symptomatic women who are pregnant or breastfeeding. The reason for this is the dense breast tissue, not the radiation exposure. If there is an indication for mammography, this should be performed straight after. Screening in this group of women is best delayed until a few months after childbirth or after breastfeeding has ended.
Additional techniques, such as colour Doppler, contrast ultrasound and elastography have added value with small groups, in which the operator dependency is of great importance. The reason these developments have not been implemented on a greater scale is also related to the low threshold in performing a biopsy.
Communication between the radiologist and the women should follow that, as outlined in the WGBO: it is compulsory in the WGBO for the radiologist, as a health care provider, to provide information about the results of the imaging performed, but he does not need to give a direct or definitive result (Burgerlijk Wetboek 1994 (the Dutch civil code)). The radiologist can provide the result in general terms; in the event of bad news he can indicate that the requesting physician will provide the woman with further details, given they have a better overview of all the details.

2.2.2 Reporting in relation to the Breast Imaging Reporting and Data System (BI-RADS)

The below text has made use of Kerlikowske (2003), three interobserver studies with screening populations [Caplan, 1999; Lehman, 2002; Monticciolo, 2004], three studies with selected abnormalities on mammography and ultrasound [Berg, 2002; Lazarus, 2006; Burnside 2007] and the BI-RADS atlas.
BI-RADS has been developed by the American College of Radiologists [ACR, 2003]. The system was established in 1994 and consists of an atlas, in which standardised terminology is covered for the purpose of a standardised compiled report, with the aim of improving uniformity in intercollegial communication and reducing confusion. In relation to mammography and ultrasound, the criteria from which the final assessment categories have been derived, are based on publications on the diagnostic value of these criteria and can therefore be considered evidence-based. Application of the system was initially limited by interobserver variation, this decreased as the system became more common. The percentage of mammography reports in which the BI-RADS final assessment category has been assigned is an internal indicator in the quality assurance audits of the NVvR (Radiological Society of the Netherlands).

<u>The report</u>
A good report begins with a good imaging request. This should contain information about the complaint or the symptomatology, risk profile and history as well as clinical breast examination (also see 2.1).
If more than one type of imaging is performed in one sitting, all types should be included in the same report with one integrated conclusion and final assessment category to facility clarity.

A report should be succinct and follow the structure determined by BI-RADS:
1. It should state the indication for the imaging study;
2. Describe the breast composition in a semi-quantitative manner (not: very good, good, moderate, poor):
    - ACR 1 The breast is almost entirely fat (< 25% breast tissue);
    - ACR 2 There are scattered fibroglandular densities (25-50% breast tissue)
    - ACR 3 The breast tissue is heterogenously dense (51-75% breast tissue)
    - ACR 4 The breast tissue is extremely dense (> 75% breast tissue)
3. Describe any new findings or changes compared to previous images, including size and localisation. Correlation with symptomatology.
4. Concluding description followed by a BI-RADS final assessment category, showing the level of suspicion, and recommendations in relation to follow-up or additional imaging if indicated.

<u>BI-RADS final assessment categories and clarification</u>
If both mammography and ultrasound are performed, an integrated report should be formulated; the deciding factor in the BI-RADS final assessment category is the modality with the highest suspicion of malignancy.

Note that the presence of extremely dense breast tissue does not influence the BI-RADS final assessment category. In the final assessment category, the radiologist should express the extent to which an abnormality is radiologically suspect for malignancy, independent of density or the ability to evaluate the tissue.

BI-RADS 0 (Incomplete study)
Additional imaging is indicated. Examples are magnification views, ultrasound or comparison with previous studies that are not available. Many mammographic examinations performed during screening, which are eligible for referral, belong to this category. In radiology departments, this category should be applied as a provisional result and attempts towards completion should be made as fast as possible.

BI-RADS 1 and 2 (Negative and Benign)
The distinction between BI-RADS 1 and 2 is somewhat artificial, but may assist the treating physician with the discussion about a finding on the mammogram with radiological benign characteristics, such as a benign calcification or an oil cyst. Typical ultrasound BI-RADS 2 abnormalities are cysts and solid abnormalities with benign characteristics, which are stable over time. The BI-RADS 2 category is chosen if there is status after surgery, such as breast-conserving treatment, breast reduction and breast augmentation.
The percentage of malignancies in these categories should be extremely small, but will never be nil, because false negative findings are inevitable.

BI-RADS 3 (Probably benign)
This final assessment category is reserved for abnormalities on mammography or ultrasound, where the radiologist estimates the risk of malignancy to be so low (< 2%), that short-interval follow-up is deemed adequate. This usually concerns abnormalities with benign aspect, in which imaging for comparison is available, such as solid laesions (on ultrasound) with round, oval or lobulated contours, (mammographically) well-defined laesions, small groups of round or oval microcalcifications or focal asymmetry of the breast tissue.
The manner in which a BI-RADS 3 laesion is dealt with in the Netherlands differs from the recommendations by the ACR (2003), due to a difference in organisational structure. The guideline development group is of the opinion that aside from short-interval follow-up, a biopsy may also be chosen. If follow-up is chosen, then follow-up any earlier than 6 months later is generally not worthwhile [Graf, 2004; Vizcaino, 2001]. After 6 months, a recommendation may be made whether further follow-up needs to be performed after 12 and 24 months. The radiologist also has a choice here: the duration of follow-up may be applied to the age of the patient and the laesion type: in the case of a young woman with a small, typical fibroadenoma, one-off follow-up after 6 months is sufficient. Complete follow-up through to 24 months can be chosen for an older woman with a cluster of probably benign microcalcifications. If the laesion remains stable over time, the final assessment category can be changed to BI-RADS 2 (benign).
The most important disadvantage of follow-up is the chance that the patient does not follow this recommendation. This was the case for 16-18% of patients in various studies [Varas, 2002; Zonderland, 2004].
If a biopsy is chosen (cytological punction or needle biopsy) and the results are representative and correlate with the imaging (e.g. fibroadenoma), then the diagnostics are complete and follow-up is no longer necessary.
The choice between follow-up or biopsy is dependent on the technical possibilities for biopsy, the wishes of the patient and the preference of the radiologist. On the basis of currently available literature, there are insufficient indications that MRI provides added value [AHRQ, 2006; Peters, 2008], see 2.2.5.

BI-RADS 4 (Probably malignant)
If an abnormality is assigned BI-RADS 4, it needs to be taken into account that the abnormality may still be benign. The chance of malignancy within this category can vary highly, from 2-95%; subclassifications may therefore be used as an option, namely:

- BI-RADS 4a (low suspicion)
- BI-RADS 4b (intermediate suspicion) and
- BI-RADS 4c (of moderate concern, but not classic)

This refinement is of importance with microcalcifications and benign biopsy results that are indistinct, see 4.1.3. Microcalcifications may be subdivided according to the BI-RADS assessment categories

into round and punctate, milk of calcium, amorphous, coarse heterogenous, fine pleomorphic, fine linear, and branching calcifications. The order corresponds to increasing risk of malignancy. The distribution pattern, diffuse distribution, regional, clustered, linear or segmental, may play a role in determination of the risk of malignancy. In a retrospective study of 115 biopsies, Burnside (2007) described a good correlation between the morphology of microcalcifications and the estimated risk of malignancy. The amorphous and coarse heterogenous microcalcifications were less often associated with malignancy (7 and 13% respectively) compared to fine pleomorphous and fine linear/branching microcalcifications (29 and 53% respectively).

The essence of assigning a BI-RADS 4 is that tissue for pathology must be obtained that correlates with the radiology. Short-interval follow-up is not sufficient, unless this has been decided by the breast care team on the basis of good arguments.

BI-RADS 5 (Highly suggestive of malignancy)
This category is assigned to an abnormality that is highly suggestive of malignancy, with a greater than 95% likelihood of malignancy. There are often secondary characteristics of malignancy. If the obtained pathological material still yields a benign result, there needs to be consultation within the breast care team whether there may have been a sample error.

BI-RADS 6 (Biopsy- proven malignancy)
The number of patients with large tumours or locoregional extended disease who are treated pre-operatively with neoadjuvant chemotherapy or radiotherapy is on the increase. The effect of such therapy is monitored using imaging. This category has been created for this group of people, because the typical abnormalities may disappear as a result of therapy, while there may still be malignant tissue in the breast. This category is therefore not intended for imaging for patients that have already undergone surgery.

Table 1. Final assessment categories: BI-RADS mammography and ultrasound

Final assessment category	Description
0	Incomplete examination: additional imaging evaluation indicated and/or prior mammograms for comparison
1	Normal, there is nothing to comment on
2	Benign finding, e.g. a cyst, a known or calcified fibroadenoma or postoperative status
3	Probably benign finding: The radiologist thinks the laesion is benign, but prefers confirmation by means of a short-interval follow-up (6 months) or by means of a punction
4	Probably malignant, suspicious laesion: 4a. low suspicion, malignancy cannot be excluded 4b. intermediate suspicion of malignancy 4c. moderate suspicion, not classic
5	Highly suggestive of malignancy
6	Biopsy- proven malignancy

Conclusion

Level 1	For good quality breast care, clear and systematic reporting of radiological examinations is essential. The routine assigning of BI-RADS final assessment categories reduces interobserver and intraobserver variability. A1 ACR 2003 A2 Caplan 1999, Lehman 2002, Monticciolo 2004

Remaining considerations
Patients referred by the national breast screening programme form a separate group. They (usually) do not have any symptoms, but an abnormality on the screening mammogram. Section 1.3.2. describes how this should be dealt with. For most patients, the mammogram and ultrasound can be used to explain the referral indication and assign a definitive, diagnostic BI-RADS final assessment category. For a small proportion, the abnormalilities that are cause for referral are not detected on the

mammogram in the hospital and can at the most be interpreted as fibroglandular tissue. A BI-RADS 1 can then be assigned and patients can immediately return to the national breast screening programme. In a few cases, e.g. with focal asymmetry, a BI-RADS 3 (probably benign) can be assigned and a 6 month follow-up recommended, after which the patient returns to the national breast screening programme. Given this concerns asymptomatic women from the general population with low suspicion of malignancy, an MRI is also not indicated in this group.

There must not be more than two working days between performing the examination and reporting. Requesting mammograms that have been taken elsewhere must also not delay reports, any comparisons performed at a later point in time may be mentioned in an appendix. Assigning a BI-RADS 0 may only be applied if the comparison with previous mammograms is absolutely necessary for the conclusion. Each radiology unit should consider striving for a comprehensive system in relation to requesting previous mammograms from elsewhere and follow-up recommendations. Recommendations by a radiologist are not binding, although it is adviced that a multidisciplinary decision for a change in patient management is also recorded in an appendix. Finally, it remains important to also communicate personally unexpected findings with the requesting physician.

Recommendations

Mammography indications:

- Screening within the framework of the national breast screening programme
- Screening in relation to increased risk
- Within the framework of symptomatology (in women and men > 30 years)
- Within the framework of metastases of an unknown primary malignancy: only if there are clinical or pathological signs for malignancy

Ultrasound indications:

- Examination of first choice for young (< 30 years) symptomatic women (and men if applicable)
- Examination of first choice for symptomatic women who are pregnant or breastfeeding
- Additional examination to further characterise a mass detected on a mammogram
- Additional examination to further analyse a palpable abnormality that is indistinct or occult on the mammogram
- Additional examination to further analyse a non-palpable finding on a mammogram
- Additional examination to further analyse an incidental laesion found on MRI
- For the purposeof an ultrasound-guided punction or biopsy

Operating and reporting on mammography and ultrasound:

- If mammography is indicated for young, pregnant and breastfeeding women after having undergone an ultrasound, this should be performed directly afterwards
- The radiology report should correlate the symptomatology with the integrated radiology findings
- If multiple imaging types are performed during one visit, an integrated report should be made, in which the examination with the highest suspicion for malignancy should be the deciding factor
- The report should be completed with a conclusion and recommendations, in which the BI-RADS final assessment category must be assigned

BI-RADS 3

- Assigning the final assessment category BI-RADS 3, probably benign, is reserved for the group of abnormalities that the radiologist thinks is benign, i.e. the chance of malignancy is less than 2%.
- The manner in which a BI-RADS 3 laesion is dealt with may differ and is dependent on the possibilities in relation to punction, but also the wishes of the patient and preference of the radiologist. On this basis, a choice should be made between a punction or short-term follow-up (6 months). In the case of a fibroadenoma, a single follow-up in 6 months is sufficient; for microcalcifications, follow-up in 6 months is recommended, and then further follow-ups after 12 and 24 months.
- If a patient has a BI-RADS 3 laesion, and is referred by the national breast screening programme, a punction should be chosen (where possible) so that the patient can be directly referred back to the national breast screening programme if the result is benign.
- Additional MRI for BI-RADS 3 laesions as an alternative for follow-up of biopsy is not recommended.

BI-RADS 4 and 5
The manner in which a BI-RADS 4 and 5 laesion is dealt with is uniform: tissue sampling for pathology is mandatory. By exception with BI-RADS 4 abnormalities, short-interval follow-up after 6 months may be chosen if decided by the breast care team on the basis of good arguments.

2.2.3 Imaging and punction of cysts

The BI-RADS atlas distinguishes between uncomplicated cysts and complex cystic laesions. Mendelson (2001) also mentions complicated cysts. Uncomplicated cysts have a thin wall and are entirely anechoic. Complicated cysts contain a homogenous hypoechoic content, sometimes with a fluid interface; complex laesions are partly cystic, partly solid, with thickened walls, thickened septa and intracystic solid masses. The atlas classifies uncomplicated cysts as BI-RADS 2 (benign), impalpable uncomplicated cysts or clusters of microcysts as BI-RADS 3 (probably benign) and complex cysts as BI-RADS 4 (suspicious), the solid components often consist of papillary proliferations, see 4.1.3.
Ultrasound is highly specific and therefore the technique of choice. By far most cysts are uncomplicated, the diagnosis can be made by ultrasound with > 99% certainty [Boerner, 1999; Kerlikowske, 2003; Vargas, 2004]. The aspirate of 660 uncomplicated cysts in a study by Smith (1997) did not yield any malignant cells. Atypical cells were found in 5%, but all these cysts were found to be benign as well when additional was performed. In prospective follow-up studies of the various types of cysts, a malignancy is only encountered sporadically (see the table below).

Results for ultrasound of cysts

Author	Material	Follow-up	Malignancies
Smith 1997	660 uncomplicated cysts	Aspirate	0%
Lister 1998	63 uncomplicated cysts	Follow-up/Aspirate	0%
Venta 1999	308 complicated cysts	Follow-up/Aspirate/ cytology or histology if possible	0.3% (intracystic papilloma with 3 mm DCIS)
Thurfjell 2002	267 benign cysts	Follow-up for 3 years	0.4% (cyst found to be IDC after 3 years)

In a retrospective study by Berg (2003), punction of 150 uncomplicated, complicated and clustered cysts did not yield a malignancy. Punction of 71 complicated cysts resulted in 18 cases of malignancies. Especially a thickened wall or excentrically located solid component, containing more than 40% of the total laesion, is predictive of malignancy [Venta, 1999]. In an additional prospective study, Berg (2005) described that clustered microcysts occur quite commonly and are not malignant.

Conclusions

Level 1	The diagnostic reliability of ultrasound with an uncomplicated cyst is very high. A1 Kerlikowske 2003 B Boerner 1999, Thurfjell 2002, Vargas 2004

Level 3	The chance of a malignancy with uncomplicated cysts, as well as with clustered microcysts and complicated cysts is negligibly small. B Berg 2005 C Smith 1997, Berg 2003

Level 3	Pathological analysis of aspiration fluid from cysts that are uncomplicated, clustered or complicated is not worthwhile. B Lister 1998 C Smith 1997

Level 3	The chance of malignancy in a complicated cyst is small, but cannot be excluded, especially if there is a thickened wall or excentrically located mass.

	C Venta 1999, Berg 2003

Remaining considerations

Cysts may be the cause of painful, palpable abnormalities. The diagnosis can be made on the basis of ultrasound only. A punction may be offered to relieve painful, palpable cysts.

Recommendations

Ultrasound is the examination of choice to establish the diagnosis *cyst*, this applies to uncomplicated (anechoic) cysts, complicated (homogenous hypoechoic) cysts and clusters of microcysts and is independent of size and findings on palpation.
A punction may be performed for relief. A BI-RADS 2 (benign) may be assigned to this group.
Pathological examination of the aspirate is not indicated.

Complicated cysts have a small chance of malignancy. This chance increases with marked wall thickening or the presence of a solid component.
If benign characteristics dominate, BI-RADS 3 (probably benign) may be assigned with a choice of follow-up after 6 months or aspiration.
If suspicious characteristics dominate, BI-RADS 4 (suspicious) must be assigned and a punction needs to be performed: aspiration and, if possible, histology of the solid component.
Pathological examination of the aspirate is indicated here.

2.2.4 Imaging and punction of fibroadenoma

According to the BI-RADS atlas, a homogenous, solid mass with well defined margins, oval shape and parallel orientation is in line with a fibroadenoma. Skaane (1998) and Stavros (1995) add a thin hyperechoic pseudocapsule to this. If it concerns a new finding, these laesions are assigned the final assessment category BI-RADS 3 (probably benign). Known, longer existing laesions are classified as BI-RADS 2 (benign).
On the other hand, a BI-RADS 4 (probably malignant) should be assigned if not all typical characteristics are present, because a malignant tumour cannot be excluded in the case of atypical characteristics.
The fibroadenoma is the most common tumour in young women. 72% of 287 palpable laesions in women under 30 years of age were fibroadenomas [Vargas, 2005]. It is also the most common laesion in girls in puberty [Kronemer, 2001]. In a screening population of 117,729 women over 35 years of age, 51 fibroadenomas developed in 6 years; there were 4 in women between 50 and 52 years of age [Foxcroft, 1998]. The influence of hormonal fluctuations is not fully clear, but it is known that fibroadenomas may fluctuate in size and regress during menopause.
Ultrasound is more specific than mammography in establishing the radiological diagnosis. In their prospective study, Skaane and Stavros achieved an almost 100% accuracy in the group fibroadenomas, which met all the typical characteristics. From the below literature overview it appears that after adequate imaging technique, the choice is either a follow-up after 6 months or a punction (cytology or needle biopsy) for confirmation.

Fibroadenoma: imaging technique results

	Material	Follow-up	Malignancy
Graf 2004	157 BI-RADS 3 laesions, some palpable, some non-palpable	Follow-up after 6 months to 2 years, needle biopsy or excision	No malignancies
Apestequia 1997	145 BI-RADS 3 laesions, non-palpable	Follow-up after 12 months or cytology	2/145 malignancies (1.38%)
Carty 1995	78 fibroadenomas, confirmed by cytology	Follow-up up to 5 years or excision	No malignancies
Dixon 1996	219 fibroadenomas, confirmed with cytology	Follow-up up to 2 years or excision	No malignancies

Phyllodes tumour

A fibroadenoma consists of epithelial and stromal components. Rapid size increase in combination with increased growth of the stromal component, so that the tumour becomes more heterogenous, raises suspicion for a phyllodes tumour.
Gordon (2003) followed 1,070 fibroadenomas confirmed by punction. For 179 laesions, volume

measurements were performed multiple times. An increase in size to 1 cm of all 3 dimensions within a 6 month period was deemed acceptable in all age categories. A size of more than 3 cm and cystic components was more indicative of phyllodes tumour. These can become very large, up to 20 cm. Phyllodes tumours display overlapping characteristics with fibroadenomas on a mammogram and ultrasound, the pathological characteristics also overlap [Liberman, 1996; Yilmaz, 2002]. The diagnosis phyllodes tumour may be made using a histological biopsy, but excision is necessary to differentiate between benign and malignant phyllodes tumour.

Multiplicity

Patient management in the case of multiple fibroadenomas consists of careful ultrasound examination according to the abovementioned criteria by Stavros (1995) and Skaane (1998). Multiple fibroadenomas are described with cyclosporine use [Son, 2004]. Punction of one of the laesions (often the largest) in combination with a follow-up of 6 months of the remaining laesions is sufficient.

Removal

Excision of a fibroadenoma is no longer considered necessary. Different percutaneous methods have been developed to remove the fibroadenoma in a minimally invasive manner, as long as the location is suitable and the fibroadenoma no larger than 3 to 4 cm. In doing so, it is not always necessary for the fibroadenoma to be removed in its entirety. Both regression and recurrence are described [Grady, 2008]. Cryoablation in 64 patients with a follow-up of at least 12 months (a follow-up of 2.6 years for 37/64) showed good results in Kaufman (2004, 2005) as well as percutaneous ultrasound-guided vacuum-assisted excision in 56 and 109 patients respectively in Sperber (2004) and Krainick-Strobel (2007). In this last study, total removal was possible for 86%, and there was scar formation in 19%. Comparison of a group (n=51) who underwent surgical excision with a group (n=47) who underwent ultrasound-guided percutaneous vacuum-assisted excision [Wang, 2009] resulted in favour of the last group, especially due to much better cosmetic results, also after hematoma formation.
It is important, prior to the procedure, for the diagnosis fibroadenoma to be established with certainty. In the study by Matthew (2007) of 76 patients who underwent the procedure, 3 patients were found to have a malignancy. Prior to the procedure, cytology in these patients did not yield a clearly benign diagnosis.

Conclusions

Level 2	The reliability of ultrasound in diagnosing fibroadenoma that meets all typical characteristics, is very high. A2 Stavros 1995 B Skaane 1998

Level 2	Fibroadenomas may fluctuate in size. An increase in size to 1 cm of all 3 dimensions within a 6 month period is not alarming. A2 Gordon 2003 C Dixon 1996, Carty 1995

Level 3	With a fibroadenoma of more than 3 cm or with cystic components, a phyllodes tumour cannot be excluded and a histological biopsy is indicated. C Liberman 1996, Yilmaz 2002

Level 3	Percutaneous ultrasound-guided vacuum-assisted excision of a fibroadenoma is a safe procedure with good cosmetic result. The diagnosis should be established prior to the procedure. B Wang 2009, C Krainick-Strobel2007, Matthew 2007

Remaining considerations

The solid character of fibroadenomas causes more concern than a cystic abnormality and the fear of making an interpretation error and the subsequent false negative finding is great. It is therefore important only to assign a BI-RADS 3 to laesions with all the typical characteristics of a fibroadenoma.

Furthermore, ultrasound is known to be operator-dependent and published studies may paint a flattering picture, also about percutaneous removal.

Recommendations

The ultrasound diagnosis *in line with fibroadenoma* is only allowed if there is a homogenous, solid mass with well defined margins, oval shape and parallel orientation.

f he ultrasound diagnosis *in line with fibroadenoma*a BI-RADS 3 (probably benign) can be assigned; a choice can be made between follow-up in 6 months or a (cytological or histological) punction.

In case of multiple fibroadenonomas punction of one of the laesions (often the largest) in combination with a follow-up of 6 months of the remaining laesions is sufficient.

No distinction is needed between palpable and non-palpable fibroadenomas.

Laesions that do not have all the typical characteristics of a fibroadenoma, must always be assigned BI-RADS 4 (suspicious laesion). Optionally, the BI-RADS category 4a may be assigned (low suspicion, malignancy cannot be excluded).
A (cytological or histological) punction must be performed for these laesions. This applies to fibroadenomas that

- do not fully meet the above description
- that are greater than 3 cm with cystic components or that have grown per dimension more than 1 cm per 6 months, because they cannot be distinguished with certainty from phyllodes tumours

When a phyllodes tumour is suspected, histological biopsy is preferred. The suspicion should be reported on the pathology request form.

2.2.5 Imaging of silicone prostheses

There are no evidence-based guidelines or meta-analyses about screening and diagnostics in patients with silicone protheses. Most data is derived from (long-term) retrospective cohort studies.
Retrospective cohort studies show that the incidence of breast cancer in the presence of prostheses is not higher and survival is not poorer than expected [Deapen, 2007]. In some studies, the incidence is even lower. A Finnish study included 2,171 women; 30 developed breast cancer out of 33.7 expected carcinomas (SIR 0.9. 95%CI 0.6-1.3). A Danish study compared 2,763 women with silicone prostheses with a control group; less breast cancers were found here too than expected (SIR 0.7. 95%CI 0.5-1.0). The breast cancer stage and survival in these 2 studies were comparable to that in the general population [Pukkala, 2002; Friis, 2006]. Handel (2007) compared 129 carcinoma in women with silicone prostheses with the general population and found more palpable abnormalities, invasive tumours, positive lymph nodes and false negative mammograms. Follow-up was a maximum of 23 years; no difference in survival was found. Tumour detection was usually by means of physical examination (palpable abnormality); mammography was the most reliable imaging technique, followed by ultrasound.

Conclusions

Level 1	It has been demonstrated that the incidence of carcinoma does not increase in the presence of prostheses, but remains the same or is lower than in the general population. A2 Deapen 2007, Pukkala 2002, Friis 2006

Level 1	It has been demonstrated that cancer stage and survival in women with prostheses are comparable to the stage and survival in the general population. A2 Deapen 2007, Pukkala 2002, Friis 2006, Handel 2007

Level 3	Carcinomas in women with prostheses are more often detected as palpable abnormalities, they are more often invasive with lymph node metastases and false negative mammograms. A2 Handel 2007

Remaining considerations

Patients with silicone prostheses form a heterogenous group. The extent to which the prostheses mask the fibroglandular tissue varies greatly, in general overprojection reduces with increasing age, due to an increase in fatty tissue in the breast. Other factors also play a role in the ability to perform and evaluate a mammogram: capsule formation, large prosthesis in a small breast and prepectoral localisation are unfavourable, but performing and evaluating a mammogram in the case of postpectoral localisation is generally not a problem. Digitalisation of the mammogram also has a positive influence here.

The chance of rupture with the old generations of silicone prostheses (which contain an almost fluid core) is much greater than with the most recent prostheses, consisting of much firmer cohesive gel. Due to their more anatomical shape, they are much more formable and pliable, this is tested during the production process. They have a much lower chance of rupture than the older types: 98% was rupture-free after 5 years and 83-85% after 10 years [McLaughlin, 2007].

Mammography is generally considered the method of choice. Only a minority in the national screening programme cannot be evaluated, see 1.2.2. In the radiology departments of hospitals, the responsibility lies with the radiologist. The radiologist should provide further instructions to the technician when the mammogram is made: in applying compression, the consistency and location of the prostheses (pre- or retropectoral) should be taken into account. The technician should strive for images according to Eklund and an extra projection direction, for example mediolateral [Eklund, 1988].

Ultrasound is indicated as an addition to mammography for palpable abnormalities, both for the detection of leakage and for masses. There are no good studies available on ultrasound as screening method with prostheses. In the 14-centre study by Berg [2008], no women with implants were included. This study did show that in individual cases screening with ultrasound may be worthwhile, if screening using mammography does not work, see 1.1.4.

In the United States, MRI is approved by the FDA as method to determine leakage or rupture with asymptomatic patients, but the evidence for this is doubtful, partly due to the quality of third generation prostheses. However, MRI is very sensitive in determining a rupture if there are symptoms [McCarthy, 2008]. MRI as screening method in women with prostheses and with the risk profile of the general population is not recommended, because there are no indications that their prognosis is worse if breast cancer develops.

Regular breast self examination is not recommended in the general population, see 1.1.1. However, because most carcinomas in women with prostheses are discovered by palpation, this method may be worthwhile here.

Recommendations

There is no standard procedure available for women with silicone prostheses.

The guideline development group is of the opinion that the radiologist, together with the laboratory technician, must determine the choice and sequence of clinical imaging on the basis of consistency, relative size and localisation of the prosthesis.

<u>*Screening*</u>

Women with silicone prostheses between 50-75 years of age are eligible for participation in the national screening programme. Only if mammography does not work or the mammogram cannot be evaluated, they are advised to have their screening examination conducted in the hospital radiology department. At the hospital, it is expected that the radiologist and technician perform additional imaging. The radiologist may decide to screen using ultrasound (if required).

Screening with MRI is not recommended.

<u>*Diagnostics:*</u>

Mammography and ultrasound are performed if there are symptoms.

If mammography does not work, ultrasound is the procedure of choice.

2.2.6 Imaging: MRI

Breast cancer can be detected by means of MRI with intravenous administration of Gadolineum. The pathophysiology is largely based on angiogenesis: there is an increase in the number of blood vessels and permeability of the vessel wall. The process is complex, benign abnormalities (fibroadenomas) and parenchyma may also stain [Kuhl, 2000]. The evaluation of an abnormality is based on a

combination of morphology, enhancement and the kinetics of the enhancement [ACR, 2003].
The following patterns can be distinguished within the group of enhancing abnormalities: :

- focus, dot-like enhancement < 5 mm
- mass, 3 dimensional space-occupying process
- non-mass-like enhancement, enhanced area with a specific distribution pattern, e.g.segmental

The kinetics of the enhancement can be subdivided into 3 types:

- Type I: linear and persisting over time
- Type II: plateau, occurs 2-3 minutes after injection
- Type III: washout of the contrast, occurring 2-3 minutes after injection

The technique is highly sensitive, but this has an unfavourable influence on the specificity. A drawback of the high sensitivity in combination with low specificity is the occurrence of incidental or accidental findings: this is the case if there is enhancement of a laesion measuring 5 mm or greater, which is not expected on the basis of earlier images, such as elsewhere in the breast or contralateral. Incidental laesions are seen more often with younger women and in the presence of dense breast tissue. The incidence depends on the study population and varies from 16-41% [Deurloo, 2005; Teifke, 2003]. In the prospective study by Morakkabati-Spitz (2005), non-mass-like enhancement was seen with a segmental or linear distribution pattern in 50 of the 1,003 (5%) patients. In 17 patients this concerns DCIS, the positive predictive value of this type of contrast image for DCIS in this study is 34% (17/50) with a specificity of 96%.
Correlation with mammography and ultrasound is necessary to further characterise these laesions generally starting with 2nd look ultrasound. In a series of 7 retrospective cohort studies, the success percentage in identifying these laesions was 22.5 - 82% [LaTrenta, 2003; Sim, 2005; Linda, 2008; Demartini, 2009; Meissnitzer, 2009; Destounis, 2009; Abe, 2010]. If a corresponding laesion on ultrasound was found, the percentage of malignancies was 28.6 - 42.8%. If no correlation was found, this percentage was much lower: 6.3 - 20%. The chance of malignancy was greater for a mass compared to non-mass-like enhancement, as the mass was larger, if the laesion was in the proximity of the malignant index tumour and as this index tumour was larger. The corresponding laesion often has a noticeable benign aspect, with round oval shape and parallel orientation, though often with ill-defined margins [Abe, 2010].

In the presence of a corresponding laesion on ultrasound, the nature of the laesion can be determined by ultrasound-guided biopsy. If there is no corresponding ultrasound, patient management depends on the indication for the MRI.

Indication preoperative MRI

The prospective MARGIN study [Elshof, 2010] was conducted amongst 690 women with PA proven breast cancer and with a wish for BCT. They underwent a preoperative MRI. The additional laesions were subdivided on the basis of location; however, this subdivision is arbitrary and specifically aimed at determining the surgical plan: multifocal (maximum diameter of the index tumour and additional laesion of 3 cm), multicentric (maximum diameter index tumour and additional laesion greater than 3 cm) and contralateral. Second-look ultrasound was only performed for the last 2 groups. In the case of multifocality, the size of the lumpectomy was adjusted. If a corresponding laesion was not found during second-look ultrasound, a follow-up was considered as sufficient, because these laesions were classified as BI-RADS 3. The follow-up was an average of 58 months, in which no local recurrences or primary tumours were detected. It is assumed that this can be also attributed to radiotherapy and adjuvant chemotherapy.
In the case of BI-RADS 4 laesions and laesions that are decisive for surgical management, this approach is insufficient and MRI-guided biopsy is indicated.

Indication for MRI screening

In MRI screening a stricter work-up is indicated, see 2.3.1. If an additional laesion is classified as a BI-RADS 3, shirt interval follow-up is recommended: for menstruating women, this may be done in another phase of menstruation and can be performed in as short a period as possible. The breast tissue enhances the least between day 7 and day 20 after menstruation [Müller-Schimpfle, 1997; Kuhl, 2000]. If the women is not (or no longer) menstruating, follow-up of the size of the laesion after 6 months is indicated.
If an incidental finding consists of non-mass-like enhancement, DCIS may be suspected (BI-RADS 4). If a correlation with the mammogram does not show suspected MC, there are two possibilities: a direct MRI-guided biopsy is recommended or the MRI scan is first repeated: if the enhancement persists,

669 then an MRI-guided biopsy is still performed.

670 *MRI reporting*

671 When reporting on MRI imaging, the BI-RADS final assessment categories are also applicable, with
672 the undertstanding that this categories will be assigned in a more intuitive manner than is the case
673 with mammography and ultrasound due to the lack of evidence-based knowledge of the predictive
674 values of morphological and kinetic patterns.
675
676 *BI-RADS final assessment category with MRI imaging*

Final assessment category	Description
0	Assessment incomplete, e.g. due to movement artefacts or technical imperfections
1	No abnormal findings or enhancing patterns
2	Clear benign morphological finding with benign enhancing pattern
3	Probably benign: The radiologist thinks the laesion is benign, but prefers confirmation; a choice can be made from: ○ Repeat in another phase of the cycle, to further specify the enhancing pattern ○ Repeat in 6 months, to check the size increase ○ Second-look ultrasound, to perform ultrasound-guided punction; if the second-look ultrasound is negative, follow-up MRI in 6 months is mandatory
4	The combination of morphology and enhancing pattern is suspicious . Malignancy cannot be excluded, but the laesion is atypical. With occult laesions on mammography or ultrasound: consider MRI-guided biopsy
5	Highly suspicious of malignancy, both on the basis of morphology and enhanceing pattern. With occult laesions on mammography or ultrasound: consider MRI-guided biopsy.
6	Biopsy-proven malignancy

677
678 *Remaining considerations*

679 The availability of MRI in the Netherlands is rapidly increasing, but the scan can rarely be applied in
680 the short-term, so that the time for diagnostic work-up is often extended by 1 to 2 weeks. The increase
681 in the number of MRI's performed on suspicion of breast cancer requires adjustments by the surgeon
682 and radiologist. More attention should be given to the radiologist discussing MRI findings with the
683 surgeon, and he/she should also be available in the operating room. The number of locations where
684 MRI-guided biopsies are being performed is steadily growing, it is important that accessibility also
685 increases.
686

Level 1	Due to the high sensitivity of MRI, unexpected findings occur in 16-41% of the examinations performed. Of these, 29-43% are malignant. A2 Deurloo 2005, Teifke 2003 B LaTrenta 2003, Sim 2005, Linda 2008, Demartini 2009, Meissnitzer 2009, Destounis 2009, Abe 2010

687

Level 3	If a corresponding laesion on ultrasound is not found, the chance of malignancy is 6.3 - 20%. B La Trenta 2003, Sim 2005, Linda 2008, Demartini 2009, Meissnitzer 2009, Destounis 2009, Abe 2010

688

Level 3	If there are multifocal laesions on a pre-operative MRI scan, in which the laesion and the index tumour together have a maximum diameter of 3 cm and in which no corresponding laesion on ultrasound is found, the chance of a local recurrence after adjusted, more ample lumpectomy is acceptably small. B Elshof 2010

689

Level 3	If there is no corresponding laesion on ultrasound of additional BI-RADS 3 laesions outside the quadrant of the index laesion on a pre-operative MRI scan, surgical

	management does not need to be adjusted. The chance of recurrence is acceptably small. B Elshof 2010

2.2.7 Differentiation between benign and malignant abnormalities/further characterisation

Is it worthwhile to perform additional MRI in the group of patients in which, after imaging with mammography and ultrasound, the diagnosis breast cancer cannot be determined with certainty?

From the eight articles used full-text to assess this question, six were found suitable to answer the clinical question [Bluemke, 2004; Gibbs, 2004; Hrung,1999; Liberman, 2002; Nunes, 2001; Teifke, 2003]. The report by the AHRQ (2006) and meta-analysis by Peters (2008) were also used. The results of 44 studies are incorporated in this; these studies are largely (but not fully) in alignment with the abovementioned analysis.

The 44 studies had a sample size varying from 14 - 821, and a carcinoma prevalence of 23 - 84%. The pooled sensitivity was 0.90 (95%CI 0.88-0.92) and the pooled specificity 0.72 (95%CI 0.67-0.77). The diagnostic accuracy was influenced by the carcinoma prevalence and by the manner in which the findings were assessed: if two of the three ACR criteria (morphology, enhancing and enhancing kinetics) were used, the specificity was the greatest: 0.81. If all three were used, the specificity was 0.67 and if one criterion was used 0.74. This can be explained by the different methods of interpretation within studies and it is in line with the (as yet) young guidelines for interpretation of MRI images in the BI-RADS atlas [ACR, 2003].

On the basis of the above study results, it can be concluded that punction is necessary for a definitive diagnosis and cannot be replaced by MRI.

There are two groups in which these limitations play a smaller role:

- The scar in a postoperative breast may be difficult to assess by mammography, because similar to a malignancy there may be architectural distortion. Differentiation is simpler, because scar tissue no longer enhances after approximately 6 months [Rieber, 1997]. Enhancing of parenchyma is less likely due to radiotherapy and adjuvant chemotherapy. This group of patients therefore displays constant (high) sensitivity and improved specificity with high negative predictive value: 88.8 - 93% [Drew, 1998; Belli, 2002].
- Approximately 1% of all primary breast cancers are mammographically occult cancers and present as axillary lymph node metastases, while a primary carcinoma also cannot be detected by clinical examination and ultrasound. It is important for therapy choice to still attempt to find the primary tumour. Based on the high sensitivity of the MRI however, it is possible to detect the primary tumour using MRI for at least 70% of this group [Morrow, 1998; Obdeijn, 2000; Olson, 2000].

Conclusions

Level 1	Prospective studies have shown that the diagnostic accuracy of MRI in different populations varies from 69 – 89%. A1 Bluemke 2004, Hrung 1999 A2 Nunes 2001 B Gibbs 2004, Liberman 2002

Level 1	MRI is not good enough to replace biopsy. A1 Peters 2008

Level 2	In the postoperative breast, to differentiate between scar tissue and a local recurrence, the specificity of MRI is 89 – 93%. A2 Drew 1998 B Belli 2002

Level 2	In the case of lymph node metastases of an occult breast cancer, the primary tumour can be detected using MRI in 40-70%. B Obdeijn 2000, Olson 2000

Remaining considerations

A limitation of the available studies is the varying prevalence of abnormalities for participating patients and varying specificity. No randomised studies have been performed, this is related to the high expectations MRI has created, both in patients and with professionals in this area.

2.3 Preoperative staging

2.3.1 MRI for PA-confirmed breast cancer

Multiple reviews are available on different subtopics. On the basis of 19 studies, Houssami (2008) has evaluated how often extra malignancy is found and what the effect is on surgical management. Brennan (2009) analysed 22 studies to determine the percentage mammographic occult contralateral malignancy. Mann ((1), 2008) evaluated 21 studies to determine the value of MRI in invasive lobular carcinoma. Schouten van der Velde (2009) determined the value of MRI for DCIS by analysing the results of 19 studies. A number of cohort studies are also cited.

Tumour size, multifocality, multicentricity and bilaterality

Aside from personal preference of the patient, the size of the breast cancer in relation to the size of the breast is determinant for primary treatment. The size can be determined by means of clinical breast examination, mammography, ultrasound and MRI. Berg (2004) has prospectively analysed the accuracy of mammography, ultrasound and MRI for 110 women in whom 177 malignant laesions were found. The extra laesions changed the surgical management in 30% of cases. Mammography, together with clinical examination and MRI, is the most sensitive combination. Ultrasound after MRI did not provide additional value. The sensitivity of mammography was inversely proportional to the density of breast tissue and reduced from 100 to 45% for very dense breast tissue. MRI displayed a higher sensitivity than mammography and ultrasound, both for invasive and in situ malignancy. Addition of MRI led to a false-positive finding and an overestimation of tumour size in 6%.

In the prospective study by Deurloo (2006), in which candidates for breast-conserving therapy were included, MRI was significantly more often correct in determining tumour size than conventional imaging (90% versus 70%). This was especially the case if there was an irregular shape of the tumour on the mammogram, if there was a discrepancy in size, measured on mammography and ultrasound and in younger patients. Mammographically occult laesions were detected in 13% of patients.

In the prospective multicentre trial by Schnall (2005), 414 women with proven breast cancer were examined by mammography and MRI. Mammographically occult malignant laesions that were more than two cm distance from the index laesion (and therefore usually outside the boundaries of the lumpectomy) were found in 10% of women. This especially concerned women with dense breast tissue. Half of these laesions were greater than 1 cm.

DCIS

The size of DCIS is usually determined by the size of the area with microcalcifications. However, this often appears to be an underestimation [Holland, 1990]. A more accurate determination of the size of DCIS by MRI is important, because complete excision means 100% curation in the case of DCIS.

In a review, Schouten van der Velden (2009) analysed 19 studies for the value of MRI with DCIS. The sensitivity varied from 38 to 100%, in which false negative findings often involved low-grade DCIS. MRI was found to be better at indicating the size of DCIS, although a lot of overestimation occurred due to the presence of enhancing benign proliferative disorders.

The publication by Kuhl (2007) is an interesting study on the value of MRI with DCIS. She studied more than 7,000 patients for different indications using both mammography and MRI. It was a double-blind study. One hundred and sixty seven cases of pure DCIS were found and these were the subject of the study. There was a moderate sensitivity (56%) for mammography and significantly higher sensitivity for MRI (96%). MRI was especially better in detecting high-grade DCIS.

MRI was also found to be more accurate in the case of an invasive carcinoma with an extensive intraductal component (EIC). There is EIC in 30 to 40% of invasive laesions. Irradically removed EIC is an important prognostic factor for the risk of a local recurrence, probably because substantially more tumour tissue remains in these patients after lumpectomy [Holland (1), 1990; Holland (2), 1990; Voogd, 2001].

Invasive lobular carcinoma

Invasive lobular carcinomas make up approximately 10% of all breast cancers and there are indications that the incidence is increasing [Li, 2003]. A diffuse growth, without microcalcifications, is

more common than with invasive ductal carcinomas, so that the mammogram may be false negative [Arpino, 2004; Berg, 2004]. The infiltrative growing lobular carcinomas are often underestimated in size, both with mammography and ultrasound [Mann (2), 2008]. Connected to this is the fact that positive surgical margins are seen more commonly with breast-conserving treatment in the case of invasive lobular carcinoma than with invasive ductal carcinoma [Dillon 2006, de Zeeuw 2009]. However, it has never been demonstrated that ILC leads to more local recurrences, not with breast-conserving treatment, nor GRM with radiotherapy [Diepenmaat, 2009]. It appears from the review by Mann ((1), 2008) that MRI is better at indicating tumour size than mammography and ultrasound. In addition, extra ipsilateral malignant laesions were seen in 32% of patients and contralateral laesions in 7% of patients using MRI. MRI changed surgical management in 28% of cases.

Relation to evaluability of mammography

In the prospective trial by Sardanelli (2004), MRI was compared to mammography in 90 patients who were going to undergo a planned mastectomy. MRI was found to be more sensitive in the detection of multifocal and multicentric laesions with an overall sensitivity of 81 and 60% respectively. However, no significant difference in sensitivity was found in breasts largely composed of fat tissue. In the studies by Berg (2004) and Goethem (2004), the difference in sensitivity was also inversely proportional to the density of the breast tissue.

Contralateral laesions

In the multicentre study by Lehman (2007), 30 contralateral tumours (3%) were found in 969 women with a recent diagnosis of unilateral breast cancer, which were clinically and mammographically occult. The review by Brennan (2009) shows suspicious abnormalities in the contralateral breast are seen in 9.3% of women with recently diagnosed breast cancer, in which more than half are found to be false positive. A total of 131 malignant laesions were found in 3,253 women (4%). Of these laesions, 35% concerned DCIS; 65% were invasive with an average diameter of 9 mm. While the prognostic value of detecting these laesions is difficult to estimate, simultaneous detection of contralateral malignancy can spare women a second round of therapy.

Conclusions

Level 1	On average, MRI is a better approximation of the precise tumour size than clinical breast examination, mammography and ultrasound, especially with dense breast tissue. A1 Houssami 2008, Brennan 2009, Mann 2008, Schouten van der Velden 2009 A2 Berg 2004, van Goethem 2004, Deurloo 2006

Level 2	The difference in accuracy between MRI and mammography is dependent on the density of the breast tissue. The difference is small for fatty breasts. A2 Berg 2004, Sardanelli 2004, B Van Goethem 2004, Schnall 2005

Level 1	When determining the tumour size using MRI, overestimation is more common than underestimation. The percentage of overestimation in tumour size by MRI varies strongly; it is smallest with invasive lobular carcinoma and the largest with DCIS. A1 Houssami 2008, Mann 2008, Schouten van der Velden 2009 A2 Deurloo 2006, Berg 2004

Level 1	Compared to mammography and ultrasound, MRI has the highest accuracy in pre-operative determination of additional tumour foci and bilaterality. This applies to invasive ductal carcinoma and invasive lobular carcinoma. A1 Houssami 2008, Brennan 2009, Mann(1) 2008

Level 1	The sensitivity of MRI with DCIS is highly variable and there may be a substantial overestimation.

	MRI has a higher negative predictive value than mammography in relation to multicentricity, residual tumour and detecting an invasive component. MRI has the highest accuracy in determining the presence and size of high grade DCIS and an extensive intraductal component. A1 Schouten van der Velden 2009 A2 Kuhl 2007, Hwang 2003

What is the effect of preoperative MRI?

The rapid introduction of MRI is largely the result of great accuracy in relation to tumour size, multifocality and multicentricity and has lead to MRI increasingly being added to the preoperative work-up of patients eligible for BST.

This may lead to changes in surgical management, which means a mastectomy is performed instead of a lumpectomy, or a more extensive lumpectomy or an extra lumpectomy. Morrow (2004, 2006) has made critical side notes about this development. Does this more extensive surgery actually result in an improvement for the patient? Does preoperative MRI contribute to a reduction in the number of reoperations, to less recurrences or to a better prognosis?

Effects on the pre-operative process

In a retrospective study by Bleicher (2009) involving 577 patients, of which 130 underwent a preoperative MRI, it was noticeable that the pre-operative process with these 130 patients took more than 22 days longer (p=0.011), while there was no statistically significant difference in positive surgical margins after surgery (21.6% with MRI and 13.8 % without MRI, p=0.20). The percentage of conversions to mastectomy was higher, but this difference was also not statistically significant (9.8% with MRI and 5.9% without MRI, p=0.35). The longer duration of the pre-operative process is usually the result of the work-up of additional findings. In the study by Lehman (2007), 121 biopsies were required for the detection of 30 contralateral tumours.

Effect on surgical management

Berg (2004) reports that surgical management was changed in 30% of cases, Van Goethem (2004) 43%, Deurloo (2006) 22% and Mann ((2), 2008) 28% of exclusively ILC patients.

Houssami (2008) reports that the effect on surgical management is mentioned in 13 of 19 studies: mastectomy is performed instead of lumpectomy in 8% and more extensive surgery in 11% (not further specified, this concerned more ample excision, or an extra excision but also mastectomy). On the basis of false-positive findings, an unjustified mastectomy was performed in 1% of women and more extensive surgery in 5%.

Effect on the frequency of reoperation

Only a proportion of studies provide information about the effect of preoperative MRI on the number of irradical lumpectomies. Grobmeyer (2008) reports a low percentage (10%) of positive surgical margins. Pengel (2008) compared the number of irradical lumpectomies in a group of patients with and without preoperative MRI. This was 14% in the MRI group and 19% in the non-MRI group. Mann (2010) retrospectively evaluated the re-excision rate with ILC: this was 27% in the non-MRI group and significantly lower (9%) in the MRI group. The final mastectomy percentage was also lower in the MRI group (48% versus 59%).

Turnbull (2010) published results for the only randomised study conducted (so far) in this area. It concerns an English multicentre study in which 45 hospitals and 107 surgeons participated. The primary endpoint was the percentage of reoperations. The percentage of reoperations in 800 patients with and 800 patients without preoperative MRI were compared and were found to be practically the same: 18.7 versus 19.3%.

Effect on the risk of recurrence and prognosis

There is little known yet about this. There was no difference in the frequency of local recurrence in a retrospective study by Solin (2008): 3% in women with preoperative MRI and 4% in women without MRI. There was also no difference in survival: 86% in women with preoperative MRI and 86% in women without MRI. The differences in patient populations were not significantly different, the patients with MRI were a little younger (53 years versus 56 years) and had slightly more favourable tumour characteristics.

The additional tumour foci that were detected using MRI confirm what has been known for some

time, namely that breast cancer is often multifocal and multicentric [Holland, 1985]. It is therefore plausible that tumour is regularly left behind during a lumpectomy. Despite this, clinical trial data show that the prognosis of patients undergoing BST is the same as patients undergoing a mastectomy [van Dongen, 2000; Fisher, 2002] and the recurrence percentage is low. Clearly, postoperative radiotherapy and chemotherapy attribute to this. Patients in these trials did not undergo preoperative MRI, from which the conclusion could be drawn that survival advantage is not gained from detecting multifocality using MRI. In relation to the risk of local recurrence, it must be noted that the risk is clearly higher for young women [Vrieling, 2003; Bartelink, 2007] and that the prognosis of patients with a local recurrence is clearly poorer than for patients who do not experience a recurrence [Voogd, 2001; Clarke, 2005]. De Bock (2009) analysed the data of 3,601 women with stage I and II breast cancer included in 3 EORTC trials. Patients with a local recurrence were found to have three times the risk of developing distant metastases than patients who did not develop a recurrence. Young age and breast-conserving therapy were the most important prognostic factors for developing a local recurrence. The expectation is that implementation of MRI specifically with young women will favourably influence survival, while in women of 70 years and older no survival advantage is expected. However this has not yet been demonstrated.

Conclusions

Level 1	Preoperative MRI may lead to a longer pre-operative process and has lead to more extensive surgery, both in terms of local excision with BCT and the percentage of mastectomies. A1 Houssami 2008, Brennan 2009 B Bleicher 2009

Level 1	Preoperative MRI has not lead to a significantly lower percentage of reoperations, except with ILC. A1 Turnball 2010 B Bleicher 2009, Mann (2) 2008

Level 1	After primary therapy (consisting of mastectomy or BCT), the chance of a local recurrence is the greatest with young women and breast-conserving therapy. These recurrences worsen the prognosis and reduce survival. A1 Voogd 2005, Clarke 2005, Bartelink 2007, de Bock 2009 A2 Vrieling 2003

Remaining considerations

After an enthusiastic introduction of MRI in the preoperative work-up of patients who are eligible for BCT, the added value is currently up for discussion and the indication is therefore controversial. It appears to be difficult to translate the extra information obtained by means of MRI into better surgical results. It is also possible that the role of additional radiotherapy and adjuvant chemotherapy with eradication of additional foci is being underestimated.

While sufficient information will be gained with conventional imaging for the majority of patients to perform breast-conserving treatment, it has become clear that subgroups will benefit from preoperative MRI. More randomised studies are required to define these subgroups.

If additional laesions are detected using MRI, for which PA is required, extension of the pre-operative process is sometimes unavoidable.

Recommendations

<u>Performing the MRI</u>

- Standardised reporting including BI-RADS final assessment categoriesis required.
- Incidental, additional findings must be classified separately.
- An incidental, additional finding must be correlated with mammography and (second-look) ultrasound, during which PA material can be obtained.
- If an ipsilateral incidental finding is present with a preoperative patient (multifocal or multicentric) and no corresponding laesion on ultrasound or mammographyis found, a practical approach can

be chosen by the breast care team and planned surgical management does not need to be amended per se.

- The following applies to the remaining additional findings:
  - If a corresponding laesion is not found and it concerns a BI-RADS 3 laesion, a repeat MR in another phase of the menstruation or after 6 months is indicated
  - If a corresponding laesion is found and it concerns a suspicious malignant mass (BI-RADS 4 or 5), which may drastically change surgical management, this is eligible for MRI-guided biopsy.
  - If a corresponding laesion is not found and it concerns a non-mass-like enhancement (BI-RADS 4), which may drastically change surgical management, this is eligible for MRI-guided biopsy
  - In the remaining cases, a one-off repeat of the MRI in a different phase of the cycle or in 6 months may be chosen, before proceeding to MRI-guided biopsy

Indications for MRI:

Screening:

- Screening with MRI is indicated for women with a very high risk (RR 6-8)
- There is insufficient basis to recommend annual MRI screening for women with increased risk without gene mutation, other than in a research context
- MRI screening of women from the general population with dense breast tissue or with silicone prostheses is not recommended

Preoperative staging:

- Routine preoperative MRI is not recommended.
- Preoperative MRI is recommended for invasive carcinoma, if the woman would like to be eligible for BCT, and:
  - there is a discrepancy in size on clinical examination, mammography and ultrasound, or
  - there is invasive lobular carcinoma, unless there is a unifocal mass on a fatty mammogram

  This recommendation applies especially to young women
  The added value for women over 70 years of age is minor
- Preoperative MRI is recommended with DCIS, if the woman would like to be eligible for BCT, and:
  - there is high grade DCIS, in which there is indistinctness about the tumour size
  - there is DCIS with suspicion of (micro)invasion

Differentiation between benign and malignant abnormalities/further characterisation:

- MRI as additional imaging technique in the case of a problematic mammogram or ultrasound should be applied cautiously. If a punction is indicated on the basis of mammography and ultrasound, this punction indication will not be made unnecessary by MRI examination
- MRI is recommended as additional diagnostic tool for suspicious abnormalities of the postoperative breast or positive axillary nodes and an occult primary tumour on mammogram and ultrasound

Determining the effect of neoadjuvant chemotherapy

- MRI as additional imaging technique is recommended to accurately record the tumour size before and after neoadjuvant chemotherapy (unless it can be clearly determined using mammography and ultrasound)

2.3.2 For which patients is preoperative and ultrasound of the axilla indicated as triage test for the SN procedure?

Preoperative staging of the axilla using ultrasound, selectively supplemented with ultrasound-guided punction is applied when breast cancer is suspected. In 2006, a systematic review was published of prospective cohort studies [Alvarez, 2006], in which cytological punctions were performed. In one study, histology was also obtained in difficult cases. The sensitivity of ultrasound with non-palpable nodes, based on morphology, varied between 26.4% (95%CI 15.3 – 40.3%) and 75.9% (95%CI 56.4 – 89.7%).

In the meantime, the meta-analysis by Houssami (2011) has become available. Thirty-one studies were included with data of 2,874 punctions in 6,166 patients. An overall sensitivity was calculated of 79.6% (95%CI 74.1 - 84.2), specificity of 8.3% (95%CI 97.2 – 99.0), and PVW 97.1% (95%CI 95.2 – 98.3). The average percentage of insufficient punctions was 4.1%.

The sensitivity was higher if the punction was performed with nodes *suspicious* on ultrasound compared to *visible* nodes. Suspicious characteristics varied in different studies, the most important were cortical thickness and asymmetry of the cortex. The procedure prevented an unnecessary SN procedure in 19.8% of all women; in 17.7% of the women if the lymph nodes were not palpable. The chance of a positive punction result of the nodes is significantly greater if the diameter of the primary tumour is greater than 21 mm: OR 2.57 (95% CI 1.29-5.09).
The sensitivity and specificity of histology (4 studies) were a little higher than of cytology (24 studies): a sensitivity of 83.4% (95%CI 71.6 - 90.9) and specificity of 100% for histology, versus 78.6% (95%CI 72.2 – 83.7) and 98.0% (95% CI 96.7 – 98.8) respectively for cytology. However, the difference was not significant (p=0.41) and it seems more relevant for the choice of histology or cytology to let it depend on the expertise of the pathologist. The comparative study between cytology and histology by Rao (2009), included in the meta-analysis, showed no statistical difference in sensitivity; however, histology was twice as expensive. In the study by Deurloo (2003), also included in the meta-analysis, the best predictor of lymph node metastasis by ultrasound was the maximum cortex thickness, in which the optimal cut-off point was found to be > 2.3 mm.

Conclusions

Level 1	Selective preoperative punction of abnormal axillary nodes on ultrasound leads to a reduction in the number of SN procedures by 19.8%. A1 Houssami 2011

Level 1	The results of cytology and histology (sensitivity and specificity) are comparable: the difference is not significant. A1 Houssami 2011

Level 3	During ultrasound examination of axillary nodes, a cortex thickness >2.3 mm is an optimal cut-off point for an acceptable cytology yield. B Deurloo 2003

Remaining considerations

Ultrasound with cytology of the axillary nodes is not a stressful procedure. The procedure can be applied with breast abnormalities that are assigned BI-RADS 4 or 5 before a definitive pathology diagnosis is available. Cytology of axillary nodes does not appear to interfere with the SN procedure, although systematic studies are lacking.

Recommendations

Ultrasound of the axilla is indicated in the case of pathologically proven (or suspected) breast cancer (BI-RADS 4 or 5), supplemented with punction of a suspected node.

Cytological punction of a lymph node is recommended if the cortex thickness is 2.3 mm or more and if the cortex is asymmetrical.

2.3.3 FDG-PET-CT of PA-proven breast cancer

In asymptomatic patients without locally advanced disease, staging is largely limited to clinical examination. In patients with stage III breast cancer, staging is performed with imaging. So far, these patients usually undergo skeletal scintigraphy, ultrasound of the liver and chest X-ray [Aukema, 2009]. A relatively new technique is positron emission tomography (PET) with the glucose analogue F-18-fluorodeoxyglucose (FDG), currently often used in combination with computer tomography (CT). FDG-PET is an accurate technique in oncological practice in staging and re-staging of recurrent disease, in the detection of occult tumours and the evaluation of residual laesion after therapy [Juweid, 2006]. It is a non-invasive examination of the entire body. By combining anatomical and functional information, integrated PET-CT systems have a better accuracy than FDG-PET only or FDG-PET in combination with a separate CT for the detection of malignant abnormalities [Antoch, 2004, Poeppel 2009]. FDG-PET is highly sensitive for the detection of lytic skeletal metastases, but sclerotic laesions may be missed with this technique.
The CT component contributes to a higher specificity, also in the case of skeletal abnormalities.
The diagnostic value of FDG-PET-CT is greater in the staging and re-staging of patients with breast

cancer than the value of FDG-PET or CT only [Fueger, 2005; Czernin, 2010]. FDG-PET-CT has gained an increasing role in recent years in the different diagnostic aspects of breast cancer.

Detection of primary breast cancer

The sensitivity of FDG-PET for the detection of subcentimetre laesions is low, approximately 57% [Lavayssière, 2009]. Avril (2000) had an overall sensitivity of 80.3% with 144 patients. The detection of T_1 tumours was decidedly lower than for T_2 tumours, 68.2% and 91.9% respectively. Fuster (2008) studied 60 patients with tumours > 3 cm. FDG-PET-CT detected all laesions but FDG-PET-CT visualised only 14 of the 19 multicentric and/or multifocal tumours compared to MRI. The relatively limited spatial resolution of PET and the variable uptake of FDG in breast tumours play a role in this moderate result. Well-differentiated and slow growing tumours have a lower metabolic activity and , as a result, are more often false negative. FDG-PET therefore has a higher sensitivity for invasive ductal carcinoma than for invasive lobular carcinoma. Non-invasive tumours such as ductal and lobular carcinoma in situ (DCIS and LCIS) generally have a low uptake of FDG or are even negative. There is a correlation between uptake and aggressiveness of the tumour [Lavayssière, 2009]. In a group of 116 tumours, Kumar (2006) found that smaller tumours (≤ 1 cm) and low-grade were powerful independent predictors of false-negative examinations. In a systematic review of 13 studies (n=16-144/study), in which an FDG-PET was performed in patients with suspected breast cancer, FDG-PET had a (predicted) sensitivity of 89% and a (predicted) specificity of 80%. The (individual) risk of a false negative result was too great to omit a biopsy in patients with a negative FDG-PET [AHRQ, 2001]. The sensitivity of the examination is therefore too low for detection of a primary breast cancer in routine staging.

Staging lymph nodes

Accurate staging of axillary nodes is important to determine the prognosis and select the right patients for additional treatment. Studies that have shown that the value of FDG-PET(-CT) in determining the axillary node status show a wide range of sensitivity and specificity. In a systematic review of 26 studies (n=2,591), an average sensitivity of 63% (95%CI: 52-74%) was found and an average specificity of 94% (95%CI: 91-96%) for PET or PET-CT [Cooper, 2011]. The average sensitivity was 11% (5-22%) for micrometastases (≤ 2 mm; 5 studies; n=63) and 57% (47%-66%) for macrometastases (>2 mm; 4 studies; n=111). FDG-PET(-CT) has a lower sensitivity and specificity than the SN procedure. Replacement of the SN procedure by FDG-PET may spare patients the negative effects of the SN procedure but results in more false negatives with a greater recurrence rate. In short, FDG-PET(-CT) does not play a meaningful role as standard non-invasive procedure during staging of clinically negative axilla. However, specificity is very high. The seven FDG-PET-CT studies in this review (n=862) have an average specificity of 96% (95%CI: 90-99%). On this basis, omitting the SN procedure and performing a direct ALND in patients with a positive axillary node on FDG-PET-CT, in which the procedure was performed for another reason, can be considered [Cooper, 2011; Aukema, 2009].

Detection of extra-axillary lymph nodes is important for lymph node staging and any adjustment that may need to be made to the treatment plan. Aukema (2010) found PET-positive extra-axillary lymph nodes in 28% (17/60) of patients with stage II-III breast cancer, of which 7 could be evaluated using ultrasound and were pathologically proven. Radiotherapy was adjusted in 7 patients (12%).

Staging – detection of distant metastases with primary breast cancer

A complete diagnostic work-up for the detection of distant metastases consisting of chest X-ray or CT, skeletal scintigraphy and ultrasound of the liver is not indicated for most patients with primary breast cancer stage I and II but is in fact indicated for patients with stage III breast cancer [Puglisi, 2005]. In a prospective study, Hoeven (2004) researched the value of FDG-PET in 48 patients with locally advanced breast cancer and negative conventional work-up. Metastases was suspected in 10 patients. Further work-up confirmed 4 metastases. Fuster (2008) conducted a prospective study with 60 patients with large (>3 cm) primary breast cancer and compared FDG-PET with conventional imaging. FDG-PET had a sensitivity and specificity of 100% and 98% respectively for the detection of metastases and conventional imaging of 60% and 93%. In a larger retrospective study, Mahner (2008) studied 199 patients with locally advanced breast cancer (n=69) or suspected recurrence (n=50). FDG-PET detected distant metastases with a sensitivity, specificity and accuracy of 87%, 83% and 86% respectively. For conventional imaging (chest X-ray, ultrasound of the abdomen and skeletal scintigraphy) this was 43%, 98% and 74% and for CT this was 83%, 85% and 84%. The diagnostic accuracy of FDG-PET for the detection of distant metastases is better than that of conventional imaging but comparable to that of CT. The diagnostic information provided by FDG-PET and CT was

also found to complement each other in this study. This data suggests that one FDG-PET(-CT) examination may potentially replace conventional imaging [Koole, 2011].

Re-staging – detection of locoregional recurrence and distant metastases

Patients with a locoregional recurrence of breast cancer can sometimes still be treated with curative intent using surgery. The presence of distant metastases determines the treatment plan and prognosis to a large degree. That is why adequate detection of distant metastases is crucial. Isasi (2005) reported, in a meta-analysis of 16 studies and 808 patients, a median sensitivity of 93% and a median specificity of 82% for FDG-PET in the detection of recurring breast cancer (local, regional and distant). The pooled sensitivity was 90% (95%CI: 87%-93%) and the pooled percentage of false positives was 11% (95%CI: 7%-15%), after excluding outliers.

In a systematic review of 28 studies, Pennant (2010) studied the value of FDG-PET(-CT) in the detection of recurring breast cancer (local, regional or distant). The size of the studies varied from 10 to 291 patients (median 45). FDG-PET had a significantly higher sensitivity and specificity for the detection of locoregional recurrence and distant metastases compared to conventional imaging, 89% and 93% versus 79% and 83% respectively. FDG-PET-CT had a significantly higher sensitivity compared to CT (95% versus 80%) but not a significantly higher specificity (89% versus 77%). FDG-PET-CT had a significantly higher sensitivity compared to FDG-PET (96% versus 85%) but the specificity was not significantly higher (89% versus 82%). FDG-PET and FDG-PET-CT (the latter on the basis of 1 study) showed no significant difference in sensitivity or specificity compared to different MRI techniques. The overall sensitivity, on a patient basis of FDG-PET-CT (n=5) and FDG-PET (n=25), was 96% (95%CI: 89%-99%) and 91% (95%CI: 86%-94%) and the overall specificity was 89% (95%CI: 75%-95%) and 86% (95%CI: 79%-91%). It should be noted that the evaluated studies were generally small and retrospective. In addition, subgroup analysis was conducted on all studies and not only on comparative studies.

This data suggests there is a higher diagnostic accuracy for the detection of locoregional recurrence and distant metastases when FDG-PET is added to conventional imaging.

FDG-PET-CT has added diagnostic value compared to FDG-PET and CT only, in the detection of recurring breast cancer. Change in the treatment plan varied in the different studies from 11% to 74% (median 27%). These changes include (not) starting hormonal therapy and chemotherapy. In three studies, change in the treatment plan was only scored if this change was a direct result of FDG-PET(-CT) examination. Estimations of the frequency in change varied in these studies from 11 to 25%.

It can be concluded from the review by Pennant (2010) that it is still too early to fully replace conventional staging by FDG-PET-CT. FDG-PET-CT already appears to be justified when metastatic disease is suspected after unclear findings on conventional imaging. FDG-PET-CT also appears to be valuable as an addition to current practice when a recurrence is suspected.

Dirisamer (2010) found a higher sensitivitiy (93%) for FDG-PET-CT compared to FDG-PET (84%) and CT (66%) only in 52 patients with a suspected recurrence (regional and distant). FDG-PET-CT was correct in 96% of patients, FDG-PET in 85% and CT in 73%. All missed laesions on CT concerned lymph nodes (< 10 mm).

In a study in the Netherlands, the impact of FDG-PET-CT on treatment was evaluated in 56 patients with proven locoregional recurrence [Aukema, 2010]. FDG-PET-CT detected additional tumour locations in 32 patients (57%). Distant metastases were detected in 11 patients using conventional imaging and in 23 patients with FDG-PET-CT (significant difference). FDG-PET-CT detected additional laesions in 25 patients (45%) that were not visible with conventional imaging. FDG-PET-CT had an impact on the treatment plan in 27 patients (48%) because more extensive locoregional disease or distant metastases were detected. Extensive surgery was prevented and a switch made to palliative treatment in 20 patients (36%). The sensitivity, specificity, accuracy, PPV and NPV of FDG-PET-CT were 97%, 92%, 95%, 94% and 96% respectively. Aukema concludes that FDG-PET-CT added to conventional imaging plays an important role in the staging of patients with locoregional recurrence.

Conclusions

Level 3	The sensitivity of FDG-PET(-CT) is too low for detection of a primary breast cancer. C AHRQ 2001

Level 3	FDG-PET(-CT) does not play a decisive role in staging of clinically negative axilla and cannot replace the SN procedure. C Cooper 2011

Level 3	Omitting the SN procedure and performing a direct ALND in patients with a positive axillary node on FDG-PET-CT, in which the procedure was performed for another reason, can be considered. C Cooper 2011, Aukema 2009

Level 3	FDG-PET(-CT) may potentially replace conventional staging. C Fuster 2008, Mahner 2008, Koole 2011

Level 3	In the case of (suspicion of) local, regional or distant metastasis of an invasive breast cancer, FDG-PET(-CT) has greater diagnostic value than conventional staging, with impact on treatment. C Pennant 2010, Isasi 2005, Fueger 2005, Dirisamer 2010

Remaining considerations

An increasing number of hospitals in the Netherlands are performing FDG-PET-CT. Due to collaboration agreements, the modality is available to all patients.
At almost all locations, this leads to replacement of conventional staging by FDG-PET-CT, both for stage III and IV breast cancer, for neoadjuvant therapy and if a (local, regional or distant) recurrence is diagnosed or suspected.
This has consequences for treatment of the patient, despite the fact that there is still no literature data on long-term results. Due to the high sensitivity and specificity of FDG-PET-CT for axillary lymph node metastases, the procedure also has consequences for recommendations for axillary node staging in the Netherlands. It is still too early to omit ultrasound and punction and immediately move across to axillary node dissection or for a binding recommendation for FDG-PET-CT. Aside from high sensitivity, many abnormalities are also found, which later do not appear to be due to metastases. A clear strategy has not yet been developed to deal with this, because a pathological diagnosis cannot always be obtained.
In relation to the large chance of false-positive findings in the case of small aspecific abnormalities on FDG-PET-CT, these should be disregarded and treatment can remain curative in intent.

Recommendations

FDG-PET-CT can replace conventional staging for primary breast cancer (skeletal scintigraphy, ultrasound of the liver, chest X-ray and/or CT).

FDG-PET-CT is recommended with stage III primary breast cancer.

FDG-PET-CT may be considered with stage II primary breast cancer within the framework of neoadjuvant treatment.

Aside from local conventional imaging, FDG-PET-CT may be considered as an additional procedure in the case of complaints that are suspicious for locoregional recurrence or distant metastases.

In patients with a positive axillary node on FDG-PET-CT as unexpected finding, the chance of lymph node metastasis is high and additional ultrasound examination with punction is indicated.

In relation to the large chance of false positive findings, the guideline development group is of the opinion that in case of small aspecific abnormalities on FDG-PET-CT these should be disregarded and treatment can remain curative in intent.

Loc(oregion)al treatment

3.1 Treatment of Ductal Carcinoma in Situ (DCIS)

The increase in the number of patients with Ductal Carcinoma In Situ (DCIS) is partly due to the national breast cancer screening programme. DCIS is diagnosed in approximately 1,800 patients annually. DCIS is an intraductal proliferation of malignant cells in which invasion of the stroma has not yet occurred and is generally considered a pre-stage of an invasive ductal carcinoma, although it is uncertain what percentage of untreated cases will develop into an invasive carcinoma [Lakhani, 2006]. Lobular Carcinoma In Situ (LCIS) is considered a risk factor for the development of invasive carcinoma and is not treated as a malignancy.

3.1.1 Preoperative diagnosis of DCIS

It is estimated that 80-85% of DCIS is non-palpable and is detected on the basis of mammographic findings, usually on the basis of microcalcifications [Lakhani, 2006]. This underlines the importance of good mammography [McKay, 2000]. However, extension of microcalcifications on the mammogram does not always appear to correlate with pathological metastasis of the tumour [Holland, 1990]. In diagnostics in relation to microcalcifications, vacuum-assisted biopsies are preferable due to a lower underestimate rate. Pre-operative MRI may be considered, if the woman would like to be eligible for BCT, if there is high grade DCIS and the tumour size is unclear and (micro)invasion is suspected. If the pre-operative diagnosis is certain, the chance of radicality of the excision increases [Verkooijen, 2002]. Invasive carcinoma is still found on excision in approximately 20% [Fahrbach, 2006; Meijnen, 2007]. A large meta-analysis estimated the chance of invasive growth at 25.9% (95%CI 22.5-29.5%). The chance is related to the type of biopsy needle (11G vs 14G, p=0.06), the grade of DCIS (high grade versus low grade, p<0.001), the size of the laesion on the mammogram (>20 mm vs ≤ 20 mm, p<0.001), the mass on the mammogram (mass vs microcalcifications only, p<0.001) and if the growth is palpable (palpable vs. non-palpable, p<0.001 [Brennan, 2011].

Given the abnormality is often non-palpable, it is difficult to determine peroperatively if the abnormality has been fully removed and specimen radiography is indicated.
The chance of lymph node metastases is small in abnormalities < 2.5 cm and in low-grade DCIS in patients over 55 years of age [Fahrbach, 2006; Huo, 2006; Meijnen, 2007; Julian, 2007]. In the case of a DCIS > 2.5 cm in diameter, as determined by histological biopsies, the chance of lymph node metastases due to missed invasive growth was 7% [Meijnen, 2007; Brennan, 2011]. If postoperative invasive foci are encountered that are larger than 5 mm, the chance of lymphogenous metastasis is > 5% and lymphogenous staging is still recommended [Schneidereit, 2003; Seidman, 1995].

A sentinel node procedure (SN procedure) should be considered for [Fahrbach, 2006; Huo, 2006; Meijnen, 2007]:

- patients with a preoperative diagnosis of DCIS for whom a mastectomy is indicated due to size
- patients with a small DCIS who are eligible for BCT, in which there are risk factors for an invasive component:
    - younger than 55 years
    - solid component on the mammogram
    - suspicions on the basis of histological biopsies
    - moderate or poorly differentiated DCIS in biopsies

The SN procedure should take place at the same time, prior to the resection of the DCIS. Certainly in the case of a mastectomy, performing an SN procedure in the second instance is less reliable and therefore undesirable.

Conclusions

Level 3	The dimensions of DCIS are difficult to determine preoperative, and there may be a discrepancy between the extent of microcalcifications and pathological tumour size. C Holland 1990

Level 3	If postoperative invasive foci are encountered that are larger than 5 mm, the chance of lymphogenous metastasis is > 5% and lymphogenous staging is still recommended. A2 Schneidereit 2003

Level 3	For pure DCIS, diagnosed by excision biopsy, the chance of lymph node metastasis is extremely small. B Julian 2007

Level 3	In patients in whom DCIS is determined using histological biopsies of laesions greater than 2.5 cm, the presence of lymph node metastasis is at least 7%. B Meijnen 2007

Level 1	The chance of diagnosing invasive ductal carcinoma with DCIS is related to the type of biopsy needle (11G vs 14G), the grade of DCIS (high grade versus low grade), the size of the laesion on the mammogram (> 20 mm vs ≤ 20 mm), the mass on mammography (mass vs microcalcifications only) and if the growth is palpable (palpable vs. non-palpable). A1 Brennan 2011 B Meijnen 2007

3.1.2 Treatment of DCIS

Surgical treatment

Treatment of DCIS requires multidisciplinary collaboration. A decision can be made within multidisciplinary consultation if BCT or a mastectomy should be recommended, depending on whether complete excision with good cosmetic results is possible [McCormick, 1991].
In addition, the following conditions are important for optimal treatment result of breast-conserving treatment of DCIS:

- a unifocal laesion
- evaluable mammogram
- the size of the laesion in relation to the size of the breast is such that a complete and cosmetically acceptable resection of the DCIS area is anticipated. This is often not possible with laesions > 4 cm. In the case of larger laesions and the wish for breast-conserving treatment, the possibility of oncoplastic techniques should be considered and discussed with the patient.

Removal of the entire breast (mastectomy) and breast-conserving treatment (BCT) are associated with an almost 100% chance of curation [Westenberg, 2003; Bijker, 2006; Wapnir, 2011]. Given the apparent paradox that invasive breast cancer can be treated with BCT in the majority of cases, while the pre-stage (DICS) would require removal of the entire breast, much research has been conducted on the possibilities of breast-conserving treatment.
The results of the SweDCIS, NSABP B17, EORTC 10853 and UK/ANZ studies show a high percentage of laesions detected by mammogram (40-70%). The breast cancer-related death of patients with DCIS is relatively limited and varies in studies from 1% to a maximum of 4.1% in 10 years in the EBCTCG review. Death is independent of primary treatment [Bijker, 2006; Cuzic, 2011; EBCTCG, 2010; Fisher, 1993; Fisher, 1998; Viani, 2007; Wapnir, 2011].
During BCT for DCIS, the aim must be tumour-free resection margins. With DCIS, the chance of irradicality after the diagnosis is known is approximately 30%, this is due to the fact that the tumour is often non-palpable and there is an inherent discrepancy between the mammographic and pathological dimension. If the resection margins are not tumour-free following re-excision, a re-excision or mastectomy is recommended.

Radiotherapy after excision of DCIS

In the meantime, 4 large randomised studies have been performed with long-term follow-up in which the role of (not) administering radiotherapy after excision of DCIS has been researched [Fisher, 1998; Emdin, 2006; Bijker, 2006, Cuzick 2011]. In all these trials together, postoperative breast irradiation halves the chance of ipsilateral recurrence, but does not improve the disease-free and total survival [EBCTCG, 2010]. Half of recurrences found in trials are again DCIS, and the other half are invasive carcinomas. The results of all DCIS trials show the same picture [EBCTCG, 2010].
No (large) subgroups can be identified from the randomised studies in which radiotherapy could have been safely omitted [Bijker, 2001; Mokbel, 2006; Viani, 2007]. Ample excision margins in combination with very extensive excision margin analysis also does not make radiotherapy unecessary per se,

certainly not with grade III tumours [Hughes, 2009]. The predictive factors for locoregional recurrence after BCT for DCIS in the EORTC trial [Bijker 2001] are:

- microscopic, small tumour-free margins
- grading (grade II, III)
- clinical symptoms on presentation
- no radiotherapy (50 Gy)
- no clinging micropapillary type
- age ≤ 40 years

Others also found the margin surrounding the excised tumour tissue to be the most important predictive factor [Dunne, 2009].

The optimal radiotherapy dose in BCT of DCIS is not known and is currently being studied in a randomised, international trial. The locoregional recurrence rate after radiotherapy of approximately 10% after 5 years is quite high. The current locoregional recurrence rate for BCT of invasive carcinoma, in which a boost is generally administered to the tumour bed is < 5% after 5 years. The recurrence usually develops in the area of the original laesion. Administering a boost after BCT of DCIS could therefore also be worthwhile. Several authors report administration of a boost on the tumour bed [McCormick, 1991; Schwartz, 2000; Silverstein, 1999].
In a retrospective study of the Rare Cancer Network, it was concluded that the administration of a higher dose (boost) reduced the chance of a recurrence in younger patients (< 45 years; follow-up 72 months) [Omlin, 2006]. It appears from retrospective and prospective studies that radiotherapy may also be effective in tumour-containing surgical margins. In the EBCTCG meta-analysis, the rate of ipsilateral recurrence in patients with an incomplete excision was also high after radiotherapy (24.2% after 10 years) [EBCTCG, 2010]. After a non-radical mastectomy, radiotherapy of the chest wall is indicated (50 Gy / 2 Gy fraction or equivalent), also with a boost, depending on the estimated amount of residual tumour.

Adjuvant hormonal therapy after excision of DCIS

In the NSABP B-24 and UKCCCR study (2003), it is reported that tamoxifen (administered after conserving treatment) reduces the chance of recurring DCIS [Fisher, 1999]. Based on the point of departure that conserving treatment of DCIS is only indicated in tumour-negative resection margins, it is concluded that the advantage reported in the NSABP B-24 study is deemed too limited to be clinically relevant [Wapnir, 2011]. It must also be concluded on the basis of the results of the English study that there is little evidence for the use of tamoxifen in conserving treatment of DCIS after an R0 resection.

Conclusions

Level 1	The breast cancer-related death of patients with DCIS is relatively low (a maximum of 4.1% in 10 years). This is independent of the primary treatment: mastectomy versus breast-conserving. A1 Bijker 2006, Cuzick 2011, EBCTCG 2010, Fisher 1993, Fisher 1998

Level 3	A tumour-positive resection margin is the most important predictive factor for local recurrence with BCT of DCIS. C Bijker 2001, Silverstein 1993, Silverstein 1998

Level 1	The addition of radiotherapy after a local excision of DCIS results in a significantly lower chance of a local recurrence. A1 Bijker 2006, Fisher 1998, EBCTCG 2010, Emdin 2006, UKCCCR 2003

Level 3	The administration of a higher dose (boost), particularly in younger patients, appears to reduce the recurrence rate. C Omlin 2006

Level 1	Adjuvant therapy with tamoxifen in the breast-conserving treatment of DCIS, removed with tumour-free resection margins, leads to a limited improvement in local tumour

	control and not to a survival advantage. A2 EBCTCG 2010, Fisher 1999, UKCCCR 2003, Wapnir 2011

Remaining considerations

It should be made clear to the patient with DCIS that it concerns a pre-stage of breast cancer, in which it is not yet invasive and not yet metastatic. The chance of curation is high but a complete excision of the abnormality is important. This is achieved with a great degree of certainty by mastectomy, while BCT is possible if the abnormality can be removed with free excision margins. It must also be explained that regular check-ups with mammography are indicated.

The same considerations apply to *M. Paget* of the nipple as with DCIS [Bijker, 2001; Fisher, 1993-2000].

Recommendations

An SN procedure should be considered in the case of:

- patients with the preoperative diagnosis DCIS, for whom a mastectomy is indicated in relation to size
- patients with a small DCIS who are eligible for BCT, in which there are risk factors for an invasive component:
  - younger than 55 years
  - solid component on the mammogram
  - suspicion on the basis of histological biopsies
  - moderate or poorly differentiated DCIS in biopsies

The treatment of DCIS is mastectomy or BCT, consisting of microscopic complete tumour excision and radiotherapy, in which a boost may be considered, particularly for younger patients.

Contraindications for BCT:

- Multicentricity (the presence of DCIS in multiple quadrants of the breast)
- Residual disease: mammographic evidence or tumour-positive resection margin

Axillary staging is not indicated with pure DCIS in the excision sample.

If postoperative invasive foci are encountered that are larger than 5 mm, lymphogenous staging is recommended.

Adjuvant (hormonal) treatment after breast-conserving treatment (R0 resection and radiotherapy) is not recommended.

The same treatment recommendations apply to *M. Paget* of the nipple with underlying DCIS as with DCIS.

3.2 Primary locoregional treatment of stage I-II invasive breast cancer

This chapter discusses locoregional treatment of breast cancer, with classification $T_{1-2}N_{0-1}M_0$ (stage I and II, excluding $cT_3N_0M_0$) [UICC, 2010; Sobin, 2003; Wittekind, 2002]. Locoregional treatment may consist of breast-conserving therapy (BCT) or mastectomy and is combined with an axillary node staging procedure. The histological subtype does not play a meaningful role in this: it therefore also applies to lobular carcinoma [Arpino, 2004].

A mastectomy is performed if it is the preference of the patient or if there is a contraindication for BCT due to an expected poor cosmetic result or a high chance of a local recurrence. An axillary lymph node dissection (ALND) is performed if there are cytological or histological positive nodes, if the sentinel node is positive or there is a contraindication for conducting an SN procedure. Radiotherapy is an inherent component of BCT: if BCT is chosen, there must not be any contraindications for radiotherapy.

3.2.1 Dissemination detection

The chance that distant metastases are detected using any form of imaging technique is low [Ciatto, 1985; Ravaioli, 2000; Samant, 1999; van der Hoeven, 1999]. Tumour markers, such as CA15-3, CEA

and CA27.29 have no value as predictive factor [Ebeling, 1999]. This is in line with the ASCO guideline 2007.
Of course, it may be worthwhile for individual patients to expand diagnostics on clinical indication. With locoregional metastatic disease, the chance of finding asymptomatic metastases is higher (see Chapter 7). This also applies to a postoperative stage that is disappointing: if tumours are greater than 5 cm and/or there are more than 3 positive nodes, the chance of finding metastases is approximately 3-5% [Samant, 1999; Ravaioli, 1998; Kim, 2011; Puglisi 2005]. Which imaging techniques may play a role in dissemination detection is outlined in section 2.3: staging.

Conclusion

Level 3	Performing pre-operative dissemination research as a standard does not provide additional value for patients with $cT_{1-2}N_{0-1}$ breast cancer. C Ciatto 1985, van der Hoeven 1999, Samant 1999

Recommendations

Preoperative dissemination research is not recommended in the case of $cT_{1-2}N_{0-1}$ breast cancer.

Symptoms that may indicate metastases should be evaluated.

Dissemination research is recommended for a high postoperative stage.

3.2.2 Breast-conserving therapy (BCT)

BCT is defined as: a liberal locoregional excision of the tumour that is combined with an intervention for axillary node staging, followed by radiotherapy of the breast.

The aim of BCT is to obtain survival similar to that after mastectomy, with an optimal cosmetic result of the treated breast and as small as possible chance of a locoregional recurrence. Choosing between BCT and a mastectomy should be a multidisciplinary process, in which the findings and considerations of the surgeon, radiologist, pathologist and radiotherapist are determinant. If on medical grounds there is a preference for one of the two treatments, the advice and considerations should be discussed with the patient; if the patient has a preference for one of the treatments, this should weigh heavily.

For the purpose of accurate radiotherapy, MRI compatible clips should be placed in the tumour bed in a standardised manner according to the UK protocol [Coles, 2009], i.e.: clips in 5 directions:

1. in the medial edge of the tumour bed, between the chest wall and skin
2. in the lateral edge of the tumour bed, between the chest wall and skin
3. in the cranial edge of the tumour bed, between the chest wall and skin
4. in the caudal edge of the tumour bed, between the chest wall and skin
5. at the deepest point of the tumour bed

An absolute contraindication for BCT is persistent extensive tumour positive surgical margins (including DCIS) after adequate attempts at locoregional excision. The most important aspects for the choice between locoregional treatment possibilities of the operable breast cancer are: the chance of a locoregional recurrence and, specific for BCT, the expected cosmetic result. Six large prospective randomised studies in which the treatment results of mastectomy were compared with BCT all showed that the chance of survival does not depend on the therapy chosen [EBCTCG, 2005; Sarrazin, 1984; Veronesi, 1990; Fisher, 1989; Straus, 1992; van Dongen, 2000; Blichert-Toft, 1992; EBCTCG, 2000]. While one study did find a difference in the chance of locoregional recurrence after a long follow-up period in favour of mastectomy, especially with larger tumours, this did not result in a difference in survival [van Dongen, 2000; Poggi, 2003; Kroman, 2004]. It is generally stated that a chance of a locoregional recurrence of at the most 1% per year (cumulative) is acceptable for BCT [Rutgers, 2001]. This is well possible in the Netherlands: the five-year locoregional recurrence percentage after BCT in the entire population is <3% [van der Heiden, 2010].

Most recurrences after BCT are due to growth of the residual tumour [Bartelink, 2001; Kurtz, 1989; Voogd, 1999]. Renewed tumour growth in the treated breast in these cases is assumed to derive from microscopic tumour foci that have remained behind in the breast after surgery. In two-thirds of mastectomy samples, tumour foci of an invasive and non-invasive nature were found around the tumour. Of these tumour foci, 43% were more than 2 cm outside the tumour. There was also no

difference between primary tumours smaller or larger than 2 cm in relation to the number of tumour foci and distance in relation to the tumour [Holland, 1985]. In other words, independent of the tumour size, there is a chance that tumour remains in the breast after surgery. Radiotherapy should destroy these tumour cells. However, if the number of tumour cells is too extensive, patients may be confronted with a greater chance of a local recurrence.

The most important factor that predicts the chance of a locoregional recurrence is a tumour-positive surgical margin [Park, 2000]. Different series show follow-up recurrence percentages of 2% to 8% with tumour-free surgical margins and 9% to 27% with tumour-positive surgical margins, after 5 to 10 years follow-up. The highest percentages are found in the series with the longest follow-up and if the tumour reaches extensively (*more than focal*) into the resection surface [Park, 2000]. More than focal tumour-positive resection surfaces or the lack of margin tests (for example, if a carcinoma is unexpectedly found in a diagnostic biopsy) are indications for a re-excision; a residual tumour is then found in more than half of cases [Schnitt, 1987; Gwin, 1993; Kearny, 1995; Schmidt-Ullrich, 1993].
The chance is especially great in tumours surrounded by an extensive DCIS component (67%) and with multinodular or diffuse invasive lobular carcinomas (50%) [Schnitt, 1987]. It is unclear if a re-excision is worthwhile if the tumour extends focally to and into a resection surface; however, the locoregional recurrence risk is elevated in this case so that adjustment of the radiotherapy dose appears to be a good alternative [Park, 2000; Clarke, 1992; Romestaing, 1997].

Extensive lymphangio-invasive growth may also present a higher risk of residual tumour and as a result may lead to an increased locoregional recurrence percentage. This is found in various studies [Veronesi, 1995; Borger, 1994; Voogd, 2001]. However, the amount of lymphangio-invasion is difficult to classify and does not give a measure of the risk of residual tumour load. Lymphangio-invasion is also an important risk factor for locoregional recurrence after a mastectomy, so that the choice between BCT and mastectomy should not be made on the basis of this factor.

An important independent risk factor for locoregional recurrence after BCT is age. The chance of a locoregional recurrence after BCT is inversely proportional with age. While a young age ($\leq$ 40 years) is a factor for recurrence after BCT, no difference has been found in retrospective series in survival if BCT is selected instead of mastectomy; young age is associated with a poor survival prognosis, which does not appear to be influenced by locoregional therapy [Nixon, 1994; Vrieling, 2001; Elkhuizen, 1998; de la Rochefordiere, 1993; van der Sangen, 2010]. The conclusion is that young age is not a contraindication for breast-conserving treatment [Zhou 2004].

Radiotherapy and BCT

Omitting radiotherapy results in a strong increase in the incidence of locoregional recurrences. Radiotherapy is therefore considered an inherent component of BCT. No subgroups have been defined in which radiotherapy can be omitted [EBCTCG, 2005; Fisher, 2002].

In the Netherlands, a boost is generally administered on the tumour bed after radiotherapy of the entire breast. Results of the EORTC study 10882/22881 (boost - no boost) indicate that the chance of developing a local recurrence after radiotherapy of the breast followed by administration of a boost/no boost is 6.2% and 10.2% respectively after a median follow-up duration of more than 10 years [Bartelink, 2001; Bartelink, 2007]. Survival in both groups was not significantly different. The boost gives a significant equal relative decrease in the local recurrence percentage in all age groups, but the absolute advantage is greater with decreasing patient age. In patients under 40 years of age, the boost decreased the ten-year local recurrence percentage from 23.9% to 13.5%. In older patients, the boost also provided a significantly better control; however, the absolute difference was approximately 4% after 10 years: from 12.5% to 8.7% in patients of 41-50 years, from 7.8% to 4.9% in patients of 51-60 years and from 7.3% to 3.8% in patients over 60 years. This involved a follow-up of 10 years, so this may still change over time. It should be noted here that an additional boost has a negative influence on the cosmetic result. There is still no data available for the cosmetic aspect after ten years. The advantage provided by the boost should be offset against the age, comorbidity, and the chance of a reduction in cosmetic effect.

Radiotherapy leads to a smaller chance of a local recurrence for each subgroup of BCT patients; this leads to the greatest reduction with young women, the advantage with older women (R0; met tamoxifen) is limited to a few percent after 5 years [Vinh-Hung, 2004; Vinh-Hung, 2003; Fisher, 2002; Hughes, 2004].

There is a significant relationship between reduction in five-year locoregional recurrence percentages and survival advantage after 15 years [EBCTCG, 2005]. It appears from this meta-analysis that, in the hypothetical absence of other causes of death, the occurrence of four locoregional recurrences results in the occurrence of 1 breast cancer death after 15 years.

Hypofractionation

Evidence-based to June 2011:

What are the differences in locoregional control, cosmetic result and survival between hypofractionation irradiation schedules and the current (long-term) irradiation schedules in patients who have undergone breast-conserving treatment?

In a systematic review of good quality, two randomised trials were identified and meta-analysed [Lehman, 2008]. Hypofractionation (more than 2 Gy per fraction) was compared to conventional irradiation (1.8 to 2 Gy per fraction) in a population of 2,644 patients with $T_{1-2}N_0M_0$, and tumour-free margins in the resection sample. Hypofractionation did not influence the five-year survival (RR: 0.97; 95%CI 0.78-1.19), cosmetic (RR: 1.01; 95%CI 0.88-1.17) or local control (difference in local recurrence-free survival: 0.4%, 95%CI -1.5-2.4%). Toxicity for the skin (after five years, RR: 0.99; 95%CI 0.44-2.22) and toxicity for the subcutaneous tissue (RR: 1.0; 95%CI 0.78-1.28) were comparable. The ten-year results of one of the included trials again showed no difference between hypofractionation or conventional fractionation [Whelan, 2010].

The START Trial A compared three different irradiation schedules: 41.6 Gy in 13 fractions (3.3 Gy per fraction, 5 weeks), 39 Gy in 13 fractions (3.0 Gy per fraction, 5 weeks) vs. 50 Gy in 25 fractions (2 Gy per fraction, 5 weeks) [Bentzen, 2008]. There were 2,236 women with $pT_{1-3a}N_{0-1}M_0$ enrolled in the study, including 15% mastectomy patients; 61% of patients received a boost, 78% received tamoxifen and 34% adjuvant chemotherapy. The outcomes after 5 years did not differ concerning (local) recurrence, survival or side effects. The START Trial B compared two irradiation schedules 40 Gy in 15 fractions (3 weeks) vs. 50 Gy in 25 fractions (5 weeks) (n=2,215) [Bentzen, 2008]. The outcomes after 5 years did not differ concerning (local) recurrence or side effects. A surprising finding was the better survival in the 40 Gy group (HR death 0.76; 95%CI 0.59-0.98). The authors could not find a reason for this result and expected it was a coincidence. For both trials, the cosmetic results and quality of life data in subgroups were analysed and reported separately after 5 years (n=2.208) [Hopwood, 2010]. Scores for body image, and the arm or shoulder symptoms did not differ for the different irradiation regimes. Breast symptoms were examined in eight different items. For the item 'negative skin change', women in the 39 Gy and the 40 Gy groups scored better than women in the 50 Gy groups (HR 0.63; 95%CI 0.47-0.84, and 0.76; 95%CI 0.60-0.97 respectively). No differences were demonstrated between the groups for the other seven items.

The equivalence of hypofractionation and standard fractionation appears to apply to patients with $pT_{1-3a}N_{0-1}M_0$ tumours, although there are subcategories with relatively few patients within these classifications. One trial compared local recurrences within particular subgroups [Whelan, 2010]. Hypofractionation was equivalent to standard fractionation for women under 50 years or over 50 years, for tumours greater or smaller than 2 cmcm, for oestrogen-receptor positive and negative tumours, and for patients who had or had not received systemic therapy. In the subgroup with high-grade tumours, there were more local recurrences in the hypofractionation group (16.6% vs. 4.7%; HR: 3.08; 95%CI 1.22-7.76). In answer to this finding, the 8-year results of the START Trial A and B were analysed post hoc for high grade tumours, in which no difference was found in local recurrence (HR: 0.83; 95%CI 0.56-1.23) [Haviland, 2010].

Gene mutation carriers

There is no absolute contraindication for breast-conserving treatment with a demonstrated BRCA1 or 2 gene mutation (see section 1.3.1). These women have a greater chance of a second primary breast cancer (especially contralateral) and possibly a somewhat greater chance of an ipsilateral recurrence, but this does not influence survival [Pierce, 2010; Kirova, 2010].

Radiotherapy in women > 50 years of age

Given the chance of locoregional recurrence after BCT is dependent on age, various studies have looked at the necessity of radiotherapy after a breast-conserving treatment in older women. A randomised trial [Fyles, 2004] examined the locoregional recurrence percentages after radiotherapy plus tamoxifen versus tamoxifen only in 769 women over 50 years of age undergoing BCT due to a tumour smaller than 5 cm. In doing so, it appeared that the addition of radiotherapy to tamoxifen

reduced the locoregional recurrence percentage from 7.7% to 0.6% after 5 years. With radiotherapy, the 5-year disease-free survival increased from 84% to 91%. An RTOG study randomised in the same manner [Hughes, 2004], this time with women older than 70 years with pT_1N_0 ER+ breast cancer. This resulted in a five-year locoregional recurrence percentage of 1% with radiotherapy and tamoxifen and 4% with tamoxifen only.
Locoregional recurrence percentages in the SEER database were also examined for women > 70 years with tumours ≤ 2 cm ER+/unknown, pN_0 who did or did not undergo radiotherapy within the framework of BCT [Smith, 2006]. Radiotherapy reduced the locoregional recurrence percentage after 8 years from 8% to 2.3%. This shows that with older women, radiotherapy also plays an important role in locoregional control after BCT, however possible comorbidity in older women should be taken into account with each individual choice.

Partial breast irradiation

Seventy to eighty percent of local recurrences are localised in the original tumour area. This has lead to development of partial breast irradiation in which only the tumour area is irradiated and not the entire breast. Guidelines have been formulated by the ESTRO (www.estro.org) and ASTRO (www.astro.org) to outline to whom partial breast irradiation may apply; these are low-risk patients for local recurrence, such as older patients, tumour ≤ 2 cm, N_0, radical surgical margins, ER+, no extensive DCIS around the invasive ductal carcinoma. Published data so far show promising results. In one-institute series, follow-up data has already been published, including that of Vicini with brachytherapy with 3.8% recurrences after 10 years and in the ELIOT series (2006) with intra-operative radiotherapy with 2.1 % recurrences.
Only a few randomised trials have been published so far. Polgar (2007) compared brachytherapy with complete breast irradiation. In this study, five-year recurrence percentages of 4.7% vs. 3.4% were seen. Results of the TARGIT trial were recently published in which complete breast irradiation was compared to intra-operative partial breast irradiation. Recurrence percentages of 0.9% and 1.2% respectively were found in this study with a median follow-up of only a bit over 2 years [Vayda, 2010]. However, extremely low risk patients were included in this study (median age of 63 years, 90% ER+, < 2 cm), some of whom were furthermore also treated hormonally (more than 60% of patients) and chemotherapy (10% of patients). In addition, there was only extremely superficial irradiation of the tumour bed in this study, in contrast with many other forms of partial breast irradiation. There are currently still many ongoing randomised trials with various techniques of partial breast irradiation, including studies with postoperative external radiotherapy. The role of partial breast irradiation will become clearer in coming years.

Conclusions

Level 1	BCT is a safe therapy, because the chance of survival is comparable to that of mastectomy. Omitting radiotherapy with BCT has an unfavourable influence on locoregional control and survival. A1 Sarrazin 1984, Veronesi 1990, Fisher 1989, Fisher 2002, Straus 1992, van Dongen 2000, EBCTCG 2000, EBCTCG 2005, Vinh-Hung 2003, Vinh-Hung 2004, Hughes 2004, Fyles 2004, Poggi 2003, Kronan 2004

Level 1	A boost aside from radiotherapy of the entire breast improves local control in all patients. The absolute advantage of a boost after complete resection reduces with increasing age. A1 Bartelink 2001, Bartelink 2007

Level 1	Young age (≤ 40 years) is an independent (negative) risk factor for the occurrence of a local recurrence after BCT. A1 Bartelink 2001, Bartelink 2007, Voogd 2001, Arriagada 2005 C Elkhuizen 1998, de la Rochefordiere 1993, van der Leest 2007 van der Sangen 2010

Level 3	The presence of more than focal tumour metastasis in the resection surface is the most important risk factor for the occurrence of a locoregional recurrence after BCT. The same applies to the DCIS component.

	C Borger 1994, Park 2000

Level 2	A BRCA 1/2 gene mutation is not a contraindication for BCT. The risk of a locoregional recurrence is lightly elevated, but this does not influence survival. B Pierce 2010, Kirova 2010

Level 3	A good cosmetic result after BCT can be achieved in at least 70% of patients; the result is better when a boost is not given and better in the case of a small excision volume. A2 Vrieling 1999 C De la Rochefordiere 1992

Level 2	Partial breast irradiation leads to good results in select patient groups with a low a priori risk of local recurrence. A2 Polgar 2007 B Vaidya 2010 C Vicini 2006

Level 1	Hypofractionation with postoperative irradiation of a $pT_{1-3a}N_{0-1}M_0$ breast cancer with tumour-free resection margins leads to a comparable five-year survival, local control and cosmetic result compared to conventional irradiation schedules. A1 James 2008 A2 Bentzen 2008 (A), Bentzen 2008 (B), Hopwood 2010, Whelan 2010

Remaining considerations

Hypofractionation reduces the treatment with radiotherapy and is therefore an improvement, in terms of hospital logistics as well as the physical burden on the patient.

Given the still relatively short follow-up of most randomised studies, partial breast irradiation is only recommended within a research context for now.

Recommendations

BCT should only be offered to the patient if a good cosmetic result and an equally good locoregional tumour control can be expected.

If BCT is offered, fractionated radiotherapy of the entire breast with or without a boost should form an integral part of treatment.

Reoperation is indicated if there is more than a focal tumour positive resection surface (of the invasive and/or DCIS component). This is the most important risk factor for the occurrence of a local recurrence.

MRI compatible clips should be placed in a standardised manner in the tumour bed for the purpose of obtaining accuracy in radiotherapy.

The advantage provided by the boost should be offset against the age, comorbidity, and the chance of a reduction in cosmetic effect.

If the chance of a recurrence < 1% per year in patients older than 50 years and without additional risk factors, the boost may be omitted after an R0 resection.

Hypofractionation of the postoperative irradiation of the breast may be applied in women with a $pT_{1-3a}N_{0-1}M_0$ breast cancer and tumour-free resection margins.

Partial breast irradiation should, given the still relatively short follow-up, preferably be applied within a study context.

3.2.3 Mastectomy

If BCT is deemed contraindicated and if preferred by the patient, mastectomy including adequate axillary staging is the appropriate treatment. The chance of a locoregional recurrence varies strongly in the different (retrospective) literature series, depending on the T and N classification [Valagussa, 1978; Ragaz, 2005; Recht, 1999; Jager, 1999]. In a recent analysis based on population in the Netherlands, 3% recurrences are seen after 5 years [van der Heiden, 2010].

Radiotherapy

On the basis of literature data there are arguments for and against considering radiotherapy after mastectomy in the case of T_3 tumours [Ragaz, 2005; Jager, 1999; Overgaard, 1997; Overgaard, 1999; Recht, 2001; Taghian, 2006; Migano, 2007]. There is still insufficient data available to use extranodal growth of axillary metastases as independent criterion as indication for postoperative radiotherapy for breast cancer [Recht, 2001; Gruber, 2005; Jager, 1999]. Of course, tumour metastasis in a surgical margin is an indication for postoperative radiotherapy. There is limited literature data on the clinical significance of the width of tumour-free margin and the chance of a locoregional recurrence. A few studies state a narrow margin (< 2 mm) is a predictor of locoregional recurrence [Wallgren, 2003; Jagsi, 2005].

Postoperative radiotherapy reduces the chance of a locoregional recurrence by a factor of 3 to 4 [EBCTCG, 2000]. There is a relationship between the reduction in locoregional recurrence and long-term survival. At a five-year locoregional recurrence percentage of >15%, postoperative radiotherapy leads to a five-year survival improvement of approximately 5% [Punglia, 2005].
EBCTCG data and other studies [Darby, 2005; EBCTCG, 2005; Hooning, 2006; Hooning 2007; Taylor, 2006; Taylor, 2007] have also shown that radiotherapy in earlier times lead to higher than expected death due to cardiac morbidity. This applies especially to tumours on the left side and parasternal irradiation. It is expected that with current techniques (including Deep Inspiration Breath Hold technique) in which the heart can be spared as much as possible, the absolute effect of radiotherapy on survival is higher.

An important criterion to determine the chance of locoregional recurrence is the number of axillary node metastases. Postoperative radiotherapy is accepted for high-risk patients with ≥ 4 positive nodes. In two prospective studies, the chance of a ten-year locoregional recurrence after mastectomy including ALND and adjuvant systemic therapy was approximately 15% for patients with 1-3 axillary node metastases and approximately 30% for the 4+ patients.

These findings are confirmed by the EBCTCG (2010) meta-analysis. Aside from survival advantage and reduction in locoregional recurrences at ≥ 4 positive nodes, this has now been confirmed for 1-3 positive nodes. A point of criticism of the EBCTCG overview and abovementioned studies (especially the Danish series and British Columbia studies) is that there was an extremely high locoregional recurrence percentage (30% and 26% respectively). This may not be in line with the current situation. Approximately 30% of patients in the non-irradiated groups of the two Danish studies (with a 12 year follow-up) developed a locoregional recurrence. This suggests that surgical treatment was insufficient in many cases. No ALND's were performed in Denmark as is common in the Netherlands, but samples of level I and II were taken. However, others reported that even after adequate ALND's (in the case of mastectomy including ALND) and adjuvant medication-based therapy in subgroups, there was still a large chance of a locoregional recurrence if post-operative irradiation was not administered [Ragaz, 2005; Recht, 1999; Jager, 1999; Katz, 2001].
Survival advantage was originally demonstrated in the high risk groups, i.e. patients with 4 or more positive nodes. In an update of the Danish studies in the subgroup of patients in whom 8 or more nodes were removed, it appears that patients with 1-3 tumour-positive nodes had a similar survival advantage after radiotherapy than the N_4+ patients (9% absolute after 15 years) [Overgaard, 2007].

It is important to select patients who have an expected locoregional recurrence percentage of ≥ 15% over 5 years, given these patients may benefit from radiotherapy, both in terms of their locoregional control and overall survival. Not only the lymph node status but also the combination with other factors may be considered here. Wallgren (2003) studied more than 5,000 patients after mastectomy including ALND who were treated in one of the seven International Breast Cancer Group randomised trials. This group consisted of lymph node positive and negative patients who did not (pN_0) or did undergo systemic therapy (pN+). The factors for locoregional control were studied within this group. In addition to the number of positive nodes, tumour-related factors such as vaso-invasive growth, size of

the tumour (< 2 cm) and grade III tumours were predictors of a locoregional recurrence. Especially vaso-invasive growth has been confirmed in other studies [van Tienhoven 1999, Voogd 2001]. Jagsi (2005) looked at predictive factors of locoregional recurrence after mastectomy including ALND. Three of such factors in lymph node-negative patients appeared to give a locoregional recurrence percentage of 40% after 10 years. Other studies also confirmed the possible role of radiotherapy in N_{1-3}. Ragaz published the 20-year results of the British Columbia trial in 2005. In this study, 318 premenopausal patients with an invasive breast cancer and positive node status were randomised over two groups: radiotherapy + chemotherapy (n=164) or chemotherapy only (n=154). After 20 year follow-up, the locoregional disease-free survival was 90% in the radiotherapy group and 74% in the control group. Subdivided according to node status, this was 91% and 79% for patients with 1-3 positive nodes and 84% and 59% for patients with four or more positive node (p=0.6). The SUPREMO trial is currently underway, which studies the value of chest wall irradiation in intermediate risk patients.

In some cases it is unclear, if there is an indication for local radiotherapy, if the regional node areas (axillary, parasternal, infra and supraclavicular regions) should also be irradiated [Recht, 2001]. In trials from which the EBCTCG (2005) overview derives its data, the node areas were often routinely irradiated. However, the chance of manifestation of a recurrence in the node areas is small, so that radiotherapy of the regional node areas may be overtreated for many patients [Recht, 2001].

Conclusions

Level 1	Patients with large tumours (> 5 cm) and/or extensive lymph node metastases (≥ 4 positive nodes), also have an increased chance of a locoregional recurrence after radical surgery and systemic therapy. A2 Ragaz 2005, Overgaard 1997, Overgaard 1999 C Recht 1999, Recht 2001, Jager 1999, Katz 2001

Level 1	Postoperative locoregional radiotherapy reduces the chance of a locoregional recurrence by two-thirds and leads to an improved chance of survival [EBCTCG, 2000]. A1 EBCTCG 2000, Whelan 2000 A2 Ragaz 2005, Overgaard 1997, Overgaard 1999

Level 1	Aside from local control, locoregional radiotherapy also significantly improves overall survival after 15 years, if the locoregional recurrence risk after 5 years is 15% or more. A1 EBCTCG 2005

Level 1	Postoperative locoregional radiotherapy improves locoregional control and overall survival with 1-3 positive nodes. A2 Ragaz 2005, Overgaard 1997, Overgaard 1999 B Overgaard 2007

Level 3	A combination of various tumour-related predictors for locoregional recurrence (young age, N status, vaso-invasive growth) leads to an increase in the risk of locoregional recurrence. C Wallgren 2003, Voogd 2005, Jagsi 2005

Recommendations

Indications for radiotherapy of the chest wall after ablative surgery:

- a tumour-positive resection surface of the primary tumour, irradicality
- cT_4, pT_4
- pT_3, depending on one or more of the following risk factors, angio-invasive growth, grade III, and/or age ≤ 40 years

Postoperative radiotherapy of the chest wall after ablative surgery may be considered in the case of:

- 1-3 positive nodes and combination with one of the following characteristics: angio-invasive

growth, grade III, age ≤ 40 years and tumour size ≥ 3 cm
- pN_0 and combination with three of the following characteristics: angio-invasive growth, grade III, age ≤ 40 years and tumour size ≥ 3 cm

Indications for locoregional postoperative radiotherapy (both after BCT and modified radical mastectomy):
- 4 or more positive nodes
- Tumour-positive axillary top

3.3 Regional treatment for breast cancer

Regional treatment for breast cancer has the following aim:
- an optimal regional tumour control
- improved survival
- obtaining prognostic information

The SN procedure is the method of choice for the identification of lymph node metastases in patients with axillary lymph nodes that are not clinically suspect or not suspect on ultrasound imaging [Krag, 2010].
A complete axillary node dissection (ALND) for this purpose should be considered obsolete. An ALND can only be conducted if the SN procedure is unsuccessful. Non-invasive methods do not appear reliable in predicting axillary node status. A wait-and-see approach can be chosen, if the chance of lymph node metastases is less than 5%. This percentage is based on the accepted false negativity of the SN.

3.3.1 The sentinel lymph node procedure

The different studies show that with the necessary experience, an SN procedure can be performed in more than 95% of patients and the procedure is reliable in predicting the presence or absence of axillary node metastases in 95% of cases (distribution 84-100%) [Sandrucci, 1999; Konstantiniuk, 2007; Straver, 2010]. For T_1 tumours, phase III studies with sufficient follow-up have demonstrated that the SN procedure is a safe alternative to the ALND, if the SN is tumour-negative [Veronesi, 2006; Krag, 2010]. This is confirmed in various non-randomised studies in the Netherlands in which T_2 tumours were also included (1,467 patients, median follow-up 30-65 months) [de Kanter, 2006; Heuts, 2007; Torrenga, 2004; Kuijt, 2007]. The best results are obtained with use of the combination of preoperative lymphoscintigraphy with radiocolloid, and peroperative injection with Patent Blue. The SN can then be found with the aid of a gamma probe and guided by blue-coloured afferent lymph vessels.

The SN procedure is indicated for patients with a $T_{1\text{-}2}N_0$ breast cancer. Please refer to section 3.1.1 for the SN procedure in DCIS, see Chapter 7 for the SN procedure in neoadjuvant systemic therapy and Chapter 11 for the SN procedure during pregnancy. In contrast to ALND, the SN procedure leads to substantially less functional impairments of the musculoskeletal system [Cairns, 1999; Chetty, 2000; Veronesi, 2003; Fleissig, 2006; Ashikaga, 2010].

<u>Multifocal/multicentric tumours</u>

The dilemma here is formed by uncertainty in relation to lymph drainage from the tumour. Some studies argue that each tumour has its own lymph drainage pattern, so that determination of the injection location for the radioactive substance is difficult in these patients [Estourgie, 2004] with the result that the radioactive substance does not indicate the actual drainage; the sentinel lymph nodes may be missed and the percentage of false negatives increases [Ozmen, 2002; Tousimis, 2003; Veronesi, 1999]. For this reason, it is argued that a cautious approach should be taken when performing an SN procedure in the case of multicentricity [Schule, 2007].
Other researchers argue that the lymph drainage pattern of the entire breast is uniform and the radioactive substance can be injected at many locations in the breast and that multifocality/multicentricity is not a contraindication for performing an SN procedure [Knauer, 2006].
A recent review concludes that the value of an SN procedure with large and multifocal/multicentric tumours is uncertain, especially due to the lack of randomised studies in these groups and due to the heterogenous results of non-randomised studies. On the basis of this review, it cannot be concluded in these cases that the SN procedure is automatically contraindicated. One should realise however, that there is an already greater a priori chance of lymph node metastasis with multicentricity and multifocality, as is the case with large tumours [Spillane, 2011].

Absolute contraindications for the SN procedure:

- axillary node metastasis demonstrated by punction

Relative contraindications for the SN procedure:

- ≥ T3 and/or multicentric: Experience with the SN procedure in tumours greater than 5 cm, or multicentricity over a distance of > 5 cm is small and the benefit achieved is limited due to the large chance of axillary node metastases [Lyman, 2005; Spillane, 2011]
- previous (recent) axillary surgery

Radiotherapy of the axillary region as alternative for ALND in positive SN

In the 1980's, the NSABP trial B04 randomised 1,097 operable patients with a clinically negative axillary between mastectomy with axillary node dissection, mastectomy with locoregional radiotherapy and mastectomy without axillary treatment [Fisher, 1985; Fisher, 2001]. The 25-year follow-up data from this trial showed a better locoregional control in the node negative group was provided by mastectomy with locoregional irradiation (5%) than mastectomy with ALND (9%) or mastectomy without axillary treatment (13%) (difference between the 3 curves: p=0.002), and no difference in metastasis-free survival or total survival. In the same trial, 586 patients with clinically positive axillary nodes were randomised between mastectomy with ALND or mastectomy with locoregional radiotherapy. In this node positive group, there was no difference between axillary surgery or radiotherapy in locoregional control, metastasis-free survival or survival [Fisher, 1985; Fisher, 2001]. Deutsch (2008) studied the long-term morbidity of axillary treatment in the NSABP B04 trial. The percentage of patients with lymphoedema after mastectomy with ALND was 58%, after mastectomy only 39% and after mastectomy plus radiotherapy 38%. The morbidity of combined treatment (ALND and radiotherapy) is even higher than that of ALND only [Larson, 1986; Ryttov, 1988]. The 15-year results of another randomised comparative study with 658 patients with an N_0M_0 breast cancer (smaller than 3 cm) were published in 2004 [Louis-Sylvestre, 2004]. In this study, one group received ALND after surgery and the other group axillary, periclavicular and parasternal radiotherapy after surgery. Both groups received radiotherapy of the breast, in which part of the axillary is implicitly irradiated along with the rest. The ten-year disease-free survival in both groups was 72% (15 years: 64.3 vs 65.5). After 15 years, isolated axillary recurrences were found in 1% of cases in the ALND group and in 3% in the radiotherapy group (p=0.04). After a 15-year follow-up, there was no significant difference between the two groups in the occurrence of locoregional recurrences. Twenty-one percent of patients in the ALND group had lymph node metastases on surgery. The proportion in the radiotherapy group would have been comparable. In the AMAROS study, 26% of patients undergoing an ALND after a positive SN had additional positive nodes in the ALND sample [Straver, 2010]. Extrapolating this data, it appears that irradiation of the axilla is a good alternative for the treatment of the axilla in the case of a positive SN. Not only the axilla but also the periclavicular region was irradiated in the AMAROS study. This study has recently been closed and the results are awaited.

Conclusions

Level 1	There is no difference in survival, disease-free survival or locoregional control between surgery or radiotherapy of the axillary and periclavicular lymph nodes with an operable breast cancer with clinical tumour-negative axilla. A2 Fisher 2001, Louis-Sylvestre 2004

Level 3	There does not appear to be a difference in survival, disease-free survival or locoregional control between surgery or radiotherapy of the axillary lymph nodes with an operable breast cancer with a clinical tumour-positive axilla. A2 Fischer 2001

Level 3	The chance of lymphoedema and other late morbidity is higher after ALND than after axillary radiotherapy. A2 Deutsch 2008

Axillary lymph node dissection (ALND)

Axillary node dissection is generally reserved for treatment of the axilla when lymph node metastasis has been demonstrated, such as a positive sentinel lymph node or a tumour-positive picture based on punction. ALND gives substantial morbidity, in which pain complaints, dysesthesia, functional

impairments of the shoulder joint and lymphoedema of the arm are the most serious. However, a complete ALND gives a recurrence percentage of less than 3% [van der Ploeg, 2010].

3.3.2 Treatment of patients with micrometastases or isolated tumour cells in the sentinel lymph node and/or axillary nodes

Clinical question, evidence-based to June 2011

Quite a lot of observational studies show the prognostic importance of the presence of micrometastases and isolated tumour cells in the axillary nodes and/or sentinel lymph node (SN). A recent meta-analysis of cohort studies showed that the presence of axillary node metastases of 2 mm or smaller is accompanied with a poorer survival than the absence of such metastases (pooled HR for death: 1.44; 95%CI 1.29-1.62) [de Boer 2010]. In another meta-analysis of the same group, a risk of 12.3% of non-SN metastasis was found in the presence of isolated tumour cells in the SN (total pooled risk: 12.3%; 95%CI 9.5-15.7) [van Deurzen, 2008; Straver, 2010]. In a systematic review by Cserni (2004), percentages of 10-15% additional axillary metastases were seen for the group of patients with a micrometastasis or isolated tumour cells. For the first 2,000 patients participating in the AMAROS study, it appeared the percentage of additional axillary metastases was 18%, both with micrometastases and isolated tumour cells [Straver 2010]. A number of different centres developed a nomogram to help predict the risk of non-SN metastases in the presence of axillary node micrometastases or isolated tumour cells, in which those of the Memorial Sloan-Kettering Cancer Centre and the Tenon score seem to be the most reliable for this specific group of patients [Coutant, 2009]. From a recent study in the Netherlands it appears that the nomogram of the Memorial Sloan-Kettering Cancer Centre, applied to 168 women with a positive sentinel node who underwent an axillary node dissection, is of insufficient predictive value in order to determine the treatment plan in individual cases [van den Hoven, 2010].

Given patients with micrometastases or isolated tumour cells in the SN form a separate prognostic population, it raises the question if they should be treated in the same manner as patients with axillary node macrometastases. In some of the cases there was displacement of epithelial cells [Bleiweiss, 2006; van Deurzen, 2009 (1); van Deurzen, 2009 (2)]. It is not clear here if marginal sinus metastases have the biological properties to be or become tumour forming.
The results must be seen in the light of the chance of metastasis in the non-sentinel nodes in an axillary lymph node dissection if no tumour is found in the SN biopsy itself. This chance is generally about 7%. In the study by Krag (2007), the percentage of false-negative SN biopsies was even 9.8%. In a pooled meta-analysis of 14,959 patients [van der Ploeg, 2008] there is an acceptable axillary node recurrence percentage of 0.3% after a median follow-up of 34 months in patients with an SN negative status. This is 0.7% after 95 months follow-up in the NSABP B-32 trial [Krag, 2010].

<u>Axillary node dissection</u>
Randomised studies that have researched the benefit of a complete axillary lymph node dissection (ALND) in patients with micrometastases or isolated tumour cells in the axillary nodes and/or SN have not been published yet. Ten comparative observational studies researched the benefit of ALND in patients with micrometastases in the axillary node [Pernas, 2010; Wasif, 2010; Bilimoria, 2009; Bulte, 2009; Cox, 2008; Haid, 2006; Schulze, 2006; Fan, 2005; Jeruss, 2005; Liang, 2001], while seven comparative observational studies were found for patients with isolated tumour cells in the axillary node [Pugliese, 2010; Giobuin, 2009; Cox, 2008; Schulze, 2006; Calhoun, 2005; Jeruss, 2005; Jakub, 2002].

The largest retrospective cohort study compared 3,674 patients with axillary node micrometastases who only underwent an SN biopsy with 6,585 patients who, in addition, also underwent an ALND [Bilimoria, 2009]. No differences were found in the 5-year survival (corrected HR: 0.95; 95%CI 0.70-1.27; p=0.75) and axillary recurrence percentage (0.4% after SN biopsy vs. 0.2% after SN biopsy and ALND, p=0.18). The hazard ratio was corrected for age, T classification and tumour grade (amongst other things). It is necessary to mention a few important side notes for this study. It concerns a cancer registry database, in which it can be presumed there was an underregistration of (axillary) recurrences. In addition, there was no multivariate correction for the use of systemic therapy. Another large retrospective cohort study was also based on cancer registry data [Wasif 2010]. This study was aimed at understanding to what extent ASCO guidelines are followed, especially the recommendation to perform a routine ALND in patients with micrometastases in the SN. Of the 5,353 enrolled patients with micrometastases in the SN, 2,160 (40.4%) underwent no additional ALND. No difference in total

survival was found between patients who did or did not undergo an additional ALND (89% after SN biopsy vs. 90% after SN biopsy and ALND, p=0.98). However, these results were not corrected for primary tumour characteristics or the use of systemic therapy. Data on (axillary) recurrence was not reported by the authors.
Similar findings for survival [Cox, 2008] and recurrence [Bulte, 2009; Cox, 2008; Fan, 2005; Haid, 2006; Jeruss; 2005; Liang; 2001, Pernas; 2010; Schulze, 2006] were found in smaller cohort studies. Cox (2008) compared the outcomes of 2,108 patients with a negative SN with those of 151 patients with isolated tumour cells (see below) and 122 patients with micrometastases in the SN. General and disease-free survival were not significantly worse in the group with micrometastases. Within the group with micrometastases, no difference was found in general survival between patients treated with or without additional ALND. After a (short) median follow-up of 1.7 years, axillary recurrences were also not found in the group who were only treated with an SN biopsy. In a small prospective study, Pernas (2010) compared the outcomes of 14 patients with micrometastases in the SN and treated with an additional ALND with that of 45 patients who only underwent an SN biopsy. One patient in the group treated with additional ALND developed an infraclavicular recurrence. After a median follow-up of 60.4 months, the group who were only treated with an SN biopsy were recurrence-free. The number of patients with micrometastases in the SN in the other studies varied from 9 to 45 [Bulte, 2009; Fan, 2005; Haid, 2006; Liang, 2001; Schulze, 2006]. After a follow-up varying between 13.5 and 47 months, these patients remained free of axillary recurrence, independent of treatment with ALND. Only Fan (2005) reported a recurrence in the group who were only treated with an SN biopsy, but without clarifying where. None of these studies corrected for primary tumour characteristics or the use of systemic therapy.
Incidentally, non-comparative studies also found low axillary recurrence percentages (0-3%) in patients who only underwent an SN biopsy [Fournier, 2004; Langer, 2009; Yegiyants, 2010].

In a retrospective analysis of a prospective database, Pugliese (2010) compared 76 patients with isolated tumour cells in the axillary node who had only undergone an SN biopsy with 95 patients who also underwent an ALND. After a median follow-up of 6.4 years, no axillary node recurrences were found, 3 local recurrences and 6 distant recurrences. Eight of the 9 recurrences were determined in patients treated with SN biopsy and ALND. The five-year recurrence-free survival of the total cohort was 97% (95%CI 92.1 - 98.6). Other authors also found low axillary recurrence percentages of 0% [Calhoun, 2005; Jakub, 2002; Jeruss, 2005; Giobuin, 2009; Schulze, 2006] to 2.3% [Cox, 2008] of patients with isolated tumour cells in the axillary node who only underwent an SN biopsy. Only one comparative study reported survival figures for patients with isolated tumour cells [Cox, 2008]. In this study, 44 patients underwent only an SN biopsy and 107 patients an SN biopsy and ALND. While the authors do not report any figures, the Kaplan-Meier curve shows a significantly worse survival in the group who only underwent an SN biopsy (p=0.02).
None of these studies corrected for primary tumour characteristics or the use of systemic therapy.

Finally, a large study was conducted by the Memorial Sloan-Kettering Cancer Centre in which 6 of the 287 patients (2%) with a positive SN who only underwent an SN biopsy developed an axillary recurrence in comparison with 6 of the 1,673 patients (0.4%) who also underwent an axillary node dissection (p=0.004) [Park, 2007]. In patients with an H&E-positive SN (predominantly micrometastases), the axillary recurrence percentage without ALND was 5% after 23 months. This study also did not correct for primary tumour characteristics or the use of systemic therapy.

<u>Axillary irradiation</u>
None of the studies specifically compared the effect of irradiation or non-irradiation in patients with micrometastases or isolated tumour cells in the SN.

Conclusions

Level 2	There are indications that omitting an axillary node dissection in at least a proportion of patients with SN micrometastases does not lead to a reduction in survival or an increase in the number of axillary recurrences. It is difficult to see from the current literature which patients this involves. B Bilimoria 2009, Cox 2008, Pernas 2010, Wasif 2010, Giuliano 2010

Level 2	It is plausible that omitting an axillary node dissection in patients with isolated tumour cells in the SN does not lead to an increase in the number of axillary recurrences.

	B	Pugliese 2010, Cox 2008, Calhoun 2005, Jakub 2002, Jeruss 2005, Giobuin 2009, Schulze 2006

Remaining considerations

Four randomised studies have been published so far with and without ALND in patients with a negative SN [Veronesi, 2010; Zavagno, 2008; Canavese, 2009; Krag, 2010]. Omitting ALND is considered safe in the case of a negative SN. In this study, patients with isolated tumour cells were considered node positive, and therefore underwent an ALND as a standard. The limited data that has been published so far in relation to axillary management if isolated tumour cells in the SN are found has been derived from observational series, and show a low recurrence percentage. Another retrospective analysis of 6,838 patients treated between 1998 and 2004 also shows little influence on the breast cancer-specific survival of an axillary node dissection in patients with micrometastases [Yi, 2010]. In an analysis in the Netherlands (the MIRROR study), the regional recurrence percentage in patients with SN isolated tumour cells who did not undergo ALND also appeared acceptable (2% after 5 years of follow-up). In the ASCO guideline, ALND is not recommended as a standard with SN-isolated tumour cells.

In the pre-SN era, no difference was found in the NSABP B04 trial in clinically node-negative patients in relation to survival between an ALND, regional irradiation or omitting both [Fisher, 1985]. Reed (2009) suggests that the extremely low axillary recurrence percentage generally described in literature after breast-sparing treatment could be linked to radiotherapy of a proportion of level I and II of the axilla in mantle-fields. In the EORTC study 10981/22023 (the AMAROS study), closed in April 2010 with almost 4,800 patients, in which all patients with a positive SN received axillary treatment, randomised between surgery or radiotherapy of the axillary and periclavicular region, the total number of axillary recurrences strongly fell behind expectations (personal communication). While it has not been unequivocally proven yet, the guideline development group deems it likely on the basis of available literature and experience from the AMAROS study that axillary irradiation could be an alternative to an axillary node dissection in patients with metastasis/metastases in the SN for whom treatment of the axillary is considered necessary.

For the time being, ASCO does standard recommend an ALND in patients with SN micro/metastases. The series reported so far do show a low regional recurrence percentage, but these series are partly biased due to patient selection, small patient numbers, short follow-up duration, or underreporting of recurrences during follow-up (cancer registration databases) [Pepels 2011].

The ACOSOG (American College of Surgeons) Z-11 study was recently published [Giuliano, 2010; Giuliano, 2011]. This concerned a prospective study in which patients with a positive SN (≥ 3 SN+ excluded) were randomised between ALND or no further axillary treatment in patients who underwent BCT. In this study, 891 patients were evaluated with a median follow-up of 6.3 years; no significant difference was found in local or regional recurrence (0.5% after ALND, 0.9% after SN procedure). Adjuvant systemic therapy was administered in 97% of cases. The authors concluded that it is justified to omit an ALND in patients who undergo a BCT, receive adjuvant systemic therapy and with a positive SN.

Recommendations

Specific recommendations about axillary treatment can be found in section 3.3.3.

Specific recommendations about adjuvant systemic therapy in the case of (sub)micrometastases can be found in Chapter 5.

3.3.3 Axillary , periclavicular and parasternal radiotherapy

There is not much literature on the relationship between the number of positive nodes and the chance of a regional recurrence. In most studies, there is an indication for postoperative radiotherapy of the high axillary and periclavicular node chain if there are ≥ 4 positive nodes. Axillary recurrences are extremely rare after level I-II ALND. The number of axillary recurrences is also extremely low with positive nodes after surgery only. This has lead to less irradiation of the axilla. Given the periclavicular node area is the most common location for recurrence growth after the breast or chest wall, this node area is usually irradiated in high-risk patients (≥ 4 positive nodes, positive axillary top).

Medial and central tumours give a high chance of parasternal node metastases. It has also been demonstrated that medial and central tumours are associated with a poorer prognosis [*Zucali, 1998;*

Gaffney, 2003]. Parasternal recurrences are only found in extremely rare cases. The treatment of the parasternal node chain has been a point of discussion for a long time. A patient group also cannot be defined in subgroup analyses for which this treatment would be beneficial. Given the effect of radiotherapy on survival is visible after 15 years in EBCTCG data, a longer follow-up may in fact show a difference.

Conclusions

Level 2	With a clinically negative axilla, a sentinel node procedure can be used to determine the axillary node status in breast cancer smaller than 5 cm with a reliability of at least 95%. B de Kanter 2006, Heuts 2007, Torrenga 2004, Kuijt 2007, Straver 2010

Level 1	The chance of metastases in the remaining axillary nodes with a positive SN is approximately 50% when macrometases has been demonstrated and approximately 20% if micrometastases have been demonstrated. A1 Cserni 2004

Level 3	The chance of metastasis in non-SN nodes with isolated tumours cells in an SN reduces as the primary tumour decreases in size. There is currently insufficient data to indicate when this chance is < 5%. C Barranger 2005, Bolster 2007, Calhoun 2005, Cserni 2007, den Bakker 2002, Gray 2004, Lambert 2007,Rahusen 2001, Turner 2000, van Deurzen 2007

Level 2	The chance of an axillary recurrence with a negative SN is less than 0.5%. B Naik 2004, van der Ploeg 2008 C Blanchard 2003, Jeruss 2005, Rosing 2006, Smidt 2005, Krag 2010

Level 2	Performing an ALND after a positive SN has not been demonstrated to provide survival advantage. B Bilimoria 2009, Yi 2010, Giuliano 2010

Level 3	Patients with a tumour-positive SN who undergo BCT and receive adjuvant systemic therapy receive no benefit from an ALND in relation to the chance of an axillary recurrence. B Giuliano 2010

Level 2	Axillary recurrences are extremely rare, both after ALND and primary radiotherapy. Most axillary recurrences appear to occur in the first three years after primary treatment. B Louis-Sylvestre 2004, Hoebers 2007

Remaining considerations

Conducting the SN procedure in patients with a status after breast augmentation with the help of intramammary prosthesis appears possible and reliable [Gray, 2004]. Peri- and intratumoural injections have been used in the Netherlands since the introduction of SN biopsy [Estourgie, 2004]. These largely follow the physiological drainage of the breast and are especially important with tumours at a deeper location and if there is attention for extra-axillary SN's [Estourgie, 2004]. If there is only interest in the axillary lymph nodes, superficial injection techniques are a good alternative [Veronesi, 2006; Rutgers, 2004; Borgstein, 2000; Rodier, 2007]. If the radiocolloid is injected intra or peritumoural, parasternal drainage is found in almost 20% of cases using scintigraphy [van Rijk, 2006]. In old series in which surgery was expanded with a parasternal lymph node dissection, metastasis was exclusively found in these nodes in almost 10% of patients, especially in medial located tumours larger than 2 cm [Veronesi, 1983]. No univocal advice is given in literature for routine

biopsy of a parasternal SN [Rutgers, 2004; Fabry, 2004; van der Ent, 2001; Lyman, 2005; Wouters, 2007]. In individual cases it can be decided to perform a biopsy of these sentinel lymph nodes. If metastases are detected, this implies a poor prognosis and parasternal radiotherapy and administering adjuvant systemic therapy is recommended.

Recommendations

Pre-operative

The SN procedure is indicated for patients with a $T_{1-2}N_0$ breast cancer for the purpose of lymph node staging.

The SN procedure may also be conducted safely if multifocality at a distance of <5 cm is determined prior to surgery.

Relative contraindications for the SN procedure (i.e. the SN procedure may be considered, but the value is limited):

- $\geq T_3$ and/or multicentricity determined prior to surgery
- earlier (recent) axillary surgery

Absolute contraindications for the SN procedure (i.e. axillary node dissection level I and II is indicated):

- Axillary node metastases determined by ultrasound and punction
- If an SN procedure cannot be performed for other reasons

Postoperative

Additional treatment is not recommended for patients with isolated tumour cells in the SN (on the basis of low regional recurrence percentages).

Patients with micrometastases in the SN have a risk of approximately 20% of non-SN involvement. The risk of non-SN involvement is additionally dependent on the primary tumour characteristics. The chance of recurrence depends on the application of radiotherapy and adjuvant systemic therapy. The best strategy for axillary treatment per patient should therefore be discussed during multidisciplinary consultation:

- irradiation of the breast only (implicitly including a large part of level 1 and 2 of the axilla) if adjuvant systemic therapy is also administered
- axillary radiotherapy
- ALND

In the case of limited macrometastases in 2 SN's at the most, omitting an ALND in patients who will undergo a BCT and receive adjuvant systemic therapy may be considered.

With more extensive macrometastasis, treatment of the axilla (ALND or radiotherapy) is indicated.

3.4 Primary and secondary breast reconstruction

Possibilities for a breast reconstruction have improved in the last 25 years thanks to development in surgical and prosthetic techniques. The number of reconstructions has also increased [Berger, 1994]. Breast reconstruction supports the recovery of patients to a great extent because it reduces the psychological, social and sexual morbidity associated with loss of the breast [Fischbacher, 2002; Pusic, 2007; Zweifler, 2001; Al-Ghazal, 2000; Sandelin, 1998]. Patients who have undergone a breast reconstruction are generally satisfied with the result and have more self-confidence, especially on a psychosocial level [Zweifler, 2001; Sandelin, 1998]. Reconstruction restores the feeling of 'being female' and leads to a more complete body perception because wearing an external breast prosthesis becomes unnecessary [Reaby, 1998; Rowland, 1995].
Despite these benefits, the percentage of patients undergoing a breast reconstruction is low: approximately 15% [Rowland, 1995]. The most important cause of this is patients not knowing about the possibility of reconstruction prior to undergoing mastectomy [Zweifler, 2001; Reaby, 1998; Pusic, 1999].

3.4.1 Primary or secondary breast reconstruction?

The best point in time for the breast reconstruction is not known [Al-Ghazal, 2000; Gilliland, 1983; Rosato, 1980]. Factors that play a role in the decision-making as to whether to perform a primary or

secondary reconstruction are the tumour stage and the chance of postoperative radiotherapy [Christante, 2010]. Primary or direct breast reconstruction must especially be recommended to patients with a low risk of postoperative radiotherapy. Primary reconstruction leads to better cosmetic results because the skin of the breast can be spared [Fishbacher, 2002]. Studies with selected patients show that patients themselves prefer a direct reconstruction above a secondary reconstruction [Al-Ghazal, 2000; Halpern, 1990]. They experience less discomfort and feel better mentally [Al-Ghazal 2000; Rosenquist, 1984]. As they are spared a life without the breast, they are more satisfied with the final result compared to patients who have had a secondary reconstruction [Kroll, 1997; Kroll, 1995].

Conclusion

Level 3	A descriptive study has demonstrated that women who undergo a breast reconstructive directly after mastectomy including ALND are more satisfied with the aesthetic result and display a better psychosocial wellbeing than women who undergo secondary reconstruction. *C* Fishbacher 2002, *Al-Ghazal 2000, Kroll 1995, Kroll 1997*

3.4.2 Breast reconstruction and locoregional recurrence

On the basis of available literature it is unclear if the incidence of locoregional recurrence is related to the moment of reconstruction (primary versus secondary) [Petit, 2008; Kroll, 1991; Johnson, 1998; *Vaughan, 2007*]. Breast reconstruction is accompanied by an acceptable morbidity and does not influence the detection and follow-up treatment of a recurrence [Sandelin, 1998; Kroll, 1991; Vandeweyer, 2001; Noone, 1994; *Spiegel, 2003;* Taylor, 1995]. Developments in cancer safe breast-sparing operations and the improved cosmetic results have lead to the rise in skin-sparing mastectomy techniques. Sparing the skin facilitates the breast reconstruction because the skin envelope remains intact and it is easier for the inframammary fold to be restored.

On the basis of descriptive studies, it is concluded that the chance of a locoregional or systemic recurrence with a skin-sparing mastectomy followed by a direct or a delayed reconstruction is equivalent to that of treatment by means of conventional mastectomy without reconstruction [Petit, 2008; Gerber, 2009; Sandelin, 1998; Kroll, 1997; Kroll, 1991]. A post-mastectomy mammogram of the reconstructed breast is not worthwhile and even leads to some confusion if there is any fat tissue necrosis present [Holmes, 1988].

Conclusions

Level 3	There are no indications that primary or secondary breast reconstruction leads to a higher risk in breast cancer recurrence. C Petit 2008, Gerber 2009, Kroll 1991, Johnson 1998, Taylor 1995, Vaughan 2007

Level 3	No indications have been found that a skin-sparing mastectomy followed by a direct reconstruction leads to an increased chance of a locoregional or systemic recurrence in breast cancer. C Kroll 1997, Sandelin 1998, Spiegel 2003, Petit 2008,

3.4.3 Perform an autologous reconstruction or not?

The choice between a subpectorally placed prosthesis and autologous tissue in a reconstruction is dependent on the quality and vascularisation of the overlying skin remaining after the breast mastectomy, the shape and size of the breast and the preference and expectation of the patient. When the skin is of insufficient quality, skin will need to be added to ensure adequate volume. In this case, use of own tissue is a more likely choice. The level of patient satisfaction is greater over time with the autologous method than with the prosthesis method, even though the first method often leads to more scars and initially a greater morbidity. The structure of own tissue is better than that of foreign material. Incidentally, it is noticeable that patients are generally satisfied with the result regardless of the reconstruction, as long as they stand behind the decision themselves [Spear, 2000; Alderman, 2000].

Silicon prostheses

Silicon breast prostheses have been used for cosmetic and reconstructive surgery since 1962. These prostheses have been the subject of discussion, both concerning possible systemic and locoregional complications. The locoregional complications after silicon implantation such as capsular contracture and wound infection are important when choosing the method of breast reconstruction. The chance of complications increases with smoking, obesity and higher age at the time of implantation [Spear, 2000; Handel, 1995]. No causal relationship has been found between implanted silicon and systemic complaints associated with silicon [McLaughlin, 2007; Noone, 1997; Nyren, 1998].

Conclusion

Level 3	A causal relationship between implanted silicon and the occurrence of systemic syndromes has not been demonstrated. B McLaughlin 2007 C Noone 1997, Nyren 1998

3.4.4 Breast reconstruction and radiotherapy

Complications after breast reconstruction with a subpectorally placed prosthesis is more common in irradiated patients than in non-irradiated patients [Berry, 2010; Christante, 2010; *Jugendburg, 2007].* However, postoperative radiotherapy may also negatively influence the cosmetic result of a direct reconstruction, performed with the help of autologous tissue [Tran, 2001; Javaid, 2004]. Patients must be informed about this. The increased chance of complications is not a reason to remove the prosthesis as a precautionary measure when radiotherapy of the chest wall is being administered [Contant, 2000; Berry, 2010]. However, the global tendency is not to perform a direct breast reconstruction if there is an increased chance of postoperative radiotherapy, due to the elevated chance of complications and the poorer cosmetic results [Javaid, 2004; Recht, 2001; Kronowitz, 2004; Berry, 2010].

Conclusion

Level 3	Radiotherapy does not lead to significantly more complications with a breast reconstruction. C Christante 2010, Berry 2010, Jugendburg 2007

3.4.5 Oncoplastic breast-conserving therapy

The principle of breast-sparing treatment consists of the ample excision of tumour volume and irradiation of margins following surgery, striving for an optimal cosmetic result. The cosmetic result is dependent on the tumour location, resection volume and irradiation dose [Vrieling, 1999; Cochrane, 2003]. The cosmetic result is 70-82% acceptable [Vrieling, 1999; Taylor, 1995; de la Rochefordiere, 1992].

When a greater lumpectomy must be performed, this will lead to a smaller breast with a deformity [Cochrane, 2003]. Use of breast reduction plastic surgery enables a greater volume to be removed containing the cancer tissue, and the shape to be restored. Good preoperative planning between the surgeon and plastic surgeon allows adequate resection by the oncological surgeon and subsequently a good distribution of breast tissue with relocation of the nipple through the many breast reduction possibilities available to the plastic surgeon. Peroperatively placed ligaclips after resection and prior to reconstruction mark the excision location, necessary for radiotherapy [Anderson, 2005; de Lorenzi, 2010]. In this manner, an even greater volume may in fact be removed so that wider margins may be achieved without large deformity. The oncological results are comparable with results of conventional breast-conserving therapy [Mc Culley, 2005; Rietjens, 2007; Asgeirsson, 2005].

Conclusion

Level 3	Oncoplastic breast-conserving therapy enables a more ample excision to be performed so that there is less chance of residual tumour and a better cosmetic result. C Mc Culley 2005, Rietjens 2007, Andersson 2005, de Lorenzi 2010

Remaining considerations

The cosmetic results in the long term, especially as a result of the potentially larger radiotherapeutic boost area, have to be thoroughly evaluated. Perhaps these patients may even be treated without a

local boost in the case of negative tumour margins, which would benefit cosmetic results [Pezner, 2011; Kronowitz, 2007]. A contralateral symmetrisation procedure is often necessary to remedy asymmetry.

3.4.6 Nipple sparing mastectomy

It is usual for the nipple areola complex to be removed in a mastectomy. The loss of the nipple strengthens the feeling of the extent of the mutilation. The risk that the nipple is also involved in the tumour process is largely determined by the size and location of the tumour and node status. If the tumour is further than 2 cm from the nipple, is not larger than T2 or multifocal and positive lymph nodes are not suspected, then the nipple areola complex could be spared [Caruso, 2006; Lambert, 2000; Gerber, 2003; Petit, 2006]. Partial or complete nipple necrosis is a dreaded complication [Petit, 2006; Caruso, 2006; Rusby, 2007]. A frozen section is taken from the bottom of the nipple complex perioperatively during mastectomy. The nipple can be spared if the frozen section is negative. So far, good local control can be achieved with a good cosmetic result [Chen; 2009; Rusby, 2007; Gerber, 2003 en 2009; Petit, 2009]. This method can also be applied with a prophylactic mastectomy.
Additional intra-operative radiotherapy of 16 Gy on the nipple complex, the so-called ELIOT procedure, is outlined to reduce the chance of a local recurrence [Petit, 2006].

Conclusion

Level 3	A nipple sparing mastectomy is oncologically safe with smaller tumours that are not localised close to the nipple. There should be no suspicion of positive axillary nodes. C Petit 2009, Gerber 2003

Remaining considerations

The limited proportion of direct reconstructions in the Netherlands can largely be traced back to the limited information about direct reconstructive possibilities provided by the oncological specialist to the patient and subsequently to the limited availability of plastic surgery for these interventions. Nonetheless, the possibility of breast reconstruction should be discussed with patients before the oncological intervention takes place. The patient is then also informed about the fact that a corrective intervention may be performed on the other breast. For patients with a large preoperative chance that radiotherapy will be necessary following surgery, the larger chance of complications must be incorporated in the advice about (primary or secondary) reconstruction.

Recommendations

Patients who must undergo a mastectomy should be informed prior to the intervention regarding the possibilities of breast reconstruction.

Breast reconstruction must be considered for every patient with breast cancer who is undergoing surgery.

There is a slight preference for conducting a direct breast reconstruction.

Delaying breast reconstruction must be considered if the chance is great that radiotherapy will be indicated.

Pathology

Pathology analysis provides various information important for selecting the appropriate therapy. Criteria and guidelines for the best possible uniformity and objectivity in determining this information is provided in the following sections:

4.1 Preoperative cytological diagnostics
4.2 Preoperative histological diagnostics
4.3 Management plan if there is a benign or not clearly benign abnormality
4.4 Processing of and reporting on breast and axilla resection samples
4.5 Determining the PT and tumour grade
4.6 Excision margin analysis with breast-conserving therapy; indications for additional surgery
4.7 Determining hormone receptor and HER2 status
4.8 Staging by means of the SN procedure and/or ALND
4.9 Minimum criteria for the diagnosis DCIS – dd. invasive carcinoma
4.10 Evaluation after neoadjuvant chemo- or endocrine therapy

4.1 Preoperative cytological diagnostics

Cytological thin needle diagnostics

Cytological thin needle diagnostics are applied with palpable and non-palpable laesions, under palpation or under ultrasound guidance. One to two punctions are usually performed, in which multiple passages are made through the laesion using an 18-23G needle. Most studies concern both palpable and non-palpable tumours, in which the procedure takes place using ultrasound guidance or under palpation. Cytology is deemed unsuitable for diagnostics of microcalcifications. The sensitivity varies from 65-98% and the specificity from 34-100%. The results are negatively influenced if the woman is younger than 40 years of age, the tumour is smaller than 10 mm, if the procedure was conducted by an inexperienced staff member or if the evaluation is performed by an inexperienced pathologist [Boerner, 1999; Kerlikowske, 2003; Liao, 2004; Cobb, 2004]. The presence of a cyto-pathologist at the time of the procedure increases accuracy [Helbich, 2004]. In a study by Ljung (2001), the percentage of inconclusive punctions with trained physicians was 2.4%; there were no false negatives. The percentage of inconclusive punctions for untrained physicians increased to 50.4% and the percentage of false negative results to 8.3%. The results do not appear to be dependent on the discipline, but on expertise in relation to the procedure.

If cytology is compared to histology, the results are comparable in terms of sensitivity, but histology has a higher specificity and an uncertain diagnosis is less common [Westenend, 2001]. The advantage of cytology is the speed of evaluation and low costs, as well as the fact the procedure is not very invasive. In experienced hands, it can also be used to determine ER/PgR sensitivity. The disadvantages are that cytology is not able to answer all clinical questions or that the required expertise is not available to do so. The punction must also be frequently repeated as a result of the substantial percentage of insufficient results.

Conclusion

Level 2	The accuracy of cytology is comparable to that of histology, as long as it is performed and evaluated by experienced staff members. B Westenend 2001, Ljung 2001, Liao 2004

Remaining considerations

Cytology and histology overlap and partly supplement one another and their role is therefore less sharply defined in current preoperative diagnostics than in the past.

More important than the choice between cytology or histology is the consultation between the surgeon, radiologist and pathologist. They independently formulate a conclusion; the further treatment plan is determined by consensus during preoperative multidisciplinary consultation.

Recommendations

When can primarily be chosen for cytology?

Cytology is suitable for the diagnosis of evident solid laesions (masses), independent of whether these are palpable or non-palpable, such as a one-day service within the framework of a breast policlinic.

Compulsory items in the pathology report for a cytological punction

- quality and ability to evaluate
- content description
- correlation with the findings on clinical images
- conclusion, in which it is recommended to use the following categories:
  - no diagnosis, insufficient material; repeat of cytological analysis or histology indicated
  - normal breast, no abnormalities; *consultation with radiologist as to whether it is representative; repeat analysis if there is doubt*
  - benign laesion, namely …….. (specify); *a wait-and-see policy can be chosen if clinical images can be explained by findings*
  - not clearly benign or suspected malignancy
  - malignant

After cytology, histology should still be obtained if:

- the cytology result falls in the category of:
  - insufficient material
  - repeatedly negative or uncertain
  - not clearly benign or suspected malignancy
- neoadjuvant chemotherapy is indicated
- certainty about the distinction DCIS versus IDC must be obtained

4.2 Preoperative histological diagnostics

In general, a radiologist will decide during clinical imaging which technique will be used. This will depend on the nature and morphology of the abnormality. If the results of clinical breast examination, imaging and punction correspond, the accuracy of the triple-diagnostics is greater than 99%.
In doing so, it is less important how the PA material was obtained and if the laesion is palpable [Wallis, 2007]. In this regard, the term 'triple diagnostics' (which stood for palpable abnormality, imaging and cytology) has gradually broadened: the surgeon, radiologist and pathologist independently form an opinion on the basis of their findings, and further patient management is determined by consensus.
The more biopsies and the bigger the biopsies, the more certainty regarding the definitive diagnosis. With ultrasound-guided needle biopsies, the phenomenon that a good biopsy sinks in formalin can be used to evaluate quality. With microcalcifications, at least five microcalcifications must be found using radiology, preferably divided across three biopsies [Fishman, 2003; Margolin, 2004; Wallis, 2007]. When taking a biopsy of microcalcifications, the procedure should always be completed with a specimen radiography, to evaluate whether the sample is representative. In the case of larger biopsies, more complications need to be taken into account, especially hematoma formation and with the use of anti-coagulants.

After biopsy of non-palpable small abnormalities and calcifications, the abnormality may have disappeared on a mammogram; for this reason it is recommended that a marker is left behind for localisation at a later stage [Fahrbach, 2006]. This is also recommended for ultrasound-guided needle biopsies [Wallis, 2007]. A marker must always be left behind with MRI-guided needle biopsies [Schrading, 2010].
The concern for seed metastases as a result of thick needle biopsies is unfounded given the study by Diaz (1999): displaced tumour cells were found, on average in 32% of 352 biopsies, but the incidence was inversely proportional to the time between the biopsy and excision. It can be derived from this that the tumour cells can be displaced, but that they do not survive.
Each breast care team must have ultrasound-guided and stereotactic punction procedures at their disposal within their own team. The MRI-guided punction procedures are not performed everywhere, but each team must have access to a location in which the procedure is performed.

<u>Histology with ultrasound-guided thick-needle biopsy</u>

The global standard is ultrasound-guided 14G biopsy, in which an average of 5 biopsies are taken. In the multicentre study by Fajardo (2004), only ultrasound-guided procedures of non-palpable abnormalities have been evaluated. The results under palpation usually remain behind those of ultrasound-guided procedures [Agarwal, 2003; Lorenzen, 2002; Shah, 2003]. The distinction between palpable and non-palpable laesions disappears with ultrasound-guided punctions, and this aspect therefore does not play a role in most studies.
Similar to cytology, the following play a role: the size of the laesion, the expertise of the person performing the punction and the pathologist evaluating the material. Sample errors may occur if it is hard to immobilise the laesion, if the needle cannot be positioned well or if it pushes the (small)

laesion forward. Fishman (2003) took 4 ultrasound-guided 14G biopsies per tumour for 73 solid tumours: 1 biopsy was in diagnostic in 70% of cases, 2 biopsies in 92%, 3 biopsies in 96% and 4 biopsies in 100%.
In a review of 8 studies [Youk, 2007], the procedure needed to be repeated again in 10% of cases on average, because the punction results were inconclusive or discordant. The percentage of malignancies was still substantial for this subgroup: 17%. The final percentage of false negative results was low. In the follow-up, the percentage of false negatives averaged 4% (0-8%). The conclusion each time is that results are comparable with results of a diagnostic excision biopsy [Helbich, 2004; Fajardo, 2004; Youk, 2007]. This is confirmed by a systematic review by Bruening (2010).

Histology with X-ray-guided, stereotactic thick-needle biopsy

A non-palpable laesion, which can only be seen by mammogram, can be obtained by puncture using the X-ray-guided, stereotactic procedure. This can be performed using a special table, in which the patient undergoes the procedure in prone position or with an accessory piece that is attached to the mammography equipment, so that the procedure can be performed in a sitting or recovery position. The results of these procedures are comparable. This procedure is more time-consuming and invasive and is especially used with microcalcifications.
The best results are obtained after at least 5 biopsies, correspondence with the definitive PA diagnosis varies from 87-96% [Verkooijen, 2000; Helbich, 2004; Fajardo, 2004]. Here too, it can be concluded that the results are comparable with results of a diagnostic excision biopsy [Verkooijen, 2002; Helbich, 2004; Fajardo, 2004].

Histology with vacuum-assisted biopsy equipment

Vacuum-assisted biopsy equipment enables multiple biopsies to be obtained at high speed with needles of 10-11G. Thanks to the vacuum system, biopsies are greater in size and are obtained semi-automatically. As a result, the number of biopsies can easily increase to 6 lots or a multiple of this. This equipment is suited par excellence to obtaining stereotactic histologic biopsy. This procedure is more invasive than the 'usual' stereotactic thick needle biopsy and has a higher complication percentage, especially haematoma formation. Again it largely concerns microcalcifications here, and in addition radial scars and architecture distortions. The studies included by Fahrbach (2006) looked in particular at the reduction in laesion miss rates by needle biopsy and a possible improvement in the underestimate rate, i.e. if there was a reduced occurrence in the diagnosis atypical ductal hyperplasia (ADH) in the needle biopsy while a DCIS was found during excision, or the diagnosis DCIS on the needle biopsy while an invasive carcinoma was found during excision. The reference, if available, was the diagnosis of the excision and a clinical/radiological follow-up of at least 1 year if available. Most abnormalities were not palpable (97%) and consisted of microcalcifications (64%), mostly evaluated as BI-RADS 4 or 5 (90%) (Fahrbach, 2006). The biopsy was taken using prone equipment for most of the patients. The following differences were notable in comparing vacuum-assisted biopsy and conventional needle biopsy: the number of biopsies averaged 13.3 (range 10-17) in the studies with vacuum-assisted biopsy equipment and 6.6 (range 5-10) for conventional needle biopsy. The number of failed procedures was lower for vacuum-assisted biopsy equipment (1.5% vs 5.7%) and the number of non-diagnostic biopsies was also lower (0% vs 2.1%). This is also concluded in the study by Jackman (2009). However, a false negative result cannot be fully ruled out in this manner: in a German multicentre study cited by Fahrbach, in which 20 biopsies were taken using vacuum-assisted procedure for 2,874 laesions, a false negative result was still obtained in one case [Kettritz, 2004] .

MRI-guided histological biopsy

MRI-guided biopsy is indicated for BI-RADS 4 and 5 laesions, which are at least 5 mm or larger and are not found during second-look ultrasound or mammography unless the PA of the laesion has consequences for the surgical management plan. Cytology is not worthwhile: it is easy for sample error to occur due to tissue displacement. If the laesion is difficult to reach, wire guided localisation may be performed.
A prospective multicentre cohort study has been conducted [Perlet, 2006] and an increasing number of retrospective cohort studies, either with thick needle, or with vacuum systems [Han, 2008; Li, 2009; Malhaire, 2010; Peters, 2009; Schrading, 2010]. This enables a larger number of 10G biopsies to be taken, so that the sample error is reduced. A control series is recommended after the biopsy, both before and after clip placement. The technical execution requires expertise. Using console equipment instead of performing the procedure freely by hand makes the procedure faster and more accurate [Schrading, 2010].

The number of MRI series required and sliding the patient in and out of the scanner is determinant for the examination duration [Noroozian, 2009]. The technical success percentages are high and vary between 87.2-100%. False negative results occur in 2-7% of cases. This is comparable with the results of tissue biopsies under ultrasound-guidance and by stereotactic biopsy, but the series are still too small to draw a definitive conclusion. The advice by Heywang (2009) to take 24 biopsies as a standard is based on the aim of completely or partially removing the laesion. This is not always necessary; however, radiologic-pathologic correlation is required.

Conclusions

Level 3	The percentage of false negative results of histological ultrasound-guided needle biopsies is approximately 4% with 5 biopsies. The reliability is comparable to that of a diagnostic excision biopsy. A2 Fajardo 2004 C Helbich 2004, Youk 2007

Level 1	The percentage of false negative results of histological stereotactic needle biopsies is also an average of approximately 4% with 5 biopsies. The reliability is again comparable to that of a diagnostic excision biopsy. A2 Verkooijen 2002, Fajardo 2004 C Helbich 2004

Level 1	Stereotactic and ultrasound-guided histological biopsies have almost the same accuracy as open surgical biopsy. There is a lower chance of complications developing. A1 Bruening 2010

Level 1	In the population of patients with (non-palpable) abnormalities detected by screening who are eligible for stereotactic punction, the use of vacuum-assisted biopsy equipment leads to a lower underestimate rate and less missed abnormalities. A1 Fahrbach 2006 B Jackman 2009

Level 2	MRI-guided biopsies (thick needle and vacuum-assisted) have a success percentage of 87.2-100%. The number of false negatives is 2-7%. A2 Perlet 2006 B Han 2008, Li 2009, Malhaire 2010, Peters 2009

Remaining considerations

Cytology and histology overlap and partly supplement one another and their role is therefore less sharply defined in current preoperative diagnostics than in the past.

More important than the choice between cytology or histology is the consultation between the surgeon, radiologist and pathologist. They independently formulate a conclusion; the further treatment plan is determined by consensus during preoperative multidisciplinary consultation.

Recommendations

Compulsory items in the pathology report of a histological needle biopsy

- classifying diagnosis; use of the following categories is recommended:
  - benign laesion, namely …….. (specify)
  - not clearly benign, or suspected malignancy
  - malignant, namely ….. (specify: invasive, in situ, primary, metastasis, etc.)
- correlation with the clinical imaging findings (especially the presence or absence of microcalcifications)

The following may be added on indication:

- hormone receptor status and HER2
- grading (a histological biopsy is less suitable for reliable grading of the tumour than tumour excision)

When can primarily be chosen for histology?
Histology is suited to the diagnosis of poorly delineated solid laesions, architecture distortions, radial scars and microcalcifications and for additional diagnostics, as mentioned above.

In this group, both the stereotactic needle biopsy and stereotactic vacuum-assisted biopsy are a good alternative for the diagnostic excision biopsy.

Multiple biopsies should be taken during histological biopsy procedures, in order to prevent sampling error:

- a minimum of 5 biopsies is recommended if there is doubt as to whether results are representative
- use of the phenomenon that a good biopsy sinks in formalin can be used during ultrasound-guided punctions of solid laesions
- at least 5 microcalcifications need to be found radiologically during stereotactic punctions of microcalcifications, preferably divided over 3 biopsies
- a specimen radiogram must be performed as a standard component of the procedure during stereotactic punctions of microcalcifications

Each breast care team should have access to a centre where MRI-guided biopsies can be performed.

Placement of a marker is strongly recommended, especially in a stereotactic biopsy and MRI-guided biopsy.

4.3 Management plan if there is a benign or not clearly benign abnormality

After cytology, in which no specific diagnosis is obtained or in which a proliferative laesion or atypia is suspected, histology must still be performed.
The results of a histological biopsy must continually be correlated with clinical findings and imaging. If there are microcalcifications, it is a requirement that the pathologist accurately describes the microcalcifications with a fitting BI-RADS final assessment category [Burnside, 2007] and that a specimen image is made of the biopsies (see 2.2.2). The accuracy of the PA report in relation to the presence of malignancy increased in the presence of sufficient microcalcifications: a malignant diagnosis was only missed in 1% of cases with biopsies containing microcalcifications, the diagnosis was missed in 11% ($p<0.001$) of cases with biopsies not containing microcalcifications [Johnson, 2009].

There is a relationship between the percentage of false negative findings and the number of biopsies obtained. In a large retrospective cohort study, relative risks were calculated for 9,087 women with benign breast abnormalities, using a follow-up period of 15 years (median). The RR for abnormalities with atypia was 4.24 (95%CI 3.26-5.41), RR for proliferative changes without atypia was 1.88 (95%CI 1.66-2.12). Familial burden was an independent, additional risk factor; the RR for moderately elevated risk was 1.43 (95%CI 1.15-1.75%) and RR for strongly increased risk 1.98 (95%CI 1.58-2.32) [Hartmann, 2005]. If there are concordant benign findings in a woman without additional risk factors, then the risk of a missed carcinoma is therefore no greater than after diagnostic excision biopsy and not greater than in the general population.
If there is doubt about results being representative, a decision can be made to repeat the procedure, a diagnostic excision biopsy, or perform a check-up by means of mammography. The risk factors are not high enough to justify routine follow-up using MRI [Elmore, 2005]. Follow-up after 6 months is often recommended, but a drawback is that there is often insufficient compliance from patients. This was 84% for Lee (1999) and 77% for Kunju (2007).
With (a)symptomatic patients, if there is a BI-RADS 3 (probably benign), BI-RADS 4 (probably malignant) laesion or BI-RADS 5 (malignant) laesion, a punction is performed for a substantial proportion of the BI-RADS 3 and in principle for all BI-RADS 4 and 5 laesions. The number of diagnostic excision biopsies has therefore substantially decreased. The benefit is that it is not so invasive, the drawback is that the laesion is not pathologically examined in its entirety. It is therefore extremely important that the punction is representative.

False positive results from histological biopsies are also possible; it is therefore necessary when using these biopsies, for the management plan to be determined after multidisciplinary consultation. Whether or not histological biopsies of mammographic abnormalities with microcalcifications are

representative must be checked using a specimen photo. In the case of the diagnosis DCIS in a histological biopsy, there is a substantial chance of invasive carcinoma on excision.

Clearly benign PA diagnosis

If a clearly benign PA diagnosis correlates with clinical findings and imaging, additional diagnostics or follow-up is not necessary. Clearly benign PA diagnosis are: hamartoma, fibroadenoma, tubular adenoma, benign hyperplasia, sclerosing lobular hyperplasia, fibro-cystous changes, duct ectasias, apocrine metaplasia, pseudoangiomatous stromahyperplasia, normal or fibrous breast tissue [Jacobs, 2006; Johnson, 2009; Hargaden, 2008].

Not clearly benign PA diagnosis

In addition, there are PA abnormalities that are risk factors for development of a malignancy (see 1.3.1) and PA abnormalities that may accompany DCIS in the direct proximity of the obtained biopsy, so that the biopsy may therefore be deemed non-representative for the entire abnormality. These 2 categories overlap and the extent of the risk is difficult to determine, because the published series are all small and retrospective. Determining the management plan is the most difficult if there is a BI-RADS 4 abnormality or BI-RADS 4 microcalcifications. The below information is largely based on Elston (2000), van de Vijver (2003), Jacobs (2006), Johnson (2009), Lopez-Garcia (2010) and Jain (2011). The literature mentioned makes it clear that not in all cases regarding the classification of particular laesions and the clinical consequences of a pathology diagnosis (that is not clearly benign) is there international consensus.

- *Atypical ductal hyperplasia (ADH)*
  Because a common criterion for ADH is based on the size of the abnormality, it is not possible in a strict sense to make the diagnosis ADH on the basis of a needle biopsy. Furthermore, there is substantial interobserver variation when diagnosing ADH and the abnormalities found in ADH fully correspond with those of DCIS grade I. Studies that have made use of the diagnosis ADH on the basis of a biopsy, have found percentages of additional DCIS of 18-87% with the use of 14G needles and 10-39% with the use of 9-11G needles. Invasive carcinoma has also been seen in approximately a quarter of these. There is a clear relationship between the mammographic image of the microcalcifications and pathology. If so-called ADH was found in biopsies in which all microcalcifications were removed, the underestimate rate (the chance of missing a DCIS with possible invasive component) was negligibly small. If ADH was diagnosed with less than 2 foci or with incomplete removal of an area smaller than 21 mm, the underestimate rate was 4%. With more than 2 foci and incomplete removal, the underestimate rate was 38%. If there were 4 foci or more, an underestimate rate of 87% was reported.
- *Cylinder cell laesions*
  These laesions may be encountered in biopsies of microcalcifications. Especially if there is cell atypia, the laesion may be associated with low-grade DCIS. The risk is comparable with atypical lobular hyperplasia and ADH.
- *Ductal Carcinoma in Situ*
  This is a malignant diagnosis, the underestimate rate in relation to invasive growth is 10-38%. The chance increased with high-grade DCIS, if comedo necrosis is seen or if the abnormalities is accompanied with a solid or palpable component. The chance of invasive carcinoma with low-grade DCIS is comparable to an LCIS found by accident.
- *Lobular neoplasia (Atypical Lobular Hyperplasia and Lobular Carcinoma in Situ)*
  These abnormalities usually do not have a radiological substrate and can therefore be considered chance findings. As a marker for increased risk of breast cancer, they do not need to be excised; mammographic follow-up is sufficient.
  Exceptions, for when excision should take place:
  - If they occur in combination with ADH (underestimate rate for DCIS and IDC increasing to 67%)
  - If they occur with macroacinar and pleomorphic morphology
  - If they occur in combination with microcalcifications that are highly suspect on a mammogram
- *Papillary laesions*
  There is an increased frequency in ADH and malignancy in both solitary papillomas and multiple papillomas or atypical papillomatosis. Frequencies are higher with multiple papillomas and atypical papillomatosis. The risk with a solitary papilloma may be underestimated because the core biopsies are difficult to evaluate due to the fragmented tissue and there may be sampling error. If the papilloma causes nipple discharge, there is a therapeutic reason for excision.

- *Radial scar/complex sclerosing laesions*
  The diagnosis radial scar may be made using histological biopsies. This abnormality is known to be associated with invasive (tubular) carcinoma or in situ carcinoma, especially with elderly patients and larger laesions. The underestimate rate varies from 0-12% and decreases with increasing number of biopsies (12 biopsies or more).
- *Fibroepithelial laesions*
  In rare cases, an LCIS, DCIS and even invasive carcinoma is described in a fibroadenoma [Kuijper, 2001]. Given the rarity, this does not have any consequences for the management plan for a typical fibroadenoma with concordant imaging. The laesions with suspected phyllodes tumour form a separate group. These fibroepithelial tumours have histological characteristics that fit with benign, borderline or malignant tumours. These characteristics play a role in the risk of recurrence, which is 15% on average. A malignant phyllodes tumour has a favourable prognosis. The primary treatment consists of ample excision [Telli, 2007].

Conclusions

Level 1	With the biopsy diagnosis: atypical ductal hyperplasia, atypical papillomatosis or radial scar (complex sclerosing laesion), there is a clinically significant chance of simultaneous malignancy. A1 Johnson 2009, Jacobs 2002

Level 2	The chance of concomitant malignancy with atypical ductal hyperplasia is correlated with the number and aspect of the microcalcifications on the mammogram. A1 Johnson 2009 B Burnside 2007

Level 2	Ample excision is necessary for complete evaluation of a phyllodes tumour. This is also necessary to prevent a recurrence. A1 Johnson 2009 B Telli 2007

Recommendations

The following pathological biopsy diagnoses can be considered clearly benign: If this corresponds to clinical findings and images, then no further action is required:

- hamartoma
- fibroadenoma
- tubular adenoma
- benign ductal hyperplasia
- sclerosing lobular hyperplasia
- fibro-cystous changes
- duct ectasias
- apocrine metaplasia
- adenosis
- pseudoangiomatous stroma hyperplasia
- normal or fibrous breast tissue

The following pathological biopsy diagnoses cannot be considered clearly benign:

- flat epithelial atypia/cylinder cell laesions
- atypical ductal hyperplasia
- atypical lobular hyperplasia and lobular carcinoma in situ
- papillary laesions
- radial scar/ complex sclerosing laesion
- phyllodes tumour

In the case of a diagnosis that is not clearly benign, the management plan must be determined in multisciplinary consultation. It must be based on:

- the number of biopsies and how representative the results are on which the pathology report is

based
- imaging: including the extent and level of suspicion of microcalcifications, the microcalcifications on the specimen radiogram and how many microcalcifications have remained behind
- patient factors: including age, familial burden, treatment preference, co-morbidity

Depending on the above, it can be decided in multidisciplinary consultation to repeat the biopsy, perform a diagnostic excision biopsy or mammographic follow-up. Routine follow-up with MRI is not indicated.

4.4 Processing of and reporting on breast and axilla resection samples

Processing of breast samples

Optimal fixation is of great importance in removing biopsies from resection surfaces, evaluation of the tumour and determination of optimal grading, hormone receptors and HER2.

Receiving fresh samples is obligatory for optimal processing and fixation. A protocol can then be followed in which the sample, after inking of the resection surfaces (preferably following convention with different colours), is cooled for a short duration (2 x 15 min. in aluminium foil at 20°C), lamellated in 3 mm thick slices and then fixed flat between gauze. In this manner, fatty lobate resection surfaces are also sliceable and able to be evaluated.

If samples cannot be delivered fresh due to local circumstances, the laboratory needs to ensure that it is possible for there to be sufficient fixing of tissue; cutting samples without inking resection surfaces is not acceptable because it hinders reliable evaluation of the resection surfaces. Especially slow fixation leads to unreliable immunohistochemistry and in situ hybridisation.

Processing of axillary samples

The surgeon should mark the sample (medial axillary top). At least 10 nodes may be found in a standard ALND. The node that is found closest to the top marking, is the top node; each sample therefore has an axillary top node.

Processing of the sentinel lymph node

See paragraph 4.8.

Recommendations

It must be ensured that resection samples are processed at such a pace that grading and receptor analysis is not influenced by poor fixation.

A specimen radiogram of the lamellated sample is strongly recommended for the purposes of efficient sampling in the case of:
- laesions with microcalcifications or assessment for DCIS
- macroscopically invisible tumour foci
- threatened surgical margins

Compulsory items in the pathology report of a resection sample:
- histological type according to WHO, invasive and in situ
- maximum tumour diameter, according to TNM 7th ed., invasive and in situ if applicable
- grading (invasive) according to modified Bloom and Richardson
- MAI
- ER status (positive if > 10% positive tumour cells, document the %)
- PR status (positive if > 10% positive tumour cells, document the %)
- HER2 status and technique used
- minimum tumour-free margin, both for invasive carcinoma and DCIS
- if non-radical: focal or more than focal, both for invasive carcinoma and DCIS
- the side with the narrowest margin or positive surgical margin
- with neoadjuvant therapy, see paragraph 4.10.

Compulsory items on the pathology report for an SN procedure:
- number of nodes
- number of positive nodes
- number with macro-, micrometastasis, isolated tumour cells

- any massive extranodal growth

Compulsory items on the pathology report for ALND:

- number of nodes
- number of positive nodes
- number with macro-, micrometastasis, isolated tumour cells
- any massive extranodal growth
- status of the axillary top
- with neoadjuvant therapy, see paragraph 4.8.

4.5 Determining the PT and tumour grade

Tumour diameter

Tumours are staged according to the TNM classification, 7th edition. The pT is the maximum diameter of the dominant invasive carcinoma foci. This measure is used for staging, determining the prognosis and therapy evaluation and also for the indication for additional therapy.
The pT is determined by measuring macroscopically recognisable tumour, preferably in the fresh sample. In the case of star-shaped radiating tumours, only the centre of the tumour should be measured. The macroscopic measure must be compared to the microscopic findings in a central cross-section of the tumour. The largest measurement should be taken as the pT. In the case of a stellate tumour, the diameter is determined by the bulk of the tumour and not by protrusions.
If there is multinodularity, the maximum diameter of the area with the nodes are measured as pT if there is confluence. If there are separate nodes that are separated by pre-existent node tissue, the diameter of the largest foci is taken as pT. Given the turning points for the indications for adjuvant therapy lie at 1, 2 and 3 cm, these measures should therefore be avoided as much as possible by exact measurements in mm.
A pT_4 tumour is when there is ulceration of the skin by the tumour, a peau d'orange, oedema of the skin, an inflammatory aspect of the skin, metastases in the skin or metastasis into the chest wall. Some of the skin changes cannot be evaluated well in a mastectomy sample and should therefore be reported by the clinic. When there is metastasis into the skin but the above skin changes are not present during pathological analysis, the tumour is classified on the basis of the dimensions (T_1,T_2,T_3). An *M. Paget* is not considered a pT_4 in itself. When determining the metastasis into the chest wall, the pectoralis major muscle is not to be included in the calculation. When metastasis into the muscle tissue only involves the pectoralis major muscle, the pT classification is determined by the dimensions.

Grading

Aside from the pT, the tumour grade is also used to determine the indication for adjuvant systemic therapy with pN_0. All invasive carcinomas may be graded using the modified Bloom and Richardson guidelines [Rakha, 2008]. It therefore also applies to infiltrating lobular carcinoma and *special* types such as medullary, tubular and mucinous carcinoma. The method consists of three components of the tumour morphology: the extent of tubule formation, the nuclear polymorphism and mitotic activity defined as the number of mitoses per 2 mm^2. In doing so, the number of fields of view to be counted differs; this depends on the size of the fields of view associated with the microscope. A score of 1, 2 or 3 is assigned to each of these components. The histological grade is determined by the sum of these scores.
Grading requires paraffin setions of well-fixed tissue.

Level of tubule formation:	1 = > 75 %
	2 = 10-75 %
	3 = < 10 %
Nuclear polymorphism:	1 = comparable to normal epithelium
	2 = enlarged, vesicular, small nucleoli
	3 = polymorphic, vesicular, large nucleoli
Mitotic activity:	1 = 0 through to 7 mitoses per 2 mm^2
	2 = 8 through to 12 mitoses per 2 mm^2
	3 = 13 or more mitoses per 2 mm^2

The histological grade is I for the scores 3-5, II for 6-7, and III for 8-9.

Tumour excision is necessary for reliable grading of carcinomas However, because neoadjuvant

chemotherapy is increasingly being applied and the indication for postoperative adjuvant systemic therapy is partly dependent on the tumour grade, the pathologist is regularly expected to make a pronouncement about the grade of the tumour according to the modified Bloom and Richardson from the needle biopsy taken prior to the neoadjuvant chemotherapy. This is possible to a limited degree given tumour heterogeneity and the chance of underestimating the mitosis index. However, a high level of concordance is possible for evident high-grade and low-grade laesions [Harris, 2003; Park, 2008].

MAI

The cut-off points of the MAI have been converted in the same manner as that of the Bloom and Richardson grading. The mitosis index is the most important factor in the histological grade. Incorporating MAI in the compulsory items / minimum data set ensures pathologists seriously count the mitoses. However, it is not necessary for this to be reported in the conclusion.

Recommendations

Tumour size must be determined according to the TNM classification, 7th edition.

All invasive carcinomas must be graded using the modified Bloom and Richardson guidelines.

4.6 Excision margin analysis with breast-conserving therapy; indications for additional surgery

Most recurrences after breast-conserving treatment develop as a result of metastasis of the residual tumour. Metastasis in surgical margins is one of the most important predictors of residual tumour [Bijker, 2006; Dunne, 2009; Scopa, 2006]. The evaluation of radicality therefore has important clinical-therapeutic consequences. The choices between breast-conserving therapy or mastectomy, for re-excision and/or adjusting the radiotherapy dose and field size, depends on the microscopic evaluation of the radicality. In doing so, it needs to be gauged if residual tumour has remained in the breast, or if it concerns an invasive carcinoma or DCIS, and/or if it involves a small or substantial amount. The distribution and density of ducts with DCIS play a role in estimating if and how much DCIS will have remained in the patient. Irradicality per se does not mean much; this should be:

- qualified: evaluate metastasis of both the invasive carcinoma and DCIS; report for both the minimum tumour-free margin in mm in various directions
- quantified: evaluate the extent of the irradicality in mm
- also localised, where possible: specify the side with the narrowest margin, or the irradicality

Naturally, surgical margin analysis is only reliable if the excision sample is submitted in toto, with markings, and adequately processed using inking of the surgical margins and samples are removed in a focused manner.

A re-excision or a mastectomy is only indicated if it is estimated on the basis of microscopic findings in the segment excision that a substantial residual tumour may have remained behind, that this will lead to an increased chance of recurrence, and that renewed surgery will reduce this chance. This is the case with:

- invasive carcinoma (or a DCIS component) that reaches more than focal into the surgical margin
- DCIS reaching into the surgical margin
- an – unsuspected – growth pattern with satellites, in which the microscopic tumour metastasis exceeds the estimated size during macroscopy and clinical imaging (especially with ILC and strongly diffuse growing IDC).

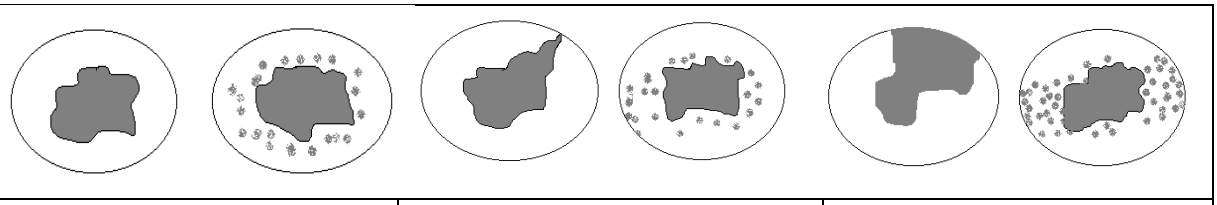
The margins are tumour-free if, in an adequately processed sample, tumour does not reach *into* any of the surgical margins. Unclear terms such as *close to* or *almost at* should be avoided. The chance of recurrence is only increased if there is evident metastasis in surgical margins.

There is focal metastasis in a surgical margin if the tumour (invasive carcinoma and/or DCIS) reaches into a limited area (≤ 4 mm) in an inked margin. This usually concerns one or more of the radiary extensions of a star-shaped carcinoma. In principle, this is *not* a requirement for renewed surgery. Local control can be achieved by adjusting radiotherapy fields and dosis.

If there is more than focal metastasis in a surgical margin, the tumour reaches into a larger area or multiple small areas in the inked resection margin. In most cases, it concerns metastatic DCIS.

Metastasis of LCIS in surgical margins is not an indication for renewed surgery, given this is generally a diffuse abnormality in which radicality is difficult due to limited excision, and the risk of recurrence with LCIS is limited. An exception to this is the polymorphic or comedo-type LCIS, which has a higher chance of local recurrence and is an indication for renewed excision.

Because it is difficult to define the terms *focal and more than focal* in an exact manner, the following diagrams have been provided for clarification:



Radical	Focal non-radical	Non-radical
→ Radiotherapy	→ Radiotherapy	→ Surgery

To reduce the risk of an invasive recurrence to an acceptable minimum, complete excision with a microscopically tumour-free margin is required during breast-conserving treatment of DCIS. The chance of recurrence depends on the width of the free margin [Silverstein, 1999].

Recommendations

The margins are tumour-free if, in an adequately processed sample, tumour does not reach *into* any of the surgical margins.

There is focal metastasis in a surgical margin if the tumour (invasive carcinoma and/or DCIS) reaches into a limited area (≤ 4 mm) in an inked margin.

The side with the smallest margin, or the irradicality must be specified.

4.7 Determining hormone receptor and HER2 status

In breast cancer treatment, analysis of oestrogen (ER), progesterone (PR) and HER2 receptors plays an important role in the adjuvant and metastatic setting. As a result, standardised receptor determination is of great importance. ER and PR are determined by means of immunohistochemistry of formalin-fixed and paraffin-embedded tumour material. Below are guidelines for the procedure of immunohistochemical staining, quality control and scoring method.

HER2 is an oncogene that is amplified in 10-15% of breast cancers. The gene codes for a membrane protein in the tumour cells. In tumours without HER2 amplification, there is usually a normal level of HER2 expression; in tumours with amplification there is usually a strong increase in expression of this protein. This has consequences for the choice of goal-oriented and conventional chemotherapy.

The determinations are performed on a representative cross-section of the tumour, and in addition any pre-existing breast tissue where possible; the material is formalin fixed and paraffin embedded. Specific requirements should be adhered to in determining the ER, PR and HER2 status, in terms of pre-analytical, analytical as well as postanalytical factors. The details fall outside the scope of this guideline.

Determining ER and PR

Scoring method

- the percentage of tumour cells with nuclear staining is estimated in the tens; the intensity is not included in the scoring method
- if the percentage is 10% or greater, the sample is referred to as ER or PR positive. ASCO recommends a threshold of 1% but there is little evidence for this
- if the ER or PR status of the tumour is negative, it is necessary to look for staining of normal epithelium of the lobs and ducts around the tumour if a proportion of the cells here stain, the negative result ER or PR may be issued; if there is no staining of normal lobs, the staining should be repeated, possibly on another sample.

Quality control and validation of the technique

- there should be a detailed staining protocol in writing, which is followed each time
- a (preferably weak) positive control should be included in each stain; if the positive control is negative or weaker than normal, the stain should be repeated
- the facility should participate in external audits to demonstrate sufficient quality of the staining technique; the SKML, NordiQC, and the UK-Neqas provide this service

HER2 analysis

There are indications that the intensity of the stain deteriorates if the section is not recent; for this reason, the stain must be performed within 2 months after a paraffin sample has been taken.

An in situ hybridisation for HER2 may be performed first, given false positive findings have been reported for HER2 to 12%, similar to immunohistochemistry [Perez, 2006].

Immunohistochemistry

Scoring method

Only membranous staining of invasive tumour cells must be evaluated as positive (in some cases there is cytoplasmic staining; this should not be included in the score).

A scoring system has been developed that categorises the stain as 0, 1+, 2+ of 3+; this system must be followed.

- 0: less than 10% of the tumour cells stain
- 1+: more than 10% of the tumour cells stain, in which there is no circumferential staining of all tumour cells and the colour intensity is weak
- 2+: more than 10% of the tumour cells display circumferential staining of tumour cells, in which the intensity of the stain is assessed as not more than moderate
- 3+: there is more than circumferential membranous staining in more than 30% of tumour cells, in which the intensity is assessed as strong

The area of the tumour with the strongest staining determines the score. There is normal expression of HER2 in tumours without amplification; this expression is usually too low to detect. If the normal lobs display membranous staining, the intensity of the entire stain is too strong and the result cannot be assessed as reliable.

Quality control and validation of the technique

- there should be a detailed staining protocol in writing, which is followed each time
- for each stain, a combination section of a negative, a 1+ and 3+ control should be included; if the positive control is negative or weaker than normal, the stain should be repeated. If the 1+ or negative control stains too strongly, the stain should also be repeated.
- the facility should participate in external audits to demonstrate sufficient quality of the staining technique; the SKML, NordiQC, and the UK-Neqas provide this service

HER2 amplification test

Given a proportion of the tumours with a 2+ staining results are still amplified, an amplification test must be performed in the case of a 2+ result. The international accepted methods for this are fluorescent *in situ* hybridisation (FISH), chromogenous *in situ* hybridisation (CISH) and a silver-based *in situ* hybridisation (SISH). Some laboratories use the Dutch MLPA (PCR-based) technique.

Some in situ kits also use the chromosome 17 centromere probe, of which the benefit is being debated. This *dual colour* ISH is scored as follows:

- Ratio HER2/centromere chromosome 17 < 1.8: no HER2 amplification
- Ratio HER2/centromere chromosome 17 > 2.2: wel HER2 amplification
- Ratio HER2/centromere chromosome 17 1.8-2.2: inconclusive for HER2 amplification (then repeat with another test)

If *in situ* hybridisation is performed without a centromere probe (e.g. CISH), the cut-off for HER2 low level and high level amplification is >6 and >10 copies of the HER2 gene or clusters respectively.

Recommendations

ER, PR and HER2 status of invasive tumours must be determined an assessed according to a standardised protocol.

The facility should participate in external audits for ER tests, PR tests and HER2 immunohistochemistry and amplification (e.g. SKML, NordiQC, UK-Neqas) to demonstrate sufficient quality of the staining technique.

4.8 Staging by means of the SN procedure and/or ALND

In the past, ALND was a fixed component of the treatment of operable invasive breast cancer. The axillary node status is an important prognostic indicator and was important in selecting adjuvant systemic therapy. In addition, the dissection formed part of local therapy. In the SN procedure, one or more nodes that are the first to drain lymph fluid from the tumour are selectively removed. The SN status predicts the chance of further axillary node metastasis and therefore determines the indication for axillary node dissection.

Given the importance of the SN status in deciding whether or not to treat the axilla, these nodes are more extensively assessed than normal, using serial sectioning and immunohistochemistry. In the different series on results of SN analysis there are large differences in processing, especially in the number of levels and the interval between each. It is clear that there is a direct relationship between the chance of tumour in the SN and the extensiveness of the analysis. A choice must be made between general feasibility and effectiveness of SN processing.

SN frozen section analysis

Frozen section analysis may be performed if desired, in which the SN should be sectioned carefully (to prevent loss of material) until a full central cross-section is obtained. The sensitivity of the frozen section is approximately 75% at a specificity of almost 100% [Jensen, 2010; Tille, 2009].

SN processing

The following is recommended for processing of the SN for purely pragmatic reasons:

- completely include lymph nodes to 0.5 cm; half lymph nodes greater than 0.5-1.0 cm lengthwise and imbed both halves in such a way that the centre side is sectioned; fully imbed nodes greater than 1 cm in lamellas.
- the paraffin blocks are sectioned at least at 3 levels with a 250 µm interval; one section of each level undergoes HE staining. Immunohistochemical analysis with antibodies against keratin (CAM5.2 or AE1/AE3) is added to this in case of HE-negative SN. For practical reasons it may be handy to perform immunohistochemistry immediately [Jensen, 2010; Tille, 2009].
- In practice, this means that almost all SN are halved and therefore sectioned at least at 6 levels

SN reporting

In relation to reporting of SN status, it is recommended that the following categories are used:

- SWK tumour-free (pN_0 (i-) (sn)).
- SWK with isolated tumour cells (ITC; solitary cells or cell clusters smaller than or equal to 0.2 mm) (pN_0 (i+) (sn)).
- SN with micrometastasis (a focus > 0.2 mm and ≤2 mm or in total more than 200 cells) (pN_1(mi)(sn)).
- SN with macrometastasis (greater than 2 mm) (pN_1 (sn)).

ALND reporting

In relation to reporting on ALND, it is recommended that the following items are mentioned:

- number of lymph nodes analysed
- number of nodes with metastases and the type of metastases (macro- (>2 mm), micro- (>0,2 -≤2 mm), ITC (≤ 0,2 mm)).
- status of the medial axillary top node
- any convolutes present
- metastasis of the tumour in the perinodal fatty tissue and, if applicable, if a resection margin is threatened

Criteria for distinguishing ITC and micrometastasis

Decision tree for distinguishing between ITC/pN_0(i+) and micrometastases/pN_1mi according to the seventh edition of the TNM classification (Cserni, 2011).

- Distance between cells/clusters, localisation in the sinus or parenchyma or metastasis outside the lymph node do not influence classification

- A cluster is a confluent focus of tumour cells in contact with other tumour cells. However, tumour cells separated by desmoplastic/fibrotic stroma are interpreted as confluent
- The upper threshold of 0.2 mm is used for clusters and 200 cells as the upper threshold for discohesive cells or almost cohesive clusters

Extensive extranodal growth

There is extensive extranodal growth if there is such a level of tumour growth in the axillary fat, that there is doubt about the radicality at the location of the axilla. In that case, there is an indication for post-irradiation of the axilla.

Recommendations

SN's must be analysed at least at 3 levels for the presence of tumour cells; if morphologically negative, also with the aid of keratin staining

SN and ALND are recorded using the TNM classification, 7th edition.

The status of the axillary top node must be reported separately.

Extensive extranodal growth must be reported.

4.9 Minimum criteria for the diagnosis DCIS – dd. invasive carcinoma

There are many classifications for DCIS. It is recommended to use the classification that is in line with that for invasive carcinoma. In doing so, lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS) are distinguished. On the basis of cytonuclear and architectural characteristics, DCIS is subdivided into good, moderate and poorly differentiated types, which form the precursors of invasive carcinomas with grade I, II and III. Well-differentiated DCIS is recognised by the micropapillary or cribriform architecture with cells with a quite clearly cubic or cylindric cytoplasma so that the small regular round nuclei do not overlap each other. There is little to no mitotic activity and apoptosis, and there is at the most minimal necrosis. Poorly differentiated DCIS is characterised by enlarged, polymorphic nuclei, evident mitotic activity, apoptosis, and often central necrosis in largely solid epithelium [Holland, 1994]. Moderately differentiated DCIS is inbetween this.
It is not always easy to distinguish hyperplastic cylinder cell laesions from well-differentiated DCIS [van de Vijver, 2003]. Especially cylinder cell laesions with atypia in a needle biopsy appear to be associated with DCIS in a subsequent resection or in the follow-up [Verschuur-Maes AH, 2011]. The WHO uses the term *flat epithelial atypia* for these laesions.

There is no consensus on the minimum size of the laesion in order to speak of well-differentiated DCIS. For practical considerations, the term *atypical ductal hyperplasia* (ADH) can be used to denote completely excised well-differentiated DCIS of a small size; arbitrarily, a maximum size of 3 mm can be used. A distinction cannot be made between well-differentiated DCIS and ADH on the basis of histogenetics. In addition, a large interobservervariation has been described as to whether a laesion can or cannot be classified as ADH. See also 4.1.3: management plan for women with a not clearly benign laesion.

In the case of DCIS, it is not possible to exclude invasion with certainty; DCIS without invasion is a diagnosis per exclusionem. For treatment purposes, distinguishing pure DCIS and DCIS with invasive carcinoma is of great importance, especially in relation to the need for axillary staging/treatment. A meta-analysis has found that DCIS patients with a positive SN never have metastases in other axillary nodes. The WHO and TNM classifications use a threshold of 0.1 cm to distinguish micro-invasive carcinoma from macro-invasive carcinoma (pT_1mic). In relation to the prognosis and therapeutic consequences (chance of axillary node metastases), this threshold is less critical, and morphologically difficult to apply; in many cases of DCIS, the boundaries of ducts are not sharp due to reactive fibrosis and lymphocytary infiltrates. For this reason, it is recommended to only diagnose invasion if the following criteria are met:

- tumour focus with the usual morphology of invasive carcinoma
- the tumour focus lies outside the loose periductal/lobular stroma

Excluding invasion requires adequate sampling; laesions smaller than 4 cm should be included fully and for more extensive ones at least 10 blocks with the laesion, preferably on the guidance of a specimen lamellogram. An invasive carcinoma focus is sometimes not found, while there are evident

tumour emboli in the vessels (especially with invasive micropapillary carcinomas). In this case, treatment should follow that of invasive carcinoma.

Recommendations

To exclude invasion in the case of DCIS, laesions smaller than 4 cm should be included fully; for more extensive laesions at least 10 blocks with the laesion, preferably guided by a specimen lamellogram.

The term *atypical ductal hyperplasia* (ADH) can be used to denote well-differentiated DCIS of a small size; arbitrarily, a maximum size of 3 mm has been chosen.

It is recommended to only diagnose invasion if the following criteria are met:

- a tumour focus with the usual morphology of invasive carcinoma
- the tumour focus lies outside the loose periductal/lobular stroma

4.10 Evaluation after neoadjuvant chemo- or endocrine therapy

Evaluation of samples after neoadjuvant therapy serves to determine the level of response, amongst other things. Adequate marking to orientate the sample in relation to the location where the tumour is or was is therefore essential. Lumpectomy samples are processed as described above. Relatively small lumpectomy samples (arbitrarily to approximately 30g) are fully included, sections are taken from larger samples and mastectomy samples on the guidance of macroscopic findings and additional information from imaging research. To determine a pathological complete response (pCR), ample sampling (at least 1 sample per cm tumour and samples in relation to the surgical margins) of the tumour bed is necessary. The sampling should be repeated if necessary. Only the invasive tumour is analysed to determine a pCR, DCIS is not considered. One speaks of a partial response when invasive tumour is encountered with regressive changes such as fibrotic scar tissue with lymphoid infiltrates, groups of foam cells or loss of node tissue. Remaining pathological parameters (size, surgical margins etc.) are determined as outlined above. The scoring system according to EUSOMA is applied to determine the response:

Response in the breast:

1.	*Complete pathological response,* either (i) no residual carcinoma or (ii) no residual invasive carcinoma but DCIS present.
2.	*Partial response to therapy,* either (i) minimal residual disease/near total effect (e.g. only a few loose tumour cells or tumour cells located in small groups) or (ii) evidence of response to therapy but with 10-50% of tumour remaining or (iii) >50% of tumour cellularity remains evident, when compared to the previous core biopsy sample, although some features of response to therapy are present (e.g. fibrosis).
3.	*No response*: no evidence of response to therapy.

Response in the lymph nodes:*

1.	No evidence of metastatic disease and no evidence of therapy-related changes in the lymph nodes.
2.	Metastatic tumour not detected but evidence of response/down-staging, e.g. fibrosis.
3.	Metastatic disease present but also evidence of response, e.g. nodal fibrosis.
4.	Metastatic disease present without evidence of response to therapy.

*: When there is a mixture of categories, e.g. 1 node with a metastasis showing no response and 1 node showing fibrosis, the worst category should be used.

Recommendations

Biopsies to 30 gram must be fully submitted; for larger samples, at least 1 section per cm of tumour or tumour bed must be submitted on the basis of macroscopy and/or specimen lamellogram.

Compulsory items in the pathology report of a resection sample after neoadjuvant chemotherapy:

- Maximum tumour diameter, invasive and / or in situ. (if present)
- Maximum diameter fibrotic area (if present)
- Distance of tumour to nearest resection margin (if applicable)
- Response to pretreatment according to EUSOMA
- Number of lymph nodes, number of lymph nodes with metastasis and lymph node response to pretreatment according to EUSOMA

Compulsory items that should be determined using the needle biopsy taken prior to neoadjuvant chemotherapy:

- histological type according to WHO
- grading according to the modified Bloom and Richardson
- ER, PR and HER2 status

Optional items that may be determined using the needle biopsy taken prior to neoadjuvant chemotherapy:

- presence or absence of angio-invasion
- presence or absence of in situ component

Risk profiling

Clinical question, evidence-based update to autumn 2010, consensus-based update to summer 2011

The goal of adjuvant systemic treatment is to prevent distant metastasis. A good selection of patients who will benefit from adjuvant treatment is important in view of side-effects and costs of these therapies. Risk profiling or prognosis stratification involves distinguishing patients with a good prognosis from patients with a poor(er) prognosis, with the aim of only selecting those patients who benefit from treatment. However, identification of patients with a good prognosis who do not need adjuvant therapy, does not imply that all patients with a poorer prognosis will not benefit from adjuvant therapy.

5.1 Prognostic factors

There are various classification systems to estimate the chance of metastasis and death of individual patients. The main ones are the Nottingham Prognostic Index (NPI) [Galea, 1992], the St. Gallen classification [Goldhirsch, 2006; Goldhirsch, 2007; Goldhirsch, 2009] and *Adjuvant!* (www.adjuvantonline.com). All these classification systems are based on traditional prognostic factors, including tumour size, lymph node status and tumour grading. In addition, the St. Gallen classification also uses age at time of diagnosis, the number of positive lymph nodes, oestrogen receptor status, the presence of peritumoural vascular invasion and overexpression of HER2. Furthermore, *Adjuvant!* offers the possibility of taking the presence of comorbidity into account at the time of diagnosis when making the prediction.

The prognostic value of the abovementioned traditional prognostic factors, as has been incorporated in the NPI, the St. Gallen classification and *Adjuvant!* has been found to be reproducible in large, independently conducted studies with unselected, non-overlapping patient populations [Boyages, 2002; Boyages, 2006; Colomer, 2004; Lundin, 2006; Olivotto, 2005]. It appears that improvement in the prognostic value of the NPI by addition of other variables such as progesterone receptor and HER2 is possible, but has not been validated [van Belle, 2010]. A side note with the St. Gallen classification system is that a disproportionate number of patients in the various validation studies with negative lymph nodes (> 70%) are classified as *intermediate risk* or *high risk* and are therefore eligible for adjuvant systemic therapy [Boyages, 2002].

Compared to other risk classification systems, *Adjuvant!* offers the advantage that an estimation is made per patient in the reduction in risk of death and risk of recurrence that may be realised with the prevailing medication-based treatments. These estimates are derived from the meta-analyses of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). In this manner, it is a valuable aid in the advising of and decision-making with the patient. The system also provides the possibility to modify estimations on the basis of additional prognostic information, including HER2 status or angioinvasive growth, for example. The risk estimations in *Adjuvant!* are based on data from several tens of thousands of patients from the Merican Surveillance, Epidemiology and End Result (SEER) registration [Ravdin, 2001]. The predictions of the system have been validated in an independent population-based series of 4,083 Canadian patients [Olivotto, 2005]. The predictions appeared to be largely accurate, with the exception of women under 35 years of age, where the estimation by *Adjuvant!* of the absolute breast cancer-related risk of death was approximately 10% too low. Partly on the basis of these findings, the predictions in *Adjuvant!* for women under 35 years of age have been adjusted. In a group of 5,380 patients in the Netherlands with a median follow-up of 11.7 years, the prediction of 10-year total survival and specific survival with *Adjuvant!* was found to be accurate, with the exception of a too low estimation in the risk of death by 4% for patients under 40 years of age, despite an earlier adjustment on the basis of the Canadian study [Mook, 2009].

Conclusions

Level 2	The prognostic value of the traditional prognostic factors, as incorporated in the Nottingham Prognostic Index, the Sankt Gallen classification and *Adjuvant!*, has been found to be reproducible in large, independently conducted studies. B Boyages 2002, Boyages 2006, Colomer 2004, Lundin 2006, Olivotto 2005, Mook 2009

Remaining considerations

Aside from traditional prognostic factors such as tumour grading, tumour size and lymph node status, numerous other tumour characteristics have been studied for their prognostic value. Factors that have also been found to be of significance in prospective study designs in predicting the prognosis of patients with a lymph node negative breast cancer are the presence of epithelial cancer cells in bone marrow, urokinase-type plasminogen activator (uPA) and the inhibitor of this (PAI-I). However, execution and standardisation of the technique to determine these factors is laborious. The Ki67/MIB1 index is an immunohistochemical proliferation variable with good prognostic value [Yerushalmi, 2010; Azambuja, 2007]. In terms of the histological grade, it has become clear that actually only the mitotic activity expressed as the MAI component of this has prognostic value [Abdel-Fatah, 2010; Genestie, 1998; Le Doussal, 1989]. The MAI has been validated in various prospective studies in the Netherlands for different subgroups [Baak, 2005, 2007, 2008, 2010].

5.1.1 Adjuvant systemic therapy in patients with micrometastases or isolated tumour cells in the sentinel lymph node

As outlined in section 3.3, many observational studies have shown the prognostic importance of the presence of micrometastases and isolated tumour cells in the axillary nodes and/or SN. A few retrospective studies have evaluated the benefit of adjuvant systemic treatment in patients with micrometastases or isolated tumour cells in the SN. In a large study in the Netherlands, 995 patients with micrometastases or isolated tumour cells and treated with adjuvant systemic therapy (hormonal therapy and/or chemotherapy) were compared to 856 patients with micrometastases or isolated tumour cells and not treated with such adjuvant therapy [de Boer 2009]. In this non-randomised study, an increase in the five-year disease-free survival was found for both patients with micrometastases and patients with isolated tumour cells after treatment with adjuvant systemic therapy (corrected HR: 0.50; 95%CI 0.35-0.72 and 0.66 95%CI 0.46-0.95 respectively). It should be noted that there was a combined endpoint in relation to local, regional and distant recurrences.

Conclusion

Level 3	There are indications that the presence of micrometastases or isolated tumour cells has a negative influence on the disease-free survival with a hazard ratio of 1.5 at a median follow-up of 5 years and that the relative risk reduction in relation to the disease-free survival with adjuvant systemic treatment in this group of patients is no different than in the general breast cancer population. B de Boer 2009

Remaining considerations

Few studies have been reported in which the effect of systemic therapy in patients with isolated tumour cells or micrometastases has been reported separately . The prognostic importance of micrometastases and isolated tumour cells is described in a recent meta-analysis of studies prior to the SN age, and more recently in studies in which patients underwent a SN procedure. The different studies report a hazard ratio of approximately 1.5 in multivariate analyses corrected for a number of primary tumour characteristics. The recurrence percentage was reduced with additional systemic therapy, comparable to the effect with larger tumours.

Recommendations

When deciding whether or not to prescribe systemic therapy in the presence of micrometastases or isolated tumour cells, correcting the risk of recurrence may be considered when using *Adjuvant!* with a factor of 1.5 (confidence interval of 1.15 – 2.13), if "0' is entered for the node status. Parallel to this, the predicted benefit in relation to the recurrence-free survival of systemic therapy will somewhat increase.

Too little is known to make a recommendation on the effect on survival.

5.2 Gene expression profiles

On the basis of patterns of gene expression, breast cancer may be subdivided into different molecular subtypes. In doing so, it has also been found possible to define prognostic profiles on the basis of gene expression profiles. These profiles include the MammaPrint® 70 gene profile or *Amsterdam signature* [van 't Veer, 2002; van de Vijver, 2002], the MammaPrint® 76 gene profile or *Rotterdam signature* [Wang, 2005] and the 21 gene profile or Oncotype DX™ panel [Paik, 2004; Paik, 2006]. This

is determined using real-time quantitative reverse transcription polymerase chain reaction (RT-PCR) in fixed tumour tissue from tissue blocks (Oncotype DX) or via DNA microarray analysis of fresh (frozen) tumour tissue (MammaPrint, Rotterdam signature), in which the activity of multiple genes in the tumour is studied. So instead of looking at tissue structures, tissue synthesis and the proteins involved, current analysis looks at the expression of selected genes measured by the amount of RNA present. The sets of genes on which these tests are based fall largely in the gene clusters of the oestrogen response and proliferation. The set of 70 genes of the MammaPrint was identified from more than 25,000 unselected candidate genes in 78 patients with $T_{1-2}N_0$ (both ER positive and negative) invasive breast cancer under 55 years of age (largely not treated with adjuvant therapy) [van 't Veer, 2002]. On the basis of the correlation with an average expression profile, a classification was made in a high or low risk profile. For Oncotype DX is derived from 250 previously selected genes to eventual 21 genes (16 cancer-related and 5 reference genes) chosen in order to determine a 10-year breast cancer recurrence [Paik, 2004]. The recurrence score (RS) was calculated on a scale of 0 to 100, with a subdivision in low risk (RS <18), intermediate risk (RS 18-30) and high risk (RS >30). This test was initially applied to 668 postmenopausal patients with N0, ER positive breastcancer who were treated with tamoxifen (NSABP B 14)

5.2.1 Prognostic value

It has been demonstrated for a number of gene expression profiles that they are significantly better at distinguishing the subgroups with a favourable or unfavourable prognosis than traditional systems based on clinical and histological parameters [van de Vijver, 2002]. The MammaPrint placed 40% of the N_0 patients in the right prognosis group; only 15% would fall in the group with a low risk according to the St. Gallen criteria. In the meantime, the MammaPrint has been validated in retrospective studies in both lymph node negative [Buyse, 2006; Bueno-de-Mesquita, 2009] and lymph node positive patients (1 to 3 lymph node metastases) [Mook, 2009], with postmenopausal N_0 patients of 55 to 70 years of age [Mook, 2010], with HER2 positive breast cancers [Knauer, 2010] and small T_1 tumours [Mook, 2010]. Compared to the traditional risk estimations, the MammaPrint is a more accurate prognostic instrument in these retrospective studies. In the prospective RASTER study, implementation of the MammaPrint was possible in 16 hospitals in the Netherlands [Bueno-de Mesquita, 2007]. The MammaPrint classified 208 (49%) of 427 N_0 patients in the poor prognosis group, while this was 69% according to *Adjuvant!*, 83% according to the St. Gallen guidelines and 42% according to the NPI (a disconcordance in 37%, 39% and 27% respectively).

The 76-gene profile has been validated in 2 studies with 378 N_0 patients who had not received adjuvant systemic therapy [Foekens, 2006; Desmedt, 2007]. The ten-year recurrence-free survival was 94% in the good prognosis group, versus 65% in the poor prognosis group [Foekens, 2006].

The 21-gene profile of Oncotype DX was validated in 651 N_0 ER+ patients who were treated with tamoxifen in the NSABP B20 trial [Paik, 2006]. In a case-control study with 790 ER+ N_0 patients, the ten-year recurrence-free survival of the low, intermediate and high-risk group was 97%, 89% and 84% respectively in patients treated with tamoxifen only [Habel, 2006]. Validation of this profile in a subgroup of 1,231 postmenopausal patients from the ATAC trial confirmed the prognostic value of this profile for both N_0 and N+ ER+ breast cancer, treated with tamoxifen or anastrazole [Dowsett, 2010].

The 21-gene profile of Oncotype DX has been specifically developed with ER+ breast cancer, and therefore not tested with ER disease. All these gene expression studies largely studied patients with invasive ductal carcinoma.

5.2.2 Predictive value

Knauer [2010] conducted a pooled retrospective analysis of 7 studies on adjuvant therapy in 541 patients. In the high-risk group, as determined using MammaPrint, a better metastasis-free five-year survival of 88% was found in the group treated with chemotherapy followed by hormonal therapy, versus 76% in the group treated with hormonal therapy only. The predictive value of the MammaPrint for the effect of adjuvant chemotherapy has not yet been proven with this retrospective non-randomised study with different chemotherapy regimens. In a subgroup of the NSABP B20 trial, in which N_0 ER+ patients were randomised between tamoxifen and tamoxifen plus chemotherapy, chemotherapy was only found to provide an advantage (by means of Oncotype DX) in patients with a high recurrence score (>30) (RR 0.26; 95%CI 0.13-0.53) [Paik, 2006]. At a low and intermediate RS, no advantage was seen with chemotherapy above tamoxifen only (RR 1.31; 95%CI 0.46-3.78 and RR 0.61; 95%CI 0.24-1.59, respectively). In a similar retrospective analysis of postmenopausal N+ ER+ patients, an advantage with adjuvant CAF chemotherapy was only seen in the group with a high RS [Albain, 2010]. While no advantage of chemotherapy could be found in the low and intermediate RS groups, a clinical advantage cannot be directly excluded given the large confidence intervals in these

groups. The predictive value of the gene profile has not been prospectively researched with newer therapeutic modalities such as aromatase inhibitors, other chemotherapy agents or trastuzumab.

Conclusion

Level 2	It has been demonstrated for a number of gene expression profiles in retrospective studies that they are better at distinguishing subgroups with a favourable or unfavourable prognosis than traditional risk estimations. B Buyse 2006, Chang 2003, Desmedt 2007, Foekens 2006, Huang 2003, Paik 2004, Paik 2006, Sotoriou 2003, van 't Veer 2002, van de Vijver 2002, Wang 2005, Bueno-de-Mesquita 2009, Mook 2009, Mook 2010, Dowsett 2010

Remaining considerations

Of the abovementioned gene expression profiles, only the MammaPrint is currently commercially available in the Netherlands. The Food and Drug Administration approved the marketing of MammaPrint in 2008. Insurers in the United States still consider the use of MammaPrint experimental. No studies are available as yet that describe the clinical results of applying MammaPrint. The MINDACT trial is a prospective randomised multicentre study in which patients with a discordant outcome for MammaPrint and clinical risk estimation according to *Adjuvant!* are randomised for following the outcome of either MammaPrint or clinical risk estimation. Inclusion for this study ended on 1 July 2011. In the American TAILORx study, N_0 ER+ patients and an intermediate risk according to the Recurrence Score were randomised between chemotherapy followed by hormonal therapy or hormonal therapy only. The results of these studies will become available in a number of years.

The St. Gallen international expert consensus panel states that validated gene expression profiles can be used as a supplement to *state of the art* histopathology, if there is doubt about the indication for adjuvant chemotherapy on the basis of traditional prognostic factors [Goldhirsch, 2009].

Recommendations

Adjuvant! (www.adjuvantonline.com) is a validated instrument for predicting the prognosis of individual patients and predicting the reduction in absolute risk of recurrence and death by adjuvant systemic therapy. For this reason, the recommendations for adjuvant systemic treatment in this guideline have been based on the tables generated with *Adjuvant!*.

Validated gene expression profiles may be used in individual cases with a *hormone sensitive invasive ductal carcinoma*, if there is doubt about the indication for adjuvant chemotherapy on the basis of traditional prognostic factors.

Adjuvant systemic therapy

Adjuvant systemic chemotherapy and/or endocrine therapy is administered as a supplement to primary locoregional treatment, with the aim of eliminating any distant metastases (occult metastases) that may be present but cannot be detected yet. Many large randomised studies and a few important meta-analyses have shown that this form of treatment provides a clear contribution to the chance of curation of women with an early stage breast cancer [EBCTCG, 2005]. The axillary lymph node status, the tumour size and grade, the age of the patient, and presence of HER2 overexpression are important for determining the risk of metastases. Aside from these classic prognostic factors, much research has been done in recent years on promising new prognostic factors that use the genetic profile of the tumour, enabling better characterisation of biological behaviour.
Each patient with a pimary operable breast cancer can, in principle, benefit from treatment with adjuvant systemic therapy. However, the chance of occult metastases is not the same for each patient. Risk profiling is necessary to distinguish patients with a good prognosis from patients with a poor(er) prognosis, with the aim of tailoring adjuvant therapy recommendations to the estimated prognosis (see Chapter 5: risk profiling).

In the past, treatment with adjuvant systemic therapy was recommended with an expected absolute ten-year survival advantage of at least 5%. The threshold for using adjuvant treatment was then placed at a ten-year chance of mortality of 20% or more, because the meta-analysis of the EBCTCG globally showed a 25% relative risk reduction in death with the adjuvant systemic therapies that were available at the time.

However, the effectiveness of current chemotherapy and hormonal therapy is greater. It appears from data from the meta-analysis of 2000 (published 2005) that the 15-year relative risk reduction in death by anthracycline-containing chemotherapy, tamoxifen or the combination of both modalities is 20-57% (see below table).

Adjuvant systemic therapy is recommended if the absolute risk of a ten-year mortality is 15% or more. With the above mentioned relative reductions in the chance of death, the absolute chance of death is subsequently reduced by 4-5% for most categories of patients. For the chance of recurrence, the minimum condition is an absolute reduction of 10%. With current adjuvant treatments, this is almost always achieved at a chance of recurrence of 25% or higher.

There are various guidelines that may help with the treatment decision: St. Gallen, NCCN, and ASCO guidelines. The drawback is that none of these guidelines gives a quantitative impression of the (disease-free) survival advantage that can be expected for the treatment selected. In the programme *Adjuvant!*, an estimation is made of the prognosis and the effect of different treatment possibilities using patient and tumour-related characteristics [Ravdin, 2001]. The program is validated in different large datasets, which can be found at (www.adjuvantonline.com) [Olivotto, 2005]. The basis of this database is formed by SEER (Surveillance, Epidemiology and End Results) data with cancer-specific survival and recurrence curves based on data from the United States. The relative advantage through reduction in the risk of recurrence and death is derived from meta-analysis of the EBCTCG and has been processed in these curves, in order to arrive at age and tumour characteristic-dependant risk estimations.

The programme distinguishes three categories of chemotherapy schedules:

- First generation schedules are 6 courses of CMF and 4 courses AC
- Second generation schedules are 6 courses CAF, 6 courses $FE_{100}C/CE_{120}F$, 4 courses AC followed by 4 courses paclitaxel, and 4 courses TC (docetaxel, cyclophosphamide)
- Third generation schedules are 6 courses TAC, 3 courses $FE_{100}C$ followed by 3 courses docetaxel, 4 courses AC followed by 4 courses docetaxel or 12 courses paclitaxel weekly and dose-dense (q 2 weeks) 4 courses AC followed by 4 courses paclitaxel

The second and especially third generation schedules have largely been studied with N+ patients.
From the hormonal interventions, tamoxifen or the combination of tamoxifen with ovarian ablation have been considered as equally effective in the premenopausal patient. For the postmenopausal patient, tamoxifen is considered as the *first generation* endocrine therapy and treatment with an aromatase inhibitor or the sequential treatment of tamoxifen followed by an aromatase inhibitor or an aromatase inhibitor followed by tamoxifen for a period of 5 years is considered as the *second generation* endocrine therapy.

The risk of death for HER2 overexpression and survival advantage for treatment with trastuzumab have not yet been included in *Adjuvant!*. In this guideline, the choice whether or not to undergo adjuvant treatment is based on the tables associated with this program, and for a large part corresponds with the 2011 St. Gallen criteria.

Eligible for treatment are:

- all patients with N+ tumours, or
- an unfavourable N_0 tumour:
  - age < 35 years except a grade I tumour ≤ 1cm
  - age ≥ 35 years with a tumour of 1,1-2 cm and ≥ grade II *or* with a tumour > 2 cm
  - if there is HER2 overexpression in a tumour ≥ 0.5 cm independent of other characteristics, systemic therapy may also be considered

Adjuvant treatment and age at diagnosis (year)	Proportional effect on annual breast cancer mortality (therapy vs. control)		15-year breast cancer mortality (M) with treatment (risk (%) and absolute advantage (%)) versus corresponding risk without treatment					
	Hazard Ratio	Proportional reduction	M=12.5 (e.g. low risk N_0)		M=25 (e.g. N_0)		M=50 (e.g. N+)	
			Risk	Advantage	Risk	Advantage	Risk	Advantage
Chemotherapy for ER- and ER+ breast cancer								
Gone (all ages)	1,00	…	12,5	…	25,0	…	50,0	…
Anthracycline (< 50 years)	0,62	38%	7,9	4,6	16,3	8,7	34,9	15,1
Anthracycline (50 - 69 years)	0,80	20%	10,1	2,4	20,6	4,4	42,6	7,4
Anthracycline (≥ 70 years)	?	?	?	?	?	?	?	…
None (all ages)	1,00	…	12,5	…	25,0	…	50,0	…
Tamoxifen (all ages)	0,69	31%	8,8	3,7	18,0	7,0	38,0	12,0
Anthracycline + Tamoxifen (< 50 years)	0,62 x 0,69	57%	5,6	6,9	11,6	13,4	25,7	24,3
Anthracycline + Tamoxifen (50 - 69 years)	0,80 x 0,69	45%	7,1	5,4	14,7	10,3	31,8	18,2
Anthracycline + Tamoxifen (≥ 70 years)	? x 0,69	?	?	?	?	?	?	?

Effectiveness of treatment with anthracycline-containing chemotherapy (6 months), tamoxifen (5 years), or both on the fifteen-year mortality rate due to breast cancer (%) in relation to ER status, age and underlying risk (10-15%, 25%, or 50%) [EBCTCG, 2005].

So far, most studies have been conducted in the general breast cancer population, in which the molecular heterogeneity of the disease has not been taken into account. On the basis of retrospective studies, hormone receptor status has been used as a guide for hormonal therapy since 2000. Developments are underway to develop tests using molecular techniques that may lead to a more personalised treatment. A good example of this is determining HER2 overexpression in order to identify the group of patients who would benefit from the addition of trastuzumab to chemotherapy. In the future, tests might become available indicating who will benefit from anthracyclins and who will benefit from taxanes.

6.1 Chemotherapy

6.1.1 Anthracycline-containing chemotherapy

Meta-analyses of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) show that chemotherapy improves the disease-free and total survival of all patients with an early stage breast cancer [EBCTCG 2005, 2008, 2010]. The therapy results in the meta-analysis are expressed in the annual reduction in RR of death and ultimate absolute ten or fifteen-year survival advantage. Treatment with 6-9 courses of anthracycline-containing chemotherapy reduces the RR of death from breast cancer, by approximately 38% per year for women under 50 years of age and approximately 20% per year for women who are 50-69 years. The reduction in RR of recurrence or death in these studies is largely independent of the hormone sensitivity of the tumour, tamoxifen use, node status and other tumour characteristics. The anthracycline-containing chemotherapy schedules are more effective than the CMF (C: Cyclophosphamide, M: Methotrexate, F: 5-Fluorouracil) regimes and resulted in a significant reduction in the recurrence rate (HR 0.89; 2p=0.0001) and death (HR 0.84; 2p<0.00001) compared to the CMF schedule [EBCTCG, 2005].

Adjuvant chemotherapy and hormone receptor status of the tumour

A few retrospective studies have shown that postmenopausal patients with a hormone-sensitive (HR+), early stage breast cancer (node negative (N_0) and node positive (N+) patients with metastasis in 1-3 nodes), only experience a limited absolute advantage with the addition of chemotherapy to standard treatment with tamoxifen [Colleoni, 2005; Pritchard, 1997; LBCSG, 1984; Goldhirsch, 1990; Fisher, 1997; Fisher, 2004; Albain, 2004; Berry, 2006; Wils, 1999; Fargeot, 2004; Namer, 2006; Conforti, 2007; Albain, 2009]. The same finding was made in the small IBCSG 11-93 study in low-risk N+ premenopausal patients with a hormone-sensitive tumour. Addition of 4 courses of A/EC chemotherapy to tamoxifen in combination with suppression of the ovarian function did not show an improvement in survival [Thurlimann, 2009]. In a retrospective analysis, the programme *Adjuvant!* also overestimated the effects of chemotherapeutic treatment added to combination hormonal therapy with tamoxifen and suppression of the ovarian function in premenopausal patients with an ER+, N+, low-risk breast cancer [Paridaens, 2010; Cufer, 2008]. However, most of these studies used first or at the most second generation chemotherapy schedules.

Studies with neoadjuvant chemotherapy also show a negative correlation between hormone sensitivity and the effect of chemotherapy, usually expressed in percentage pathological complete remission (pCR). The difference in pCR percentages in patients with hormone-sensitive versus hormone-insensitive tumours as a result of neoadjuvant chemotherapy have also been confirmed in recent studies (up to 10% vs >20%). Unfortunately, the studies do not provide data about the level of hormone sensitivity, with the exception of Bhargava, who indicates that the pCR percentages in patients with luminal A and B tumours (corresponding with an ER score >200 vs 11-199) do not differ (1.8 vs 1.4%). A consistent relationship between the presence or absence of the progesterone receptor and the effect of (neo)adjuvant chemotherapy has not been shown.
It has become clear through research on the genetic profile of the tumour that these hormone-sensitive breast cancers belong to a heterogeneous group, in which the spectrum spans from extremely low risk for which chemotherapy is not worthwhile, to a clearly increased risk of recurrence for which treatment with chemotherapy is justified [Soteriou, 2009; Bonnefoi, 2009; Albain, 2009; Albain, 2010].

Aside from adequate hormonal treatment, conventional adjuvant and neoadjuvant chemotherapy is of limited significance in patients with hormone-sensitive tumours. The favourable contribution of chemotherapy reduces with age. Third generation chemotherapy schedules appear to be more effective. There is a demonstrated reverse correlation between the effect of (neo)adjuvant chemotherapy and hormone sensitivity. However, a cut-off value for receptor activity on the basis of

which chemotherapy should (not) be recommended within the hormone-sensitive group is not known. An indication for (neo)adjuvant treatment with chemotherapy may be strengthened or weakened by other factors (such as an extremely low concentration of hormone receptors, age, condition, contraindications, grading, HER-2 etc.). If feasible , a third generation schedule is preferable.

Adjuvant chemotherapy in the elderly

There is little known about the effect of adjuvant chemotherapy in patients from 70 years of age. Two randomised studies have looked at the effect of adjuvant chemotherapy in patients 65 years and older [Fargeot, 2004; Muss, 2009]. The study by Fargeot randomised between treatment with tamoxifen with(out) 6 courses epirubicin weekly, and in the study by Muss the patients in the control arm were treated with 6 courses of CMF or 4 courses AC (standard treatment) or with 6 courses of capecitabine (experimental arm) . The addition of epirubicin to tamoxifen resulted in a 6-year disease-free survival advantage of 3.3%, without a survival advantage. Standard CMF and AC resulted in a significantly better (disease-free) survival after 3 years compared to capecitabine, especially in patients with a tumour with negative hormone receptors. Toxicity was limited in the weekly epirubicin group but substantial in the CMF treated group, with the consequence that only 62% of the patients received the planned 6 courses.

Optimal duration of adjuvant anthracycline-containing chemotherapy

While anthracycline-containing schedules are considered standard adjuvant chemotherapy, optimal duration and dose of this treatment have not been studied sufficiently. Indirect data suggests that 6-9 cycles of anthracycline-containing chemotherapy is more effective than 4 cycles. The arguments for this are:

- The meta-analysis of 2005 shows if the data for the 4 studies in which 4 or less cycles of AC or EC (C: cyclophosphamide, A: doxorubicin, E: epirubicin) were administered are omitted, this results in an increase in survival advantage provided by anthracycline-containing chemotherapy compared to chemotherapy not containing anthracycline. Treatment with 6 to 9 cycles of anthracycline-containing chemotherapy results in an approximately 25% annual reduction in RR of death compared to CMF regimes [EBCTCG, 2005].
- Three studies in which 4 cycles of AC/EC were compared with 6 cycles of typical CMF showed comparable outcomes [Fisher, 1990; Fisher, 2001; Galligioni 2000], while 6 cycles $CE_{120}F$ was more effective than 6 cycles of typical CMF [Levine, 2005].
- Six cycles FEC resulted in a better survival than 3 cycles FEC in premenopausal patients with an N+ breast cancer [Fumoleau 2003].

Based on these arguments, it is generally accepted that 6 cycles of intravenous FAC/CAF or FEC/CEF are considered standard adjuvant anthracycline-containing chemotherapy.

Optimal dose of adjuvant anthracycline-containing chemotherapy

Dose escalation

Seven studies researched the effect of dose escalation of doxorubicin, cyclophosphamide and epirubicin as adjuvant chemotherapy [Galligioni, 2000; Levine, 2005; Henderson, 2003; Budman, 1998; Fisher, 1997; Fisher, 1999; Piccart, 2001; FASG, 2001; Bonneterre, 2005]. In the CALGB 9344 study, treatment with a higher than standard dose of doxorubicin (60 mg/m^2) for 4 courses did not result in a better survival [Henderson, 2003]. In CALGB 8541 however, treatment with a cumulative dose of doxorubicin lower than 240 mg/m2 was found to be less effective [Budman, 1998]. In the NSABP B-22 and B-25 study, dose escalation of cyclophosphamide did not result in a better survival, except for the subgroup of women under 50 years with at least 4 tumour positive axillary nodes [Fisher, 1999]. Dose escalation of doxorubicin above a standard dose (of 60 mg/m^2/course) did not result in a better clinical effect, while there did appear to be a cumulative threshold value under which the effectiveness decreased [Burdette-Radoux, 2003]. Three of the four studies on the effect of high-dose epirubicin (100-120 mg/m^2) schedules in patients with an N+/high-risk breast cancer showed a better survival compared to 6 courses of typical CMF and compared to epirubicin 50-60 mg/m^2 [Galligioni, 2000; Piccart, 2001; FASG, 2001; Bonneterre, 2005].

No studies have been performed in which 4-6 cycles of (F)A_{60}C were compared with 6 cycles of (F)$E_{100\text{-}120}$C.

Dose intensification

Many studies have looked at the principle of dose intensification [Bonadonna, 2004; Therasse, 2003; Fetting, 1998; Linden, 2007; Nitz, 2005; Citron, 2003; Venturini, 2005; Burnell, 2010; Moebus, 2010]. However, most studies did not research the pure *dose-dense* principle (intensification of the

chemotherapy dose by shortening the interval between administrations) but the doses in the two study arms were not identical. Two pure dose-dense studies yielded the following results. In the CALGB 9741 study, treatment with 4 courses of AC followed by 4 courses paclitaxel in a 14-day schedule resulted in a better 4-year disease-free survival (82 vs 75%) and 4-years survival (92 vs 90%) than the same 3-weekly treatment in patients with N+ breast cancer. In the Italian study in which the effect of 6 courses $FE_{60}C$, administered with a 2- or 3-weekly interval, were compared, there was no significant difference in effectiveness between the two schedules [Venturini, 2005]. Two large studies were published recently that compared a dose-dense and intensified schedule with 3-weekly standard AC/EC and paclitaxel schedule [Moebus, 2010; Burnell, 2010]. The study by Burnell, conducted in 2104, N+ and high-risk N_0 patients, used the Canadian $CE_{120}F$ schedule as the third arm. After a median follow-up of 30 months, the 3-weekly AC/paclitaxel schedule was found to be inferior to both the intensified schedule and the Canadian $CE_{120}F$ schema. The 3-year disease-free survival was: 85%, 89.5% and 90.1% respectively. The German study compared a standard 3-weekly EC/paclitaxel schedule with all agents given as monotherapy in a 2-weekly schedule and escalated dose; the study incorporated 1,284 patients with 4 or more positive lymph nodes. The 5-year disease-free survival was 62% vs 70% ($p<0.001$) and the survival was 77% vs 82% ($p=0.0285$) respectively. In this study, an AML or MDS developed in 4 patients treated in the intensified arm.

High-dose chemotherapy
A number of studies have compared the effect of high-dose chemotherapy followed by stem cell transplantation to treatment with standard adjuvant chemotherapy. In a meta-analysis of 15 studies, an absolute disease-free survival advantage of 13% was reported after a median follow-up of 6 years. There was no survival advantage, possibly partly due to therapy-related death and an increase in the occurrence of acute myeloid leukaemia and MDS in some studies. In a few retrospective subgroup analyses, high-dose chemotherapy appeared to be mainly effective for patients with an HER-2-negative tumour and for patients with a triple negative tumour [Rodenhuis, 2006; Tallman, 2003; Peters, 2005; Wilkin, 2007; Hanrahan, 2006; Zander, 2004; Leonard, 2004; Coombes, 2005; Moore, 2007; Nieto, 2009; Farquhar, 2007]. After a follow-up of 87 months, the Dutch 4+ study shows a trend in the actuarial 5-year disease-free survival in favour of the high-dose arm of 4% for the entire group (HR 0.84; p=0.076 (two-sided)). An unplanned subgroup analysis shows a significant 5-year survival advantage of 7% for the patients with a tumour without HER-2-overexpression who are treated with high-dose chemotherapy. A second analysis in a representative sample within the HER-2-negative subpopulation shows a substantial 8-year survival advantage of approximately 50% for patients with tumours with a BRCA1-like array comparative genomic hybridisation (CGH) profile when they have been treated with high-dose chemotherapy compared to standard $FE_{90}C$ (multivariate HR 0.12; 95%CI 0.04-0.43; 5-year recurrence-free survival 78% vs 29%), while a significant difference in (recurrence-free) survival is seen between the two treatment arms in the patient group who have a tumour without a BRCA1-like CGH profile [Vollebergh, 2010].

6.1.2 Taxane-containing chemotherapy
Aside from anthracyclines, taxanes (paclitaxel and docetaxel) have been found to be very effective in the treatment of breast cancer. Neither agent shows a clinical cross-resistance with anthracyclines. Results are now available for 21 trials with first-generation taxane treatment in which approximately 35,000 women were randomised between treatment with taxane-containing and taxane-free, generally anthracycline-containing, chemotherapy. Studies differ in study structure, the type of taxane used, and the simultaneous or sequential addition of taxane to the anthracycline-containing schedule. It appears from a few pooled data analyses and a meta-analysis that taxane-containing adjuvant chemotherapy results in a small advantage in disease-free survival and survival (approximately 5 vs 3% absolute advantage respectively) compared to the control arm (generally an anthracycline-containing schedule) of the studies. This finding is independent of the type of taxane, the administration schedule, the node status and hormone receptor expression [Bria, 2006; de Laurentiis, 2008; Ferguson, 2007; Bedard, 2010; Kelly, 2010]. However, the studies can be further subdivided into:

a) studies in which the taxane-containing schedule is compared to a relatively low-dose anthracycline schedule (e.g. 4 AC or 6 FAC_{50}) and
b) studies in which the taxane-containing schedule is compared to a standard-dose anthracycline-containing schedule (e.g. 6 $FEC_{90/100}$) in the control arm

<u>First generation taxane-containing chemotherapy compared with anthracycline-containing chemotherapy</u>
The results are available for nine first-generation taxane studies in which the taxane-containing

schedule is compared with an anthracycline-containing schedule. There are 17,000 patients in these studies. The PACS 01 study included N+ patients and found a significant improvement in the five-year disease-free survival and survival (HR 0.82 and 0.73 respectively) after treatment with 3 courses FEC_{100} followed by 3 courses docetaxel compared to 6 courses FEC_{100} [Roche, 2006]. The GEICAM 9906 trial found an improvement in the 5-year disease-free survival (HR 0.74) of N+ patients in favour of the group treated with 3 courses of FEC_{90} followed by 8-weekly administrations of paclitaxel compared to 6 courses FEC_{90} [Martin, 2008]. In the ECTO study with N_0 and N+ patients, the effect of treatment with 4 courses doxorubicin in combination with paclitaxel followed by 4 courses CMF iv. was compared to the effect of 4 courses doxorubicin monotherapy prior to 4 courses CMF iv. The hazard ratio for disease-free survival and for survival was 0.73 (p=0.027) and 0.80 respectively after more than 6 years, in favour of the arm without paclitaxel [Gianni, 2009]. Both the 4-arm BIG 02-98 and Taxit 216 studies showed a better disease-free survival in patients with an N+ breast cancer, with a hazard ratio of 0.79 and 0.82 respectively for the taxane-containing study arm. The combination of 4 courses epirubicin/cyclophosphamide followed by 4 courses docetaxel was found to provide a significantly better disease-free survival compared to 6 courses FEC_{100} or 6 courses CMF (iv day 1 and 8 schedule) in the WGSG/AGO study [Nitz 2008]. The HeCOG 10/97 compared an unconventional dose-dense schedule, namely 3 courses CMF with a dose-dense schedule of 4 courses epirubicin and 4 courses CMF. While the taxane regimen was not found to provide a statistically significant advantage, the study had insufficient power to show a difference in survival. In the GEICAM 98-05 study, TAC was found to be more effective than FAC_{50} after a follow-up of more than 6 years in high-risk N_0 patients. The hazard ratio for the recurrence rate was 0.68 (p=0.01). A significant difference in survival has not (yet) been demonstrated (HR 0.76); however, the number of patients in the study who died is still very low (TAC: 26, FAC: 34) [Martin, 2010]. In two studies, the NCIC MA 21 and the UK TACT, no advantage was found in the addition of a taxane to a standard anthracycline schedule. In both studies, the anthracycline regime was superior to the typical CMF as has been found earlier in head-to-head comparisons (CEF and E-CMF) [Fountzilas, 2005; Burnell, 2009; Ellis, 2007]. From the recent (as yet unpublished) meta-analysis of the EBCTCG 2010, it appears that the combination of a taxane- plus anthracycline-containing schedule versus the same or a high dose anthraycline-containing schedule results in a reduction in breast cancer mortality of approximately 12% (RR 0.88; p=0.00001; n=44,000). Subdivided in the anthracycline strength of the studies, the RR is 0.87 (p=0.001; n=11,000) if the taxane-anthracycline schedule is compared with the same dose anthracycline in the control arm; however, if the dose of the non-taxane arm was doubled, the advantage of treatment with a taxane was lost (RR=0.95±0.06, p=0.4; n=10,000).

Second generation taxane studies

The second generation taxane studies directly compare different taxane-containing regimes in order to determine the optimal dose and the optimal schedule and type of taxanes in the adjuvant setting. CALGB 9741 tested the dose-dense hypothesis (see dose intensification). There was a clear advantage for the experimental schedule in the 4-year disease-free survival (HR 0.80). After a follow-up of almost 6 years, the risk of recurrence is still significantly lower in favour of the dose-dense arm, but the difference in survival is not significant (HR 0.85, p=0.12). The as yet unpublished BCIRG 005 study compares the effect of 6 courses TAC with 4 courses AC followed by 4 courses docetaxel in N+ patients. After a follow-up of 60 months, there is no difference in (disease-free) survival between the two study arms [Eiermann, 2008].

It appears from the results of the ECOG 1199 study that the taxane schedule may be of importance. This study randomised almost 5,000 patients with N+ breast cancer into 4 different taxane schedules according to a 2-by-2 factorial design. After 4 courses adjuvant AC, patients were randomised between 4 courses three-weekly paclitaxel or 12 courses weekly paclitaxel, 4 courses three-weekly docetaxel or 12 courses weekly docetaxel. A disease-free survival advantage was found in the study arms in which the patients were treated with weekly paclitaxel or three-weekly docetaxel, while a survival advantage was only found in the arm with the weekly paclitaxel schedule [Sparano, 2008]. Six small (neo)adjuvant studies researched the optimal sequence of anthracyclines and taxanes [Cardoso, 2001; Miller, 2005; Piedbois, 2007; Puhalla, 2008; Wildiers, 2009; Earl, 2009]. In three of the four adjuvant studies, the relative dose intensity was found to be higher in the sequence taxane followed by anthracycline. A higher pCR percentage was achieved in the two neoadjuvant studies with the taxane followed by anthracycline schedule. Data on the effectiveness in the adjuvant setting are not yet known. The optimal schedule taxane/anthracycline-containing chemotherapy is not yet known because only preliminary results of most studies have been published.

Taxane-containing, non-anthracycline-containing chemotherapy versus anthracycline-containing

chemotherapy
A large randomised study compared the effectiveness of taxane-containing chemotherapy with that of anthracycline-containing chemotherapy [Jones, 2006]. In this study, 1,016 patients (N+ and N_0) were randomised between treatment with 4 courses AC or 4 courses TC (docetaxel/cyclophosphamide). After a median follow-up of 5.5 years, there was a significantly longer disease-free survival for TC (HR 0.67).

6.1.3 Chemotherapy in combination with trastuzumab

Six randomised studies have researched the value of 1-year treatment with trastuzumab as part of the medication-based adjuvant therapy in patients with a tumour with HER-2-overexpression [Piccart, 2005; Romond, 2005; Smith, 2007; Slamon, 2007; Spielman, 2009; Joensuu, 2009]. In NSABP-B31, N+ patients were treated with 4 courses AC, followed by 4 courses paclitaxel (175 mg/m^2/3 weeks) versus the same chemotherapy to which 1-year treatment with trastuzumab was added, to be started simultaneously with paclitaxel. In the three-arm NCCTG N9831 study, N+ (after an amendment also N_0) patients were treated with 4 courses AC, followed by 12-weekly courses of paclitaxel (80 mg/m^2) as monotherapy or in combination with weekly trastuzumab for a duration of 1 year or followed by weekly trastuzumab for a duration of 1 year (sequential trastuzumab). After treatment with adequate adjuvant chemotherapy, N_0 and N+ patients were randomised for treatment with 0, 1 or 2 year trastuzumab in a 3-weekly schedule in the three-arm HERA study [Piccart, 2005; Smith, 2007]. In the three-arm BCIRG 006 study, N+ and high-risk N_0 patients in arm 1 and 2 were treated with 4 courses AC followed by 4 courses docetaxel (AC-T) as monotherapy or in combination with trastuzumab (AC-TH) for a duration of 1 year (weekly during chemotherapy, thereafter three-weekly). In the third arm, treatment consisted of 6 courses docetaxel plus carboplatin (TCH) in combination with trastuzumab for a duration of 1 year (weekly during chemotherapy, thereafter three-weekly [Slamon, 2011]. In the PACS04 study, N+ patients with a tumour with HER-2-overexpression were randomised between treatment with 6 courses FEC_{100} or epirubicin/docetaxel followed by a second randomisation between observation or treatment with trastuzumab for a duration of 1 year. In the FinHer study, patients were randomised for 3 courses docetaxel or vinorelbine followed by 3 courses FEC, in which patients with HER-2-overexpression were also randomised between receiving or not receiving treatment with trastuzumab for a duration of 9 weeks during vinorelbine or docetaxel treatment [Joensuu, 2006; 2009].

The design and therapeutic interventions of the NSABP-B31 and NCCTG N9831 studies were so similar that it was decided to evaluate the studies together in relation to the arms in which the trastuzumab was administered simultaneously with paclitaxel [Romond, 2005] After a median follow-up of 2.9 years, the hazard ratio for disease-free survival was 0.49 for patients treated with trastuzumab ($p<0.0001$). The 4-year disease-free survival for the trastuzumab group was 85.9% versus 73.1% for the control group. In the trastuzumab arm, 92.6% percent of patients were still alive after 4 years compared to 89.4% in the control arm. After a median follow-up of 4 years so far, a significant effect is seen on survival (HR 0.63; $p=0.0004$). In an unplanned interim analysis with still relatively few events, the results of the sequential trastuzumab treatment in the NCCTG N9831 study did not show significant advantage for the sequence 4 AC – 4 paclitaxel – trastuzumab compared to 4 AC – 4 paclitaxel with a hazard ratio of 0.87 for the 2-year disease-free survival.

The first results of the HERA study concern the comparison of no trastuzumab treatment vs 1 year treatment with the agent. After a median follow-up of 2 years, there was a significant survival advantage for the trastuzumab arm with a hazard ratio for disease-free survival of 0.63 ($p<0.0001$) and 0.63 for survival ($p=0.0051$). The three-year disease-free survival in the trastuzumab arm was 80.6% versus 74.3% for the control arm and the corresponding survival was 92.4% versus 89.7%. In the FinHer study, the three-year disease-free survival was also significantly better for the group of patients in the trastuzumab arm (89% vs 78%, $p=0.01$). There was also a trend for a better survival (96% vs 90%, $p=0.07$). In the BCIRG 006 study, both trastuzumab-containing treatment arms (TCH and AC-TH) showed a significant improvement in disease-free survival after a median follow-up of 3 years compared to the AC-T schedule (HR 0.67 en 0.61; $p=0.0003$ and $p<0.0001$). The 3-year disease-free survival was 87% for AC-TH, 86% for TCH and 81% for AC-T. There was also a significant improvement in survival by both TCH and AC-TH compared to AC-T (HR 0.66 and 0.59; $p=0.017$ and $p=0.004$). Only the PACS 04 study showed no improvement in (disease-free) survival as a result of the addition of trastuzumab [Spielmann, 2009].
It is still unclear what the most effective form of administering trastuzumab is: after or simultaneously with chemotherapy. There are indications that the simultaneous administration of trastuzumab with a

taxane is more effective than sequential administration. This can be seen from the comparison in risk reductions that are better in the studies in which trastuzumab was administered in combination with a taxane (NSABP B-31/NCCTG N9831 and BCIRG 006).

Trastuzumab with small (< 1 cm) N_0 tumours with HER-2-overexpression.
The majority of patients with stage I breast cancer have an excellent prognosis. It appears from multiple retrospective studies that the presence of HER-2-overexpression in this small tumour is associated with a clear increase in the recurrence rate [Rakkhit, 2009; Joensuu, 2003; Gonzalez-Angulo, 2009; Curigliano, 2009; Chia, 2008; Tovey, 2009; Black, 2006; Park, 2010; Oakman, 2010; Amar, 2010; Burstein, 2009; Verma, 2010; Banerjee, 2010; Joerger, 2011]. However, interpretation of these studies is hampered by the fact that the studies differ in relation to the endpoint chosen, the duration in follow-up, and whether or not adjuvant systemic therapy was used. No prospective study has demonstrated that treatment with trastuzumab reduces the recurrence rate with these small tumours. In a small retrospective study in the Netherlands with a short follow-up, the 70-gene profile in tumours with an ER and PR of ≥ 50% resulted in a small subgroup with a good prognosis despite HER-2-overexpression [Knauer, 2010]. The St. Gallen guideline of 2011 poses that even with the small T_{1b} tumours there may be a role for treatment with trastuzumab. For this category, the National Comprehensive Cancer Network (NCCN) guideline of 2011 recommends considering treatment with chemotherapy and trastuzumab for hormone-receptor negative tumours from $T_{1b}N_0$. For hormone-receptor positive tumours, the NCCN recommends treating these patients with hormonal therapy and trastuzumab, possibly in combination with chemotherapy. However, the treatment of these small tumours must be weighed up against the possible cardiotoxicity and uncertain absolute advantage provided by trastuzumab.
It appears from these retrospective studies that often contain small absolute numbers of patients that this group of small tumours with HER-2-overexpression is heterogenous; as a rule of thumb, the relative risk of death after 10 years as calculated with the adjuvant-on-line programme can be multiplied by a factor of 2.5.

Adjuvant treatment of the triple negative breast cancer
Approximately 15-20% of the breast cancers are so-called triple negative tumours [Perez, 2010]. This subgroup of the breast cancer is characterised by the absence of both the ER and PR and HER-2-overexpression. The tumour occurs more often at a young age, is high-grade and on presentation is often already substantial in size and metastasised to the axillary lymph nodes. The tumours have a poorer prognosis with rapid recurrences, frequent brain metastasis, and a short survival after a recurrence develops.Various neoadjuvant phase II studies have found that these tumours respond better to standard neoadjuvant chemotherapy with anthracyclines and taxanes compared to other tumour types; however, if complete remission is not achieved, there is no improvement in survival [Parker, 2009; Tan, 2008; Wang, 2009; Hugh, 2009; Sorlie, 2009; Tan, 2009; Liedtke, 2008]. In a subgroup analysis of the CALGB9741 study, doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 and paclitaxel 175 mg/m^2 every 2 weeks with G-CSF provided a risk reduction of 24% (95%CI 1-42%) in recurrence and 28% (95%CI 1-47%) in death compared to the same agents once every three weeks in the ER negative subgroup. The HER-2 status was left out of consideration in this analysis [Berry, 2006]. Research is underway on the effect of treatment with platinum analogues, intensified alkylating therapy, anti-tubulins, angiogenesis inhibitors and poly(ADP)ribose polymerase (PARP) inhibitors in this subgroup of mammary tumours. However, there is currently insufficient data to treat this group of breast cancers (outside a research context) different to the other types of breast cancer.

6.1.4 Toxicity
Secondary haematological malignancies
Patients treated with radiotherapy, alkylating chemotherapeutic agents and topoisomerase inhibitors have an increased chance of developing an acute myeloid leukaemia or myelodysplasia (AML/MDS). In a retrospective study with the data from six NSABP studies, there was an increase in the incidence of AML/MDS in the AC regimens with intensified doses cyclophosphamide, in which GCS-F support was required (Smith, 2003). The same observation has been described by Herschman (2007) with the use of GCS-F with AC chemotherapy, amongst others. In a review with data from nineteen randomised studies, Praga (2005) concluded that the chance of developing a secondary AML/MDS was 0.37% with cumulative doses of ≤ 720 mg/m^2 epirubicin and ≤ 6.300 mg/m^2 cyclophosphamide. Higher doses resulted in a 4.97% cumulative rate of AML/MDS after 8 years.

The chance of developing therapy-induced leukaemia is limited with the current standard regimes, and the (disease-free) survival advantage resulting from adjuvant treatment of breast cancer with anthracyclines and cyclophosphamide is many times greater than the loss of lives through AML/MDS.

Cardiotoxicity

The formation of free radicals and oxidative stress that occurs during treatment with anthracyclines can damage the heart. Anthracycline-induced cardiotoxicity is characterised by a slow progressive worsening in pump function without spontaneous improvement, and correlates strongly with the cumulative dose of anthracycline – *half the dose causes half the damage* [Jensen, 2006; Johnson, 2006]. There is also a clear increase in the sensitivity for heart damage with increasing age. The reduction in pump function occurs especially in the period after treatment so that monitoring of the ejection fraction during treatment is hardly effective. The individual sensitivity for anthracycline cardiotoxicity varies strongly. Shan (1996) concludes in a review that cardiac damage in some patients already occurs with cumulative doses of ≤ 300 mg/m^2, while other patients tolerate doses of ≥ 1000 mg/m^2 doxorubicin. An estimated cumulative percentage of clinical heart failure of 5% was found to occur in the study by Swain (2003) in patients treated with 400 mg/m2 and in 26% of patients treated with 550 mg/m^2 doxorubicin. In the French adjuvant study with $FE_{100}C$, clinical heart failure was observed in 2 of the 85 patients evaluated and asymptomatic left ventricle dysfunction in 18 patients [Bonneterre, 2004]. Meinardi (2002) did not observe clinical heart failure in any of the 56 patients treated in the 4+ study in the Netherlands. However, there was abnormal systolic function in 11% of patients and abnormal diastolic function in 38%, two or more years after treatment with epirubicin doses up to 450 mg/m^2. For the time being, the (disease-free) survival advantage for adjuvant treatment with anthracyclines is greater than mortality through cardiotoxicity. However, increasing use of (higher-dose) anthracycline-containing chemotherapy schedules, also at a higher age, means it is plausible that the full extent of the problem will only become clear in coming years and caution is warranted.

Cardiotoxicity may also occur after treatment with trastuzumab. This especially occurs if trastuzumab is administered closely together with anthracyclines. Well functioning HER-2 signalling is probably needed for the healing of cardiac damage induced by anthracyclines [Hudis, 2007; de Korte, 2007]. Trastuzumabas monotherapy can also be cardiotoxic. Binding of trastuzumab to HER-2 receptors in the heart limits the response to stress. Despite strict selection of patients prior to research, cardiotoxicity was seen in the four large adjuvant studies in which patients were treated with both anthracyclines and trastuzumab. Symptomatic heart failure was observed in the HERA trial in 0.6% of patients treated with trastuzumab, and in the BCIRG trial in 1.6% of patients in the anthracycline-containing arm (AC-TH) and in 0.4% in the therapy arm without anthracycline (TCH). This percentage was 3-4% in both American studies in which the trastuzumab was administered simultaneously with paclitaxel. The definition of cardiotoxicity and the associated (temporary) cessation in treatment with asymptomatic reduction in left ventricular ejection fraction (LVEF) was not identical in the studies, which makes comparison difficult. There was an asymptomatic cardiac dysfunction in the NSABPB-31 in 34% of patients (defined as at least a one-off reduction in LVEF by ≥ 10 EF points and an LVEF of < 55%) in the group treated with trastuzumab, while at least a one-off reduction in LVEF of ≥ 10 EF points of < 50% was observed in 7% of patients treated with trastuzumab [Suter, 2007].
It is unknown to what extent the cardiotoxicity of trastuzumab will be temporary. Telli (2007) outlines that there was still a significant reduction in LVEF in a substantial number of patients with a cardiac event in both the NSABP B-31 and the BCIRG studies after ≥ 6 months follow-up.

Conclusions

Level 1	Treatment with anthracycline-containing chemotherapy reduces the RR of death from breast cancer by approximately 38% per year for women under 50 years of age and approximately 20% per year for women who are 50-69 years. These anthracycline-containing chemotherapy schedules are more effective than CMF regimes and result in a significant reduction in the chance of a recurrence and death compared to the CMF schedule. A1 EBCTCG 2005

Level 2	Treatment with high-dose epirubicin (100-120 mg/m2) schedules in patients with an N+/high-risk breast cancer shows a better survival rate compared to 6 courses of typical CMF and compared to epirubicin 50-60 mg/m2.

	B Piccart 2001, French epirubicin study group 2001, Bonneterre 2005

Level 2	Addition of a taxane to anthracycline-containing chemotherapy results in a better (disease-free) survival of patients in early stage breast cancer. Improvement in (disease-free) survival with addition of a taxane to anthracycline-containing chemotherapy has been demonstrated in patients with N+ and N0 breast cancer. Subgroups cannot be distinguished (ER status, HER-2 status) in which this treatment has a more or less pronounced effect. B Henderson 2003, Buzdar 2002, Mamounas 2005, Roché 2006, Martin 2005, Gianni 2005, Goldstein 2005, Martin 2010

Level 1	Studies (NSABP-B31, NCCTG N9831, HERA, BCIRG 006) that have researched the value of 1-year treatment with trastuzumab as part of systemic adjuvant therapy in patients with a tumour with HER-2-overexpression, all show a significant reduction in the risk of recurrence and death. A2 Romond 2005, Smith 2007, Slamon 2011

Level 3	It has been demonstrated in multiple retrospective studies that the presence of HER-2-overexpression in small tumours (< 1 cm) is associated with a clear increase in the chance of recurrence. C Rakkhit 2009, Joensuu 2003, Gonzalez-Angulo 2009, Curigliano 2009, Chia 2008, Tovey 2009, Black 2006, Park 2010, Oakman 2010, Amar 2010, Burstein 2009, Verma 2010, Banerjee 2010, Joerger 2011

6.2 Hormonal therapy

6.2.1 Suppression of ovarian function

The EBCTCG-meta-analysis of 2005 analysed the effect of inactivating or suppressing ovarian function in 8,000 women under 50 years of age with a hormone-positive breast cancer. Suppressing the ovarian function was found to have a favourable effect on both locoregional control and total survival, although the authors indicate that the result is less substantial than that found in earlier analyses. The recurrence percentage after 15 years was 47.5% for women with oophorectomy compared to 51.6% for the control group (p=0.00001), and the mortality 40.3% compared to 43.5% for the control group (p=0.004).

However, retrospective analyses of different studies suggest that patients experiencing amenorrhoea after treatment with chemotherapy have a better (disease-free) survival than patients who continue to menstruate after chemotherapy [Davidson, 2001; Pagani, 1998; del Mastro, 1997]. This data has increased the interest in oophorectomy. A few large randomised studies have researched the effectiveness of chemotherapy plus inactivating ovarian function (either in or not in combination with tamoxifen) compared to the effect of chemotherapy only [Davidson, 1999; Baum, 2001; IBCSG, 2003; Baum, 2003].

A recent meta-analysis studied the effect of treating premenopausal patients with hormone-positive breast cancer using LHRH agonists, administered as monotherapy or in combination treatments [*LHRH-agonists in Early Breast Cancer Overview Group,* 2007], in which the LHRH agonist was administered after chemotherapy for a duration of 2-5 years.

The combination of an LHRH agonist plus tamoxifen as the only systemic therapy compared to no treatment resulted in a reduction in the recurrence rate of 58.4% (p<0.0001) and death rate of 46.6% (p=0.04) after a recurrence. When treatment with an LHRH agonist with or without tamoxifen was compared to treatment with chemotherapy (mainly CMF regimes), no significant difference was found in effectiveness.

Addition of an LHRH agonist to tamoxifen (n=1,013), to chemotherapy (n=2,376) or to chemotherapy plus tamoxifen (n=365), did show a trend in reduction in the chance of recurrence and death, although

the differences were not significant. Combined analysis of the last two groups (n=2,741) did show a significant reduction of 12.2% (p=0.04) in recurrence and a reduction of 15.0% (p=0.04) in mortality after recurrence.

Addition of the combination of an LHRH agonist plus tamoxifen to treatment with chemotherapy compared to treatment with chemotherapy only, did show a reduction in the chance of recurrence of 26.7% (p=0.001) and a reduction in the mortality after recurrence of 24.4% (p=0.01). Combined analysis of the effect of adding an LHRH agonist to tamoxifen, chemotherapy or the combination of both modalities resulted in a reduction in the recurrence rate of 12.7% (p=0.02) and of 15.1% (p=0.03) in death rate after an earlier recurrence. The abovementioned analyses were also performed separately for different age groups. The greatest reduction in the risk of recurrence following treatment with an LHRH agonist after chemotherapy (with or without tamoxifen) was found in women of 35 years and younger (HR 0.66); the effect was still significant in the group to 40 years of age (HR 0.77), but was no longer significant in women over 40 years. While the advantage provided by the addition of an LHRH agonist to chemotherapy was identical regardless of tamoxifen administration, so few patients were treated in studies in which tamoxifen was administered in both arms that a pronouncement cannot be made yet regarding the extent of the advantage due to addition of an LHRH agonist in this context. It must also be taken into consideration that CMF chemotherapy was administered in most studies, a regime in which a high percentage of women experienced amenorrhoea (increasing with age), so that the effect of the LHRH agonist added may have been influenced.

6.2.2 Tamoxifen

In the meta-analysis published by the EBCTCG in 2005, it was found that 1-2 years of treatment with tamoxifen compared to no treatment provided an advantage with a hazard ratio of 0.79 (SE=0.02) in relation to locoregional control (5.8% recurrences per year vs 7.1%). These results were even more pronounced after 5 years of treatment with tamoxifen: HR 0.69 (SE=0.03), i.e. recurrences in the tamoxifen groups were 3.2% vs 4.5% in the control groups.

The figures are comparable for total survival. The mortality rate after 1-2 years in the tamoxifen group was lower than that in the control groups (33.6% vs 37.7%; HR 0.85 (SE=0.02). Results are more favourable after treatment with tamoxifen for 5 years. The hazard ratio in favour of tamoxifen is then 0.76 (SE=0.03). Results over fifteen years have also become available. The recurrence percentage after 15 years was 33.2%, while this was 45.0% in the control groups for women with oestrogen-receptor positive tumours (p<0.00001). These differences were also found for the mortality rate: after 15 years, the mortality rate in all tamoxifen groups together was 25.6% versus 34.8% in the control groups (p<0.00001). For all subgroups (with different doses tamoxifen, age, menopausal status, node status, presence or absence of toxicity and different chemotherapy combinations), it was shown that there is an advantage to tamoxifen treatment.

The absolute advantage is of course dependent on the absolute risk of recurrence. The 5-year survival advantage for node-negative (N_0) low-risk patients is 3.7%, for N_0 with intermediate risk 7%, for high-risk and node-positive (N+) patients 12%. The effect of tamoxifen with an ER-negative but PgR-positive breast cancer has only been studied in a small group of patients. There is an advantage in this category, but it is limited. The advantage of adjuvant tamoxifen with an ER-, PgR-breast cancer is limited to halving the chance of contralateral breast cancer.

6.2.3 Aromatase inhibitors

The effect of treatment with aromatase inhibitors has not yet been incorporated in the meta-analysis published by the EBCTCG in 2005, but it has been in the meta-analysis performed in 2006. Systematic reviews were published in 2004 and 2007 concerning the role of aromatase inhibitors in the treatment of postmenopausal women with breast cancer [Choueiri, 2004; Eisen, 2007]. This review analysed the characteristics of anastrozole, letrozole and exemestane in the different phases of breast cancer. Three types of adjuvant studies have been conducted with aromatase inhibitors:

a) comparative studies in which tamoxifen is compared with an aromatase inhibitor after locoregional treatment and adjuvant chemotherapy, both administered for a duration of 5 years, also called upfront studies;
b) *sequential studies* in which treatment with 2-3 years tamoxifen, followed by 3-2 years of an aromatase inhibitor, or an aromatase inhibitor for a duration of 2 years followed by 3 years of tamoxifen is compared with five years of tamoxifen or five years of an aromatase inhibitor;

c) extension studies that research if continuing treatment with an aromatase inhibitor after 5 years of tamoxifen use provides a positive contribution to the recurrence-free period and survival

Studies with extended hormonal therapy after 5 years of an aromatase inhibitor or after a sequence of tamoxifen followed by an aromatase inhibitor are in progress and have yielded insufficient data for application outside a research context.

Up-front studies

There are three upfront studies worldwide: the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial began with three treatment arms. However, inclusion in the combination arm was ceased after the first interim analysis because no advantage was seen compared to tamoxifen monotherapy, while an advantage was observed for anastrozole.

The second double-blind study was organised by the Breast International Group, the BIG 1/98 study, and had four treatment arms: 5 years of tamoxifen, 5 years of letrozole, 2 years sequential tamoxifen → 3 years of letrozole or 2 years of letrozole → 3 years of tamoxifen. Both studies show an advantage for aromatase inhibitors in relation to disease-free survival (ATAC HR 0.86; 95%CI 0.78-0.95, p=0.003; BIG 1-98 HR 0.88; CI:0.78-0.99, p=0.03) but (as yet) no survival advantage after a median follow-up of 120 and 76 months respectively [Howell, 2005; ATAC, 2008; Cuzick, 2010; Thurliman, 2005; BIG 1-98, 2009].

In the BIG 1-98 study, neither of the two sequential arms showed a significant difference with 5 years of letrozole (HR 1.05 (95%CI 0.84-1.32) for tamoxifen/letrozole versus letrozole and 0.96 (95%CI 0.76-1.21) for letrozole/tamoxifen versus letrozole respectively). An advantage was mainly seen in the ATAC study in patients who had *not* received chemotherapy and patients with *negative* axillary nodes. The opposite was observed in the BIG 1-98 study. In an unplanned, retrospective analysis of PA specimens from 1,792 patients from the ATAC study (30% of the total number), no preferential advantage for anastrozole could be determined in patients with an ER+PgR- breast cancer or with a breast cancer with HER-2-overexpression [Dowsett, 2006]. In the BIG 1-98 study, letrozole prevented an early recurrence in patients with unfavourable prognostic characteristics, in which no single unfavourable prognostic factor was predictive of the effect of letrozole [Mauriac, 2007].

The third upfront study was conducted in Austria with premenopausal women who were all treated with an LHRH agonist for three years, in which patients were randomised between 3 years of tamoxifen (n=900) or 3 years of anastrozole (n=903). In addition, a second randomisation was conducted with and without intravenous zoledronate every 6 months [ABCSG-12, 2009]. After a median follow-up of 47.8 months, there was no difference in disease-free survival between patients treated with tamoxifen or anastrozole (HR 1.10; 95%CI 0.70-1.53). However, there was a significant difference between patients who had and had not been treated with zoledronate [Gnant, 2009].

Sequential studies

There are two types of sequential studies. Firstly, studies in which patients who had received tamoxifen for 2-3 years were randomised between continuing tamoxifen or treatment with an aromatase inhibitor for a total duration of 5 years. A selection occurred here, because only those patients who were still disease-free after 2-3 years of tamoxifen were included in the study. The Intergroup Exemestane Study (IES), the Italian Tamoxifen Anastrozole (ITA) study, and the Arimidex Nolvadex 95 (ARNO95) study belong to this type of sequential study.

All studies showed an improvement in the disease-free survival for sequential therapy: HR 0.75 (95%CI 0.65-0.87) after a median follow-up of 58 months in the IES [Coombes, 2006; Coombes, 2007], HR 0.35 (95%CI 0.18-0.68) after a median follow-up of 36 months in the ITA study [Boccardo, 2005] and HR 0.53 (95%CI 0.28-0.99) in the ARNO-95 [Kaufmann, 2007].

In the IES, a survival advantage was reported for 4,724 patients after omitting 122 patients with negative hormone receptors: HR 0.83 (95%CI 0.69-1.00, p=0.05). A survival advantage was also found in the ARNO95 study [Kaufmann, 2007].

In the second type of sequential study, patients at the start of adjuvant hormonal therapy are randomised between monotherapy (with tamoxifen or an aromatase inhibitor) or sequential therapy (with tamoxifen and subsequently an aromatase inhibitor or the other way around). The sequential arms of the BIG 1-98 study, the ABCSG-8 study and the Tamoxifen Exemestane Adjuvant Multicenter (TEAM) study are such a sequential study.

In the ABCSG-8 study, there was an almost significant advantage in disease-free survival between the patients treated 2 years with tamoxifen followed by 3 years of anastrozole (n=1,865) versus 5 years of tamoxifen (n=1,849); (HR 0.85; 95%CI 0.71-1.01; p=0.067) while a significant survival advantage was

observed; (HR 0,78; 95%CI 0,62-0,98, p=0,032) [Jakesz, 2008]. A meta-analysis of sequential trials in which 5 years of tamoxifen was compared to the sequential tamoxifen aromatase inhibitor, showed a survival advantage for sequential treatment [Dowsett, 2010].
No difference was found in disease-free survival and total survival in the TEAM study after a median follow-up of 61 months between patients who were treated with exemestane (n=4,868) or with a sequential treatment of 2.5-3 years tamoxifen followed by 2.5-2 years exemestane (n=4,898); (HR 0.97, 95%CI 0.88-1.08) [vd Velde, 2011]. There was also no difference in disease-free survival between exemestane and tamoxifen in this study after 2.75 years, although there was a significant advantage over time in distant metastasis in favour of exemestane. After a median follow-up of 5.3 years, a survival advantage was found in favour of IFN-a, but the difference was no longer significant after 5 years. So far it has not been possible to identify a subgroup that benefits from the use of an aromatase inhibitor from the very start.

Extension studies
The extension studies are the Mammary-17 (MA-17), the ABCSG-6A study and the NSABP B-33 study. The MA-17 randomised between letrozole or placebo after 5 years of tamoxifen and was ended prematurely because the absolute difference in disease-free survival between both arms was significantly (4.7%) in favour of treatment with letrozole [Goss, 2003]. Patients from the placebo group could subsequently choose treatment with letrozole; of these, 1,579 (73%) of the 2,268 patients who were disease-free made use of this option [Goss, 2008]. Patients who still chose letrozole treatment were generally somewhat younger, more commonly had axillary metastases during primary treatment and had received adjuvant chemotherapy more often in comparison to the 804 patients who did not end up choosing treatment with letrozole. After a median follow-up of 5.3 years, there was an advantage for the group who was still treated with letrozole (median time after tamoxifen of 2.8 years) compared to the group who did not choose to do so, both in disease-free survival (HR 0.37; 95%CI 0.23-0.61; p<0.0001) and distant disease-free survival (HR 0.39; 95%CI 0.20-0.74; p=0.004). The ABCSG-6A study and the NSABP B-33 study also showed an advantage for anastrozole after 5 years tamoxifen [Jakesz, 2007] (HR for disease-free survival 0.62; 95%CI 0.40-0.96; p=0.031) and 2 years exemestane after 5 years of tamoxifen respectively [Mamounas, 2006].

Side-effects of hormonal therapy
While the most important side-effects of tamoxifen are thrombo-embolic complications and a slight increase in the risk of developing endometrial carcinoma, the side effects of aromatase inhibitors are mostly complaints of the postural and musculoskeletal system. Aromatase inhibitors may cause irritating arthralgias, probably as a result of minor fluid accumulation in joints and tendon sheaths. In addition, osteoporosis or osteopaenia may develop due to the extremely low level of oestrogen. As a result, the incidence of osteoporotic fractures increases during use of aromatase inhibitors. Monitoring bone density and possible treatment of osteopaenia and osteoporosis consisting of a healthy lifestyle, taking sufficient calcium and vitamin D and a bisphosphonates (if required) is therefore indicated (see Chapter 12). Some studies with aromatase inhibitors have also reported an increase in the incidence of cardiovascular complications. However, the absolute percentages are low and often not significantly different than with tamoxifen treatment, for example.

Conclusions

Level 1	Adjuvant treatment with five years of tamoxifen has a favourable influence on the five- and fifteen-year survival of women with a hormone positive, stage I or II breast cancer. Locoregional control also improves as a result of treatment. A1 EBCTCG 2005

Level 1	Adjuvant treatment with 2-3 years tamoxifen followed by 3-2 years of an aromatase inhibitor, or the reverse order (a total treatment duration of five years) provides a better disease-free survival and total survival than treatment with only five years of tamoxifen, in postmenopausal women with a hormone-positive, stage I or II breast cancer. A1 Coombes 2006, Coombes 2007, Boccardo 2005, Jackesz 2005,Jackesz 2008, Choueri 2004, Kaufmann 2007, Dowsett 2010

Level 1	Adjuvant treatment with an aromatase inhibitor for a duration of 5 years leads to a better

	disease-free survival than 5 years of treatment with tamoxifen, in postmenopausal women with an HR+ stage I or II breast cancer. A1 Howell 2005, BIG 1-98 2005, Mouridsen 2009, ATAC 2008, Cuzick 2010

Level 3	Adjuvant treatment for a duration of 3 years with an LHRH agonist in combination with an aromatase inhibitor does not lead to a difference in disease-free survival compared to treatment with an LHRH agonist in combination with tamoxifen in premenopausal women. A2 Gnant 2009

Level 1	Adjuvant inactivation or suppression of ovarian function (through surgery, radiotherapy or LHRH agonists) improves the locoregional control and total survival in premenopausal women with a hormone-positive stage I or II breast cancer. A1 EBCTCG 2005

Level 1	Addition of an LHRH agonist to tamoxifen, chemotherapy or the combination of both modalities results in a better disease-free survival in premenopausal women with hormone-positive stage I or II breast cancer. The largest reduction in the risk of a recurrence due to treatment with an LHRH agonist after chemotherapy (with or without addition of tamoxifen) is found in women under 40 years of age. A1 LHRH-agonists in Early Breast Cancer Overview Group 2007

Level 1	Extended adjuvant hormonal therapy with an aromatase inhibitor after five years of tamoxifen in postmenopausal women with a hormone-positive stage I or II breast cancer, only has a favourable influence on the disease-free survival and total survival in patients with axillary node metastases. A1 Goss 2003, Mamounas 2006, Jakesz 2007

Remaining considerations
The studies mentioned on the effects of adjuvant hormonal therapy (including chemotherapy-induced loss of ovarian function) found that such treatment lead to a significant reduction in the chance of contralateral hormone-positive breast cancer (relative reduction in the chance of 30 to 70 %) [EBCTCG, 2005; Bertelsen, 2008].

In premenopausal patients with a hormone-sensitive breast cancer, inactivation of the ovarian function in combination with tamoxifen is an acceptable alternative if treatment with chemotherapy is not desirable (on medical grounds) or if the patient declines chemotherapy.
There is insufficient data indicating that variants in the CYP2D6 genotype influence the action of tamoxifen. It is therefore not recommended that the CYP2D6 genotype is determined outside of a research context.

Strong CYP2D6 inhibitors should be avoided in the use of tamoxifen. If an antidepressant is still desired, a drug should be chosen with as little inhibitory effect on CYP2D6 as possible. For selective serotonin reuptake inhibitors this concerns venlafaxine, escilatropam and mirtazapine [Sideras, 2010].

The physician informs the patient about the possibilities regarding the choice of hormonal adjuvant treatment, taking the risk profile, types of hormonal treatments (upfront aromatase inhibitor versus sequential), side effects and the possibility of preventing osteoporosis into account. The physician and patient make a choice together.
The advantage of chemotherapy is especially limited in older patients with a (small) N_0 tumour. If a second generation schedule is not possible due to comorbidity, *Adjuvant!* (AOL) may help in the decision to recommend hormonal therapy only in this category of patients.

GENERAL recommendations (chemotherapy, endocrine therapy and trastuzumab)

The contribution of chemotherapy to (disease-free) survival advantage is limited in elderly patients with an ER+/low-stage breast cancer, especially if a second generation chemotherapy schedule is not possible due to comorbidity. With such dilemmas, Adjuvant Online may help in recommending only hormonal therapy for this category of patients.

Chemotherapy

Adjuvant chemotherapy for N +/high-risk N_0 patients with a tumour without HER-2-overexpression may consist of:

Third generation schedules:

- 6 courses of TAC
- 3 courses of $FE_{100}C$ followed by 3 courses of docetaxel three weekly
- 4 courses AC followed by 12 courses paclitaxel weekly
- 4 courses of AC followed by 4 courses of docetaxel three weekly

If a third generation schedule is not desired, treatment with a second generation schedule consisting of 4 courses of $T_{docetaxel}C$ or a first-generation schedule consisting of 4 courses of AC or 6 courses of classic CMF may be considered.

Adjuvant chemotherapy in patients with a tumour with HER-2-overexpression may consist of:

4 courses of AC chemotherapy followed by 4 courses three weekly docetaxel or weekly administrations of paclitaxel; both in combination with trastuzumab. After completing chemotherapy, trastuzumab treatment is continued to a total treatment duration of 1 year.

Note: Patients with a tumour size ≥ T_{1b} (0.5-1.0 cm) with HER-2-overexpression, may also be eligible for the abovementioned treatment. Other tumour characteristics, toxicity and an as yet uncertain effectiveness should be weighed up against each other.

Given the possible cardiotoxicity of anthracyclines and trastuzumab (the chance increases with age), LVEF should be checked before starting chemotherapy and before starting trastuzumab and subsequently every 3 months until trastuzumab therapy has ended.

Treatment with trastuzumab is sensible if the **LVEF ≥ 50- 55%** before the start of trastuzumab treatment and if the **LVEF ≥ 50%** during therapy, and has not reduced by more than 10 EF points from the start value.

Hormonal therapy

Hormonal therapy in postmenopausal women with positive hormone receptor may consist of:

A sequential treatment with two to three years of tamoxifen followed by three to four years of an aromatase inhibitor (or the reverse order) or an aromatase inhibitor for 5 years.
If there is a contraindication for one of the two drugs, treatment with the other drug for 5 years is an alternative.

If bothersome arthralgias occur as a side effect of an aromatase inhibitor, another type of aromatase inhibitor may be tried or treatment with tamoxifen may be given.
There is no particular preference for one of the three registered aromatase inhibitors in the Netherlands.

Continued treatment with an aromatase inhibitor after five years is only advised after 5 years of tamoxifen plus if there is an increased risk of a recurrence after 5 years. This especially applies to patients with axillary node metastases on primary diagnosis. The optimal duration of this extended hormonal therapy is unknown. A minimum treatment duration of 2 to 3 years is recommended:

Hormonal therapy in premenopausal women with a hormone-sensitive breast cancer consists of:

- tamoxifen for 5 years or
- the combination of 5 years of tamoxifen with oophorectomy with an LHRH agonist for (2 to) 5

years, (or definitive ovarian inactivation). There is insufficient data regarding superiority of one of these two modalities, although addition of LHRH agonists to chemotherapy (with or without) tamoxifen provides a small additional advantage for women to 40 years of age.

Aromatase inhibitors do not work with intact ovarian function, and are therefore contraindicated as single hormonal therapy in premenopausal women.

Indication and recommendation for adjuvant systemic therapy:

N+	All patients, unless 70+ with a hormone receptor negative tumour (*although chemotherapy may be considered for fit 70+ patients with a hormone-negative tumour*)
Unfavourable N0:	▪ age < 35 years, except with a grade I tumour ≤ 1cm ▪ age ≥ 35 years with a tumour of 1.1-2 cm and grade II or higher *(If the tumour is 1.1-2 cm, grade II, HER-2-negative, but ER and PgR > 50%, hormonal therapy without chemotherapy may be considered for postmenopausal patients)* ▪ age ≥ 35 years with a tumour > 2 cm ▪ if HER-2-positive tumour ≥ T_{1b} (0.5-1 cm), treatment may be considered independent of other characteristics. Toxicity and an as yet uncertain effectiveness should be weighed up against each other.

The choice of systemic therapy

(for a quantitative impression of the advantage in (disease-free) survival that may be expected for the treatment selected: see the *Adjuvant!* programme (AOL)).

Hormonal therapy	
Indication	If ER+ and/or PgR+ (no maximum age)
Which hormonal therapy?	Premenopausal: ▪ ovarian inactivation (possibly LHRH agonist for 5 years) plus 5 years of tamoxifen or ▪ 5 years of tamoxifen Postmenopausal: ▪ 2-3 years of tamoxifen, followed by 3-2 years of an aromatase inhibitor or the reverse order ▪ 5 years of an aromatase inhibitor ▪ extended (after 5 years tamoxifen) 2 years aromatase inhibitor at a high residual risk (N+) For men: ▪ 5 years of tamoxifen

<table>
<tr><td>Chemotherapy</td><td colspan="2"></td></tr>
<tr><td>Indicatie</td><td colspan="2">If ER- and PgR-
▪ to 70 years, both N+ and unfavourable N0 (chemotherapy may be considered for fit 70+ patients with a hormone receptor negative tumour)
If ER+ and/or PgR+:
▪ to 70 years, both N+ and unfavourable N0.

The added value of chemotherapy alongside hormonal therapy may be limited in elderly patients, it is recommended to consider the calculated advantage using Adjuvant online.</td></tr>
<tr><td rowspan="3">Which chemotherapy?

Take the condition of the patient into account and possibly choose a lighter form of chemotherapy

Identical treatment is recommended for men</td><td>HER-2-positive

Both with N+ and unfavourable N0</td><td>▪ 4 x q3wk AC → 12 x q1wk paclitaxel or
▪ 4 x q3wk docetaxel

Both courses (at the start of taxane) in combination with trastuzumab, trastuzumab to 1 year</td></tr>
<tr><td>HER-2-negative

Both for N+ and unfavourable N0</td><td>Third generation schedule:
▪ 6 x TAC + primary G-CSF or
▪ 3 x FE100C → 3 x docetaxel or
▪ 4 x AC → 4 x q3wk docetaxel or
▪ 4 x AC → 12 x q1wk paclitaxel</td></tr>
<tr><td>If a third generation schedule is not possible or desirable</td><td>Second and first generation schedule:
▪ 4 x T(docetaxel)C
▪ 4 x AC of 6 x CMF</td></tr>
<tr><td>Trastuzumab</td><td colspan="2"></td></tr>
<tr><td>Indication for trastuzumab</td><td colspan="2">HER-2+++ (IHC) and/or FISH+; LVEF ≥ 50-55% shortly prior to starting trastuzumab</td></tr>
<tr><td>Checks</td><td colspan="2">Check LVEF before starting chemotherapy and before starting trastuzumab and subsequently every 3 months until completion of trastuzumab.

If LVEF ≥ 50% and has not reduced by more than 10 EF points from the starting value; trastuzumab treatment is justified.</td></tr>
</table>

6.3 The order of chemotherapy, hormonal therapy, trastuzumab and radiotherapy

Locoregional control and improvement in survival are the most important goals when treating primary breast cancer. Both treatment with radiotherapy and systemic therapies result in survival advantage [Huang, 2003].

There are no randomised studies that have researched the optimal order of adjuvant hormonal therapy and radiotherapy. Retrospective studies show that simultaneous administration of tamoxifen and radiotherapy does not have an effect on treatment results [Pierce, 2005; Ahn, 2005; Harris, 2005]. It applies to both chemotherapy and radiotherapy that delaying therapy until after completing the first therapy commenced is not desirable [Bellon, 2005; lorisch, 2006]. In principle, adjuvant chemotherapy and radiotherapy may be administered simultaneously. However, the experience is that simultaneous treatment with anthracycline-containing chemotherapy and radiotherapy leads to more toxicity. Simultaneous administration of these two therapy modalities is therefore contra-indicated . CMF and radiotherapy may be administered simultaneously [Dubey, 1999; Markiewicz, 1998; Fiets, 2003]. Randomised studies on the optimal order of both modalities are limited. In a systematic review, Huang (2003) showed that delaying radiotherapy for longer than 8 weeks leads to a reduction in locoregional control. Hickey (2006) based the conclusions in a Cochrane review on the results of three randomised studies. In two studies, chemotherapy followed by radiotherapy was compared to simultaneous administration of both treatments. The third study compared radiotherapy followed by chemotherapy with the reverse order [Bellon, 2005]. The conclusion of this review is that a different order in treatments does not have an effect on the (disease-free) survival if radiotherapy is commenced within 7 months after surgical treatment. Balduzzi (2010) concludes that, while the different studies appear to

yield conflicting results, it is justified to administer treatment with chemotherapy prior to radiotherapy in certain subgroups of patients with a high chance of occult distant metastases (N+ or HR patients), as long as the excision margins for these patients are sufficiently clear.

There are insufficient data on the cardiac toxicity of sequential administration of trastuzumab and radiotherapy compared to simultaneous administration. Given the potential cardiotoxicity, care should be taken into account with simultaneous administration.

Conclusions

Level 2	It is not known what the optimal order is of adjuvant chemotherapy and radiotherapy. B Hickey 2006, Huang 2003, Bellon 2005, Balduzzi 2010

Level 3	Delaying radiotherapy (after conserving treatment as well as mastectomy) for more than 8 weeks after surgery leads to an increased chance of a locoregional recurrence. This also applies if this delay is the result of adjuvant chemotherapy administered previously. B Huang 2003

Level 3	Simultaneous administration of anthracycline-containing adjuvant chemotherapy and radiotherapy leads to a greater chance of toxicity. Simultaneous administration of CMF and radiotherapy leads to a limited level of extra toxicity. C Dubey 1999, Markiewicz 1998, Fiets 2003

Recommendations

On the basis of the expected survival advantage, a pronouncement cannot be made in relation to the optimal order of radiotherapy and chemotherapy.

The simultaneous administration of radiotherapy and chemotherapy are advised against. This especially applies to anthracycline-containing schedules.

6.4 Adjuvant therapy with bisphosphonates

Two of the three published studies concerning adjuvant clodronate for breast cancer showed a survival advantage [Diel, 2008; Powles, 2006]. One study showed no difference [Saarto, 2004]. Two studies [Gnant, 2009; Eidtmann, 2010], described a disease-free survival advantage for the addition of zoledronate to standard adjuvant hormonal therapy. The Austrian breast cancer study group randomised 1,800 premenopausal women with hormone-receptor positive stage I-II breast cancer between 3 years of tamoxifen or 3 years of anastrozole, in combination with goserelin in both groups, and between receiving or not receiving zoledronic acid 4 mg i.v. 1x6 months for 3 years (2x2 factorial design). Only 5.4% of patients had received (neo)adjuvant chemotherapy. Eighty-five percent of patients had a strong hormonal therapy-sensitive tumour. There was no difference in recurrence-free survival between tamoxifen or anastrozole, but there was a 35% reduction in the chance of recurrence for the group that had received zoledronic acid (HR 0.65; 95%CI 0.46-0.92). It was also notable that aside from bone metastases, the group that had received zoledronic acid also had significantly less visceral metastases [Gnant, 2009]. Comparable results were reported for stage I-IIIa postmenopausal, ER+ and/or PgR+ breast cancer patients, who had received adjuvant letrozole for 5 years and in addition were randomised between an immediate start with zoledronic acid 4 mg i.v. 1x6 months or not until a fracture occurred or patients were at an increased risk of fracture [Eidtmann, 2010]. After a median follow-up of 36 months, an immediate start with zoledronic acid was found to give a 41% risk reduction in recurrence (HR 0.59; 95%CI 0.36-0.96; log-rank p=0.031) [Eidtmann, 2010]. The data of the AZURE study was presented during an as yet unpublished presentation at the San Antonio breast cancer symposium [Coleman, 2010]. This study randomised 3,360 patients with stage II-III breast cancer between receiving and not receiving zoledronate (6x4 mg i.v. q 3 or 4 weeks, 8x4 mg i.v. q 3 months, and 5x4 mg i.v. q 6 months) as an addition to standard adjuvant systemic therapy for a duration of 5 years. Of these patients, only 31% were more than 5 year postmenopausal, 78% were ER+, 32% had a T_1 tumour, and 95% had undergone adjuvant chemotherapy. With a median follow-up of almost 5 years, there was no difference in disease-free survival (multivariate HR 0.98; 95%CI 0.85-1.13; p=0.79). ER status was not found to play a role in analyses of subgroups defined beforehand, but menopausal status was. In women who were more than 5 years postmenopausal,

addition of zoledronate provided an improvement in survival (multivariate HR 0.71; 95%CI 0.54-0.94; p=0.017). This group showed a reduction in locoregional recurrences, as well as in bone metastases and visceral metastases. There was no added value for zoledronate in the other group. Coleman (2010) concluded that adjuvant bisphosphonates only work in an oestrogen-poor environment.

Toxicity
In one-third of patients treated with a bisphosphonate, an acute phase reaction develops after the first administration of i.v. of the monthly oral dose, including fever, muscle ache, and lymphopaenia [Watts, 2010]. Osteonecrosis of the jaw is a relatively rare, but serious complication in which jaw bone becomes exposed and does not heal within 8 weeks [Khosla, 2007]. Bisphosphonate therapy for osteoporosis rarely leads to this disorder (1 in 10,000 to <1 in 100,000 patient years), but the risk is much higher in cancer patients (1-10 per 100 patients) [Khosla, 2007]. Particular risk factors are treatment with zoledronate, pamidronate followed by zoledronate, higher cumulative doses of bisphosphonates, poor oral hygiene and interventions of the jaw bone [Hoff, 2008]. It is important to inform patients of possible side effects prior to starting treatment and to ensure any interventions of the jaw are carried out first. In case of unavoidable interventions during bisphosphonate therapy, it is recommended that prophylactic antibiotics are administered prior to the intervention [Woo, 2006]. Osteonecrosis of the jaw appears to be a rare side effect of oral bisphosphonates [Woo, 2006]. Bisphosphonates may be administered if there is a clearance of at least 30 ml/min. Renal function disorders are related to the peak dose and rarely occur with correct intravenous administration [Watts, 2010].

Conclusions

Level 2	There are indications that zoledronic acid added to standard adjuvant systemic therapy in a hypo-oestrogenic setting may reduce the chance of recurrence. A2 Gnant 2009 B Eidtmann 2010, Coleman 2010

Remaining considerations
Preclinical and partly also clinical research suggests that bisphosphonates inhibit tumour cell proliferation, inhibit angiogenesis and stimulate γδ T cell antitumour activity. In addition, they inhibit tumour cell adhesion to bone and extracellular matrix [Clezardin, 2005]. However, trial results are not univocal and the beneficial effect of these agents is probably limited to a particular subgroup of patients that cannot be clearly defined yet. Use of these agents as adjuvant therapy has therefore not yet become standard.

Recommendations
On the basis of current insights, there is no role yet for adjuvant bisphosphonates alongside standard adjuvant systemic therapy. If bisphosphonates are indicated for progressively increasing osteopaenia resulting in osteoporosis, these agents may have an additional favourable effect on the risk of recurrence.

Neoadjuvant systemic therapy for breast cancer with locoregional metastasis and operable breast cancer

In the second half of the 20th century, breast cancer with local metastasis was synonymous with irresectable breast cancer. The existence of skin oedema (peau d'orange), ulceration, skin satellites, inflammatory carcinoma (T_4), axillary node metastases fixed to each other or the chest wall, clinically detectable parasternal node metastases (N_2), a combination of these or infra- or supraclavicular node metastases (N_3) or lymph oedema (caused by the tumour growth) of the arm were signs of irresectability. Patients with these stages of the disease had an extremely poor prognosis and a high chance of a locoregional recurrence after radical mastectomy or even supraradical procedures [Haagensen, 1986; Haagensen, 1963; Dahl-Iversen, 1963]. Patients were treated with radiotherapy (only), with a complete response chance of 70-90%, but a moderate local control (50-80%) and poor survival (30-40%) [van Limbergen, 1990; Borger, 1992; van Tienhoven, 1995]. In the 70's and 80's, neoadjuvant chemotherapy and surgery were added to the treatment arsenal to improve locoregional control and in the hope of better survival [Hortobagyi, 2000]. With neoadjuvant chemotherapy, some tumours that were initially irresectable become smaller and more accessible to surgery, and local control improved.

While large local tumours (T_3;> 5 cm) belong to stage II according to the latest TNM classification, and are closer to T_2N_0 tumours in terms of prognosis than tumours with locoregional metastasis [Floyd 2006, Taghian 2006, Mignano 2007], T_3 tumours were also increasingly treated with neoadjuvant chemotherapy, surgery, radiotherapy and hormonal treatment (of hormone-receptor positive) [Hortobagyi, 2000; Valero, 1996; Eltahir, 1998]. By way of neoadjuvant treatment, the extent of the tumour metastasis could sometimes be limited. In recent years, neoadjuvant chemotherapy is increasingly being applied to earlier stage breast cancer, such as in patients with clinically positive lymph nodes and/or larger T_2 tumours. Some start with neoadjuvant chemotherapy for all patients for whom it can be established beforehand that adjuvant chemotherapy is indicated on the basis of age and/or tumour characteristics. Advantages are the ability to more often provide breast-conserving treatment, and the ability to evaluate the sensitivity of the tumour for chemotherapy (and stopping this therapy early or adjusting it if required).
However, this new treatment order for early stage breast cancer has also lead to some new dilemmas. These dilemmas concern the question which patients are eligible for this treatment, the choice of systemic therapy, the management plan if there is an absence in response or disease progression, the safety in relation to the chance of locoregional recurrence, selection for and timing of the SN procedure, and the extensiveness of local surgery and radiotherapy treatments.

There are differences between patients with an early stage (stage II) breast cancer and a breast cancer with locoregional metastasis (stage III) [Sobin, 2009] in relation to a number of aspects of treatment. Inflammatory carcinoma or mastitis carcinomatosa is a separate category, which is characterised by diffuse redness, peau d'orange and possible swelling of the entire (or at least more than a third of the) mammary (TNM Classification T_{4D}, stage III). The 5-year survival rate reported varies between 20-50%, and is mainly dependent on the definition used [de Boer, 2000; Yang, 2006; Abrous-Anane, 2011]. The neoadjuvant and subsequent locoregional treatment of both groups (stage II and III) is outlined in this chapter. Where necessary, the differences are highlighted.

Definitions:

Stage IIA:	T0-1N1 or T 2N0
Stage IIB:	T2N1 or T3N0
Stage IIIA:	T0-2N2 or T3N1-2
Stage IIIB:	T4N0-2
Stage IIIC:	each TN3

Postoperative classification is indicated by a p before the T or N classification.
Post neoadjuvant therapy classification is indicated by a y before the T, N, pT or pN classification.

7.1 Diagnostics

Prior to the first treatment, each breast cancer patient should be discussed within the framework of multidisciplinary consultation. If this leads to a recommendation of neoadjuvant chemotherapy, higher demands are made of the diagnostics prior to treatment then when primary surgery is recommended.

After primary surgery, tumour type, size, grade, hormone sensitivity, HER-2 amplification, angioinvasion, radicality of resection and lymph node positivity follow from histological diagnostics of the surgical tissue (mastectomy or lumpectomy and SN or ALND). Some of this information may be lost after neoadjuvant therapy. A histological diagnosis must therefore be made prior to treatment with a thick needle biopsy, in which the hormone receptors, HER-2 receptor and other prognostic characteristics may also be analysed. The location, size and metastasis of the local tumour must be documented carefully, also using clinical images, as well as any presence of additional tumour foci. This is best done using MRI, unless reliable determination is possible with mammography and/or ultrasound [Berg, 2004; Deurloo, 2005; Sardanelli, 2004]. Prior to treatment, locoregional treating physicians (surgeon, radiotherapist and oncologist) should see the clinical point of departure and preferably document the situation using clinical images, in order to adequately determine the clinical response. Given a (clinical) complete remission may occur, the location of the tumour needs to be marked with radio-opaque markers prior to neoadjuvant therapy; this is of benefit to both the surgeon and pathologist [Nadeem 2005, Oh 2007].

A good clinical and radiological determination of the axillary node status, including the level of the number of suspected lymph nodes prior to starting chemotherapy is also essential. The clinical or echographic suspicion of axillary node metastases must be confirmed before treatment using punction. An SN procedure after neoadjuvant chemotherapy appears to be less reliable. Xing (2006) performed a meta-analysis of 21 studies, in which 1,273 patients underwent an SN procedure after neoadjuvant chemotherapy, and found an identification percentage of 90% and a false negative percentage of 12%. A large proportion of patients in these studies initially had a $cT_{1-2}N_0$ stage. A small retrospective study in patients with axillary node metastasis cytologically documented prior to chemotherapy and clinically negative axillary after chemotherapy showed an extremely high false negative percentage of sentinel node cancer of 25% [Shen, 2007]. A more recent meta-analysis confirmed that especially the negative predictive value of an SN procedure is low after neoadjuvant chemotherapy [Van Deurzen 2009]. In contrast, no difference in reliability of the SN after neoadjuvant therapy was found in the NSABP-B27 study for patients with initial cN_0 versus cN+ breast cancer [Mamounas, 2005]. An SN procedure is therefore recommended prior to chemotherapy for clinically and radiologically node-negative tumours for optimal clarity.

Conclusions

Level 2	Approximately 88-89% of patients with positive lymph nodes and primary resectable breast cancer are detected with an SN procedure after neoadjuvant chemotherapy (false negative percentage 11-12%). B Xing 2006, Van Deurzen 2009

Level 3	An SN procedure after chemotherapy for patients with an initial T1-2N+ classification appears to be less reliable in determining downstaging. C Mamounas 2005, Shen 2007

Remaining considerations

The chance of synchronous distant metastasis in stage III breast cancer is greater than with an early stage [Samant, 1999; Ciatto, 1988; Norum, 2000]. Staging to exclude synchronous distant metastasis is therefore recommended in this situation (stage III). Both a conventional staging procedure and FDG-PET-CT may be considered. The advantage of FDG-PET is the high specificity in staging the axillary and other regional node areas, to enable further detailing of locoregional metastasis. Given there is no information about the number of positive regional nodes prior to neoadjuvant treatment and this number also cannot be reliably determined after neoadjuvant treatment, staging via FDG-PET-CT may also be considered with stage II (especially if there are clinically positive nodes).
If there are synchronous distant metastases, multidisciplinary treatment choices must be made on an individual basis, dependent on the nature and prognostic significance of the locoregional situation and distant metastases. This chapter focuses on stage II or II breast cancer, i.e. without manifested distant metastases.

Recommendations

Neoadjuvant systemic therapy is indicated for breast cancer with locoregional metastasis (stage III).

Neoadjuvant systemic therapy may also be considered for stage II mammary tumours in which there is already an indication for systemic therapy at the time of diagnosis and in which tumour reduction is desirable in relation to a preference for BCT.

Preconditions for starting neoadjuvant therapy

General
- multidisciplinary consultation
- document cTNM and treatment plan within multidisciplinary consultation
- clinical evaluation by the surgeon, radiotherapist and oncologist prior to starting chemotherapy

Breast diagnostics
- histological biopsy: determination of the tumour grade, hormone receptors and HER-2 amplification
- accurate documentation of the initial tumour size and metastasis by means of MRI (unless it can be determined well using mammography and ultrasound)
- photograph cT4 tumours in order to record metastasis in the skin
- placing a radio-opaque marker independent of whether mastectomy or BCT is chosen

Regional diagnostics
- recording axillary node status clinically and via ultrasound
- if cN1-3: cytological confirmation
- if cN0: SWK procedure preferably prior to neoadjuvant treatment

Screening for distant metastasis
- indicated with stage III breast cancer
- consider for stage II clinical N+ breast cancer

7.2 Neoadjuvant systemic therapy

7.2.1 Chemotherapy

In the overview by the Early Breast Cancer Trialists Collaborative Group [EBCTCG, 2005], it is demonstrated that adjuvant chemotherapy provides a clear survival advantage for stage II breast cancer. This has not been separately studied for tumours with locoregional metastasis (stage III), but systemic chemotherapy is generally accepted for this stage of disease. An essential question is whether neoadjuvant chemotherapy is at least as effective as adjuvant chemotherapy. Nine phase III studies were identified in a meta-analysis, in which a total of approximately 4,000 patients were randomised for the same chemotherapy, neoadjuvant versus postoperative adjuvant [Mauri, 2005]. However, most of these studies used first or at the most second generation chemotherapy schedules, sometimes in combination with endocrine therapy. Almost all studies included patients with a clinical stage $T_{1-4}N_{0-2}$. This meta-analysis did not find a difference in the survival rate (RR 1.0; 95%CI 0.90-11.2), or disease progression (RR 0.99; 95%CI 0.91-1.07).

Conclusion

Level 1	The neoadjuvant administration of first, second or third generation chemotherapy in patients with a primary operable or locally metastatic breast cancer (cT1c-4 and cN0-2) provides a disease-free and total survival that is comparable to postoperative administration of the same therapy. A1 Mauri 2005, Mieog 2007 A2 Bear 2006

Treatment plan if there is no response to neoadjuvant chemotherapy

The response rate after neoadjuvant chemotherapy is 80-90% and the risk of progression less than 5-10% [Kaufmann, 2006]. There is no clear treatment plan if there is progression (RECIST > 20% increase in diameter) during chemotherapy. The choice could be made to switch to local treatment earlier or to switch to an alternative, non-cross-resistant chemotherapy.

In the Gepartrio pilot study, patients with a clinical response after two courses of TAC neoadjuvant

chemotherapy were treated with another four courses of TAC. Patients who had no clinical response after two courses were randomised between another 4 courses of TAC or switching to vinorelbine/capecitabine [von Minckwitz, 2005]. The patients with a clinical response after two courses had a pCR in 23% of cases. In 7.3% of cases, the clinical non-responders had a pCR when continuing with TAC, versus 3.1% in patients who already switched early to a non-cross-resistant schedule. Vinorelbine/capecitabine was found to be less effective than continuing with TAC in patients with stable disease. It therefore does not seem desirable to already determine after two courses that there is insufficient response to chemotherapy.

The Aberdeen study still achieved a 55% clinical response with non-responders (stable disease or progression) on second generation anthracycline-containing neoadjuvant chemotherapy when therapy was switched to docetaxel. The patients with a clinical response to anthracycline neoadjuvant chemotherapy also had a doubling in the pCR percentage (from 15% to 31%) and an increase in the five-year survival from 78% to 93% after switching chemotherapy to docetaxel. In the subgroup without clinical response to AC chemotherapy in the larger NSABP-B27 study, there was no advantage provided by the addition of docetaxel, while patients who did have a clinical response to the disease-free survival did improve significantly (HR 0.71) [Bear, 2006]. In an MD Anderson Cancer Centre (MDACC) study, 106 patients with insufficient response (residual tumour following surgery of more than 1 cm^3) were randomised for postoperative continuation of the anthracycline-containing neoadjuvant schedule or switching to an alternative non-cross-resistance schedule (vinorelbine, methotrexate and 5-FU). The trend was better survival of patients treated with the alternative [Thomas, 2004].

7.2.2 Neoadjuvant hormonal therapy

Adjuvant hormonal therapy improves survival in both stage II and stage III breast cancer, as long as the tumour contains a positive oestrogen receptor and/or progesterone receptor [EBCTCG, 2005]. There is less known about the value of hormonal therapy in the neoadjuvant setting. No studies have been performed that compare preoperative and postoperative hormonal therapy. In relation to responders, it must be noted here that in contrast to chemotherapy, neoadjuvant hormonal therapy is added to standard adjuvant hormonal therapy.

A number of studies have been performed with neoadjuvant hormonal therapy, especially in postmenopausal patients. In a few phase II studies, clinical response percentages between 35 and 60% were found, but low pathological complete response percentages [Ellis, 2001; Mlineritsch 2008; Takei, 2008]. One phase II study randomised 180 patients between neoadjuvant exemestane, neoadjuvant anastrozole and neoadjuvant chemotherapy and found no difference in the chance of objective response (64%), chance of pathological response (3 vs 6%) and the possibility of breast-conserving surgery between hormonal therapy and chemotherapy [Semiglazov, 2007]. A few studies randomised between tamoxifen and an aromatase inhibitor. In the randomised IMPACT study, no significant difference was seen in the response rate between tamoxifen and aromatase inhibitor [Smith, 2005]. In two other randomised studies, the Letrozole P024 study and the much larger PROACT study, an aromatase inhibitor was found to give a somewhat better response percentage than tamoxifen [Eierman, 2001; Cataliotti, 2006]. In the last study, in which 451 patients participated, simultaneous administration of chemotherapy was permitted and administered to 44% of patients. The response percentages were comparable for patients who had only received hormonal therapy, or combined therapy. Similar to neoadjuvant chemotherapy, all studies mention resectability where this did not appear possible initially and/or breast-conserving surgery while a mastectomy had previously been planned.

Conclusion

Level 3	There are no randomised studies available comparing neoadjuvant hormonal therapy with the same hormonal treatment postoperative. Similar to chemotherapy, neoadjuvant hormonal therapy appears to make downstaging possible for hormone receptor-positive tumours, with an improved chance of radical surgery in stage III or BCT where mastectomy initially seemed necessary. Comparison of the response percentage between neoadjuvant tamoxifen and aromatase inhibitor is in favour of the aromatase inhibitor for postmenopausal patients.

	B	Eierman 2001, Smith 2005, Cataliotti 2006, Semiglazov 2007
	C	Ellis 2001, Mlineritsch 2008, Takei 2008

Remaining considerations

In many patients with an indication for adjuvant hormonal therapy, there is also an indication for chemotherapy. If a neoadjuvant setting is chosen due to irresectability of the locoregional disease or for the purposes of downstaging to better provide breast-conserving treatment, it seems logical to choose the therapy with the best response percentages. Chemotherapy appears to lead to better pathological response percentages than neoadjuvant hormonal therapy. While comparable response percentages in the randomised phase two trial of Semiglazov (2007) within this framework are intriguing, and although some suggest that the response percentages of hormone receptor positive, HER-2-negative tumours after chemotherapy would be worse than after hormonal therapy, there is insufficient evidence to date to make a positive choice for neoadjuvant hormonal therapy [Iwata, 2010]. Neoadjuvant hormonal therapy seems a good possibility in older and vulnerable patients. The optimal duration of neoadjuvant hormonal therapy is unclear (most studies report 3 to 6 months or more). Disease regression occurs slowly. One should strive for maximum regression and in any case not wait until the tumour is progressive again.

7.2.3 Neoadjuvant trastuzumab

A few studies have been published in which the role of neoadjuvant trastuzumab has been researched [Buzdar, 2005; Kaufman, 2006; Chang, 2010]. A randomised study of the MDACC was closed after 42 patients because the aim had been achieved, namely improvement in the pCR percentage from 26.3% to 65.2%. The three-year recurrence-free survival increased from 85% to 100% (p=0,041) [Buzdar, 2005; Buzdar, 2007]. The Noah trial randomised 228 patients with locoregional metastatic (stage III) HER-2-positive breast cancer for neoadjuvant chemotherapy with or without trastuzumab [Gianni 2010]. The clinical response percentage improved from 71 to 87% and the pCR percentage from 19 to 38%. With a median follow-up of 3.2 years, the primary endpoint improved: an increase in the three-year disease-free survival from 56 to 71% (HR 0.59; 95%CI 0.38-0.90; p=0.013). In a series of 109 patients with demonstrated axillary node metastases prior to treatment, the axillary pCR percentage was found to be 74% after neoadjuvant chemotherapy with trastuzumab [Dominici, 2010].

Conclusion

Level 2	The addition of trastuzumab to neoadjuvant chemotherapy improves the pathological complete response percentage.	
	B	Buzdar 2005, Buzdar 2007, Gianni 2010

Remaining considerations

With a doubling of the pCR percentage, neoadjuvant treatment with trastuzumab has shown encouraging results compared to no trastuzumab. No studies have been performed to see whether neoadjuvant chemotherapy with trastuzumab is better than or equivalent to postoperative adjuvant chemotherapy with trastuzumab. It is therefore attractive to add trastuzumab neoadjuvant to chemotherapy in patients with HER-2-overexpression and indication for systemic therapy, in order to be able to perform breast-conserving surgery more often.

In the study by Buzdar (2007), trastuzumab was administered for a duration of 24 weeks. Local therapy (surgery/radiotherapy) was postponed until 24 weeks after diagnosis. Now that the standard total treatment duration is one year, it is unclear what the best timing of locoregional treatment should be after neoadjuvant treatment with trastuzumab. A delay in locoregional therapy until one year after diagnosis hardly seems attractive. In general, it is therefore recommended to commence local therapy after completing chemotherapy and to continue trastuzumab postoperatively as adjuvant treatment. The choice of neoadjuvant chemotherapy with HER-2 inhibition is in accordance with the adjuvant setting.

In a series of 142 patients with a pCR percentage of 50%, the HER-2 was determined again. In 8 of the 25 patients, in which it could still be measured, HER-2-overexpression could no longer be detected [Mittendorf 2009]. For the time being, it is still unclear whether and how determining the HER-2 status again in the definitive surgical sample should influence postoperative treatment. Given it does not have therapeutic consequences for the time being, renewed determination of the HER-2 status can be left out.

Recommendations

Neoadjuvant chemotherapy

- The choice of chemotherapy depends on tumour characteristics, age and performance, in accordance with adjuvant chemotherapy
- Neoadjuvant therapy consists of 6, to a maximum of 8 courses, in accordance with adjuvant schedules
- Response evaluation should not take place earlier than after 3-4 courses, except if progression is evident at an earlier stage
- The treatment plan with stable disease is to continue chemotherapy, because a pathological response may still occur
- With evident progression during sequential anthracycline-taxane treatment (RECIST increase > 20% in largest diameter), an earlier switch must be made to a taxane
- Locoregional therapy is indicated if there is evident progression while the patient is on a taxane-containing combination

Neoadjuvant hormonal therapy

- Neoadjuvant hormonal therapy is an alternative to chemotherapy in elderly and fragile patients with hormone receptor-positive tumours.
- If neoadjuvant hormonal therapy is chosen, aromatase inhibitors are preferable to tamoxifen for postmenopausal patients.
- Locoregional therapy must generally be started after 3-6 months, no later than with a maximum response.

Neoadjuvant trastuzumab

- The addition of trastuzumab to neoadjuvant chemotherapy must be considered for patients with HER-2-overexpression who are eligible for neoadjuvant chemotherapy

Additional adjuvant therapy (after locoregional treatment)

- Continuing trastuzumab until one year after commencement
- Continuing hormonal treatment until at least 5 years after commencement

7.3 Local treatment

Treatment consists of surgery and radiotherapy. While local and regional treatment cannot always be separated, the local treatment of breast and regional lymph node stations are discussed separately in the below sections. While mastectomy or lumpectomy were always conducted together with axillary node dissection in the past, local and regional treatment are considered more as separate entities these days. This certainly applies after neoadjuvant systemic therapy, because in this situation the diagnostic aspect of the ALND no longer applies, because the initial axillary status (prior to neoadjuvant systemic therapy) is already known.

7.3.1 Surgery

Neoadjuvant chemotherapy is commenced with irresectable stage III breast cancer with the aim of making surgery possible by reducing the tumour load prior to the intervention. There are strong indications that reducing the tumour load improves the locoregional effect of radiotherapy [Yang, 2006]. Most authors recommend surgical removal of the residual tumour prior to irradiation [Machiavelli, 1998; Recht, 2000; Daveau, 2010]. A French series of 232 patients also showed the addition of surgery provides an advantage with inflammatory breast cancer (T_{4D}) [Abrous Anane, 2011]. It is possible with inoperable stage III breast cancer that the disease has not responded sufficiently to the neoadjuvant treatment and is still irresectable. Fortunately this is rare. In that case, the addition of surgery after radiotherapy is an option, but there is no evidence or consensus on this.

<u>Breast-conserving surgery after neoadjuvant therapy (instead of mastectomy)</u>

With larger operable tumours, an important reason to initiate neoadjuvant chemotherapy is to make BCT possible where this initially did not appear possible. An important question is whether clear indications can be formulated on when (not) to perform breast-conserving surgery. In the NSABP-B27 study, 87% had a clinical objective response and 26.1% a pCR (including 7.2% DCIS) to AC-docetaxel neoadjuvant chemotherapy [Bear, 2006]. In the meta-analyses of neoadjuvant versus postoperative adjuvant chemotherapy, a significant reduction in the number of mastectomies was seen with the use of neoadjuvant chemotherapy (absolute reduction 16.6%; 95%CI 15.1-18.1%) [Mieog, 2007].

It is the question as to what extent the choice for BCT in this category of patients has a negative

influence on local control. An increased risk of locoregional recurrences was found in the meta-analyses with the use of neoadjuvant chemotherapy (RR 1.22; 95%CI 1.04-1.43). This risk was only elevated in three studies, in which patients with a clinical complete remission [Mauriac, 1999] did not undergo breast surgery [Broët, 1999; Gazet, 2001; Scholl, 1994]. The relative risk in these three studies was 1.53 (95%CI 1.17-2.00). In the remaining studies together, in which breast surgery was performed, no significant elevation in risk was seen (RR 1.10; 95%CI 0.87-1.38). The poorer local control after neoadjuvant chemotherapy therefore appears to be explained by the fact that the macroscopic residual tumour or even the amount of tumour remaining in a clinical complete remission is too much for the radiotherapy alone to get under control. In a French series of 165 patients with a cCT following neoadjuvant chemotherapy, 100 patients who were treated exclusively with radiotherapy showed a trend of poorer locoregional control than the 65 patients with cCR who received a lumpectomy and radiotherapy [Daveau, 2010]. A combination of surgery and radiotherapy is therefore necessary as locoregional treatment even with a clinical complete remission [Mauri, 2005; Mieog, 2007; Daveau, 2010]. A possible additional explanation for the poorer local control after neoadjuvant chemotherapy is the postponement of locoregional treatment [Huang, 2003].
The same considerations apply in the choice of breast-conserving surgery as with primary surgical treatment. Diffuse microcalcifications throughout the breast form a contraindication, because calcifications will not disappear with neoadjuvant therapy [Buchholz, 2003; Buchholz, 2008]. Multicentric tumours also make the choice for BCT less logical unless with a good response, all the marked original tumour-containing areas can be radically excised. If a resection that is more than focal is irradical, the risk of recurrence is elevated and re-excision is recommended.
Researchers of the MDACC developed a prognostic index based on a prognostic study with 340 patients who underwent a BCT after neoadjuvant therapy, [Chen, 2005]. According to this index, patients with two or three of the following factors should have an unacceptably high risk of recurrence (12% and 18% after 5 years respectively) if they receive breast-conserving treatment after neoadjuvant chemotherapy: cN_2 or cN_3, residual pathological tumour > 2cm, lymphangio-invasion or a multifocal pattern of the residual tumour. There are also a few negative points associated with this study, the subgroup of patients with multiple factors was small. Positive excision margins were very limited in this study so that this factor could not be analysed. Patients in this study had a remission of all skin abnormalities, had no macroscopic residual tumour and no residual abnormalities on the mammogram. It therefore involved a selected group [Chen, 2005].

The prognostic index was validated using another dataset, namely 815 patients who after neoadjuvant chemotherapy had undergone surgery (BCT or mastectomy with ALND) and radiotherapy [Huang, 2006]. At a score of 0/1, the ten-year locoregional recurrences were low for mastectomy with ALND as well as BCT. At a score of 2 however, there were lower locoregional recurrence percentages for mastectomy with ALND versus BCT (12% versus 28%). For patients with a score of 3 or 4, recurrence percentages of 19% were even found after ten years following mastectomy with ALND versus 61% after BCT. BCT therefore appears safe, subject to good selection based on the abovementioned factors.

Conclusions

Level 1	In stage II breast cancer, neoadjuvant chemotherapy leads to an increase in the number of breast-conserving treatments. A1 Mauri 2005, Mieog 2007

Level 1	In studies in which local surgery was not performed following a good response to neoadjuvant chemotherapy, the risk of locoregional recurrences was higher than when local surgery was performed. A1 Mauri 2005, Mieog 2007

Level 3	After neoadjuvant chemotherapy for breast cancer with locoregional metastasis, surgical removal of the residual tumour (if possible) leads to better local control. C Pierce 1992, Mauri 2005, Mieog 2007, Daveau 2010, Abrous-Anane 2010

Level 2	After neoadjuvant chemotherapy and if BCT is chosen, patients with two or more of the following factors have an increased risk of locoregional recurrence:

	• cN_{2-3} classification before starting chemotherapy • a multifocal residual tumour • a residual tumour > 2 cm on pathology analysis • lymphangio-invasion in biopsy or in the postoperative specimen B Chen 2005, Huang 2006

7.3.2 Radiotherapy of the breast or chest wall

In principle, the same indications apply after neoadjuvant chemotherapy for postoperative radiotherapy as with patients who have not undergone neoadjuvant chemotherapy. Postoperative locoregional radiotherapy reduces the risk of locoregional recurrence and long-term survival with large tumours (≥ T_3) and tumours with more than 3 positive nodes (≥ pN_2) [EBCTCG, 2000]. Possibly also with 1-3 positive nodes (pN_1) [Overgaard, 1999; Ragaz, 2005]. However, there are a few uncertainties. The indications for radiotherapy after BCT or mastectomy with ALND and the regional node areas are traditionally partially based on postoperative pathological criteria. This pathological data is unreliable after neoadjuvant therapy.

A study of 150 patients after neoadjuvant chemotherapy and mastectomy with ALND without radiotherapy showed that both the initial clinical stage and the eventual pathological metastasis of the disease are independent predictors for the locoregional recurrence [Buchholz, 2003]. The locoregional recurrence percentage correlated with the T stage (T_{3-4}), clinical stage (stage IIIB, IV), pathological residual disease (> 2 cm) and positive nodes after chemotherapy [Buchholz, 2003]. In a follow-up study [Huang, 2004], 542 patients from 6 prospective studies that had received neoadjuvant chemotherapy, mastectomy with ALND and postoperative radiotherapy, were compared with 134 patients from the same 6 studies who had not been irradiated. While radiotherapy was not a randomised variable, this study found that radiotherapy improved locoregional control for patients with clinical T_3 and T_4 tumours, stage > IIB (T_2N_1, T_3N_0) and pathological residual disease > 2 cm. This study also found that radiotherapy improved the disease-specific survival in stage > IIIB, cT_4 and with 4-10 positive nodes. It was also found that patients with stage III who had a pCR, still had a high risk of locoregional recurrence. The study by McGuire (2007) researched 226 patients who had a pCR after neoadjuvant chemotherapy. Radiotherapy did not give an improvement in the locoregional control for patients with stage I and II disease, but the ten-year local control for stage III patients was significantly improved with radiotherapy (7.3% vs 33%; p=0.004). Postoperative radiotherapy was also associated with an improvement in the disease-free and total survival (total survival 77% vs 33%; p=0.002).

A prospective study on 132 stage I and II patients who received neoadjuvant chemotherapy followed by mastectomy with ALND without radiotherapy showed that patients with stage cT_3 or ypT_3 tumours or ypN_{2-3} had a high risk of locoregional recurrence. Patients with stage I and II tumours with 1-3 positive nodes after chemotherapy had a limited risk of locoregional recurrence [Garg, 2004]. Patient age under 40 years was also found to be a risk factor for locoregional recurrence in this series. Downstaging through neoadjuvant chemotherapy therefore does not appear to lead to a better local control [Bucholz, 2003, Huang 2004]. It therefore seems justified to recommend postoperative radiotherapy for patients who have a pN_1 classification (1-3 positive axillary nodes) after neoadjuvant chemotherapy.

<u>Regional treatment</u>

The location and extent of treatment of the regional node areas after neoadjuvant systemic therapy is even less clear than with operated primary breast cancer. Whether or not regional metastases are present is of prognostic importance. As downstaging may occur after neoadjuvant systemic treatment, it is recommended to document the regional node status using cytological punction of clinically suspect nodes or those that appear suspect on an ultrasound and/or SN procedure prior to starting neoadjuvant treatment. Similar to primary operated disease, the number of regional recurrences after neoadjuvant treatment is noticeably small. In a review and retrospective analysis of more than 4,000 patients from the MDAH, an axillary recurrence percentage of 1% was found, and literature was cited with axillary recurrence percentages between 1.0 and 2.1% after surgery and between 0.8 and 3.1% after radiotherapy. [Newman, 2000]. In a French study of 250 patients (including 100 with clinically palpable axillary nodes) who were exclusively treated with neoadjuvant chemotherapy and radiotherapy, there were only 6 axillary node recurrences (2.4%) [Jacquillat, 1990]. There are no randomised trials that have researched the optimal treatment of regional node areas after neoadjuvant

systemic therapy. The guideline development group is therefore of the opinion that standard treatment (as if no neoadjuvant treatment was administered) must be followed.

The standard for primary operable disease (stage I, II: $cT_{1-2}N_{0-1}$ or cT_3N_0) is:

- no regional treatment in the case of negative axillary/SN
- ALND or radiotherapy in the case of a positive SN
- ALND in the case of non-identified SN or primary positive nodes (cN_1)

Postoperative locoregional radiotherapy is indicated if more than 3 tumour-positive nodes are found during ALND.

Locoregional radiotherapy was the standard treatment for breast cancer with locoregional metastasis (stage III, (cT_3N_1; cT_4N_{0-1}; $cT_{1-4}N_{2-3}$) in the 60's, because (modified) radical mastectomy gave extremely poor results in the area of survival and locoregional control [Haagensen, 1963; Dahl Iversen, 1963; Kaae, 1963]. While mastectomy with ALND was performed in many phase II studies on neoadjuvant chemotherapy in order to determine the pathological CR rate, there is no evidence on the therapeutic value of doing so. An ALND is of course unable to provide a useful benefit to treatment of demonstrated node metastases in the periclavicular node area of the parasternal node chain (N3). Axillary nodes fixed together or to the chest wall may be treated with an ALND but postoperative radiotherapy is almost certainly indicated in such a situation because it usually involves more than three tumour-positive nodes. The disadvantage of ALND plus postoperative regional radiotherapy is that this combination increases arm and shoulder morbidity [Larson, 1986; Ryttov, 1988].

Remaining considerations:

An ALND may be considered in the case of downstaging N_2 disease to yN_1, in order to reduce the tumour load prior to radiotherapy. With this treatment plan, Kuerer found only 3 axillary recurrences in a series of 191 patients with initially node-positive stage III breast cancer [Kuerer 1998, 1999]. He suggested that a choice could be made between ALND or radiotherapy in the case of an axillary that has become clinically negative.

It seems sensible to only treat the parasternal node chain if a parasternal node metastasis has been demonstrated using a pathologically proven SN metastasis or has been shown to be probable on the basis of an increased uptake of an FDG-PET-CT.

Conclusions

Level 1	Radiotherapy, added to chemotherapy and surgery, reduces the chance of a locoregional recurrence by a factor of three in the case of a resectable breast cancer with local metastasis, and as a result improves the long-term (15-year) survival. A1 EBCTCG 2000 A2 Overgaard 1999, Ragaz 2005

Level 1	An improvement in locoregional control using radiotherapy has been demonstrated for classic irresectable breast cancer with locoregional metastasis, but no survival advantage. A2 Papaioannou 1983, Olson 1997

Level 2	After neoadjuvant chemotherapy, both the initial clinical disease stage and postoperative stage are independent predictors of the risk of locoregional recurrence. Even if a pathological complete remission has been achieved. B Buchholz 2008, Garg 2004, Huang 2004, McGuire 2007

Level 2	Locoregional control, disease-free survival and disease-specific survival appear to be improved by postoperative radiotherapy after neoadjuvant chemotherapy in patients with multiple risk factors (cT_{3-4}, cN_{2-3}, pN+). B Huang 2004, McGuire 2007

Recommendations

Follow-up to neoadjuvant treatment should be discussed within the framework of multidisciplinary consultation.

Breast surgery
- Omitting breast surgery is advised against, even with clinical complete remission
- cT_4 if operable after systemic treatment (also mastitis carcinomatosa, cT_{4D})

Contraindications for BCT:
- Suspected microcalcifications in multiple quadrants
- A non-radical resection that is more than focal
- The wishes of the patient regarding mastectomy

Axillary node dissection:
- Non-identified SN in the case of stage II ($cT_{2-3}N_0$);
- Clinically positive nodes in the case of stage II ($cT_{1-2}N_1$);
- With downstaging of stage III (cN_{2-3}) to yN_1.

Locoregional radiotherapy (breast, chest wall, axillary and periclavicular)
- Always locoregional with (still) inoperable local disease
- cN_{2-3} on initial diagnosis, or pN_{2-3} at the time of ALND (> 3 positive nodes)
- Stage III (cT_3N_1 or $cT_{0-2}N_{2-3}$ or cT_4) on initial diagnose, or ypT_3N+, ypT_4 at the time of surgery (possibly omitting irradiation of the lateral axillary)

Locoregional radiotherapy (breast, chest wall, periclavicular, with or without lateral axillary)
- Always locoregional with (still) inoperable local disease
- Stage III (cT_3N_1 or $cT_{0-2}N_{2-3}$ or cT_4) on initial diagnosis, or ypT_3N+, ypT_4 at the time of surgery
- In total (SN and ALND) > 3 positive nodes

Local radiotherapy (breast or chest wall):
- Always in the case of BCT
- A tumour positive resection surface of the primary tumor, irradicality
- ypT_3 and one or more of the following risk factors: angioinvasive growth, grade III, age ≤ 40 years
- ypT_2 if cT_3, and one or more of the following risk factors: angioinvasive growth, grade III, age ≤ 40 years
- Consider if ypN_1, and one or more of the following risk factors: angioinvasive growth, grade III, age ≤ 40 years

Parasternal radiotherapy may be considered in the case of:
- Parasternal metastases demonstrated by means of SN
- Parasternale FDG uptake with anatomical substrate on FDG-PET-CT scan
- Stage III without further knowledge about possible parasternal drainage

Locoregional recurrence of breast cancer

A locoregional recurrence of breast cancer is defined as a recurrence of the disease in the breast, chest wall, axillary, infraclavicular, supraclavicular or parasternal lymph node area after treatment with curative intent [UICC, 2002]. In an extensive literature overview by Clemons (2001), the overall ten-year incidence of locoregional recurrence is 13% after mastectomy and 12% after BCT. Three quarters of these recurrences are local and a quarter is regional.

The chance of developing a *local recurrence* is especially dependent on the tumour stage and after BCT also dependent on age. With DCIS, the ten-year incidence of local recurrence after BCT is 10-15% and after mastectomy 0-4%. Half of these recurrences are invasive [EORTC, 2006; Fisher, 2001]. In trials randomised between mastectomy and BCT, the percentage of local recurrence after mastectomy is generally lower than after BCT, without this influencing survival (also in the long term) [Poggi 2003, Kroman 2004]. Specifically for BCT, a young age is unfavourable for the chance of local recurrence [Poggi 2003, Kroman 2004, Bartelink 2007]. In the ten-year update of the EORTC *boost - no boost* trial, the overall local recurrence rate in patients receiving a boost was 6% and for patients younger than 40 years 13.5% [Bartelink 2007].

Reports of regional recurrences vary, which is dependent on the original disease stage, extensiveness of the axillary surgery and postoperative radiotherapy (amongst other things). In principle, regional metastasis or recurrence does not occur with DCIS. Percentages of 1-5% are reported for stage I-II breast cancer [Newman, 2000; de Boer, 2001; Voogd, 2001], and higher percentages for pT_3 or pN_2 patients (7-15%) [van Tienhoven, 1999, Jager, 1999]. The extremely rare axillary recurrence after an SN procedure is a separate situation. In an American series of more than 4,000 SN procedures, an axillary recurrence percentage of 0.25% was found with a median follow-up of 31 months [Naik, 2004]. Of the 210 patients with a positive SN who had not undergone ALND, only 1.4% developed an axillary recurrence [Naik, 2004]. A systematic review of 68 studies confirms that the axillary recurrence percentage is very low when omitting an ALND after a negative SN, but also in the case of a positive SN, as was found in the randomised American ACOZOG Z-11 study [Pepels 2011, Giuliano 2010].

The five-year locoregional recurrence rate for breast cancer with locoregional metastasis, after treatment with a combination of chemotherapy and radiotherapy, with or without surgery is 20-30% [Piccart, 1988; Hunt, 1996; Merajver, 1997]. For all groups, the locoregional recurrence rate increases as the *tumour load* (T stage, number of tumour-positive lymph nodes) increases [Clemons, 2001]. Approximately 60% of locoregional recurrences after a mastectomy occur within three years after the initial treatment, but recurrences can also still occur in the long term [Poggi, 2003; Kroman, 2004; Bartelink, 2007; Recht, 1988; Kurtz, 1990]. After BCT, the chance of a local recurrence in the long term (after approximately 7 years) seems to show a second peak [Recht 1988].

A locoregional recurrence implies a poorer prognosis, both after mastectomy [Aberizk, 1986; Mendenhall, 1988; Schwaibold, 1991] and after BCT [Voogd, 2005; Fisher, 1991; Whelan, 1994; Elkhuizen, 2001]. Different series are difficult to compare, because the original tumour stage in mastectomy series is generally higher than in BCT series. In the abovementioned review by Clemons (2001), a five-year survival of 49% on average was found after chest wall recurrences after mastectomy, and a five-year survival of 64% on average after breast recurrences after BCT. In two European phase III trials randomised between mastectomy and BCT, survival and locoregional control of the 133 patients with a locoregional recurrence after salvage treatment was found to be identical independent of the original treatment [van Tienhoven, 1999]. Two-thirds of locoregional recurrences develop in isolation both after BCT and mastectomy, i.e.: without simultaneous distant metastasis [Clemons, 2001; van Tienhoven, 1999; Jager, 1999; Recht, 1988; Kurtz, 1990; Voogd, 2005]. Local recurrences longer than five years after BCT have a better prognosis than local recurrences within five years [van der Sangen, 2006].

The five-year survival of patients with an isolated locoregional recurrence is in the order of approximately 40-65% [van Tienhoven, 1999; Voogd, 2005]. While this is not very favourable, curation certainly remains possible. Treatment of an isolated locoregional recurrence must therefore be curative in intent.

Conclusion

Level 2	After an isolated locoregional recurrence of breast cancer after BCT or mastectomy, the

	five-year survival rate is 40 - 65%. A2 van Tienhoven 1999 B Clemons 2001, Voogd 2005

8.1 Diagnostics

A locoregional recurrence after mastectomy is usually discovered during clinical examination during a routine follow-up [Rutgers, 1989]. After BCT, ⅓ of recurrences are discovered by the patient, ⅓ on imaging and ⅓ on clinical examination during a routine follow-up [Stomper, 1987; Rutgers, 1991; Sardi, 1991; Dershaw, 1992]. It is recommended that the diagnosis is confirmed using histological biopsy. Cytology may lead to false-positive results, especially with punctions from an irradiated area [Dornfeld, 1992].If there are also distant metastases, the treatment intention will change from curative to palliative. For this reason, staging is recommended (see paragraph 2.3). A contralateral mammogram to exclude a contralateral tumour is also recommended. In case of a local recurrence, lymphogenous metastasis may also have occurred. Following an earlier SN procedure, these will generally be in the ipsilateral axillary. If an ALND originally took place, node metastases may also be present in the parasternal, infraclavicular or supraclavicular region or even in the contralateral axillary [Perre, 1996]. An interesting development is the so-called *repeat SN procedure*. A number of small series have been described so far, with an identification percentage of 86% [Roumen, 2006; Newman, 2006]. In a series performed in the Netherlands, 33% (4/12) of patients were found to have a contralateral axillary on the basis of an SN procedure [Roumen, 2006]. In this series, the treatment plan for seven of the twelve patients were amended on the basis of the *repeat SN procedure*.

8.2 Treatment

The choice of treatment of an isolated locoregional recurrence (without synchronous distant metastases) depends on a large number of factors, such as primary treatment (BCT/mastectomy, whether radiotherapy, chemotherapy and/or hormonal therapy has/has not been administered), the interval between the primary treatment and recurrence, size/extent of metastasis of the recurrence and resectability.

In general, locoregional treatment with curative intent is chosen. The most important prognostic factors for survival after salvage treatment of a locoregional recurrence after mastectomy are the interval between the original treatment and the size or extent of metastasis [van Tienhoven, 1999; Aberizk, 1986; Mendenhall, 1988; Schwaibold, 1991; Jager, 1998; van der Sangen, 2003]. Unfavourable factors during the original treatment such as positive axillary nodes [van Tienhoven, 1999; Jager, 1998] and the location of the recurrence (local or regional or both) are also mentioned as prognostic factors [van der Sangen, 2003]. The interval is also the most important prognostic factor after BCT for the effect of salvage treatment, aside from the size of the recurrence, the original node status and localisation of the recurrence (local or regional) [Aberizk, 1986; Osborne, 1994; Voogd, 2005; Elkhuizen, 2001; Kurtz, 1989; Fourquet, 1989; van Tienhoven, 1999; Haffty, 1991]. A separate subgroup of recurrences can be distinguished after BCT, which may be second primary tumours [Recht, 1988; Kurtz, 1990; Kurtz, 1989; Osborne, 1994]. These are recurrences that occur late, after approximately 7 years, and/or at a different location in the breast than around the original scar. These recurrences have a much better prognosis than the recurrences localised early and/or around the original scar.

Interpretation and comparison of treatment results from different studies is difficult because the patients with a locoregional recurrence form an extremely heterogenous group and because the articles describe different subgroups. Only the isolated locoregional recurrences are assessed in the failure analysis of the EORTC and DBCG trials [van Tienhoven, 1999]. Some studies only involve local (breast) recurrences, or even only operable breast recurrences [Fourquet, 1989; Fowble 1990; Abner, 1993].

The general tendency is to choose an intensive locoregional treatment with curative intent. Depending on the prognostic factors mentioned, a five-year locoregional control of 60-70% and five-year survival of 40-65% appear feasible for such treatment of isolated locoregional recurrences [Clemons, 2001; van Tienhoven; 1999, Voogd, 2005].

8.2.1 Local treatment of the local recurrence after mastectomy

While some authors only administer high dose radiotherapy in the case of a local recurrence after

mastectomy [Aberizk, 1986; Jager, 1998; Deutsch, 1986; His, 1998], some form of surgery preceded radiotherapy in most series [Voogd, 2001; van Tienhoven, 1999; Mendenhall, 1988; Schwaibold, 1991; van der Sangen, 2003; Mora, 1996; Kamby, 1997; Willner, 1997; Nielsen, 2006]. This enables better local control to be achieved [Schwaibold, 1991; Kurtz, 1989; Nielsen, 2006]. Differences in outcomes of these retrospective studies must be interpreted carefully, due to differences in patient populations, in the therapy administered and therapy techniques. In addition, the local recurrence is irresectable in 20-40% of cases [Voogd, 2001; van Tienhoven, 1999; Schwaibold, 1991]. The best treatment results seem to be gained by as early as possible detection of the local recurrence, complete surgical removal where possible and high-dose radiotherapy in the entire mastectomy area. The following is meant with high-dose radiotherapy: in case of microscopic complete excision (R0), a dosis equivalent to 50 Gy in 5 weeks; followed by a boost in the case of incomplete (R1 or R2) or no excision.

If an isolated local recurrence occurs in the scar or regionally in an area previously irradiated, then high-dose radiotherapy is not possible. In that case, low-dose re-irradiation with hyperthermia is the treatment of choice [Vernon, 1996; Jones, 2005; Kapp, 1992; van der Zee, 1999; Hehr, 2001; Zagar, 2010]. This lead to a significantly better local control in five randomised trials than with re-irradiation alone [Vernon, 1996]. A later randomised trial for superficial tumours confirmed this [Jones 2005]. The amount of tumour is again an important prognostic factor here. There are indications that a better local control is also possible in this situation if the recurrence is first surgically removed [Kapp, 1992; van der Zee, 1999; Hehr, 2001; Oldenborg, 2010].

8.2.2 Local treatment of the local recurrence after BCT

Most literature on local recurrences after BCT concern recurrences in the breast [Fisher, 1991; Whelan, 1994; Elkhuizen, 2001; van der Sangen, 2006; Kurtz, 1989; Fourquet, 1989; Osborne, 1994; Haffty, 1991; Fowble, 1990; Abner, 1993; Dalberg, 1998; Galper, 2005; Osteen, 1994; Salvadori, 1999]. Most authors recommend salvage mastectomy as the treatment of choice, although some also deem local re-excision possible in a select group, or even re-irradiation [Osteen, 1994; Salvadori, 1999; Mullen, 1997]. In a series of 341 patients with a breast recurrence, Galper (2005) found a significantly poorer disease-free and overall survival for the 27 patients whose recurrence was again treated with lumpectomy and radiotherapy. It also applies here that most series select patients, which makes it difficult to compare results. Some (18-27%) of the local recurrences are also not operable after BCT [van Tienhoven, 1999; Salvadori, 1999; Mullen, 1997]. Re-irradiation with hyperthermia is recommended in these cases, unless high-dose radiotherapy (50 Gy of the entire breast with boost) is possible.
If the salvage mastectomy is non-radical, or there are other high risk characteristics such as lymphangitis cutis, additional re-irradiation plus hyperthermia may be considered [Kapp, 1992; van der Zee, 1999; Hehr, 2001; Oldenborg, 2010].

8.2.3 Local treatment of regional recurrences

Regional recurrences after mastectomy or BCT form a separate, heterogenous category. In principle, a regional recurrence after mastectomy is no different to a regional recurrence after BCT. This includes (in decreasing frequency), supraclavicular, axillary, infraclavicular and parasternal recurrences. There is not much literature available with recommendations for treatment, and where it is available it concerns series in which local and regional recurrences are described together as a group [van Tienhoven, 1999; Aberizk, 1986; Mendenhall, 1988; Schwaibold, 1991; Voogd, 2005; Perre, 1996; Jager, 1998; His, 1998; Mora, 1996; Kamby, 1997; Willner, 1997; Nielsen, 2006; Salvadori, 1999]. In a series of 42 isolated supraclavicular recurrences, radiotherapy showed an advantage above systemic treatment [Van der Sangen, 2003]. The treatment plan for regional recurrences in this series is in fact no different than for local recurrences, bearing in mind that it is generally less common for regional recurrences to be resectable.
In general, the same recommendations therefore apply as those formulated for local recurrences after mastectomy. For recurrences in a non-irradiated area: high-dose radiotherapy, where possible preceded by surgical removal of the recurrence. For recurrences in a previously irradiated area: re-irradiation with hyperthermia, also after surgical removal where possible.

Conclusions

Level 3	The best salvage treatment of an isolated local recurrence after mastectomy in a previously non-irradiated area, appears to be high-dose radiotherapy after surgical removal of the tumour.

	The best salvage treatment of an isolated regional recurrence after mastectomy or BCT in a previously non-irradiated area, appears to be high-dose radiotherapy after surgical removal of the tumour. C Mendenhall 1988, Schwaibold 1991, Jager 1998, Mora 1996, Kamby 1997, Willner 1997, Nielsen 2006, Van der Sangen 2003

Level 3	Salvage mastectomy provides the best local control for an isolated breast recurrence after BCT. C Kurtz 1989, Fourquet 1989, Osborne 1994, Haffty 1991, Fowble 1990, Abner 1993, Dalberg 1998, Galper 2005

Level 2	In the case of a locoregional recurrence of breast cancer after mastectomy in a previously irradiated area, low-dose re-irradiation with hyperthermia leads to a better local control than re-irradiation only. A2 Jones 2005 B Vernon 1996, Zagar 2010

Level 3	There are indications that cytoreductive surgery prior to hyperthermia with irradiation provides a better local control of a local recurrence in an irradiated area. C Hehr 2001, Kapp 1992, van der Zee 1999, Oldenborg 2010

8.2.4 Systemic treatment of a locoregional recurrence

The positive results of adjuvant systemic treatment after primary locoregional treatment of stage I and II breast cancer and the often slow growth rate of the breast cancer, so that the recurrence often does not manifest for several years, lead to the question if delayed or secondary adjuvant systemic treatment could also lead to a survival advantage. In a Cochrane systematic review, three completed and published studies were found with four randomised comparisons [Rauschecker, 2001]. One of these randomised comparisons was never reported on and the patient number in two were too small and were negative. Only the trial of the Swiss Group for Clinical Cancer Research (SAKK) randomised tamoxifen versus nothing in 178 patients. This trial showed an improvement in the 5-year disease-free survival of 36% versus 54%, but no survival advantage [Borner, 1994]. There were three trials underway at the time of the review (2001), which have been unsuccessful in the meantime due to insufficient accrual. A few studies retrospectively researched the role of additional chemotherapy, but found no or little significant difference [Danoff, 1983; Haylock, 2000]. Secondary adjuvant hormonal therapy may be recommended on the basis of the SAKK trial [Borner, 1994].

It is possible that locoregional control of non-resectable locoregional recurrences may be improved using secondary neoadjuvant chemotherapy, in analogy to primary locoregional metastatic disease (see chapter 7), but there is no evidence in the literature to this effect.

Conclusions

Level 3	Secondary adjuvant hormonal therapy improves disease-free survival when treating a locoregional recurrence. A2 Borner 1994

Level 3	There is insufficient evidence for the benefit of secondary adjuvant chemotherapy in the treatment of a locoregional recurrence. C Rauschecker 2001, Danoff 1983, Haylock 2000

Remaining considerations

There are a few situations one can imagine secondary adjuvant chemotherapy being considered for, despite the lack of evidence. In general, examples are situations in which an indication for adjuvant chemotherapy was originally lacking, and in which the tumour stage at the time of the recurrence is

such that there is an indication for it now.

- invasive recurrence with poor tumour characteristics after original treatment of a DCIS.
- breast recurrence with poor tumour characteristics, after BCT for a relatively favourable tumour, for which adjuvant chemotherapy was not originally administered. There seems to be a second primary tumour with poorer characteristics
- axillary recurrence after tumour excision, SN procedure and radiotherapy, where adjuvant chemotherapy was not originally administered

In case of locoregional recurrences that occur simultaneously with or after distant metastases, the relative importance of systemic and locoregional treatment must be considered on the basis of risk estimation. Locoregional surgery appears to improve the prognosis of primary metastatic breast cancer, it is not known if this also applies to a simultaneous locoregional and distant recurrence of breast cancer [Ruiterkamp, 2010]. In any case it must be kept in mind that an uncontrolled locoregional recurrence is associated with a large morbidity and that locoregional treatment has a better chance of preventing this than systemic treatment alone.

Recommendations

Patients with an isolated locoregional recurrence of breast cancer are treated with curative intent as follows:

- a recurrence in the spared breast: salvage mastectomy
- a local recurrence after mastectomy and/or an isolated regional recurrence after mastectomy or BCT, in a previously non-irradiated area: high-dose radiotherapy, where possible preceded by surgical removal of the tumour
- a chest wall recurrence in a previously irradiated area: re-irradiation, with hyperthermia, after surgical removal where possible.
- if the hormone receptors are positive: secondary adjuvant hormonal treatment

After salvage mastectomy with R1 resection or lymphangitis cutis, additional re-irradiation and hyperthermia may be considered

Secondary adjuvant chemotherapy may be considered in a few situations.

- invasive recurrence with poor tumour characteristics after DCIS
- breast recurrence with poor tumour characteristics, after BCT, where adjuvant chemotherapy was not originally administered
- axillary recurrence after tumour excision, SN procedure and radiotherapy, where adjuvant chemotherapy was not originally administered

Supportive care, information

Discovering there is a locoregional recurrence is an emotionally loaded event for patients. It should be explained to the patient, preferably in the presence of a partner or trusted person, that the prognosis has therefore worsened and that additional research is required to exclude metastasis. The assistance of a specialised nurse is essential.

Continuity of care

After treating the locoregional recurrence, the treatment provider should be alert for questions from the patient and problems in relation to processing the setback. The chance of a recurrence or metastasis is quite high, especially in the first few years. A new follow-up period is therefore desirable for both these reasons.

Metastasis and concentration, infrastructure

Hyperthermia is only possible at a few locations in the Netherlands (Amsterdam, Rotterdam, Tilburg). You can find more information about this at www.hyperthermie.nl.

Diagnostics and treatment of metastatic breast cancer

Distant metastatic breast cancer should be considered as an incurable disease. The median survival after the metastasis has been determined is approximately 2 years [Bloom, 1962; Ellis, 2000; Hayes, 1995; Wood, 2005]. However, there is a large heterogeneity in survival; varying from a few months to many years [Falkson, 1990; Giordano, 2004; Greenberg, 1996; Hayes, 1995; Yamamoto, 1990]. An important goal in the treatment of metastatic breast cancer is maintaining or improving quality of life by resolving or preventing complaints.
The five-year survival of metastatic patients has increased from 15% in the period 1989-1994 to 23% in the period 2005-2009, due to the increase in new hormonal and cytostatic treatment options. A small number of patients with hormone-sensitive tumours or complete remission after chemotherapy display an extremely long and stable remission after systemic treatment [Bloom, 1962; Ellis, 2000; Hayes, 1995; Wood, 2005].

9.1 Diagnostics

Metastasis is found in 75% of patients on the basis of complaints [Rutgers, 1989]. Diagnostics is aimed at the nature of the complaints and findings during physical examination. If metastasis is detected after the patient presents with complaints, complete staging must be performed (see paragraph 2.3). The goal of this is to detect other and threatening tumour localisations, determine a prognosis and evaluate the effect of treatment. The localisation and extent of the metastasis may influence the choice of therapy.

Imaging Complaints of the postural and musculoskeletal system
Metastasis to the skeleton occurs in 85% of all patients with metastatic disease [Wood, 2005; Ellis, 2000]. The skeleton is also often the first localisation of metastases, with a preference for the spinal column and pelvis followed by ribs, skull and femur [Hamaoka, 2004].
The skeletal scintigraphy is sensitive and provides a good overview of the entire skeleton, it is the examination of choice and is supplemented with skeletal photos of symptomatic and abnormal areas. This may be further expanded with an MRI scan. A CT scan is the preferred method for evaluation of rib laesions, possibly as part of FDG-PET-CT if complete staging is indicated.

Chest complaints
Intrathoracic metastases of breast cancer often spread to the lungs, pleura, mediastinum and airways. A chest X-ray is recommended for inventory purposes. However, a CT scan of the chest is the most important modality. Pleuritis carcinomatosa is the first symptom of metastasis in 20% of all patients with metastatic disease, frequencies of 15-25% are reported for lung metastasis. Solitary lung laesions appear to be the result of primary bronchial carcinoma in approximately half of cases [Casey, 1984]. Histological confirmation is therefore necessary for adequate staging and planning. The mediastinal lymph nodes are often affected in disseminated disease. Size is the most important criterion for CT evaluation, which is a limitation of the sensitivity. FDG-PET-CT may therefore be of additional value here. Pericardial and myocardial metastases are not common and are usually diagnosed using echocardiography.

Abdominal complaints
In 40-50% of all patients with metastatic disease there is involvement of the liver [Wood, 2005; Ellis, 2000]. Liver metastases are rarely solitary. Ultrasound is suitable as a screening method, but a CT scan of the abdomen is the examination of choice if there is clinical suspicion of metastases. CT can also be used to evaluate the effect of systemic therapy. MRI may contribute to the differentiation of aspecific laesions [Shah, 2009].

Neurological complaints
Brain metastases occur in 6-16% of patients with a metastatic disease [Wood, 2005; Ellis, 2000]. CT detects most brain metastases, but MRI has a higher sensitivity. If epidural metastases are suspected, MRI is superior. Tumour cells in the cerebrospinal fluid are indicative for meningitis carcinomatosa, see also www.oncoline.nl/hersenmetastasen.

Histological analysis
If metastasis is suspected, the diagnosis should in principle be histologically verified in order to confirm and characterise the metastatic disease. Hormone receptors and HER-2-overexpression may display a dynamic pattern in the course of the metastatic disease. Difference in PgR, ER and HER-2

receptor status between primary tumour and metastasis is described in 25%, 10% and 3% of patients respectively [Thompsom, 2010; Hoefnagel 2010]. Loss of hormone receptors may predict insensitivity to hormonal treatment [Kuukasjarvi, 1996] but cannot be excluded due to sampling error. Given the therapeutic consequences, current histological information is desirable. Histological or cytological confirmation is indicated with a solitary metastasis in order to exclude other causes of the abnormality, such as a second primary tumour.

Laboratory analysis
Laboratory tests are performed for two reasons:
- in case of specific complaints
- to provide direction to further tests/examination and choice of therapy

Determinations should at least include the following: blood count, liver functions, renal function, calcium and albumin. Existing data on tumour markers for early diagnostics provide insufficient support for routine use [Harris, 2007]. The tumour markers CA27.29, CA15.3 or CEA may be used as a parameter of disease activity when there are no parameters that can be measured well (such as with sclerotic skeletal metastases) [ASCO, 2007]. Marker increase can sometimes allow progression to be determined earlier than with other parameters; however, this does not provide a survival advantage. Without clinical or radiological progression it is generally insufficient reason to change the treatment plan.
A promising new development is measurement of circulating tumour cells (CTC's) as parameter for the response to therapy. The number of CTC's determined prior to starting systemic therapy for metastatic breast cancer appears to be a prognostic factor. The number of CTC's after each course has been found in a few studies to be a measure for the final outcome concerning PFS and OS. CTC's may be used in the near future as parameter for therapy response in the case of difficult to evaluate disease (e.g. only bone metastases) if accessible to everyone, and if a test validated for this purpose is used [Liu, 2009; Nakamura, 2010; Nole, 2008; Pierga 2011; Miller, 2010].

Conclusions

Level 3	Skeletal scintigraphy is the examination of choice in the event of clinical suspicion of skeletal metastases, supplemented with conventional images of symptomatic and abnormal areas and MRI where required. C Ellis 2000, Frederick 1997, Layer 1999, Nishimura 1999, Sheafor 1999, Hamaoka 2004

Level 3	Chest X-ray and ultrasound are the examination of first choice on clinical suspicion of chest or abdominal metastases. On radiological suspicion this is followed by chest CT or abdominal CT. C Costelloe 2009

Level 3	Histological confirmation of the diagnosis metastatic breast cancer is also desirable for determination of hormone receptor and HER-2-overexpression, and to exclude a benign abnormality or other primary tumour. C NCCN guidelines 2010, ESMO guidelines 2010

Level 3	If other parameters are lacking, tumour markers (CA 27.29, CA 15.3 or CEA) may be used to evaluate the effect of system therapy. C ASCO guidelines 2007

Remaining considerations
Introduction of FDG-PET-CT has replaced conventional staging almost everywhere. However, a clear strategy has not yet been developed to deal with aspecific possible false-positive findings. See also paragraph 2.3.3.

Recommendations
Conventional diagnostics is recommended on clinical suspicion of a metastasis.

After the diagnosis metastasis, complete staging is recommended.

Histological confirmation of the diagnosis metastatic breast cancer is recommended, also for determination of hormone receptor and HER-2-overexpression, and to exclude a benign abnormality or other primary tumour.

Tumour marker determinations of CA27.29, CA15.3 or CEA are recommended if there is no measurable/evaluable disease in order to evaluate the effect of treatment.

9.2 Systemic therapy

9.2.1 Hormonal therapy

Patients with a metastatic ER+ and/or PgR+ breast cancer are eligible for hormonal therapy. The clinical benefit (number of patients with response + stable disease) of first-line hormonal therapy varies from approximately 50% with ER+/PgR- tumours to approximately 70% with ER+/PgR+ tumours [Clark, 1988]. The median duration of the clinical benefit is 12-18 months, but can be extremely variable [Clark, 1988]. The response to hormonal therapy is sometimes slow, an observation period of 3 months or longer may be required to observe regression [Muss, 1994]. Patients with rapid disease progression or extensive visceral metastases are therefore usually primarily treated with chemotherapy. The choice of hormonal therapy depends on the menopausal status of the patient, the toxicity profile of the medication and the interval after adjuvant hormonal therapy [Falkson, 1991; Dickson, 2000]. The response rate is approximately the same for all hormonal treatments. A patient is eligible for second-line hormonal treatment if there is a response or stabilisation to first-line endocrine therapy. However, the response rate decreases by approximately 50% with each subsequent line [Klijn, 2001]. Hormonal therapy may also be considered as consolidation therapy after chemotherapy. The recommended sequence in hormonal manipulation of metastatic breast cancer is summarised in the schedule below . Phase III studies show that for first-line therapy for postmenopausal patients, the aromatase inhibitors anastrozole, letrozole and exemestane are of increased value compared to tamoxifen [Bonneterre, 2000; Mouridsen, 2001; Nabholtz, 2000; Paridaens, 2004]. This increased value consists of a higher response rate, a longer time to progression and a longer survival period and less thrombo-embolic complications. This increased value is a reason to recommend aromatase inhibitors as first-line therapy in postmenopausal patients [Lonning, 2000; Mauri, 2006]. After failure of a non-steroidal aromatase inhibitor, a response may sometimes occur with the steroidal aromatase inhibitor exemestane [Paridaens, 2004]. In a randomised study, the anti-oestrogen fulvestrant (in a dose of 250 mg i.m./4 weeks) was found to be almost as effective as tamoxifen in the first line and as anastrozole in the second line [Gibson, 2007; Howell, 2004]. This agent also shows activity in the third or fourth line [Osborne 2002]. Since then, a higher dose (500 mg) and loading schedule has been found to enable a significantly longer time to progression to be achieved compared to the earlier standard dose of 250 mg [Di Leo, 2010]. The role of progestatic agents compared to fulvestrant is not yet clear.

Conclusions

Level 1	For premenopausal patients with a metastatic, hormone receptor-positive breast cancer, the combination tamoxifen with LHRH in the first-line provides a longer disease-free survival than treatment with only one of the two. A1 Klijn 2001

Level 1	For postmenopausal patients with a metastatic, hormone receptor-positive breast cancer, aromatase inhibitors (steroidal and non-steroidal) in the first-line provide a higher remission percentage and a longer disease-free survival than tamoxifen. A2 Bonneterre 2000, Mauri 2006, Mouridsen 2001, Nabholtz 2000, Paridaens 2004

Recommendations

Patients with a metastatic ER+ and/or PgR+ breast cancer are eligible for hormonal therapy. The choice of hormonal therapy is determined by the menopausal status of the patient and the toxicity profile of the therapy (see the below schedule).

In the case of rapid progression, and especially with visceral metastases, treatment with chemotherapy is preferable.

Hormonal therapy schedule

Hormonal line	**Therapy**	
	Premenopausal	**Postmenopausal**
1	Induction of postmenopausal status (if LHRH, preferably combined with tamoxifen)	A: Non-steroidal aromatase inhibitors B: Steroidal aromatase inhibitors**
2	Same as postmenopausal patients	Anti-oestrogens
3*	If a postmenopausal status is achieved, combination/ treatment with aromatase inhibitors is possible	A: Steroidal aromatase inhibitors** B: Non-steroidal aromatase inhibitors Progestagens Fulvestrant (500 mg per 4 weeks)

* There is insufficient data on the optimal sequence of hormonal intervention in the third line. In exceptional situations, administration of pharmacological doses of oestrogens or androgens in the last instance may be considered

** There are no studies that have demonstrated the superiority of steroidal versus non-steroidal aromatase inhibitors

9.2.2 Chemotherapy

Chemotherapy is the treatment of choice if:

- the hormone receptors are negative
- hormonal therapy no longer appears to be effective
- there is rapid disease progression
- extensive and rapidly growing visceral metastases have developed (lung, liver, lymphangitis)
- there is serious pancytopaenia as a result of mass bone marrow metastasis

The response rate of chemotherapy is comparable with hormonal therapy, but is often associated with a more rapid effect. If breast cancer recurs more than 6-12 months after completing adjuvant chemotherapy, the same combination may be considered with a reasonable response rate, depending on the schedule used (caution with cumulative doses of anthracyclines: doxorubicin 450 mg/m^2 and epirubicin 900 mg/m^2), partly dependant on the age and comorbidity. In case of a recurrence within this period, it is advisable to apply another schedule. For patients with a tumour with HER-2-overexpression: see paragraph 9.2.3: Focused therapy.

Anthracyclines and taxanes, combinations and sequence

The response rate with the standard chemotherapy schedules as first-line treatment is approximately 40-60% with a median response duration of 8-12 months [Bontenbal, 1998]. First-line chemotherapy may consist of an anthracycline-containing schedule (FAC, FEC, AC, EC etc.) or taxanes (paclitaxel/docetaxel). The response chance is greater and the response duration and time to progression is longer in most studies with use of anthracycline-containing schedules compared to CMF chemotherapy, for example [Bontenbal, 1998]. However, only a few studies have found that anthracycline-containing chemotherapy provides a survival advantage compared to CMF [Fossati, 1998].

There are nine studies that have compared an anthracycline + taxane-containing combination with a standard anthracycline-containing schedule, FEC or FAC, AC or EC [Biganzoli, 2002; Bontenbal, 2005; Jassem, 2001; Langley, 2005; Luck, 2000; Mackey, 2002; Nabholtz, 2003; Sledge, 2003; Tubiana-Hulin, 2003]. The anthracycline/paclitaxel combinations (five studies) are at least as effective as the standard anthracycline-containing schedules, with a trend to higher response percentages in the anthracycline/paclitaxel arm of the studies. One study shows a significant improvement in the time to progression and survival for the anthracycline/paclitaxel combination [Biganzoli, 2002; Jassem, 2001; Langley, 2005; Luck, 2000; Sledge, 2003]. Out of 4 studies that have compared an anthracycline/docetaxel schedule with standard, anthracycline-containing chemotherapy, it appears the combination anthracycline/docetaxel in all studies leads to significantly higher response percentages and in three studies also to a longer *disease-free* survival. Survival is longer in two

studies with the anthracycline/docetaxel combination [Bontenbal, 2005; Mackey, 2002; Nabholtz, 2003; Tubiana-Hulin, 2003]. The combination anthracycline/docetaxel is therefore effective, but the difference in neutropenic fever with standard courses (20-30% vs 2-10%) means such a schedule cannot be applied without support with growth factors.
Sequential treatment with an anthracycline and a taxane has only been compared to a combination of both agents in a few randomised studies [Conte, 2004]. There was no difference in survival despite higher response percentages and a longer disease-free survival with combination therapy in one study. The meta-analyses concerning the efficacy of the anthracycline/taxane combinations versus standard chemotherapy schedules show that the combinations do lead to a longer progression-free survival, but there is no increase in total survival [Ghersi, 2005; Seidman, 2004; Piccart-Gebhart, 2007]. Studies with liposomal doxorubicin in the first-line have also been published since [GEBU, 2010].
Capecitabine has been found to be an effective agent after pre-treatment with anthracyclines and taxanes [Ershler, 2006]. A combination with docetaxel leads to a longer PFS and OS than with capecitabine alone [O'Shaughnessy, 2002]. This combination is currently being compared to the sequential application of both agents (NCT00415285). Docetaxel in combination with capecitabine was more effective than docetaxel with epirubicin, with a PFS of 12 vs 7 months, median survival 37 vs 27 months [Bachelot, 2009]. However, a combination of capecitabine with gemcitabine was found to be as effective but less toxic than capecitabine with docetaxel [Chan, 2009].

In summary:

- Anthracyclines and taxanes are the most effective agents for metastatic breast cancer
- Previous adjuvant therapy (time interval, cumulative dose anthracyclines), the requirement for a higher response rate and longer response duration versus more toxicity (combination versus sequential treatment) must be taken into account when choosing the first- and second-line chemotherapy.
- Multiple studies have shown that a weekly schedule of paclitaxel is more effective than three-weekly administration [Jones, 2005; Piccart-Gebhart, 2007; Sparano, 2007; Tabernero, 2004], while a three-weekly schedule of docetaxel is in fact more effective than a weekly regimen [Jones, 2005; Sparano, 2007].

Conclusions

Level 3	The response rate with standard chemotherapy schedules as first-line treatment is approximately 40-60% with a median response duration of 8-12 months. The response chance is greater and the response duration and time to progression is longer with use of anthracycline-containing schedules compared to CMF chemotherapy, for example [Bontenbal, 1998]. B Bontenbal 1998

Level 1	Taxoids are less effective than an adequately dosed anthracycline. The addition of a taxoid to an anthracycline-containing therapy does extend the progression-free interval, but not survival. A1 Ghersi 2005, Piccart-Gebhart 2007

Level 3	Capecitabine has been found to be an effective agent after pre-treatment with anthracyclines and taxanes. C Ershler 2006

Recommendations

Chemotherapy is the treatment of choice if:

- the hormone receptors are negative
- hormonal therapy no longer appears to be effective
- there is rapid disease progression
- extensive and rapidly growing visceral metastases have developed (lung, liver, lymphangitis)
- there is serious cytopaenia as a result of mass bone marrow metastasis

Anthracycline-containing schedules are the preferred primary treatment.

Liposomal doxorubicin may be considered with anthracycline pre-treatment.

Subsequent lines of chemotherapy

The choice of treatment schedule, sequence of treatment, combination or sequential

Patients with progression after an earlier response, who have been treated previously with an anthracycline/taxane, are eligible for renewed treatment, depending on the condition of the patient (performance status), treatment wishes, age and comorbidity. There is little to no comparative research between contemporary alternatives such as capecitabine [O'Shaughnessy, 2002; Seidman, 2002; Ershler, 2006], vinorelbine [Kerbrat, 2007; Ejlertsen, 2004], gemcitabine [Chan, 2005; Martin, 2007], (pegylated) liposomal doxorubicin (PLD) [Keller, 2004; O'Brien, 2004; Sparano, 2007; GEBU, 2010] or mitoxantrone [Namer, 2001]. There is therefore no recommended optimal choice or sequence. The response percentages and duration of the response to these agents after pre-treatment are usually limited [Seidman, 2002]. Capecitabine is usually chosen in the third-line (after anthracycline and taxane). When remission or a stable situation has been achieved, treatment can be continued after the first 6 courses, as long as it does not seriously affect the quality of life in a negative manner. However, usually no more than 6-9 courses are administered. The survival advantage of a combination is furthermore rarely compared with sequential application of the same agents, which usually results in less side-effects with a better quality of life [Carrick, 2005; Jones, 2006; Miles, 2002; Ershler, 2006]. Pleural fluid or ascites may cause delayed excretion of methotrexate through accumulation of the agent in this third space with an increase in mucositis and myelotoxicity.

Conclusion

Level 1	The combination of two cytostatic drugs provides a higher response rate and longer progression-free interval than sequential treatment, but also more side-effects. Addition of a third drug leads to more toxicity, but not a survival advantage. A1 Carrick 2005, Jones 2006

Recommendation

After progression during first-line chemotherapy, there is no recommendation for an optimal choice of sequence for the subsequent lines of chemotherapy. The choice between a combination of cytostatic drugs, or sequential administration should be made on the basis of the remission rate, toxicity and quality of life.

Dose escalation should not be applied outside a research context.

9.2.3 Focused therapy

HER-2 blockade

10-15% of breast cancers display overexpression of HER-2 [Baselga 2000]. These patients are eligible for treatment with trastuzumab. In phase II studies, treatment with trastuzumab monotherapy resulted in an objective response in 10-20% of the intensively pre-treated patients, with a response duration of approximately 9 months [Cobleigh 1999, Estrevez 2003]. In the study by Vogel (2002), trastuzumab monotherapy was administered as first-line treatment. The response rate in this study was approximately 35% with a median response duration of more than 12 months. On the basis of phase II studies, trastuzumab has furthermore been found to increase the efficacy of various cytostatic drugs [Burstein 2001, Marty 2005, Slamon 2001]. Combinations of trastuzumab with paclitaxel, doxorubicin and docetaxel showed a longer (progression-free) survival in randomised phase II/III studies [Slamon 2001, Chan 2007, Geyer 2006]. Patients with HER-2-overexpression are eligible for treatment with trastuzumab, preferably in combination with chemotherapy. Patients who have already received anthracycline-containing adjuvant chemotherapy, are eligible for a combination of a taxane or vinorelbine with trastuzumab. Combination with anthracyclines should be avoided due to the increased chance of cardiotoxicity. A combination with liposomal doxorubicin does appear possible, however [Sparano 2007].

The combination of trastuzumab with other cytostatic agents such as vinorelbine also appears to be more effective than treatment with these agents alone [Bartsch, 2007; Chan, 2007]. Treatment with trastuzumab monotherapy is not recommended, but the treatment after completing cytostatics courses

may be continued. If resistance to trastuzumab has occurred, continuing trastuzumab in subsequent treatment lines is more effective; this was found in two randomised phase III studies [von Minckwitz, 2009; Blackwell, 2010]. The combination of capecitabine with trastuzumab improved the response rate and time to progression, compared to capecitabine alone (respectively 48% vs 27%; p=0.011; 8.2 vs 5.6 months, p=0.034) [von Minckwitz, 2009]. The combination trastuzumab with lapatinib improved the clinical benefit and progression-free survival compared to lapatinib alone (respectively 24.7% vs 12.4%; p=0.01; HR 0.73; p=0.008) [Blackwell, 2010]. Multiple retrospective analyses support this finding [Fountzilas, 2003; Tripathy, 2004; Gelmon, 2004]. Disease progression during treatment with trastuzumab is often in the form of metastases in the central nervous system, but a favourable effect of screening with a brain MRI or prophylactic cranial irradiation has not been demonstrated. Lapatinib may have a preventative effect here [Geyer, 2006].

The combination of trastuzumab with hormonal therapy was researched in the TanDEM study [Kaufman, 2009]. In this study, 207 postmenopausal women with both hormone receptor-positive and HER-2-positive metastatic breast cancer were randomised between anastrozole with or without trastuzumab. The response rate, progression-free survival and clinical benefit improved with the combination (respectively 20.3% vs 6.8%, p=0.018; 4.8 vs 2.4 months, p=0.0016 and 42.7 vs 27.9%, p=0.026). The combination letrozole with lapatinib showed comparable improvements [Johnston, 2009]. As a result, the addition of HER-2 blockage in patients with an indication for hormonal therapy is of added value and may be considered in patients with a tumour displaying aggressive clinical behaviour while chemotherapy treatment was not the first choice.

The cardiotoxicity of trastuzumab is usually reversible with conservative measures. Re-introduction of trastuzumab in patients after a break due to (a)symptomatic cardiotoxicity was feasible in 62%-88% of patients, without renewed worsening of the LVEF [Guarneri, 2006; Ewer, 2005]. If this was the case however, then continuation of trastuzumab was still possible in 50% of patients because the LVEF stabilised at a lower level [Ewer, 2005]. This data supports the long-term use of trastuzumab in which the favourable effects weigh up against the controllable (cardio)toxicity.

A HER-2 blockade using lapatinib may be applied in patients that have become resistant to trastuzumab. In combination with capecitabine, this extends the time to progression by several months [Blackwell, 2010; Geyer, 2006]. Symptomatic brain metastases were less common in the lapatinib treatment arm of this study.

Conclusions

Level 1	In patients with a metastatic breast cancer with HER-2-overexpression, the combination trastuzumab with an anthracycline or a taxane (both paclitaxel and docetaxel) as first-line therapy has been found to be more effective than monotherapy. A2 Chan 2007, Marty 2005, Slamon 2001

Level 1	Addition of trastuzumab to taxanes or vinorelbine-containing chemotherapy in the first-line increases the remission rate and extends the progression-free interval and survival in patients with HER-2-positive tumours. A2 Chan 2007, Marty 2005, Slamon 2001

Level 1	When trastuzumab resistance develops, continuing the HER-2 blockade in combination with subsequent treatment is more effective than subsequent treatment without HER-2 blockade. A2 von Minckwitz 2009, Blackwell 2010

Level 1	Addition of HER-2 blockade to hormonal therapy improves the response, the progression-free survival and clinical benefit in patients with a hormone-receptor and HER-2-positive tumour. A2 Kaufman 2009, Johnston 2009

Recommendations

In patients with a HER-2-positive metastatic breast cancer who have already received anthracycline-containing therapy, the combination trastuzumab with vinorelbine or a taxane (both paclitaxel and docetaxel) is preferable as first-line therapy.

In patients with a HER-2-positive metastatic breast cancer who develop trastuzumab resistance, continuing the HER-2 blockade in follow-up treatments is preferable to a follow-up treatment without HER-2 blockade.

In patients with a metastatic breast cancer with both hormone receptor and HER-2-overexpression, the combination of HER-2 blockade with hormonal therapy is preferable to hormonal treatment only.

Bevacizumab

Bevacizumab is a monoclonal antibody that binds the circulating vascular endothelial growth factor (VEGF). As a result, binding of VEGF to the VEGFR-1 (Flt-1) and VEGFR-2 (KDR) receptors present on the surface of the endothelial cells is inhibited. The reduced activity of VEGF inhibits the new formation of blood vessels in tumours, which slows the tumour growth.

Three phase III studies have researched the value of adding bevacizumab to first-line chemotherapy in patients with metastatic breast cancer. In the E2100 study by Miller (2007), bevacizumab was added to a weekly schedule with paclitaxel as first-line treatment. The median progression-free survival of patients treated with bevacizumab and paclitaxel was 11.8 vs 5.9 months respectively for paclitaxel only (HR 0.60; p<0.0001). With a median follow-up duration of 22.6 months, the median survival was 26.7 vs 25.2 months (HR 0.88; 95%CI 0.66-1.03; p=0.137). After one year, 82.3% of patients were still alive versus 73.8% (p=0.007).
In the AVADO study, bevacizumab was added to a three-weekly schedule of docetaxel in the first-line. In the RIBBON 1 study, the combination bevacizumab with capecitabine, anthracycline-containing chemotherapy or a taxane (other than paclitaxel) was compared to chemotherapy only. A significant improvement in response rate and an increase from 1 to 2.9 months in progression-free survival was found in both studies, but there was no extension in general survival [Miles, 2010; Robert, 2011]. Bevacizumab in combination with weekly paclitaxel as first-line chemotherapy therefore has added value, and is registered by the EMA for this indication.

Bevacizumab in combination with capecitabine has originally been studied as a second- or third-line therapy in patients with metastatic breast cancer [Miller, 2005]. The combination was compared to capecitabine only. While combination therapy is more effective than capecitabine only (response rate 20 vs 9%), this did not result in a significant extension of the progression-free (4.9 vs 4.2 months) or general survival (15.1 vs 14.5 months). Addition of bevacizumab to second-line chemotherapy consisting of a taxane, gemcitabine, capecitabine or vinolrelbine in the RIBBON-2 study lead to few extra side effects and resulted in an extension of the progression-free survival of 5.1 to 7.2 months [O'Shaugnessy, 2008]. The value of bevacizumab in the second or later line is still unclear.

Conclusion

Level 3	Addition of bevacizumab to weekly paclitaxel in the first-line is more effective than treatment with paclitaxel only. Bevacizumab extends the progression-free survival, with an increase in side effects; there is no increase in survival. B Miller 2007

Recommendation

When paclitaxel is chosen as first-line treatment, it is worthwhile to add bevacizumab to this therapy.

9.3 Bisphosphonates

Skeletal metastasis of a breast carcinoma may lead to pain, hypercalcaemia, pathological fractures and vertebral fractures with myelum compression. Treatment with intravenous bisphosphonates reduces the incidence of these complications by approximately one-third. The interval to the next complication is also extended by several months [Hillner, 2003; Theriault, 1999; Kohno, 2005; Rosen, 2003; Pavlakis, 2005]. Multiple studies have shown that bisphosphonates may improve quality of life and extend the progression-free period of the breast cancer [Hillner, 2003]. Studies that have compared the efficacy of intravenous bisphosphonates are unfortunately still lacking [Theriault, 1999; Kohno, 2005].

The side effects are generally mild. Approximately one-third of patients experience an acute response within 2 days after administration of intravenous bisphosphonates, which disappears after 24 to 48 hours, consisting of fever, flu-like symptoms and bone pain. Bisphosphonates should not be administered too rapidly intravenously and the renal function should be monitored regularly due to the chance of damage to the renal tubules and renal insufficiency (0.1-1%) [Hillner, 2003]. Another possible side effect of intravenous administration of bisphosphonates over a long period of time, especially zoledronate and pamidronate, is osteonecrosis of the jaw after dental interventions. If possible, the carious teeth should be checked prior to treatment or preferably within 1 or 2 months [Woo, 2006]. Oral bisphosphonates may give gastrointestinal complaints in particular, partly because they must be ingested with water prior to the meal without other medication (that often contain calcium lactate as filler). Good instructions for taking oral bisphosphonates are therefore important.
It is still unclear what is the best point in time to commence treatment. In addition, it is unknown what the optimal dose, the optimal dose interval and the optimal duration of treatment is with bisphosphonates. For the time being, it is recommended to start as soon as bone destruction has been detected and to continue treatment until the condition of the patient deteriorates substantially [Pavlakis, 2005; Body, 2004].

Conclusion

Level 1	Bisphosphonates reduce the progression and morbidity of bone metastases. A1 Hillner 2003, Pavlakis 2005 A2 Theriault 1999, Kohno 2005, Body 2004

Recommendation

In the event of bone metastasis, treatment with bisphosphonates is recommended, both in combination with hormonal therapy and chemotherapy.

9.4 Treatment with comorbidity

Reduced organ function must be taken into account with cytostatic treatment, especially in the case of older patients. Disturbed liver function leads to problems with the breakdown and excretion of taxanes, anthracyclines, vinorelbine and gemcitabine. Dosis reduction is certainly indicated with increased bilirubin levels. It is still controversial if a dose adjustment is also necessary for cyclophosphamide. Reduced renal function (which may also be the case with a normal serum creatinine level in the elderly) may give problems with the administration of methotrexate and capecitabine. The cardiotoxicity of anthracycline may be strengthened by age, previous irradiation, diabetes, hypertension and previous treatment [Mary, 2007; Ryberg, 2007]. The maximum tolerated dose of epirubicin appears to be lower in this category of patients than the usual cumulative dose of 900 mg/m^2.

Conclusion

Level 2	Treatment of patients with a metastatic breast cancer and comorbidity is complex: cardiotoxicity of anthracyclines, age, previous irradiation, diabetes, hypertension, disturbed organ function, comedication and previous treatment may play an important role in this [Mary, 2007; Ryberg, 2007]. B Mary 2007, Ryberg 2007

9.5 Hereditary breast cancer

Inhibitors of DNA excision repair, the so-called PARP (poly(ADP-ribose) polymerase) inhibitors, have been found to be effective in carriers of a BRCA1/2 mutation, but the drugs used for this purpose (iniparib and olaparib) have not yet been registered for this indication [O'Shaugnessy, 2010]. So far, the same palliative treatment schedules are applicable to this group.

9.6 Palliative surgery and radiotherapy

Radiotherapy plays an important role in the treatment of complaints caused by breast cancer metastases. Both single and more fractionated irradiations may be effective here to reduce or prevent complaints. Palliative radiotherapy of the primary tumour in the breast may be considered with (threatening) ulceration. In some cases palliative surgery is indicated.

The most important indications for palliative radiotherapy and/or surgery are:

Painful skeletal metastases or (threatening) pathological fractures

Radiotherapy is an effective treatment modality for painful bone metastases; the majority of patients experience a significant reduction in pain and in 33-50% the pain even disappears completely [Chow, 2007; van der Linden, 2004]. In most cases, also in patients with an expected better prognosis [van der Linden, 2006], a single irradiation (8 Gy) is sufficient, which may be repeated over time (if required) [Sze, 2004]. In the case of extensive osteolytic laesions in long bones with chance of a pathological fracture [van der Linden, 2003] or vertebral metastases with risk of damage to the myelum without neurological complaints, a higher dose in a fractionated schedule is generally chosen. Aside from pain reduction, the aim of treatment is also induction of remineralisation to strengthen the bone [Koswig, 1999]. Given the morbidity of a spontaneous fracture, a prophylactic surgical stabilising intervention must first be considered in the event of threatening pathological fractures in long bones. If a fracture has already occurred, a surgical stabilisation must first be performed, in combination with postoperative radiotherapy to prevent luxation of the osteosynthesis material by local tumour progression [Townsend, 1995]. A vertebroplasty may also be considered for vertebral collapse through osteolytic metastases in order to strengthen the vertebra [Mendel, 2009]. Emergency radiotherapy is indicated for progressive cranial nerve deficit due to osseous skull base metastasis to prevent irreversible deficit.

Epidural myelum or caudal compression with spinal metastases

Haste is of the essence in patients with neurological complaints due to myelum or caudal compression, given the increased chance of irreversible neurological deficit when waiting longer. Recovery in function may be substantially more favourable in some cases after emergency neurosurgical intervention followed by radiotherapy, than after radiotherapy only [Patchell, 2005]. However, in that case there needs to be vertebral metastases on a few levels at the most, a good condition, a reasonable life expectancy, limited disease activity elsewhere and the patient should be under 65 years of age [Chi, 2009]. As a result, the majority of patients are not eligible for surgery. Preferably, radiotherapy should be administered as fast as possible because the treatment result is strongly dependent on the neurological residual function and the speed with which the neurological complaints developed [Rades 2002]. If the patient is still ambulant, but has progressive deficit, emergency radiotherapy (within 24 hours) may lead to recovery or stabilisation of the neurological deficit. There is no haste with stable neurological complaints that have existed for a longer period of time. If paraplegia has already occurred, a large percentage of these patients will remain bedridden [Rades, 2006]. It is important with neurological complaints to start as soon as possible with high-dose oral/iv dexamethasone in order to counteract compression of the oedema component. Short-term radiotherapy (1-2x8 Gy, or 5x4 Gy) is the treatment of choice for patients with a moderate prognosis (<1 year) [Maranzano, 2009]. A higher dose, e.g. 30 Gy in 10 fractions, should be considered if there is a better prognosis and limited disease activity [Rades, 2010].
For futher considerations, see the national Guideline *Spinal epidural metastases* at http://oncoline.nl/spinale-epidurale-metastasen.

Brain metastases

Brain metastases often cause serious neurological symptoms that strongly reduce quality of life. After diagnosis, the patient is started on dexamethasone to reduce tumour-induced oedema and therefore intracranial pressure. The aim of irradiation is reduction or stabilisation of metastases and neurological deficits, reduction in dexamethasone-dependency and a limited survival advantage [Bezjak, 2002, Tsao, 2005]. A feasible method to estimate the prognosis and the resulting value of palliative radiotherapy is the GPA classification [Sperduto, 2011].
A small percentage of patients have a solitary brain metastasis. More intensive local treatment may lead to a significant improvement in survival. A metastasectomy may be considered here. Stereotactical irradiation is a good alternative to surgery in patients with 1 to 3 metastases, a diameter of < 4 cm, who have little other disease activity [Akyurek, 2007; Rades, 2007; Kocher, 2011]. If a recurrence develops at a later stage, additional stereotactical or total brain irradiation may be administered [Chang, 2009].
For futher considerations, see the national Guideline *Brain metastases* at http://www.oncoline.nl/hersenmetastasen.

Meningitis carcinomatosa

Where there are neurological deficits due to tumour depositions in the meninges, treatment may

consist of radiotherapy at locations causing clinically threatening symptoms. This generally concerns the entire brain up to and including the base of the skull, sometimes also the entire myelum and/or cauda equina. Given the blood-brain barrier usually does not function when a patient has meningitis carcinomatosa, systemic therapy may also be effective. This is partly dependent on the condition of the patient and any disease activity elsewhere partly determines the modality chosen.
For futher considerations, see the national Guideline *Leptomeningeal metastases* at http://www.oncoline.nl/leptomeningeale-metastasen.

Progressive, ulcerating and/or bleeding breast cancer or lymph node metastases

Radiotherapy has a favourable influence on locally progressive, ulcerating and/or bleeding primary tumours or on metastases in the skin, subcutis or lymph nodes. A single dose of 6 Gy or 20 Gy in 5 fractions may have a good analgesic and/or haemostatic effect. With larger and/or ulcerating laesions, a higher dose fractionated irradiation schedule is chosen, depending on the condition of the patient. A combination of hyperthermia and local radiotherapy may be considered in patients who have already received irradiation to a high dose [Zagar, 2010].

Tumour infiltration of the brachial plexus

Tumour infiltration of the brachial plexus is usually the result of periclavicular lymph node metastasis. Early diagnosis is important to prevent serious, chronic pain complaints and neurological deficit with loss of arm/shoulder function. High-dose radiotherapy provides some of patients with good palliation of pain and prevents (further) neurological deficit.

Orbital and intraocular metastases

Both orbital and choroidal metastases form an indication for radiotherapy. This treatment has a favourable influence on ptosis and eye movements and leads to a reduction in pain complaints, maintaining or even recovery in vision for most patients [Wiegel, 2002]. There may be an indication for emergency intervention, depending on the severity and progression of complaints.

Conclusions

Level 1	Radiotherapy is effective for palliation of pain complaints caused by skeletal metastases. A2 Chow 2007, van der Linden 2006, van der Linden 2004, Sze 2004

Level 1	A single dose of 8 Gy and 6x4 Gy results in the same and substantial reduction in pain in the majority of patients. A2 van der Linden 2006, Sze 2004

Level 1	Neurological deficits indicating epidural myelum/caudal compression are an emergency indication for dexamethasone and radiotherapy. Primary neurosurgical/orthopaedic intervention is preferable for patients with a good prognosis and condition, limited vertebral metastasis and other disease activity, and an age < 65 years. In many cases, radiotherapy may prevent further neurological deficit as a result of epidural myelum/caudal compression and lead to a recovery in function. A2 Patchell 2005, Chi 2009, Maranzano 2009 B Rades 2002, Rades 2006, Rades 2010

Level 1	Radiotherapy may prevent further neurological deficit as a result of brain metastasis, lead to a recovery in function and a limited increase in survival. A2 Koch 2011, Chang 2009 B Bezjak 2002, Verhagen 2006, Sperduto 2010

Recommendations

With (pain) complaints on the basis of metastasis, palliative short-term radiotherapy should always be considered. This applies to metastasis in the brain, lymph nodes, skin/subcutis and skeleton, for example. Local radiotherapy may be considered with complaints of the primary tumour in the breast.

In principle, short-term palliative radiotherapy may be repeated if complaints return.

Administering a single dose of 8 Gy is preferable to combat pain complaints caused by skeletal metastases. If there is extensive osteolysis or a threatening fracture, a fractionated schedule to 20-30 Gy is preferable. A stabilising osteosynthesis should always be considered for long bones.

If there is limited intracerebral metastasis (1-3 metastases, diameter < 4 cm), stereotactical irradiation should be considered instead of irradiation of the entire brain.

Emergency radiotherapy (within 24 hours after diagnosis) is indicated for epidural myelum/caudal compression demonstrated by MRI to prevent progression of neurological complaints and these complaints becoming irreversible. Radiotherapy may lead to a recovery in function.

In patients with vertebral metastases and a good prognosis, the combination with neurosurgical/orthopaedic intervention must be considered. If the patient is not eligible for surgery, a higher total dose should be considered (30 Gy), to prevent complaints from recurring.

9.7 Treatment of specific problems

Life expectancy of patients with breast cancer has increased due to the vastly improved treatment of breast cancer and metastases. The consequence of treatments and symptoms of progressive disease is the possibility of a broad scale of non-tumour-specific complaints. An extensive set of national multidisciplinary guidelines can be found at www.pallialine.nl - the database with guidelines for palliative care by the CCCN. Guidelines in the area of symptoms, the end of life, as well as other guidelines for palliative care can be found on Pallialine. Examples of the treatment of common specific problems are:

Extravasation of anthracyclines

Infusion of dexrazoxane as soon as possible after accidental extravasation of doxo/epirubicin is indicated to prevent local necrosis and ulcerations [Mouridsen, 2007].

Ascites

Ascites formation with peritonitis carcinomatosa may be treated with relieving punctions. If portal hypertension is (part of) the reason for ascites, salt limitation and diuretics (spironolactone with loop diuretics) may be administered. Pleural fluid or ascites may cause delayed excretion of methotrexate through accumulation of the agent in this third area with an increase in mucositis and myelotoxicity.

Pleuritis carcinomatosa

After additional diagnosis, relieving punction may be considered alongside (adjustment of) systemic therapy if the diagnosis metastatic breast cancer is certain. If pleural effusion recurs rapidly or does not respond well to systemic treatment, drainage with pleurodesis may be applied.

Pericarditis carcinomatosa

If pericarditis carcinomatosa is associated with haemodynamic consequences, treatment with pericardiocentesis is performed, possibly followed by pericardial effusion or fenestration.

Male breast cancer

Approximately 0.6% of all breast cancers develop in men. The incidence of carcinoma is low, but in the last 25 years has increased from 0.57 in 1989 to 1.06 per 100,000 in 2009. In 2009, 106 men were diagnosed with breast cancer in the Netherlands. Men with a gene mutation; especially BRCA2 have an increased risk. It also occurs with *M. Cowden*. But even with this familial history (with RR 2-4), , screening of men is not indicated. Other known risk factors are the syndrome of Klinefelter, acquired or endogenous hyperoestrogenism and prior irradiation of the thorax, such as with *M.Hodgkin,* for example. The average age is 67 years, 7 years higher than for women. Compared to breast cancer in women, breast cancer in men is more often low-grade and oestrogen receptor-positive [Anderson, 2010]. Due to the extremely low incidence, prospective randomised studies in men with breast cancer

are lacking [Korde, 2010; Ottini ,2010].

10.1 Imaging

There are no prospective studies on imaging in men. Chen (2006) has published on imaging and Giordano (2005) on epidemiology, imaging and treatment. A carcinoma almost always presents as an excentric, palpable abnormality and nipple or skin retraction occurs more rapidly than with women. Imaging is the same as in women: mammography, supplemented by ultrasound and punction if the findings are inconclusive. All histological variants of breast cancer may occur [Jepson, 1998], but there is usually an invasive ductal carcinoma, presenting as an excentrically located spiculated mass . Microcalcifications are much rarer than in women, cysts in men are more often complex as a result of intracystic papillary proliferation.
The most common differential diagnosis of a palpable, generally painful, retromamillary swelling is gynaecomastia, in contrast to cancer with central retromammary location and usually bilateral. The mammogram is diagnostic: nodular breast tissuein recent gynaecomastia (less than 1 year) and dendritic or interspersed with fat in gynaecomastia that has existed for a longer period of time. Gynaecomastia may also be diagnosed by ultrasound, but it is more difficult to exclude malignancy. There is no clear relationship between gynaecomastia and breast cancer, but there is between gynaecomastia and a disturbed ratio between oestrogen and testosterone levels. Clinical signs of gynaecomastia are therefore no indication for imaging in men, under 30 years of age.
The indication for imaging in suspected gynaecomastia is usually the asymmetric presentation and painfulness of the retromammillary swelling. Malignancy should be excluded in older men. A bilateral mammogram is the examination of choice to diagnose gynaecomastia, MLO images are often sufficient. It is a benign abnormality, and can therefore be classified as BI-RADS 2 (benign).

10.2 Primary treatment

The treatment of breast cancer in men is derived from the treatment plan for women [Margaria, 2000]. The SN procedure also appears to be safe and reliable for men [Gentilini, 2007; Flynn, 2008]. Optimal locoregional treatment is advocated, in which both BCT and mastectomy with SN procedure may be considered. Postoperative irradiation after mastectomy must always be considered because the margins in relation to the anatomically smaller breasts are more limited [Kamila, 2007].
There are no randomised studies on the effect of adjuvant systemic therapy in men. Adjuvant systemic therapy is recommended in accordance with the treatment plan for premenopausal women older than 35 years. There is insufficient experience with the treatment of breast cancer using aromatase inhibitors in men. In theory, this treatment might not be sufficiently effective because the production of oestradiol by the testes (approximately 20% of the amount of circulating oestrogens) is aromatase-independent [Volm, 2003]. Therefore, tamoxifen and no aromatase inhibitors are recommended as adjuvant hormonal therapy [Arriola, 2007; Goss,1999; Ravardi-Kashani, 1998].
Compared to women, men with breast cancer seem to have a poorer prognosis, in line with differences in biology, pathology, initial T/N status and ethnicity. Studies from the United States indicate a poorer prognosis for black men, compared to Caucasian men with breast cancer [Crew, 2007; Nahleh, 2007]. Compared to women, men with breast cancer clearly have a greater risk of developing a second primary breast cancer [Auvinen, 2002; Bagchi, 2007; Satram-Hoang, 2007].
Consultation of a clinical geneticist is indicated in male breast cancer, because the chance of a BRCA1/2 mutation is at least 10%. Follow-up after treatment is the same as for women, including mammography (see chapter 12).

10.3 Metastatic breast cancer

There are no randomised studies on the effect of systemic therapy for male metastatic breast cancer, but the treatment plan here is also derived from that for woman [Giordano, 2002]. Regarding hormonal treatment of metastatic breast cancer for men, the guideline that applies to premenopausal women should be followed.

Conclusions

Level 2	The average age of breast cancer in men is 67; 7 years higher than for women. The incidence of breast cancer in men is increasing, but is much lower than the screening threshold in the Netherlands. B Chen 2006, Giordano 2005, Anderson 2010

Level 2	Compared to women, men with breast cancer have a clearly greater risk of developing a second primary breast cancer. B Auvinen 2002, Bagchi 2007, Satram 2007

Level 2	Compared to women, men with breast cancer seem to have a poorer prognosis, also locoregionally. B Nahleh 2007, Kamila 2007

Recommendations

Screening

There is no indication for screening of men.

Imaging

Imaging in men may be conducted in the same manner as with women:

- younger than 30 years: ultrasound, clinical signs of gynaecomastia are no indication for imaging
- over 30 years of age: mammography, supplemented by ultrasound and punction if the findings are inconclusive

Consultation of a clinical geneticist is indicated in male breast cancer, because the chance of a BRCA1/2 mutation is at least 10%.

Primary treatment

Men with breast cancer may be treated in the same manner as women with breast cancer

- with the SN procedure
- optimal locoregional therapy by means of BCT or mastectomy
- if adjuvant is applicable: no aromatase inhibitors; do use tamoxifen, orchidectomy and LHRH analogues

Aftercare and treatment of metastatic disease

- in accordance with the treatment plan for women
- see chapter 9 for metastatic disease
- see chapter 12 for aftercare

Pregnancy and fertility

More than 5% of women diagnosed with breast cancer are under 40 years of age (www.kankerregistratie.nl). As a result of the social trend to postpone pregnancy until later in life, we are increasingly becoming confronted with breast cancer occurring during pregnancy or with breast cancer in a young woman who would still like to have children.
Radiotherapy, chemotherapy and endocrine therapy can all have an influence on fertility. Treatment of breast cancer during/around the pregnancy period is most certainly multidisciplinary. a perinatologist and neonatologist must also be involved aside from the breast care team. Given the possible influence of treatment methods on not only the expectant mother, but also her unborn child, specific measures and optimal alignment are needed. See chapter 12 for Hormone Replacement Therapy (HRT) and contraception after breast cancer.

11.1 Pregnancy associated breast cancer

Pregnancy associated breast cancer (PABC) refers to breast cancer that occurs during pregnancy or in the first year after pregnancy. The incidence of PABC is estimated at 0.2-3.8% of all breast cancers [Wallack, 1983] and it occurs in 1 in 3,000-10,000 pregnancies [Pavlides, 2005; Ring, 2005; Sauders, 1993; Wallack, 1983]. PABC confronts patients and treating physicians with a diagnostic, therapeutic and ethical dilemma. Determining the diagnosis is complicated by the changes in the breasts that develop as a result of the pregnancy and through limitations in the diagnostic possibilities, so that a delay in diagnosis is fairly common. Traditionally, breast cancer during the period of pregnancy or lactation is associated with a poor prognosis [Gemignani, 2000; Gwyn, 2001; Haagensen, 1943; Keleher, 2001; Moore, 2000]. In a recent review on the basis of an international consensus meeting, it was found that the frequency of BRCA1/2 mutations is almost twice as high (9 instead of 5%) amongst PABC patients. In addition, hormone-receptor negative and HER-2-positive tumours are more common in this population [Amant, 2010]. In studies that correct for these factors and disease stage, no difference was found in the prognosis of breast cancer between pregnant and non-pregnant women, especially in patients with a low-stage breast cancer [Gemignani, 2000; Gwyn, 2001; Keleher, 2001; Moore, 2000]. The poorer prognosis is therefore not based on an unfavourable influence by the pregnancy, but on an unfavourable stage as a result of late detection of the disease. The recommendation to terminate the pregnancy is therefore not justified in order to improve the prognosis of the breast cancer [Anderson, 1996; Clark, 1989; Gemignani, 2000; Petrek, 2004].

Conclusion

Level 3	The poorer prognosis of pregnancy associated breast cancer is not based on an unfavourable influence by the pregnancy, but on an unfavourable stage as a result of late detection of the disease and unfavourable tumour characteristics in this young subpopulation. C Gwyn 2001, Keleher 2001, Moore 2000, Amant 2010

11.1.1Diagnostic investigations

A pregnancy associated breast cancer is difficult to diagnose. The breasts change as a result of the pregnancy (or lactation). Glandular tissue proliferates, and feels different (both for the patient and physicians). A lump in the breast in women of an age during which pregnancy usually occurs is generally benign, certainly during or shortly after pregnancy. From a differential diagnostic perspective, galactoceles, abscess, cyst, hyperplasia or fibroadenoma must be considered. Proliferation of the glandular tissue has an unfavourable influence on the evaluation of imaging research. Ultrasound is the method of choice in case of a palpable abnormality, followed by mammography if required. See also paragraph 2.2.

Radiological imaging

Radiological research is possible during pregnancy. The foetal radiation exposure (for most of the prevailing forms of imaging lies far under the threshold dose (100 milliSievert (mSv)). Especially if the uterus is not located within the bundle (or within 10 cm of the bundle), the doses received by the foetus is so low that there is no notable risk. In addition, the intention is always to keep theradiation dose as low as possible (*As Low As Reasonably Achievable*, the ALARA principle). The interpretation of mammographies during pregnancy is complicated by the increased density of the breast tissue. The most important indication is the evaluation of microcalcifications. A patient can be offered a lead

apron, particularly for peace of mind, because the foetal dose during mammography is negligible. The interpretation of an ultrasound of the breasts and axilla is not influenced as much by the pregnancy as is mammography.

Nuclear medicine imaging

The prevailing nuclear medicine diagnostic methods for breast cancer, the SN procedure, skeletal scintigraphy and FDG-PET make use of isotopes that do not pass the placenta [McCollough, 2007; Zanotti-Fregonara, 2009]. The main foetal radiation exposure involved in these imaging methods are that the isotopes are excreted renally, and may remain for some time in the urinary bladder. The recommendation for a pregnant woman who has an indication for a nuclear medicine investigation is therefore to drink a lot of water and urinate frequently in the first day after the investigation has been performed [ICRP, 2001; Russell, 1997]. The table shows the estimated maximum foetal radiation dose for a number of prevailing diagnostic procedures for women with breast cancer [EC, 1998; Fenig, 2001; ICRP, 2001; Kal, 2005; Nicklas, 2000; Russell, 1997; Streford, 2003; Valentin, 2003].

Foetal radiation exposure for a number of prevailing diagnostic procedures in the first trimester of pregnancy. The threshold dose for non-stochastic damage to the foetus is 100 mSv.

Diagnostisch procedure	Foetal exposure in milliSievert (mSv)
Mammography in 2 direction	< 0.001
Chest X-ray	< 0.01
X-ray of the lumbar spine	1.7
Pelvic X-ray	2.0
Abdominal X-ray	1.4
CT Abdomen	10-30
SN procedure	< 0.007
Skeletal scintigraphy**	< 4.5
FDG-PET**	10-15

** Radiation exposure decreases with duration of the pregnancy

MRI scan with intravenous gadolinium

Opinions are divided about MRI with gadolinium contrast during pregnancy. The European Society of Radiology has found the procedure is probably safe. However, this method is discouraged in the United States of America. No teratogenous effects on the foetus have been described for gadolinium-containing contrast medium. It passes the placenta, but after 48 hours it could no longer be detected in animal studies [Muller, 2011]. Different authors state that MRI with gadolinium is safe during lactation, because the amount of gadolinium absorbed by the child is negligibly small [Kok, 2004; Webb, 2005; de Wilde, 2005]. Like mammography, an MRI of the breasts is more difficult to interprete, because there is a strong increase in colouration due to high hormone levels and increased blood flow [Talele, 2003].

As described earlier in paragraph 2.3, staging investigations for metastases are not indicated for stage I and II breast cancer. For locally advanced breast cancer, conventional staging can be conducted without risk. The foetal dose of FDG-PET-CT consists of an FDG-PET and a CT component, together considerably higher (20-45 mSv) than that of conventional staging.

Conclusions

Level 1	The following radiological and nuclear medicine diagnostic methods are possible during pregnancy without a notable risk of damage to the foetus: mammography, chest X-ray, an ultrasound of the breast, axilla and liver, skeletal scintigraphy, SN procedure*. The foetal dose of FDG-PET-CT consists of an FDG-PET and a CT component, rendering the fetal dose considerably higher (20-45 mSv) than conventional staging. A1 ICRP 2001 B McCollough 2007, Zanotti-Fregonara 2009 C Kal 2005, Streford 2003 Russell 1997

* The use of patent blue is advised against during the SN procedure.

Level 3	The feasibility of MRI with gadolinium contrast in pregnant or lactating women is (still) unclear. The imaging may be performed if indicated, without the application of special measures. C Webb 2005

Fine needle aspiration and histological needle biopsy

Cytological analysis and a histological biopsy are reliable analyses during pregnancyHowever, both false-negative results (sampling errors), due to the large and congested breasts, and false-positive results, due to increased proliferation of glandular tissue, are possible. The pathologist must therefore be informed of the fact the patient is pregnant [Mitre, 1997]. There is virtually no data available on the influence of pregnancy on the determination of hormone receptors. Immunohistochemical assays detect both bound and unbound receptors and should be reliable during pregnancy.

Recommendations

Diagnosis and treatment of pregnancy associated breast cancer is most certainly multidisciplinary; aside from the breast care team, a perinatologist and neonatologist must also be involved.

Radiological diagnostic procedures are possible, taking the ALARA principle into account

- Mammography and ultrasound for locoregional diagnosis
- Conventional staging (chest X-ray, liver ultrasound and skeletal scintigraphy) only in the case of locally advanced disease or suspected metastasis (complaints)
- As a standard, MRI (with intravenous gadolinium) and FDG-PET-CT are not recommended

Cytology and histology are possible. The pathologist must be informed about the pregnant or lactating status

11.1.2 Treatment

Similar to diagnostics, the treatment of PABC must be based on multidisciplinary consultation. Discussion within the multidisciplinary team prior to treatment is essential in order to ensure optimal coordination of the different treatment modalities, the sequence of these and any obstetric steps. A treatment sequence should be chosen that couples a maximum chance of cure for the patient with a minimum risk of foetal damage. This is highly dependent upon the stage of the pregnancy at which the diagnosis is made. No randomised studies have been performed on the treatment of breast cancer during pregnancy. The recommendations hereunder are therefore largely based on retrospective studies and case histories.

Surgery during pregnancy

If the changing physiology of the woman during pregnancy is taken into account, anaesthesia and surgery may be safely performed [Ni Mhuireachtaigh, 2006; Moran, 2007]. Possible disadvantageous effects of surgery on the foetus are more often the result of hypoxia, hypotension and hypoglycaemia than teratogenous effects of anaesthetics. These conditions and therefore also the associated undesirable foetal consequences can usually be prevented. A left lateral tilt position prevents compression of the vena cava, this applies especially if the uterus is larger (after 24 weeks). Postoperative pain may lead to an increase in maternal oxytocin release, and therefore preterm contractions. This can often be prevented using adequate analgesia [de Buck, 2008].

A mastectomy or BCT may be performed in the local treatment of breast cancer during pregnancy [Navrozoglou, 2008]. The SN procedure is a safe alternative for an ALND in women with a $cT_{1-2}N_0$ tumour. In 2004, Gentilio (2004) found that administered ^{99m}TC sulfur colloid especially concentrates in the location of the injection and the lymph nodes. Keleher (2004) has calculated that the foetal dose, if the mother is injected with 92.5 MBq ^{99m}TC sulfur colloid, is 4.3mSv. This falls well within safety margins. Allergic reactions have been reported for patent blue (blue patent V). This agent is better avoided during pregnancy [Khera, 2008, Gentilini 2004].

Radiotherapy during pregnancy

In contrast to what is often said, even therapeutic radiotherapy during pregnancy is not a priori impossible. It must be realised that the foetus is more sensitive to any damage and that any damage is more severe the earlier the stage in pregnancy. On the other hand, the uterus is small during early pregnancy and lies further from the radiation fields, so that it is often easier to limit the total foetal dose

[Kal, 2005].
The risks may be subdivided in deterministic and stochastic effects. Examples of deterministic effects are an increased chance of deformities of organs (at 2-8 weeks of pregnancy), or mental retardation (of 8-15 weeks and to a lesser extent at 16-26 weeks of pregnancy). These effects are dose-dependent and have a threshold dose. In its regular reports, the International Committee for Radiological Protection (ICRP) expresses these risks in chance per millisievert (1 Sievert (Sv) corresponds to 1 Gray (Gy), see the below table) [ICRP, 2001; Valentin, 2003]. In the ICRP-90 report, a threshold dose of 100 mSv (in one administered dose) is reported for these side effects [Valentin, 2003]. Stochastic effects, in particular the induction of tumours, may (in principle) occur on damage of one cell nucleus and do not have a threshold dose. In the third trimester, (a part of the) foetus is closer to the radiation fields and the chance of tumour induction is therefore relatively high. Some people therefore advise against radiotherapy in the third trimester [Amant, 2010].

The dose to the uterus during radiotherapy is dependent on the size of the radiotherapy fields used and the distance of the uterus to the fields [van der Giessen, 1996; van der Giessen, 2001; Kase, 1983; Stovall, 1995]. This dose is usually low and may differ somewhat per radiotherapy machine. It may also be reduced by a factor 3 or 4 using shielding measures. If radiotherapy is being considered for a pregnant patient, the uterus dose must be calculated and measured using a phantom, with and without shielding [van der Giessen, 2001]. A decision can then be made in consultation with the patient whether or not to postpone radiotherapy. For example, during radiotherapy of the breast or chest wall with a reference dose of 50 Gy in 5 weeks, the calculated maximum dose at the location of the foetus may be 0.03 Sv at 8 weeks pregnant to 0.2 Sv at 24 weeks pregnant. By applying the appropriate shielding, the (physical) dose at the location of the foetus may be reduced by a factor of 3 or 4 to 0.05-0.07 Sv = 50-70 mSv. In this example, the threshold dose of 100 mSv mentioned in the ICRP-90 report is not exceeded. The chance of tumour induction would be a maximum of $1.5 * 10^{-4} * 70 = 0.0105$ or 1%.

Risks of irradiation exposure by the foetus

Pregnancy term	Risk	Risk estimation	Threshhold dose
Pre-implantation *0-8 days*	early abortion	10^{-3} mSv^{-1}	unknown
Organogenesis *2-8 weeks*	organ abnormalities	$4*10^{-4}$ mSv^{-1}	100 mSv
Brain development* *8-15 weeks*	mental retardation	$4*10^{-4}$ mSv^{-1}	100mSv
Development of brain support tissue *16-25 weeks*	mental retardation	10^{-4} mSv^{-1}	100 mSv
Maturation *25-40 weeks*	growth retardation**	(< 10^{-4} mSv^{-1})	100 mSv
Tumour induction *Entire pregnancy*	juvenile cancer	$1.5*10^{-4}$ mSv^{-1}	none

* Retardation can also be quantified as a loss of approximately 30 IQ points per Sievert
** Uncertainty about the role of radiation; growth retardation is a general result of stress

The abovementioned deterministic risks must be weighed up against the spontaneous chance of congenital abnormalities, which is approximately 4%. The increased chance of tumour induction must be related to the general chance of malignancy in children (0-15 years) in the Netherlands of 0.2%.
In good consultation with the multidisciplinary team and patient, risks for the foetus must be weighed up against the risks of (further) delaying radiotherapy, such as a reduction in the chance of locoregional control [Huang, 2003].

Conclusions

Level 1	Good estimates of the irradiation risk for the foetus can be made. The nature and size of these risks are dependent on the stage of pregnancy. The threshold dose for deterministic effects is 100 mSv.

	There is no threshold dose for stochastic effects. A1 ICRP 2003 C Kal 2005

Level 3	The uterus dose as a result of a planned therapeutic radiotherapy can be accurately calculated and measured using a phantom. It may also be reduced by a factor of 3 or 4 using shielding measures. C van der Giessen 1996, van der Giessen 2001

Adjuvant systemic therapy during pregnancy

There are no prospective randomised studies on the effects of (adjuvant) systemic therapy on the foetus. All information has been obtained from retrospective studies and case histories.

Chemotherapy

Administration of chemotherapy during organogenesis is associated with an increased chance of a spontaneous abortion and congenital abnormalities of the foetus [Doll, 1989; Ebert, 1997]. In the study by Ebert (1997), most of the 15 women who had a spontaneous abortion were treated with methotrexate. A few larger studies described foetal effects of chemotherapy during the second and third trimester of pregnancy in patients with breast cancer [Berry, 1999; Giacalone, 1999; Ring, 2005]. In the French retrospective study in which 18/20 patients were treated with different types of chemotherapy, no foetal malformations were observed [Giacalone, 1999]. In the (non-randomised) prospective study from the MDACC, Berry (1999) treated 24 pregnant patients with a median four courses of FAC chemotherapy over a period of 8 years. He did not find an increase in congenital abnormalities or complications during pregnancy in this group of patients. The median pregnancy duration at birth was 38 weeks. The birth weight, the Apgar score and health of the children directly after birth were normal. Ring (2005) described the experiences of five London hospitals in which 16 pregnant patients were treated with anthracycline-containing chemotherapy and 11 patients with CMF (cyclophosphamide, methotrexate, fluorouracil). One child was born with a hemangioma on the abdomen (possibly unrelated). None of the children had a birth weight under the 10th percentile for the pregnancy duration. Two children had breathing difficulties, and five were admitted to the high neonatal care unit. An international panel has recently reviewed existing literature on chemotherapeutic agents used for breast cancer during pregnancy. The most commonly used schedules were FAC/FEC and AC. The authors arrive at the conclusion that these chemotherapy schedules are relatively safe during pregnancy, as long as they are not administered any earlier than an amenorrhoea duration of 14 weeks [Amant, 2010].

However, there is still uncertainty about possible negative effects on development of the central nervous system, intra-uterine growth retardation, the chance of premature birth, cardiac damage to the foetus, and possible genetic abnormalities in the descents of these children [Epstein 2007, Gwyn 2005]. In 2001, Aviles published data on the health and development of 84 children exposed in utero to combination chemotherapy, administered for a haematological malignancy in the mother. After a median follow-up of 18.7 years, there were no abnormalities in physical, neurological and psychological development in the 84 first generation children, nor in the 12 second generation children. Hahn (2006) held a telephone survey amongst carers of 40 children in the age bracket 0-13 years, and found no problems in this group related to chemotherapy in utero. Van Calsteren (2006) could not determine a developmental defect in a small group of 10 children from 0 to 6 years (although there was a trend in a somewhat thinner ventricular wall in children exposed to chemotherapy in utero). The development of children born healthy after exposure in utero to chemotherapy for breast cancer therefore appears to be normal in most cases, but the follow-up of this group is still too short for a definitive conclusion.

Mir (2007) published a review about the use of other agents. No congenital abnormalities were found in nine documented case histories on paclitaxel. This also applied to six women who received docetaxel and five treated with vinorelbine. These agents were administered during the second or third trimester. The median follow-up of the children varied between 16 and 23 months. Three children, whose mother received chemotherapy in the last three weeks before birth, had anaemia or neutropenia. Amant (2010) concluded that, while information is still limited on the safety of taxanes, these agents can probably be administered with limited risk during the pregnancy.

Supporting therapy
In some cases, supporting medication is indicated during chemotherapeutic treatment. If required, metoclopramide, alizapride, 5-HT antagonists, NK1-antagonists, corticosteroids, GCS-F and erythropoietin may be administered during pregnancy [Gralla, 1999; Amant, 2010]. Extra attention must be given to the type of corticosteroid; methylprednisolone and hydrocortisone are better metabolised in the placenta than dexa/betamethasone, so that a smaller amount reaches the foetal circulation [Blanford, 1977]. Long-term follow-up of children who received multiple antenatal doses of betamethasone for lung maturation, shows an increase in attention problems and spasticity [Crowther, 2007]. Methylprednisolone or hydrocortisone is therefore preferable in the use of corticosteroids as anti-emetic or to prevent an allergic reaction.

Chemotherapy in relation to the birth
Chemotherapy should not be administered later than at 35 weeks of pregnancy. Neutropenia during birth and long-term exposure of a newborn to chemotherapy, administered shortly before birth, increases the chance of complications for mother and child [Amant, 2010]. It is preferable to aim for a full-term baby (≥ 37 weeks).

Hormonal therapy
Studies with animals have shown that tamoxifen use during pregnancy may lead to congenital abnormalities in the foetus [Chamness, 1979; Diwan, 1997]. Six cases have been described with tamoxifen-use during pregnancy [Barthelmes, 2004; Isaacs, 2001; Koizumi, 1986; Ökzüzoglu, 2002; Tewari, 1997]. One child was born with abnormalities of the genitals and a second child, who was also exposed to other potentially toxic substances, had a craniofacial defect. No abnormalities were found with the four other children. Additional but less detailed information has been obtained by the manufacturer of tamoxifen [Cullins, 1994]. From 50 pregnancies that developed during tamoxifen-use, 19 healthy children were born, 10 had a congenital abnormality, 8 pregnancies ended in an abortion and no details are available for the remaining 13. Abortions and congenital abnormalities have been described after exposure of the foetus to LHRH analogues [Goldhirsch, 2004; Jimenez-Gordo, 2000]. On the basis of this (although limited) information, hormonal treatment (tamoxifen or LHRH analogues) should be advised against during pregnancy.

Trastuzumab
Fourteen cases have been described in literature of full-term newborns, exposed to trastuzumab in utero. Oligo- and/or anhydramnion was observed in 8/14 cases. Four neonatal deaths were described, secondary to respiratory and renal failure. This may be explained by the fact that HER-2 expression is extremely strong on foetal renal epithelium, and is strongly influenced by trastuzumab [Press, 1990]. Another hypothesis is that trastuzumab causes inhibition of vascular endothelial growth factor (VEGF), which regulates the production and re-absorption of amniotic fluid[Pant, 2008]. The administration of trastuzumab is not recommended in pregnancy [van der Sangen, 2008].

Conclusions

Level 3	Methotrexate during pregnancy may lead to damage of the foetus or an abortion. C Doll 1989, Amant 2010

Level 3	Treatment with FAC/FEC or AC chemotherapy may, if indicated, be used during the second and third trimester of the pregnancy, but not after the 35th week of pregnancy due to neonatal neutropenia and the risk of maternal and neonatal infection. C Berry 1999, Giacalone 1999, Ring 2005, Amant 2010

Level 3	Administration of taxanes and vinorelbine during the second and third trimester of pregnancy does not appear to lead to congenital abnormalities, but experience with these is limited. C Mir 2007, Amant 2010

Level 3	Congenital abnormalities have been described with the use of tamoxifen and with LHRH analogues during pregnancy.

	C Barthelmes 2004, Goldhirsch 2004, Isaacs 2001

Level 3	Trastuzumab during pregnancy may interfere with renal development of the foetus. C Mir 2007, Amant 2010

Remaining considerations
The discovery of breast cancer during pregnancy is for patients, their partners and their doctors a complicated and emotionally stressfull event that leads to many questions and may confront treating physicians and patients with ethical dilemmas.
The pregnancy does not have an unfavourable influence on the course of the disease. Full treatment for breast cancer during pregnancy is possible without a notable burden on the foetus, even if the breast cancer is detected early in pregnancy. Terminating the pregnancy is not needed in order to ensure the mother can be adequately treated for her breast cancer. This should be clearly communicated to the patient.
Imaging diagnostics should not be avoided for the sake of the pregnancy, but mammography and MRI are less reliable. It is essential that all diagnostics and treatment recommendations are discussed first in the context of multidisciplinary consultation, in which a perinatologist is also involved.

Recommendations
Treatment of breast cancer during pregnancy is possible, the pregnancy does not appear to influence the prognosis and does not need to be terminated for the sake of treatment.

Treatment is dependent on the stage of the disease and pregnancy. Prior to treatment, recommendations must be discussed within a multidisciplinary team, also involving a perinatologist and a neonatologist.

Surgery
- mastectomy or BCT
- SN procedure, if indicated, **without patent blue**, is possible in all stages of pregnancy

Radiotherapy
If radiotherapy is applied, the following steps are necessary:
- Calculation and measurement of foetal dose using a phantom and calculation of foetal risks
- Apply shielding measures for the pregnant uterus

Chemotherapy
- Chemotherapy with FAC/FEC or AC during the second and third trimester of pregnancy is possible if postponement cannot be justified in relation to the mother
- Little is known about taxanes administered during pregnancy
- Methotrexate must be avoided during pregnancy
- Chemotherapy must not be commenced or continued after 35 weeks of pregnancy, due to risk of:
  a) neutropaenia during or shortly after birth (mother and newborn)
  b) limited detoxification by the newborn

Supporting therapy
Methylprednisolone or hydrocortisone are preferable when using corticosteroids.

Hormonal therapy
- Tamoxifen is contraindicated
- LHRH analogues are contraindicated

Trastuzumab
- Trastuzumab is contraindicated

11.2 Pregnancy and breast-feeding after breast cancer

Pregnancy

Risks for the mother
Many patients and treating physicians are hesitant about the desirability of pregnancy after breast cancer treatment. As a result of high hormone levels during pregnancy, the growth of any micrometastases of a hormone-sensitive tumour may be stimulated.
A number of retrospective, largely case control studies have researched the effect of pregnancy on the (disease-free) survival in women previously treated for breast cancer [Upponi, 2003; Mueller, 2003; Blakely, 2004 Gelber, 2001]. Almost all studies show that pregnancy after breast cancer treatment does not have a negative effect on the (disease-free) survival. This conclusion remains controversial because of possible selection bias (*healthy mother* phenomenon) and the retrospective nature of the studies.

Risks for the unborn child
If pregnancy occurs within 6 months after radiotherapy, there is a theoretic chance that mutations in mature egg cells will lead to congenital abnormalities. This risk is dose-dependent and can be calculated [ICRP 2001, Valentin 2003]. The size of this risk is usually negligible in the case of irradiation. Whether chemotherapy has such an effect on mature egg cells is not known. An earlier treatment with chemotherapy, consisting of CMF or doxorubicin, does not lead to an increased chance of congenital abnormalities, but is associated with an increased chance of premature births (10-29%, HR 1.7) [Del Mastro, 2006]. Reliable data on the late effect of treatment with taxane-containing chemotherapy or with trastuzumab is still lacking.
Seven cases have been described involving pregnancies that occurred during tamoxifen use. In two of these, severe congenital abnormalities developed; one was a craniofacial defect and the other involved congenital abnormalities of the urogenital tract [Cullings 1994, Tewari 1997, Koca, 2010]. In the latter case, a causal relationship between tamoxifen use during conception and the first weeks of pregnancy has certainly not been excluded [Tewari 1997]. Pregnancy should be advised against during hormonal treatment, and if pregnancy occurs during tamoxifen use, this should be ceased and the risks discussed with the patient.

Other considerations
The estimated prognosis of the breast cancer is a point of attention for the patient and her partner. After all, if the prognosis is poor for the expectant mother then the child runs the risk of losing his/her mother at a young age. Less relevant but also not negligible is the increased chance of other malignancies after breast cancer treatment, such as ovarian cancer, certainly in women with a family history of this disease (HR 1.21-1.64) [Prochazka, 2006; Hooning, 2006].

<u>Breastfeeding</u>
Clarity is lacking amongst physicians and patients on the desirability of breastfeeding by a women who has had a child after being treated for breast cancer. As far as the literature is concerned, breastfeeding does not seem to give an increased risk of recurrent breast cancer or worsening of the prognosis. In a series of 94 patients who had one or more children after breast cancer treatment with matched controls, it was found that further prognosis was better amongst the women who had had children than amongst the controls [Gelber, 2001]. In this cohort, the prognosis amongst the 27 women who had breastfed was better than that of the 25 women who had not done so and the 42 for whom the breastfeeding status was not known [Azim, 2009]. The authors note that these results may be biased, but conclude that breastfeeding does not have a negative influence on prognosis. The results are in line with the protective effect of (long-term) breastfeeding on the a priori chance of breast cancer. Women may be concerned that they are unable to provide enough breast milk, or that the treated breast produces breast milk that is damaging to the baby. Breast milk may contain fat soluble medication (e.g. taxanes) during or within a few weeks after chemotherapy, and breastfeeding is advised against in this period. After mastectomy there is only one breast and this can provide sufficient breast milk. After BCT, breastfeeding from the treated breast is possible in approximately 30-40% of women, and is not damaging for the nursing infant, but it may be painful [Azim, 2010; Freund, 2009].

Conclusions

Level 3	Pregnancy after treatment for breast cancer does not appear to have an unfavourable influence on the prognosis of the disease. C Blakely, 2004; Gelber, 2001; Mueller, 2003; Upponi, 2003

Level 3	Breastfeeding after treatment for breast cancer does not appear to have an unfavourable influence on the prognosis of the disease. C Azim, 2009; Gelber, 2001

Recommendations

Pregnancy and breastfeeding after breast cancer treatment does not need to be discouraged. The importance of prognosis in relation to her desire to have children should be discussed, however.

Pregnancy during tamoxifen use is advised against.
If pregnancy does occur during tamoxifen use, the agent should be ceased and possible risks should be discussed with the patient.

11.3 Fertility after breast cancer treatment

Infertility as a result of chemotherapy is experienced by patients as a serious side effect with loss of quality of life [Rodriguez-Wallberg, 2010]. In a retrospective study of 657 premenopausal patients with breast cancer, it was found that 26% had not been informed about the risk of infertility as a result of treatment [Partridge, 2004]. According to Jenninga (2008), quality of life after treatment, including the ability to start a family, must be incorporated in the treatment plan for breast cancer patients. Information about the influence of treatment on fertility and the possibilities to preserve fertility should be provided to patients as early as possible, so a patient may become well informed by a fertility specialist and there is enough time to keep all options open, such as freezing egg cells, embryo's or ovarian tissue.

11.3.1 Causes of infertility after breast cancer

Chemotherapy

The most important determinants of loss in ovarian function through chemotherapy are the age at which the patient is treated with chemotherapy, the dose and number of cycles of the chemotherapy administered [Petrek, 2006; Lee, 2006]. Alkylating therapy, especially cyclophosphamide, has a negative effect on fertility. It is also possible for anthracyclines, taxanes and platinum analogues to have negative effects [Tham, 2007; Perez-Fidalgo, 2010]. Premenopausal patients treated with cyclophosphamide have a reduced ovarian function after such treatment, corresponding to a physiological reduction over a period of 10 years. Reduced ovarian reserve after chemotherapy does not need to be associated with amenorrhoea [Petrek, 2006; Walshe, 2006; Gerber, 2008].

Hormonal treatment

A hormone receptor-positive breast cancer is diagnosed in 60% of premenopausal patients, for which long-term adjuvant hormonal treatment (tamoxifen, LHRH analogues) is recommended. Pregnancy is discouraged during this treatment. The ovarian reserve reduces exponentially from the age of 35 [Faddy, 2000]. By postponing their desire to have children, women run an extra risk of infertility due to increased age.

Radiotherapy

The radiotherapy dose in the treatment of breast cancer is generally not so high that infertility is to be expected [Wallace, 2005; Wo, 2009].

Preservation of fertility

The guideline "Cryopreservatie van ovariumweefsel" (ovarian tissue cryopreservation) concludes that the following can be chosen prior to chemotherapy: laparoscopic oophorectomy with subsequent cryopreservation, or freezing egg cells or embryos after IVF treatment [NVOG, 2007]. Controlled ovarian stimulation during IVF treatment is dependent on the cycle of the patient. Patients who use oral contraceptives at the time of a breast cancer diagnosis, must be advised to continue these sinceit saves time for IVF treatment. If there is an oestrogen receptor-positive tumour, an alternative stimulation protocol with tamoxifen or other agents rather then estrogens should be considered [Huang, 2007].
A good ovarian reserve is a condition for all three possibilities (IVF, egg cell vitrification and ovarian cryopreservation). IVF seems preferable for women with a male partner and egg cell cryopreservation for women without a partner. The procedure for harvesting egg cells takes 2-4 weeks as long as the woman has not stopped taking oral contraceptives. A laparoscopic oophorectomy for cryopreservation does not require hormonal preparation like the other two methods.

Early referral to a specialised fertility preservation centre is a condition for a successful clinical trajectory. Specialised centres can be found at www.nnf.nl.

Other interventions

There are two diametrically opposed views about the possibility of protecting ovarian function during chemotherapy by means of ovarian suppression (GnRH analogues or LHRH analogues) [Blumenfeld, 2007; Lawrenz, 2010; Oktay, 2007]. Most studies use the occurrence of chemotherapy-induced amenorrhoea (CIA) as outcome measure, instead of fertility and the associated chance of conceiving a child. The Zoladex Rescue of Ovarian Function (ZORO) study did not show a difference in CIA [Gerber, 2011]. The PROMISE GIM6 study showed that temporary ovarian suppression by triptorelin (GnRH analogue) in premenopausal women with early stage breast cancer provides a reduction in risk of CIA [Del Mastro, 2011]. However, the average age of this study population was relatively old (39 years) and the patients were only observed until one year after chemotherapy. As a result, use of GnRH analogues to protect ovarian function cannot be recommended on the basis of current data available, certainly not as fertility preservation.

Conclusions

Level 3	Chemotherapy-induced infertility affects quality of life. C Partridge, 2004; Rodriguez Wallberg, 2010

Level 3	Prior to chemotherapy, it is possible to perform IVF, egg cell cryopreservation or ovarian cryopreservation to protect against infertility. C Lee, 2006, Gerber 2008, NVOG 2007*

Recommendations

Premenopausal women with breast cancer should be informed as early as possible about possible infertility after cancer treatment, and the possibilities to deal with this.

If there is a desire to retain fertility, the woman should receive an early referral to a centre with expertise in fertility preservation techniques (these can be found at www.nnf.nl). In this case, any oral contraceptives being taken should be continued to save time for IVF or egg cell cryopreservation.

Aftercare and follow-up

In practice, the terms *aftercare* and *follow-up* are not always clearly distinguished from one another. The term *follow-up* is used for both situations. In its report 'Aftercare in oncology' ('Nacontrole in de oncologie', 2007), the Health Council defines the terms aftercare and follow-up with the following side-notes:
The term aftercare could suggest that there is always a clear moment at which treatment ends and aftercare begins. Treatment increasingly consists of a series of different forms of therapy: surgery, radiotherapy and medicinal therapy. Each of these modalities are eligible for follow-up. It is therefore not uncommon that aftercare after one treatment overlaps with the active execution of another. Of course this complicates the systematic basis of aftercare, but it is the reality.
The physical and psychosocial problems weave through this, which may play a role from the moment breast cancer is suspected, during primary treatment and in the follow-up.
The Health Council also recommended researching possibilities for more involvement by the first-line in aftercare and follow-up, see chapter 13 for more details.
The medical, paramedical as well as psychosocial aspects are discussed in this chapter.

Aftercare is an essential part of individual patient care during and after treatment of cancer. It consists of three elements:

- The detection of new manifestations of treated breast cancer or new malignancies associated with the breast cancer
- Providing information, guidance, addressing complaints and symptoms, detecting direct or late effects of disease and treatment and attention for social consequences
- Evaluation of the medical procedure and its consequences. The initiative for contact with this goal in mind may be made by both the physician and the patient

Aftercare has the primary objective of limiting disease burden by improving quality of life and extending life span. Aftercare is also precautionary care: the physical and psychosocial consequences of cancer and cancer treatment may already occur directly after diagnosis and during treatment. Timely treatment of complaints through early surveillance, starting directly after diagnosis, may reduce disease burden and prevent worsening. Partly on the basis of the report by the Institute of Medicine (IOM, 2008), Ganz (2011) emphasises the importance of attention for the 3 P's*: palliation* of present and continuing symptoms , *prevention* of late effects of cancer treatment or the occurrence of second tumours and the *promotion* of healthy behaviour.

In the meantime, the report by the Health Council has prompted formulation of the guideline Cancer rehabilitation: http://www.oncoline.nl/herstel-na-kanker [CCCN, 2011]. This guideline predominantly contains recommendations on giving shape to aftercare in the hospital setting in the first year following completion of treatment. Using an individual aftercare plan, choices are made in consultation with the patient for further guidance, aimed at limiting physical and psychosocial damage as a result of the illness.

Follow-up is defined as the programmatic approach to aftercare that consists of recurring contact moments between the patient and his/her treating physicians in relation to the treated form of cancer.

12.1 Detection of new cancer manifestations

Detection has the aim of early detection of the locoregional recurrence or a second primary tumour in order to strive for a better survival of patients with a previous breast cancer.

12.1.1 Locoregional recurrence

Factors that determine an increased risk of a local recurrence after BCT and mastectomy

For women over the age of 40, the risk of a local recurrence is less than 10% after 10 years [Elkhuizen, 1998, Bartelink, 2007]. In a non-randomised retrospective analysis of EORTC trial data, a locoregional recurrence was documented in 5.9% of patients undergoing a mastectomy compared to 10.8% of patients receiving breast-conserving treatment [van der Hage, 2003]. Similar to earlier meta-analysis, no difference was seen in survival between BCT and mastectomy [Morris, 1997; van der Hage, 2003].
A factor that leads to an increased risk of a locoregional recurrence both after BCT and mastectomy is

the presence of angioinvasive growth; the risk in both groups is approximately twice as high when this is the case [Voogd, 2001].
Both after mastectomy and BCT, the recurrence rate is inversely proportional to the age at the time of primary diagnosis; after 75 years of age it is extremely rare. The risk is twice to four times as high for women who experienced their first breast cancer before 40 years of age than women who developed breast cancer after 50 years of age [Elkhuizen, 1998; Bartelink, 2007; van der Leest, 2007; De Bock, 2006; van der Sangen, 2010]. A clear period in which most recurrences develop after BCT cannot be indicated: the risk is constant in the first 10 years, approximately 0.5-1% per year [Bartelink, 2007]. Adjuvant systemic therapy reduces the risk by approximately 30-50% [Rose, 1989; Haffty, 1991; Levine, 1992; Haffty, 1994; EBCTCG, 1998; Park, 2000; Buchholz, 2001; van der Leest, 2007].
Two-thirds of locoregional recurrences develop in isolation both after BCT and mastectomy, i.e. without simultaneous distant metastasis [Jager, 1999; Rangan, 2000]. Despite adequate treatment, 60% of patients still develop distant metastases with time [Recht, 1988; van Tienhoven, 1999].

Factors that determine an increased risk of a local recurrence after BCT

Factors that are determinant for an increased risk of a locoregional recurrence exclusively after BCT are the presence of an extensive in situ component, especially with irradical removal of the tumour, and an age under 40 years on diagnosis [Voogd, 2001; Arriagada, 2005].

Locally advanced breast cancer

The five-year locoregional recurrence percentage for *locally advanced breast cancer* after treatment with a combination of chemotherapy, radiotherapy and almost always also surgery is 20-30% [Piccart, 1988; Merajver, 1997]. Approximately 60% of locoregional recurrences after a mastectomy occur within three years, although recurrences are also observed after many years [Jager, 1999].

The value of detecting the local recurrence in relation to prognosis

It was initially thought that the prognosis of a recurrence in the breast after BCT was better than that of a chest wall recurrence after mastectomy, but this is not the case [Whelan, 1994; van Tienhoven, 1999]. A longer interval between the primary treatment and development of the recurrence is positively correlated with a favourable prognosis of salvage treatment [van der Sangen, 2006]. In addition, the size/extent is also mentioned as prognostic factor [Haffty, 1991; van Tienhoven, 1999]. In a meta-analysis of 2,263 patients, Lu (2009) found a better survival if the recurrence was detected by mammography or clinical breast examination, or in patients without symptoms, than if the patient presented with symptoms (HR 2.44; 95%CI 1.78-3.35 vs. HR 1.56; 95%CI 1.36-1.79). This argues for a treatment policy that strives for detection of the locoregional recurrence as early as possible. However, the extent to which a long-term routine follow-up (after five years of annual clinical examination and mammography) would ensure this is not known. Different studies have been conducted to study which part of current monitoring is the most effective in relation to detecting the locoregional recurrence: routine clinical examination by the physician, mammography, breast self-examination/breast awareness by the patient [McCready, 2005].

Methods of detection

In a systematic review and meta-analysis of 5,045 patients, de Bock (2004) found that approximately 40% of recurrences were discovered through mammography and/or clinical examination. A distinction could not be made in this study between the contribution made by clinical examination or mammography. Other series found that the recurrence rate detected by mammography after BCT only lies between 15% and 42% [Grosse, 1997; Rutgers, 1989; Montgomery, 2007]. In older studies (before 2000), Montgomery found that only 15% was detected by mammography and 46% by regularclinical examination. These ratios were reversed in the new studies (after 2000) due to improved mammographic techniques: here 40% were detected by mammography and only 15% by regularclinical examination. The authors concluded that there is no evidence that regular clinical examination leads to a survival advantage. Other studies have also shown a downward trend in the contribution of clinical examination by the physician [Drew, 1998; Kramer, 1998]. However, a study by (2010) showed that it may lead to earlier detection of a recurrence in women under 60 years of age, but it could not be demonstrated if this also leads to an improvement in survival. Thirty to forty percent of potentially treatable recurrences are noticed by the patients themselves, despite the fact that clinical examination of the breast after BCT may be problematic as a result of scar retraction or irradiation [Montgomery, 2007].
In summary, approximately 40% of recurrences are detected due to improved quality of mammography, approximately 40-50% by the patients themselves, and 10-20% via regularclinical

examination. A meta-analysis has shown that early detection of a recurrence in an asymptomatic patient leads to an improvement in survival. Mammography clearly plays a greater role in this early detection than regularclinical examination.

The early detection of a chest wall recurrence after mastectomy is dependent on clinical examination by the physician or patient themselves. Specific imaging or laboratory tests have no added value in early detection [Rutgers, 1989]. An axillary recurrence is usually discovered by the physician, and not by the patient [Montgomery, 2007].

12.1.2 Detection of a 2nd primary tumour

The risk of developing contralateral breast cancer varies in the entire group of patients from 4 to 8 per 1,000 women per year (0.4-0.8%). In patients with a BRCA1/2 mutation, the risk of a second contralateral tumour is much higher: in the order of approximately 2-3% per year [Malone, 2010; Metcalfe, 2011]. It can generally be stated that the risk increases as the age of diagnosis of the first breast cancer decreases, when the first tumour is of the lobular type and when there is a positive family history and/or genetic predisposition [Storm, 1986; Vaittinen, 2000]. If the first breast cancer is diagnosed before the age of 45, there is a 25% risk that a contralateral tumour will manifest before the age of 75. The associated risk factors are largely the same as the risk factors for a first primary tumour (see chapter 1). Modern radiotherapy techniques do not appear to increase the risk of contralateral breast cancer [Obedian, 2000].
Both chemotherapy [Bernstein, 1992; Broet, 1995] and hormonal therapy (tamoxifen, aromatase inhibitors) reduce the risk of a second primary tumour by approximately 30-50% [Rose, 1989; Haffty, 1991; Levine, 1992; Haffty, 1994; EBCTCG,1998; Park, 2000; Buchholz, 2001; van der Leest, 2007]. Such a reduction in risk also applies to mutation carriers, although there is no data available on large prospective studies.
In addition to clinical examination, annual mammography contributes to early diagnosis and a better prognosis of the second primary carcinoma [Mellink, 1991; Kaas, 2001]. In older patients (> 60 years) it seems justified to extend the mammography interval to two years after a disease-free interval of at least 10 years [Kaas, 2001]. If the primary surgical treatment consisted of mastectomy, the mammographic follow-up may be organised via the national breast screening programme.
In patients over 75 years of age with a disease-free interval of at least 5 years, it may be decided not to conduct further mammographic follow-up, because screening at this age does not meet the criteria of mortality reduction while retaining a reasonable balance of benefits and disadvantages [Boer, 1995].

Conclusions

Level 1	It has been demonstrated that a combination of various tumour-related predictors for locoregional recurrence (young age, N status, angioinvasive growth) lead to an increase in the risk of locoregional recurrence. A2 Wallgren 2003, Voogd 2005, Jagsi 2005

Level 1	Factors that are determinant for an increased risk of a locoregional recurrence exclusively after BCT are the presence of an extensive in situ component, especially with irradical removal of the tumour, and an age under 40 years on diagnosis. A2 Voogd 2001, Arriagada 2005

Level 3	A clear period in which most recurrences develop after BCT cannot be indicated: the risk of a local recurrence is constant in the first 10 year at approximately 0.5-1% per year. A2 Bartelink 2007

Level 2	Although two-thirds of locoregional recurrences present as isolated disease, it appears that 60% of patients still develop distant metastases despite treatment with curative intent. B Recht 1988, van Tienhoven 1999

Level 2	Mammography and possibly also clinical examination contribute to early diagnosis of second primary breast tumours (applies to the general population). B Mellink 1991, Robinson 1993, Roubidoux 1995, Kaas 2001

Level 3	Detection of a recurrence via mammography or clinical examination in asymptomatic patients leads to a survival advantage. B Lu 2009

Level 3	Approximately 40% of recurrences after BCT are detected via annual mammography, approximately 40-50% are detected by the patients themselves, and 10-20% via regular clinical examination. C de Bock 2004, Montgomery 2007, Lu 2010

New developments: MRI

Little is known yet about the role of regular breast MRI scan in the detection of recurrent disease . In a retrospective study in a patient population of 476 patients with primary breast cancer, Gorechlad (2008) determined that a follow-up MRI probably would not have provided a survival advantage to any of the patients with a local recurrence or second primary tumour, given the small dimensions of the local recurrences and the second primary tumours and the extremely good disease-free survival of those with a recurring tumour (10 of the 11). The local recurrences were small and independent of the detection method of the first tumour (also high density on the mammogram). It should be noted that the average follow-up in this study (5.4 years) is relatively short and that it concerns a patient population with an average risk. The American Society of Clinical Oncology does not support follow-up using MRI [Khatcheressian, 2006]. MRI does play a role in problem-solving; it may play an additional role if the scar cannot be distinguished with certainty from a recurrence, if there are unusual post-irradiation signs, if the tumour bed cannot be visualised on mammography, and with autologous breast reconstructions, because the negative predictive value in these situations is high [Preda, 2006; Rieber, 2003].

Level 3	Given the low risk of a local recurrence or a second primary tumour, and given the good survival after a second primary tumour in the current, general population, follow-up with MRI is not expected to improve survival. *C Gorechlad 2008*

12.1.3 Distant metastasis

The risk of developing distant metastases correlates with the T and N stageof the primary tumour and is favourably influenced by treatment of the primary breast cancer (surgery, radiotherapy, adjuvant systemic therapy). Manifestation of distant metastases means the disease can no longer be cured [Harris, 1986]. Survival of patients with detectable asymptomatic distant metastases was found to be the same as that of a group of patients with symptomatic disease [Joseph, 1998]. There are 2 large randomised studies that have compared survival of patients receiving standard follow-up versus patients receiving intensive follow-up. The standard follow-up consisted of mammography and clinical examination; intensive follow-up involved regular full staging by skeletal scintigraphy, chest X-ray, with or without ultrasound of the liver and laboratory tests [Roselli del Turco, 1994; GIVIO investigators, 1994]. The two studies did not show a difference in survival. In the study by the GIVIO investigators, a difference was also not found in the quality of life; in the study by Roselli del Turco a difference was also not seen in disease-free survival. These two RCT's were part of the Cochrane review by Rojas (2005). The conclusion was therefore that follow-up consisting of mammography and clinical examination is as effective as more intensive follow-up with laboratory tests and additional imaging, both in terms of survival, disease-free survival and quality of life. These findings are further confirmed in a more recent review by Hayes (2007).

The Cochrane review also showed that follow-up conducted by a trained general practitioner is as effective as follow-up by a medical specialist, in relation to quality of life and timely detection of distant metastases.

Conclusion

Level 1	Intensive follow-up (using laboratory tests and standard imaging) with the intention of detecting asymptomatic distant metastases is not expected to provide a survival advantage. A1 Rojas 2005, Hayes 2007 A2 Roselli del Turco 2004, GIVIO investigators 2004

The recommendations and follow-up schedules can be found at the end of this chapter.

12.2 The consequences of breast cancer: screening and treatment

This paragraph discusses the consequences of (the treatment of) breast cancer that are not directly related to manifestations of the breast cancer itself. Guidance provided during adjuvant therapy with trastuzumab is detailed in chapter 6.

12.2.1 Screening

Aftercare begins with systematic detection of complaints. In the guideline Screening for psychosocial distress (www.oncoline.nl/detecteren-behoefte-psychosociale-zorg), the Distress Thermometer is recommended as screening instrument for detection of (psychosocial) complaints [CCCN, 2010]. The Distress Thermometer assists care providers with insight in the severity and nature of problems experienced by patients on a physical, emotional, social, spiritual and practical level. In addition to this, screening and diagnostic instruments may be employed for specific complaints (for example, nutritional problems, depression, coping capacity

12.2.2 Locoregional effects: reduced shoulder function, lymphoedema and postmastectomy pain syndrome.

Physiotherapeutic treatment of locoregional effects of breast cancer and the scientific basis for this are outlined in detail in the Breast Cancer Evidence Statement, which can be found at www.kngfrichtlijnen.nl [KNGF,2011]. The below texts and conclusions are based on this.

Reduced shoulder function

Patients who have undergone axillary node dissection and/or axillary radiotherapy have the highest risk of mobility limitations of the upper limbs, reduced strength, sensibility disorders, lymphoedema and seroma. Patients who underwent an axillary node dissection, have more mobility limitations after two years and more lymphoedema than patients who received an SN procedure. A difference in strength was no longer found between the two groups after two years [Kootstra, 2010]. Starting exercise therapy on day 5-7 after surgery has a positive effect on the prevention of seroma. Exercises under guidance of a physiotherapist give a significantly better shoulder function and a better quality of life than doing so independently. Exercise therapy (including resistance exercises) does not exacerbate lymphoedema and stimulates lymphatic drainage.

Conclusions

Level 1	Axillary node dissection and/or axillary radiotherapy increases the risk of mobility limitations of the upper limbs, reduced strength, sensibility disorders, lymphoedema and seroma. This stabilises after 2 years. A1 Kootstra 2010, KNGF Evidence Statement Borstkanker 2011

Level 1	Limited execution of shoulder exercises in the first week following surgery leads to less wound fluid and seroma. Exercise therapy has a positive effect on the prevention of lymphoedema and the execution of ADL. A1 KNGF Evidence Statement Borstkanker 2011

Recommendations

It is recommended to refer patients who have undergone axillary treatment (axillary node dissection and/or axillary radiotherapy) to a physiotherapist for an outpatient consultation 5-7 days after treatment.

It is recommended to resume normal physical activities one week after surgery, taking the wound healing process into account. Fear of exercise must be prevented.

Within the framework of cancer rehabilitation it is recommended to discuss the topic physical training with each patient during treatment. There are no general medical reasons to hold back in physical training during treatment for cancer. Weight training may be worthwhile as part of this training; the training can be organised in such a way that an increase in muscle mass is achieved or at least maintained.

Lymphoedema

Studies have demonstrated that when patients receive postoperative physiotherapy and there is surveillance for lymphoedema, a rapid start can be made with the combination therapy of manual lymph drainage, compression therapy, exercise therapy and skin care (Complex Decongestive Therapy, CDT). The oedema is then less severe than with later detection and treatment. No evidence has been found that preventative treatment with manual lymph drainage is an effective intervention to prevent lymphoedema. In the case of subclinical lymphoedema (volume increase of 5-10%), a therapeutic elastic stocking for three months appeared to be an effective aid in reducing oedema. Compression is an essential component in the treatment of lymphoedema. Research on compression therapy (short compression bandages) in patients with moderate (20-40%) and severe lymphoedema (> 40%) showed that compression lead to significant reduction in oedema (OR 6.4). CDT is an effective treatment method in lymphoedema of the arm. Wearing a therapeutic elastic stocking can stabilise oedema or provide a possible improvement. The therapeutic elastic stocking does need to be worn for life.

Conclusions

Level 1	In patients with an increased risk, regular measurement of both arms in the first year after surgery leads to early detection of lymphoedema. A therapeutic elastic stocking for a duration of 3 months is an effective aid if the volume increase is between 5 and 10%. A1 KNGF Evidence Statement Borstkanker 2011

Level 1	Compression therapy, as a component of CDT, leads to a significant volume reduction in lymphoedema of the arm. A1 KNGF Evidence Statement Borstkanker 2011 B Damstra, 2009

Level 1	The treatment of lymphoedema must be closed with wearing a therapeutic elastic stocking for life. A1 KNGF Evidence Statement Borstkanker 2011

Remaining considerations

If there are no limitations in ADL with underlying disorders in muscle and joint function, a patient referral to a skin therapist instead of to a physiotherapist may also be considered.

Recommendations

During the end evaluation of the physiotherapeutic treatment, it is recommended that the risk factors are discussed with the patient. If there are functional complaints or signs of lymphoedema it is recommended to make renewed contact with the treating physiotherapist.

It is recommended to refer the patient with oedema to a physiotherapist trained in oedema physiotherapy. In the treatment of lymphoedema it is recommended that a therapeutic elastic stocking is worn for life.

Postmastectomy Pain Syndrome (PMPS)

Postmastectomy Pain Syndrome (PMPS) is defined as pain in the surgical area or in the ipsilateral

arm, present at least 4 days per week with an intensity of > 3 on the numeric pain scale. The *intercostobrachial nerve* is usually involved. The pain complaints can occur immediately after surgery or months later: a pressing, burning sensation on the back of the arm, the front side of the chest wall and axilla, accompanied with anaesthesia. Secondly, there is the risk of limitation of the shoulder function through immobility. According to a study by Vilholm (2008), the prevalence of PMPS is 23.9% and the OR of developing PMPS after surgery is 2.88. Risk factors for the development of chronic pain are prior treatment for breast cancer (OR 8.12), a tumour location in the upper lateral quadrant (OR 6.48), a young age (OR 1.04), ALND (OR 1.99). More pain was reported after supraclavicular radiotherapy or in the axillary.
The complaints may vary from disruptive to extremely strong. The use of unidimensional validated measuring instrument like the VAS [Gracely, 1978], NRS [Jensen, 2003] and VRS [Caraceni, 2002] are recommended in the national multidisciplinary guideline Pain and cancer (www.oncoline.nl/pijn-bij-kanker), both for the surveillance of pain and evaluation of the effect of treatment. Aside from the use of measuring instruments, a careful pain history should be taken and clinical examination conducted, to get a complete picture of the patient's pain.
Treatment is symptomatic.

Conclusion

Level 3	Risk factors for the development of postmastectomy pain syndrome are prior treatment for breast cancer, tumour location in the lateral upper quadrant, younger age and axillary node dissection. B Vilholm 2008

Recommendations

The use of unidimensional measuring instruments is recommended in the treatment of pain in patients with cancer, both for the surveillance of pain and evaluation of the effect of treatment.

The guideline development group is of the opinion that aside from the use of measuring instruments, a careful pain history should be taken and clinical examination conducted, to get a complete picture of the patient's pain. Additional diagnostics are performed if required for a better analysis.

Measuring pain is the collective responsibility of physicians, nurses and the patients themselves. Deciding on one of the different treatment methods must take place after providing information to and consultation with the patient. To this end, patients can contact professionals at the outpatient clinics, the (oedema) physiotherapist and (if there are unexplained complaints and no result with oedema therapy) the pain outpatient clinics.

12.2.3 Consequences of premature menopause and/or (neo)adjuvant hormonal therapy

Hormone replacement therapy

Hormone replacement therapy (HRT) is logically the most effective method for combating the complaints of premature menopause, however HRT is strongly advised against in patients who have been treated for breast cancer with curative intent. The reason for this can be found in the finding that HRT in healthy women increases the risk of developing breast cancer, particularly when oestrogen-progestagen combinations are used [Chlebowski, 2003]. The strongest argument against the use of HRT is the finding in randomised trials that HRT increases the risk of a recurrence in women treated for breast cancer with curative intent [Holmberg, 2004]. In the randomised (Liberate) study with over 3,000 patients, tibolone was also found to reduce vasomotor complaints and osteoporosis but also toincrease the recurrence rate [Kenemans, 2009]. Menopausal complaints can have substantial impact on the quality of life. Careful consideration with the patient, of the severity of the complaints and the specific risks of interventions for the situation involved must lead to solutions that are tailored to the specific complaint. Moreover, HRT in combination with tamoxifen is not effective against menopausal complaints. The use of non-hormonal alternative medication is effective and promising: serotonin reuptake inhibitors (SSRI's: venlafaxine (low dose 37.5-75 mg), paroxetine and fluoxetine) or GABA (low dose 300-900 mg).
A Cochrane review of 16 randomised studies was conducted in which clonidine, gabapentine and certain antidepressants appeared effective in reducing the frequency and severity of hot flushes. However, the results may be an overestimation due to the high dropout of patients in the studies [Rada, 2010]. The use of paroxetine and fluoxetine in combination with tamoxifen must be avoided.
Problems with vagina mucosa may be treated locally with non-hormonal moisturising creams and

lubricants (KY gel, Hyaluronic acid, estriol cream short-term). If a young women receives adjuvant hormonal therapy after having had breast cancer, and would like to fall pregnant, this can thwart hormonal therapy.

Conclusion

Level 1	HRT increases the risk of breast cancer in healthy women. HRT increases the recurrence rate after treatment of breast cancer. A2 Chlebowski 2003, Holmberg 2004, Kenemans 2009

Level 1	Clonidine, gabapentine and certain antidepressants appear effective in reducing the frequency and severity of hot flushes. A1 Rada 2010

Remaining considerations

The use of hormonal contraception is advised against on the basis of the same arguments as with HRT. A Mirena spiral may be considered in the case of hormone receptor-negative tumours. Substantiating literature is still lacking.

Prevention of bone loss and osteoporosis

The guideline 'osteoporose en fractuurpreventie' (osteoporosis and prevention of fractures) [CBO, 2010] describes risk factors for the presence of osteopaenia, osteoporosis and associated fractures. A summary of the aspects important to the treatment of patients with breast cancer is provided below.

Hormonal therapy and osteoporosis

Especially hormonal effects of adjuvant treatment may increase the chance of bone loss in women with breast cancer. This is due to the (increased) depletion of oestrogens, important for an optimal condition of trabecular and (to a lesser degree) cortical bone. Premature (temporary) loss of ovarian function as a result of ovariectomy, LHRH analogues or chemotherapy leads to a reduction in bone mineral density (BMD) of 4-10% in the first years [Bruning, 1990; Delmas, 1997; Saarto, 1997; Shapiro, 2001; Greenspan, 2007; Gnant, 2008, Hershman 2010]. The bone density (partially) recovers again after the menstrual cycle returns [Gnant, 2008]. With the use of aromatase inhibitors in postmenopausal women, the chance of extra bone loss and fractures is significantly higher than with use of tamoxifen or placebo [Coleman, 2007; Perez, 2006; Eastell, 2006; Confravreux, 2007; Forbes, 2009; Rabaglio, 2009]. In contrast, the effect of selective oestrogen receptor modulators (SERM's) on bone metabolism is less clear: tamoxifen induces limited bone loss (up to 4% after 3 years) in premenopausal women [Powels, 1996; Vehmanen, 2006]. With use of an LHRH analogue plus tamoxifen, bone loss (-11.6% after 3 years) is smaller than during the combination LHRH and an aromatase inhibitor (-14% after 3 years) [Gnant, 2008]. Most SERM's have a protective effect on bone in postmenopausal women, including a reduction in the chance of hip fractures [Powles, 1996; Vehmanen, 2006, Vestergaard, 2008, Cooke 2008].

Measures for patients with an increased risk of bone loss and fractures consist of recommending sufficient exercise [Schwartz, 2007; Martyn-St James, 2008] and sufficient ingestion of calcium and vitamin D. In addition, medication-based interventions may be used. Addition of zoledronate to patients treated with LHRH analogues plus tamoxifen or anastrazole may prevent the bone loss resulting from endocrine treatment (maximum of 1 SD in T score (*10% loss*) after 3 years) [Gnant, 2008; Hershman, 2010]. Greenspan (2007) found that treatment with risedronate significantly reduced bone loss as a result of chemotherapy-induced loss in ovarian function. Bisphosphonates have been proven effective in the prevention of bone loss during use of aromatase inhibitors in postmenopausal women as demonstrated by Confravreux with risedronate (2007), Brufsky with zoledronate (2008), and Lester with ibandronate (2008). However, the effects of bisphosphonates on the prevention of fractures in patients with breast cancer are less clear. Valachis (2010) found in a meta-analysis of 14 randomised trials that treatment with bisphosphonates in patients receiving adjuvant hormonal therapy did not lead to a significant reduction in fractures.

Denosumab inhibits the ligand-activated Receptor Activator of the Nuclear factor Kappa B (RANK-L) on (pre-) osteoclasts, and as a result the osteoclast activity and bone loss. In postmenopausal women with osteoporosis or with a bone density of T -1 to < T -2.5 and use of aromatase inhibitors and use of denosumab (60 mg s.c. per half year), there was a statistically significant increase in bone density in the spine or outside by 7-9% and 3-6% respectively [Ellis, 2008; Smith, 2009; Cummings, 2009]. At

the same time, the number of fractures decreased by approximately 70% [Smith, 2009; Cummings, 2009]. Registration for denosumab concerns women with osteoporosis and also postmenopausal women who use aromatase inhibitors. Denosumab is therefore an alternative for bisphosphonates, certainly if contraindications or other limitations exist for the latter. An important objection is still that possible long-term implications of long-term inhibition of RANK-L are unknown.
One should realise that prospective research on the effectiveness of most of these recommendations in the target group (patients with breast cancer) has not been conducted.

Diagnostics
The bone mineral density (BMD) is usually measured by means of Dual Energy X-Ray Absorptiometry (DEXA) at the location of the lower thoracic spine and/or the hip. The terms osteopaenia and osteoporosis are used when the BMD, independent of the localisation, are >1 and >2.5 SD lower respectively than the average BMD of young adults (T-score).
Vertebral fractures can be identified using standardised imaging techniques of the lateral spine.

Indications for measurement of the BMD
The guideline for osteoporosis and fracture prevention [CBO, 2010] provides recommendations for the indication for performing a BMD measurement and for therapeutic interventions, these are detailed in the recommendations.

Indications for therapy
The ASCO guideline for women with primary breast cancer [Hillner, 2003] recommends treatment with bisphosphonates at a T score of ≤ -2.5, independent of the presence of fractures, but is a lot more held back at T scores of -1 to -2.5 than the guideline on osteoporosis and fracture prevention [CBO, 2010]. The therapy advice in the latter guideline has been chosen for the recommendations.

Duration of treatment with bone resorption inhibitors, follow-up and compliance
In the guideline on osteoporosis and prevention of fractures, a treatment duration of 1.5-5 years is mentioned. Bisphosphonate treatment was continued in most women with breast cancer during the period of adjuvant hormonal therapy. Evaluation of the BMD during treatment with bisphosphonates is recommended with caution in the osteoporosis guideline, and then every 2 to 3 years. Special attention should be given to the compliance of oral treatment with bisphosphonates. This was only an average of 50% after 1-2 years in the fracture studies [Kothawala, 2007]. The same recommendations apply to denosumab.

Level 1	Early onset menopause, premenopausal use of tamoxifen and postmenopausal use of aromatase inhibitors are risk factors for the development of osteoporosis. A2 Delmas 1997, Saarto 1997, Shapiro 2001, Greenspan 2007, Gnant 2008, Coleman 2007, Perez 2006, Eastell 2006, Hershman2010, Forbes 2009, Rabaglio 2009 B Confavreux 2007 C Bruning 1990

Level 1	Health providers should strive for optimisation of calcium and vitamin D intake in all women with an increased risk of bone loss. The recommendation for sufficient exercise also applies here. A1 CBO 2010

Level 1	There has been sufficient evidence that the use of bisphosphonates significantly limits bone loss as a result of oestrogen depletion through the treatment of breast cancer. This has also been demonstrated for denosumab in postmenopausal women using aromatase inhibitors. A2 Delmas 1997, Saarto 1997, Greenspan 2007, Gnant 2008, Brufsky 2007, Lester 2008, Ellis 2008 B Confavreux 2007

Level 1	It has not been clearly demonstrated that treatment with bisphosphonates during

	hormonal adjuvant therapy also leads to the prevention of fractures. A1 Valachis 2010, Ellis 2008

Recommendations

The following is advised for all patients with breast cancer who undergo adjuvant systemic treatment:

- sufficient exercise, especially walking and the prevention of immobility, and
- sufficient intake of calcium (1,000 – 1,200 mg d.d.), i.e. aside from basic nutrition the patient requires four units of dairy or slices of cheese, or supplementation using calcium tablets

The Health Council recommends that women > 50 years with a light skin colour who spend sufficient time outside use extra vitamin D (*vitamin D2 = ergocalciferol or D3 = colecalciferol):* 10 microgram d.d. = 400 IE. For women > 50 years with a dark skin colour or with body covering clothing this should be 20 microgram d.d. = 800 IE. This enables the current target value of 50 - 75 nMol/L for the vitamin D level in blood (*25 OH vitamin D level = calcidiol level)* to be achieved.

BMD by means of a DEXA scan is recommended for:

- non-traumatic (vertebral) fractures
- postmenopausal women being treated with aromatase inhibitors
- women after a premature menopause < 45 years
- women using tamoxifen during premenopause
- If there are (combinations) of other risk factors as mentioned in table 1

Moment of BMD measurement:

- For postmenopausal women - in the starting phase of treatment with aromatase inhibitors
- For premenopausal women - a year after loss of ovarian function if being treated with tamoxifen only

Follow-up measurement during hormonal treatment:

- Aside from stimulating physical activity and supplementing calcium and vitamin D as mentioned above, follow-up measurement is recommended (each time) after 1 to 2 years, if there is a T score of -1 to 2.5 without having experienced fractures and/or without treatment with bone resorption inhibitors. At a T score > -1 (normal), this period may be longer
- If non-traumatic fractures occur
- Every 2-3 years during use of bone resorption inhibitors

Treatment with bone resorption inhibitors

- Treatment with bisphosphonates for a duration of 2 to 5 years is recommended at a T score of ≤ -2.5 (= osteoporosis)
- Treatment with bisphosphonates for a duration of 2 to 5 years is recommended at a T score of -2 to -2.5 in the case of:
  - fractures
  - a premature menopause
  - tamoxifen use during premenopause
  - use of aromatase inhibitors in the postmenopause
- At a T score of -1 to -2.5, an estimation of the fracture risk for the coming 10 years by means of the WHO Fracture Risk Assessment Tool (http://www.shef.ac.uk/FRAX) may help the patient and physicians in assessing the patient for treatment with bisphosphonates.
- Patients > 50 years with recent non-traumatic vertebral fractures are eligible for treatment, independent of the T score
- Long-term *(> 3 months, > 7.5 mg dd)* use of corticosteroids is an indication for treatment with bone resorption inhibitors
- Motivational support is essential for good compliance in oral therapy with bisphosphonates (and other treatments)

Which bone resorption inhibitor?

- All modern bisphosphonates available have a proven favourable effect on the BMD and on the prevention of vertebral fractures and usually also on non-vertebral fractures. The first choice for fracture prevention in women (without therapeutic oestrogen depletion) is oral alendronate

and risedronate; ibandronate and zoledronate are good alternatives and can also be administered in i.v. form
- In patients with breast cancer, loss of bone density may be corrected with zoledronate, risedronate or ibandronate and clodronate
- In postmenopausal women with breast cancer who use aromatase inhibitors, bone density may also be corrected using denosumab (s.c. injection)

12.2.4 Psychosocial complaints and fatigue

Symptoms in the patient, partners and children

25-33% of breast cancer patients have been found to experience clinically relevant distress [Kootstra 2008, Ganz 2002, Ganz 2003, Burgess 2005].
Problems reported include:

- pain, fatigue and sexual problems in the physical domain
- anxiety, depression, insecurity, post-traumatic stress symptoms and loss of control in the emotional domain
- loss of contacts and work in the social domain
- questions about “why me” and “why now” and fear of dying in the existential/spiritual domain
- difficulty with household tasks and care of children in the practical domain

The psychosocial and processing issues in the majority of patients may occur from the moment of diagnosis, but especially in the first year after treatment: the prevalence of depression and anxiety in cancer *survivors* reduces again in the course of the first year to levels comparable to that of the general population [Ganz, 1996]. A small subgroup still has demonstrably more symptoms after a few years [Ganz, 1996]. However, other psychosocial complaints may take a lot longer, such as the fear that the cancer will return, a negative body image or problems in the sexual domain. However, in studies these complaints do not translate into a poorer evaluation of the patient’s own quality of life [Ganz, 1996; Gulliford, 1997].
Young breast cancer patients, patients who receive radiotherapy and/or chemotherapy, those who were already emotionally vulnerable prior to diagnosis, patients with comorbidity, patients who experience insufficient social support, and patients with a low income are at higher risk. Confrontation with breast cancer also shows positive effects such as post-traumatic growth and “benefit finding” [Mols, 2005].
The earlier documented increased chance of heart and vascular disorders associated with radiotherapy appears to be less with the radiotherapy techniques currently being used. The late effects of radiotherapy have consequences for aftercare: radiofibrosis influences movement and increases the risk of lymphoedema [Collette, 2008]. As a result, there are large differences in quality of life [Vaittinen, 2000; Hayes, 2007; Montazeri, 2008].

Literature shows that partners, just like patients, respond with increased anxiety and depression to the diagnosis of cancer. Between 20% and 40% indicate they experience increased clinical psychological stress. Over time, anxiety and depression reduce to normal levels.
Of the children, 20-25%, a substantial proportion being children of a mother with breast cancer, indicate they experience more clinical emotional and behavioural problems and 29% indicate they experience post-traumatic stress symptoms when they hear a parent has cancer. The problems also decrease in children during the course of the first year after diagnosis when the treatment has positive effects, but approximately one-third continue to experience long-term emotional and behavioural problems and/or post-traumatic stress symptoms. Especially adolescent daughters and sons of primary school age are at risk. Parents themselves often do not seem to be well aware of the problems the children experience as a result of being confronted with cancer [Pitceathly 2003, Hagedoorn 2007, Visser 2004, Huizinga, 2005, Gazendam 2011].

Conclusions

Level 2	25-33% of patients treated for breast cancer continue to experience clinically relevant distress up to a few years after diagnosis and particular problems such as pain, lymphoedema, menopausal problems, fatigue and sexual complaints remain for a longer period of time. B Kootstra 2008, Ganz 2002, Ganz 2003, Burgess 2005

Level 2	It has been shown that fatigue, poorer physical functioning, disturbed body image and a

	lower quality of life are the most frequent complaints as a result of radiotherapy and chemotherapy. B Vaittinen 2000, Hayes 2007, Montazeri 2008

Level 3	Patients, their partners and children may suffer long-term from problems in various areas as a result of the parent's cancer diagnosis. C Pitceathly 2003, Hagedoorn 2007, Visser 2004, Huizinga 2005, Gazendam 2011

Interventions for psychosocial complaints and fatigue

Guidance within programmatic follow-up

Traditionally, patients largely receive follow-up at an outpatient clinic by way of follow-up visits. An English study showed that patients were especially satisfied about follow-up visits due to the peace of mind they provide. It did appear that the tone of physicians was sometimes overly positive and focused on the short-term, while nurses were more active in noticing unanswered questions and giving verbal and written information [Beaver, 2005]. The need for more information and the preference for additional tests correlate with the anxiety level of the patient [de Bock, 2004]. The fact that patients expect to have a higher chance of longer survival when metastases are discovered in an earlier stage, leads to a higher demand for tests for detection of metastases. This indicates that patients are not adequately informed about the primary aims of aftercare [de Bock, 2004].

Various studies have shown that frequent routine outpatient visits are insufficient to provide psychosocial support [Allen, 2002]. Pennery (2000) even outlines that outpatient visits are a source of anxiety and concern. Given visits to outpatient clinics place a lot of demand on the time of medical specialists, various studies have been conducted on alternative forms. Telephone follow-ups by a specialised nurse [Koinberg, 2004] or aftercare by the general practitioner [Grunfeld, 1996; Grunfeld, 2006; Gulliford, 1997] have been shown to be at least as effective as aftercare by the medical specialist, in terms of patient satisfaction as well as quality of life and time to detection of a recurrence. It appears from the randomised MaZorg study [Kimman, 2010; Kimman 2011 (1)(2)] and a comparable study in the UK that replacing the 3 monthly outpatient visits with telephone follow-up by the specialised nurse leads to an equally high quality of life and patient satisfaction compared to frequent outpatient follow-up.

Psychological interventions

Literature is not clear on the effectiveness of psychological interventions. Some evidence has been found for a few psychosocial interventions; this sometimes concerns a positive effect of an intervention for a specific problem such as a reduction in depression, anxiety, pain or fatigue, for example. It involves cognitive behavioural therapy, psychoeducation, problem-solving therapy, relaxation and professionally-guided social support groups. The review by Gottlieb (2007) (consisting of 44 empirical studies, including 32 RCT's and 20 of which were breast cancer patients) shows positive effects by social support groups guided by professional care providers on the psychosocial functioning of cancer patients [Newell, 2002; Osborn, 2006; Gielissen, 2006; Rowland, 2009; Bloom, 2008; Gottlieb, 2007]. Both partners and children who indicate suffering from clinically elevated problems may benefit from a psychological intervention. This intervention may be focused on an individual, a couple or system/family [Pitceathly, 2003; Hagedoorn, 2007; Visser, 2004; Huizinga, 2005; Gazendam, 2011]

The most effective component of group interventions was the informative and educative aspect [Helgeson, 2000]. An education group programme was therefore compiled for the MaZorg study, in which the following aspects were discussed:

- the normal effects of diagnosis and treatment
- coping strategies
- symptoms that patients can detect by self-examination
- who patients can turn to in case of problems

An economic evaluation of the MaZorg study showed that telephone follow-up in combination with an educative group programme < 3 months after completing treatment was a cost-effective strategy, compared to telephone follow-up with the group programme, or outpatient follow-up with or without the group programme. This applied to all patients who received treatment with curative intent [Kimman, 2010; Kimman 2011 (1)(2).

Cancer rehabilitation

Aside from guidance by nurse specialists and informative group programmes, cancer rehabilitation has been found effective in reducing and dealing with residual complaints. The majority of studies on rehabilitation concerns patients with breast cancer. In the relevant guideline, the description of cancer rehabilitation is based on the definition by the Dutch Healthcare Insurance Board (College van Zorgverzekeringen (CVZ)): care that is focused on the functional, physical, psychological and social problems associated with cancer, including aftercare and rehabilitation. For more information, see the guideline Cancer rehabilitation on www.oncoline.nl/oncologische-revalidatie [CCCN, 2011].

Contact with fellow patients

Only a few studies have looked at the effect of non-professional guided support groups. The reasons breast cancer patients participate in support groups is to become more knowledgeable about the disease, the treatment and effects of treatment in daily functioning, sharing emotions and concerns, and to learn about the manner in which others adjust to the disease, through fellow patients [Samarel, 1997; Helgeson, 1999]. A clear conclusion cannot be drawn about the effectiveness of this in achieving these aims. Partly given the importance of mutual recognition and acknowledgement of problems and complaints, the importance of social support and the negative effects of social isolation, the last form deserves sound attention.

The Dutch Breast Cancer Patient Organisation known as Borstkankervereniging Nederland (BVN) and the Dutch foundation Stichting de Amazones are the most important support groups for breast cancer patients. For women with hereditary breast cancer, there is the working group erfelijke borst-eierstokkanker ('hereditary breast-ovarian cancer', www.BRCA.nl). The BVN has documented quality criteria for diagnosis and treatment from the patient perspective [BVN, 2003]. With the Monitor breast cancer care, BVN combines patients' experiences with information about the care programme offered by different hospitals. In doing so, they support patients in their choice of the hospital for treatment.

The Dutch foundation Stichting de Amazones is focused on young women with breast cancer. They provide specific information for this patient group and offer them the possibility to search for fellow patients with a similar type of diagnosis or treatment. The foundation Stichting Mammarosa has the aim of providing information about breast cancer to women of foreign origin, and improving communication with this group.

Resuming work

There is an increasing insight that work, aside from being a burden, is also an important stabilising factor in most people's lives and is a source of pleasure and adds meaningfulness to people's existence [Blauwdruk Kanker en Werk ('Blueprint Cancer and Work'), 2009 www.nvab-online.nl].

Lifestyle advice

Lifestyle is defined as: actions people take to improve/maintain his/her health by, for example, regularly exercising and eating healthily. Little is known as yet about the relationship between lifestyle and physical and psychosocial complaints in the period after ending treatment. The results available appear to ascribe a more prominent role to lifestyle than is often assumed. A healthy diet and regular exercise appear to reduce complaints of fatigue, anxiety and depression. A healthy lifestyle also reduces the risk of recurrence, cardiovascular diseases, diabetes, osteoporosis and premature (both cancer and non-cancer related) death. Especially for obesity, results show a negative effect in breast cancer patients: women who are overweight have a poor prognosis. Many patients are not aware of the important role a healthy lifestyle plays in later health complaints. However, improvement in lifestyle is extremely important in this group, given their greater chance of developing physical and psychosocial complaints [Kellen, 2009; Stull, 2007; McTeirnan, 2010; Azambuja, 2010; Toles, 2008; Muraca, 2010].

Conclusions

Level 3	On the one hand, routine frequent outpatient follow-up gives peace of mind, but on the other, it also induces anxiety and stress. C Pennery 2000, Beaver 2009

Level 1	Alternative forms, such as telephone follow-ups by a specialised nurse, aside from annual mammography, lead to a patient satisfaction and quality of life that is at least as high as outpatient aftercare by the medical specialist. A2 Kimman 2010, Kimman 2011 (1)(2) Beaver 2009

Level 3	Literature is not clear on the effect of psychological interventions for people with cancer. Some types of therapy do seem to have an effect on reducing specific complaints, such as fatigue and anxiety. C Newell 2002, Lepore 2006

Level 2	Participation in a social support group/contact with fellow patients may be an important source of support and information for the patient. B Samarel 1997, Helgeson 1999

Level 2	The role of lifestyle is greater than is usually assumed. Positive effects have been determined for a healthy diet and regular exercise. B Kellen 2009, Stull 2007, McTeirnan 2010, Azambuja 2010, Toles 2008, Muraca, 2010

Recommendations

Medical specialists and specialised nurses should actively pay attention to complaints and early effects of cancer and treatment using systematic early surveillance. Other professionals may be engaged to assist with this. It is recommended that agreements are made about the tasks involved.

It is recommended that during the entire treatment, also during aftercare, patients are regularly informed about social support groups and contact with fellow patients.

It is recommended that lifestyle advice is a fixed component of aftercare, because a healthy lifestyle reduces the risk of a recurrence and other health complaints and has a positive effect on fatigue, anxiety and depression.

12.2.5 Care for the patient with metastatic disease

Life expectancy of patients with breast cancer has increased due to the vastly improved treatment of breast cancer and metastases. The consequence of treatments and symptoms of progressive disease are a broad scale of non-tumour-specific complaints. An extensive set of national multidisciplinary guidelines may be found at www.pallialine.nl - the database with guidelines for palliative care by the CCCN. Guidelines in the area of symptoms, the end of life, as well as other guidelines for palliative care can be found at Pallialine.

12.2.6 Recommendations: follow-up

Schedule 1: Aftercare in the first 5 years after diagnosis/last mammography before surgery

	Patients without BRCA1/2 mutation		Patients with BRCA1/2 mutation		
	Clinical examination	Mammography	Clinical examination	Mammography	MRI
Location	Hospital		Hospital / P.E.T.		
	1 year	annualy	1 year	annually	annually

Note 1: The first mammography and/or MRI after treatment must be performed approximately one year after the last mammography/MRI before surgery
Note 2: Follow-up with MRI is not recommended for the general population
Note 3: Especially in the first year, attention should be given to psychosocial guidance. See chapter 13 for the individual aftercare plan.

Schedule 2: Aftercare (at least) 5 years after diagnosis/last mammography before surgery

	Patients without BRCA1/2 mutation		Patients with BRCA1/2 mutation
≤ 60 years at the time of	after mastectomy	after BCT	after mastectomy or BCT

follow-up			
Location	Hospital		Hospital / P.E.T.*
Clinical examination	-	annually	annually
Mammography	annually	annually	annually
MRI	-	-	annually

60-75 years at the time of follow-up			
Coordinated by:	national breast screening programme	general practitioner	hospital / P.E.T.
Clinical examination	-	annually	annually
Mammography	every two years**	every two years	depending on the ability to evaluate the mammography, annually or every two years

> 75 years at the time of follow-up	consider ceasing follow-up

*: Outpatient clinic for Hereditary Tumours
**: Once every two years

Note 1: If the patient has undergone a mastectomy, she can return to the national breast screening programme after 5 years and if she is older than 60 years. The specialist must actively refer her back to the national breast screening programme, because otherwise she will not be notified.
Note 2: If the patient has undergone a BCT, she can be referred back to the general practitioner for annual clinical examination after 5 years and if she is older than 60 years; mammography is performed every 2 years via the hospital in which the patient has received follow-up thusfar, because of positioning and evaluation problems associated with the operated and irradiated breast.The specialist must actively refer her back to the general practitioner.
Note 3: The duration of the follow-up should be determined in consultation between the physician and patient. When a patient is referred back, this must be accompanied by clear instructions for aftercare and what to do in case of complaints, see chapter 13.

12.3 Evaluating the medical process

The most important parameters for evaluation of long-term quality of care are survival and locoregional recurrence. These parameters can be retrieved using the civil registry and the Dutch National *Pathology* Registry (PALGA) respectively. If something needs to be evaluated further (such as quality of life, cosmetic, lymphoedema, shoulder function) then different strategies can be employed, such as:

A) asking patients to visit once every 5 or 10 years, and setting up a so-called *late effects outpatient clinic*, or
B) only evaluate within a protocolled research setting

For this guideline it is sufficient to say that attention needs to be given to evaluating one's own medical process and training, but that an efficient strategy still needs to be developed for this.

Organisation of care

A number of reports have been released in recent years that are relevant to the care of breast cancer patients, such as Doorbraakproject mammacarcinoom (breakthrough project for breast cancer), VBOC-advies (VBOC advice), NPK rapport (NPK report), NFK-advies (NFK advice), IGZ rapport project zichtbare zorg (IGZ report on visible care project) and Nacontrole in de oncologie (follow-up in oncology). As a result of these changes, there is a need for an overview and clarity/structure. In all reports there is an increasing demand for an outline of the breast cancer care path and for a case manager, a fixed point of contact within this care path. Given the required competences, the breast cancer nurse specialist together with the treating physician and oncology nurse specialist seem to be the most suited to this role in the second-line (see the website of the Special Interest Group (SIG) for job descriptions and competences of the clinical nurse specialist and breast care nurse: Mammacare in perspectief (Breast care in perspective)).
On the basis of the report by the Health Council (2007), the KWF has published an advisory report: Nazorg bij kanker: de rol van de eerste lijn (Cancer aftercare: the role of primary care). This report addresses the role of primary care. In general, the general practitioner is often also relied on in the phase after primary treatment for cancer. This applies especially to cancers with a long survival, such as breast cancer and for patients with comorbidity. There is a need for a proactive approach by the general practitioner and for assistance with the coordination of aftercare. The general practitioner is often unable to provide this; inadequate communication between the first- and second-line and lack of time appear to play a role in this. Here too, the KWF advises the introduction of case managers and scenarios are detailed in which the general practitioner watches over the medical aspects and the doctor's assistant or nurse practitioner looks after the non-medical aspects. Expanding the capacity of the first-line, improvement in information transfer, and increasing support by advancing expertise – these are conditions that must be met in order to substantially improve the contribution by primary care to cancer care.

13.1 The diagnostic phase

Diagnostics for and guidance of patients with breast pathology should be performed by the breast care team. Treatment and guidance of patients diagnosed with breast cancer is conducted by the same team. At a minimum, this team consists of a surgeon, radiologist, pathologist, radiotherapist, medical oncologist and clinical nurse specialist/nurse practioner. It must be possible to engage a clinical geneticist or a plastic surgeon if required.

It is preferable that the diagnosis of breast pathology takes place at a multidisciplinary breast policlinic with a limited time before results are accessible (5 working days at the most). The policlinic is organised in such a manner, that all diagnostic examinations/tests (palpation by the surgeon or clinical nurse specialist/nurse practioner, clinical imaging and cytology or histology) can be performed on one day. This especially applies to palpable tumours.

It applies in all cases that the number of visits to the breast policlinic should be kept to a minimum. Results can often be disclosed on the same day. This applies, in particular, to patients where an abnormality is not found or who have a benign abnormality. The policlinic always strives to minimise the interval between diagnostic tests and making the result known (at least 90% of results should be available within 5 working days).

The breast care team has weekly multidisciplinary consultation. Diagnostic findings are discussed as a team during this consultation. The clinical nurse specialist/nurse practioner should be structurally present during this meeting. Prior to this consultation, each person formulates an opinion independent of the others. The aim of the consultation is:

- To develop the best possible treatment plan and harmonisation of patient guidance in case of breast cancer
- To develop the diagnostic plan when there is uncertainty about the diagnosis, or together determine with certainty that it does not concern a malignancy
- To discuss patients who have been found to have metastases
- To discuss other situations in the area of breast pathology, in which multidisciplinary alignment is desirable

See the NABON-Nota [NABON, 2008] for more information.

Guidance

The patient should be informed about the diagnosis *malignancy* by the surgeon or breast care nurse specialist in a professional manner. It is recommended that patients bring a family member along when the results are discussed. After this, a consultation with a specialised breast care nurse is offered. During this consultation, the specialised breast care nurse provides information, support and guidance in making a decision regarding treatment. During a second conversation with the surgeon, possibly in the presence of the specialised breast care nurse, the final treatment plan is decided together with the patient. Follow-up appointments are made and the patient should be informed how to reach the breast care team professionals involved and for which questions or issues.

Structural accessibility

In accordance with the Law on Medical Treatment Agreement (Wet op de Geneeskundige Behandelingsovereenkomst, WGBO), sufficient time should be taken to discuss the different pre-treatment examinations/tests with the patient, why a patient may or may not be eligible for particular examinations/tests and it should be clear to the patient who she can go to if she has further questions. Research has shown that a breast care nurse specialist is pre-eminently suited to the role of coordinator of diagnostics at the breast policlinic. In this role, she can function as the point of contact together with the specialised breast care nurse, which improves the continuity and quality of care [Braithwaite, 2005; Burnet, 2004; Raatgever, 2002]. The diagnostic process is complex, especially for patients who require multidisciplinary care during the process, such as in the case of familial breast cancer or a locoregional metastatic breast cancer. This concerns not only the organisation but also the actual guidance of patients. A random evaluation of 72 breast care teams in England showed that the most important factors that contribute to a good functioning breast care team are a team in which members jointly carry responsibility, the workload is acceptable (p=0.009) and where there is a clinical nurse specialist/specialist breast care nurse in the team (p=0.003) [Haward, 2003].

Conclusion

Level 3	The presence of a clinical nurse specialist/nurse practioner contributes to the quality of functioning of the breast care team. B Haward 2003

Recommendations

Breast care should be performed by a breast care team.

The breast care team has a multidisciplinary consultation at least once per week.

Diagnostic findings are discussed as a team during the pre-treatment multidisciplinary consultation. At a minimum, a surgeon, radiologist, pathologist, radiotherapist, medical oncologist and clinical nurse specialist/nurse practioner should be present. It must be possible to engage a clinical geneticist or a plastic surgeon if required.

The aim of the pre-treatment multidisciplinary consultation is:

- To formulate the best possible treatment plan and harmonisation of patient guidance in case of breast cancer
- To determine the management plan in case there is uncertainty about the diagnosis: determine if further diagnostics are required or if it can be jointly determined with great certainty that it does not concern a malignancy

13.2 The treatment phase

The chosen treatment is determined by the patient, who is fully informed about the benefits (sparing the breast) and the disadvantages (side effects) of the treatment proposed, preferably in combination with written and/or internet information. Age and general condition are included in the considerations. The increased risk of a second primary tumour if there is a mutation of the BRCA1/2 gene or a strongly burdened family history must, if applicable, be discussed with the patient. It must also be discussed that choosing a mastectomy in combination with ALND does not influence the risk of a contralateral carcinoma and survival. It must be made clear that radiotherapy is an inherent component of the BCT (see chapter 3).

The possibilities for direct or secondary reconstruction must be discussed with the patient prior to treatment. In women under 40 years of age, the consequences of fertility treatment and possibilities in

case there is a desire to have children are a fixed item when discussing treatment (see chapter 11).

Various studies [Kellen, 2009; Swenson, 2009; McLaughlin, 2005; Box, 2002; Chlebowski, 2002; Harris, 2001] have shown the importance of pre-treatment risk estimation and/or detection of any existing complaints. It is recommended to detail any existing shoulder complaints, comorbidity, BMI and pain prior to treatment. Monitoring lymphoedema is effective with circumference measurements of both arms every 10 cm. A referral to an oedema physiotherapist is recommended at a circumference difference of more than 5%.

Providing the patient with information is an essential component of treatment. The provision of information within a multidisciplinary setting must be univocal, so that each professional knows what information has been provided to the patient, when and who is responsible for doing so. It is important to draw the patient's attention to healthy behaviour regarding exercise and nutrition, as well as risk factors that may cause or worsen health problems. Lifestyle and occupation/work should also be discussed. Care of the wound, scar and skin is important, because infections and traumas are risk factors for development of lymphoedema. To avoid fear of exercise, it is important to separate information about lymphoedema from exercise behaviour. The lymphatic system is explained, and information is provided about early detection and risk reduction strategies.

Conclusions

Level 1	It is worthwhile to get details on existing shoulder complaints, comorbidity, high BMI and pain prior to treatment. A1 Chlebowski 2002 A2 Box 2002, Harris 2001, Kellen 2009 B Swenson 2009, McLaughlin 2005

Level 1	Providing information after an axillary node dissection on the use of the affected arm is important to promote recovery and prevent lymphoedema. Information regarding physical activities, a healthy diet and weight management leads to a positive change in lifestyle. A lifestyle with moderately intensive exercise gives a longer survival. A2 Harris 2001, Kellen 2009 B Swenson 2009, McLaughlin 2005, Box 2002

<u>Breast surgery in a short admission programme</u>

A short admission programme was setup in the Maastricht University Medical Centre, in which an outpatient admission or 24-hour admission was combined with a care programme in which the patient received careful and repeated information and the postoperative care was organised with input from the patient and in collaboration with home care organisations where required [de Kok, 2007]. This programme is safe, cost-effective and patient-friendly. It resulted in a reduction in the average length of admission from 3.6 to 1.1 days. Day surgery was considered possible for more than 90% of the patients programmed for breast surgery and 65% of patients received day surgery. Given the size of the surgical trauma is limited, even with MRM, the clinical care required is limited [Bundred, 1998; Purushotham, 2002].

Pressure on the social network of the patients increases when breast surgery is provided in a short admission programme. These patients also have a greater need for information about home use and removal of drains, prostheses, exercises and physiotherapy [de Kok, 2010]. A sound care package must be compiled, also in consultation with the patient, home care, physiotherapist and general practitioner, before this care can be implemented as a standard.

Conclusion

Level 2	A care programme, consisting of careful and repeated provision of information to the patient, close collaboration with home care organisations and an outpatient admission or 24-hour admission for surgical interventions, is safe, cost-effective and patient-friendly.

	A2	Bundred 1998
	B	de Kok 2007, de Kok 2010

Recommendations

The guideline development group recommends establishing the organisation of care around surgical procedures in such a way, that:

- information is repeatedly provided that is tailored to the specific phase of treatment
- this verbal information is supported with written information and/or a website

If a comprehensive care package can be compiled in consultation with the patient, home care, physiotherapist and general practitioner, breast surgery can be recommended in a short stay admission programme. Conditions are:

- home care is involved in planning of the surgery
- the use of opiates are avoided during surgery
- there are clearly formulated criteria to describe recovery, and therefore for discharge
- this information is also available in writing or via a website
- the postoperative phase has a decision moment for discharge, in which the patient has an important input
- the specialised nurse maintains regular postoperative (telephone) contact with the patient

If this package cannot be guaranteed, then outpatient admission or 24-hour admission cannot be recommended.

13.3 The aftercare phase

Chapter 12 outlines which aspects in the aftercare phase need to be covered, how often the patient needs to be checked and what should happen during these check-ups in relation to physical examination and additional examination/tests. However, it is not sufficient to lapse into the routine of the schedules outlined in chapter 12; on the one hand, because important aspects in care are inadequately highlighted, and on the other hand, because healthcare services should not be unnecessarily burdened.

Chain care and individual aftercare plan

Chain care is the coherent entity of efforts provided by different care providers under a recognisable delineation of responsibilities, in which the client process is central and in which as much alignment is sought with the client's environment. A chain care is formed consisting of diagnostics, treatment and guidance, but also of prevention, early detection and self-assessment. It is a plea for appointing a case manager to ensure there is a well coordinated safety net, the individual aftercare plan [Health Council, 2007; IGZ, 2009].

The individual aftercare plan contains at least information about:

- physical and psychosocial effects of disease and treatment
- desirability and content of the aftercare
- the moment of reconsideration and remaining points of attention:
  - possible late effects of treatment
  - signals that should give rise to consulting a physician
  - agreements about the coordination and task division between care providers

The aftercare plan makes good transfer to more comprehensive care possible [Institute of Medicine, 2005]. Additional care programmes may be found at www.oncoline.nl/oncologische-revalidatie, www.herstelenbalans.nl and www.oncoline.nl/herstel-na-kanker. It is recommended that return to work is discussed and integrated in treatment goals. See www.oncoline.nl/kanker-en-werk [NVAB, 2009].

Care after completing aftercare in the hospital

The duration of aftercare in the hospital should be determined in consultation between the physician and patient. The choice of duration cannot be made without giving substance to the primary aspects of aftercare, such as patient information and care. Even more, because the patient loses contact with the healthcare providers in the hospital after completing follow-up and the patient and general practitioner do not always know what the long-term effects will be of the cancer and treatment [KWF, 2011]. After completing aftercare in the hospital, it should be agreed who will remain the contact person and the

general practitioner should be notified of this.

Conclusion

Level 4	An individual aftercare plan enables systematic identification of problems, it provides direction to aftercare, it provides clarity about the tasks and responsibilities of the health care professionals involved and supports communication between professionals. D Institute of Medicine, 2005

Remaining considerations

The effect of aftercare plans on a reduction in cancer-related morbidity and mortality, on an improvement in knowledge about the disease and treatment and quality of life, and on adhering to a healthier lifestyle has not been researched.

Recommendations

Chain care

The guideline development group recommends that an individual aftercare plan is created for each patient, made available to the patient, general practitioner and other parties involved.

The guideline development group is of the opinion that it should be assessed, together with general practitioners and breast care teams, if and when aftercare is best coordinated by the general practitioner or case manager in the hospital. If it is decided that the general practitioner should play a greater role in this, then a fast, complete information transfer and competence advancement by the general practitioner including professional supporting staff is essential. Partial adoption of cancer aftercare by the general practitioner means an increased burden and makes an expansion of the capacity of the first-line essential.

It should be clear for the patient, general practitioner and all health care providers in each phase of and after treatment who the main treating physician is, who is coordinating the aftercare and who is the point of contact.

Which healthcare provider takes up that role can be decided in the breast care team.

The clinical nurse specialist/nurse practitioner works according to the role description and competences under supervision of the medical specialist who is the main treating physician in the aftercare process.

As an example, the following structure may be chose:

1) patients who are only treated surgically, are monitored by the surgeon or a clinical nurse specialist
2) patients who have received surgery and radiotherapy, are either only monitored by the surgeon, or only by the radiotherapist-oncologist (or by a clinical nurse specialist)
3) patients who receive or have received chemotherapy are monitored by the medical oncologist or a clinical nurse specialist
4) patients who receive or have received hormonal therapy are monitored by the medical oncologist or a clinical nurse specialist
5) patients who receive or have received a HER-2 blockage are preferably monitored by the medical oncologist, who also takes up the aftercare for the duration of treatment
6) for patients with a BRCA1/2 mutation treated for breast cancer, it may be desirable to also continue to make visits to the Hereditary Tumours consultation, in order to adequately take advantage of new developments

Aftercare interventions

- Especially in the first year there needs to be attention for psychosocial guidance.
- Resuming work should be discussed and stimulated
- Physicians and clinical nurse specialist/nurse practitioner should be up to date on referral possibilities for psycho-oncological care, social support group / contact with fellow patients and rehabilitation programmes.

Patients who would like to make use of this should be informed about these options.

Aftercare duration

The duration of aftercare should be determined jointly by the physician and patient. It should be agreed who will be the ongoing contact person and the general practitioner should also be notified of this.

1. Abe H, Schmidt RA, Kulkami K, Sennett CA, Mueller JS, Newstead GM. Axillary lymph nodes suspicious for breast cancer metastasis: sampling with US-guided 14G core-needle biopsy-clinical experience in 100 patienst. Radiology 2009;250:41-9.
2. Abe H, Schmidt RA, Shah RN et al. MR-directed ("second-look") ultrasound examination for breast lesions detected initially on MRI: MR and sonographic findings. AJR Am J Roentgenol, 2010;194:370-7.
3. Aberizk WJ, Silver B, Henderson IC, Cady B, Harris JR. The use of radiotherapy for treatment of isolated locoregional recurrence of breast carcinoma after mastectomy. Cancer 1986; 58: 1214 8.
4. Abner AL, Recht A, Eberlein T, Come S, Shulman L, Hayes D, et al. Prognosis following salvage mastectomy for recurrence in the breast after conservative surgery and radiation therapy for early stage breast cancer. J Clin Oncol 1993; 11: 44 8.
5. Abrous-Anane S, Savignoni A, Daveau C, Pierga JY, Gautier C, Reyal F, Dendale R, Campana F, Kirova YM, Fourquet A, Bollet MA. Management of inflammatory breast cancer after neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys. 2011;79:1055-63
6. Adler NE, Page AE (eds). Washington, DC, The National Academies Press, 2008 Institute of Medicine (IOM): Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs.
7. Agarawal JP, Swangsilpa T, van der Linden Y, Rades D, Jeremic B, Hoskin PJ. The role of external beam radiotherapy in the management of bone metastases. Clin Oncol (R Coll Radiol) 2006;18(10):747-60.
8. Agarwal T, Patel B, Rajan P, Cunningham DA, Darzi A, Hadjiminas DJ. Core biopsy versus FNAC for palpable breast cancers. Is image guidance necessary? Eur J Cancer 2003; 39: 52-6.
9. Agency for Healthcare Research and Quality Effectiveness of non-invasive diagnostic tests for breast abnormalities. AHRQ Publication No.06-EHC005-EF, 2006. (www.ahrq.gov)
10. Ahern V, Barraclough B, Bosch C, Langlands A, Boyages J. Locally advanced breast cancer: defining an optimum treatment regimen. Int J Radiat Oncol Biol Phys 1994; 28: 867 75
11. Ahn P.H., H.t. Vu, D. Lannin, et al. Sequence of radiotherapy with tamoxifen in conservatively managed breast cancer does not affect local relapse rates. J Clin Oncol. 2005;23:17-23.
12. Aiello EJ, Buist DS, et al. Rate of breast cancer diagnoses among postmenopausal women with self-reported breast symptoms. J Am Board Fam Pract 2004; 17: 408-15.
13. Akyurek S, Chang EL, Mahajan A, Hassenbusch SJ, Allen PK. Stereotactic radiosurgical treatment of cerebral metastases arising from breast cancer. Am J Clin Oncol 2007;30(3):310-4.
14. Alagaratnam TT, Wong J. Tamoxifen versus chemotherapy as adjuvant treatment in stage III breast cancer. Aust N Z J Surg 1986; 56: 39-41
15. Albain K. ,Barlow W., O'Malley F. et al., Concurrent CAFT versus sequential CAF-Tchemohormonal therapy (cyclophosphamide , doxorubicin, 5-fluorouracil, tamoxifen) versus T alone for postmenopausal, node-positive, estrogen and/or progesterone receptor-positive breast cancer: mature outcomes and new biologic correlates on phase III intergroup trial 0100 (SWOG-8814), Proc SABCS 88 (2004), p. 1 (Abstract 37).
16. Albain KS, Barlow BE, Shak S, Hortobagyi GN, Livingston RB, Tien Yeh I, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol 2010;11: 55-65.
17. Albain KS, Barlow WE, Ravdin PM 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, 19: 374(9707):2055-63.
18. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, Van't Veer MB, Bartelink H, van Leeuwen FE. Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol. 2003;21:3431-9.
19. Allen A: The meaning of the breast cancer follow-up experience for the women who attend. Eur J Oncol Nurs 2002, 6(3):155-161.
20. Allen SM, Shah AC, Nezu AM, Nezu CM, Ciambrone D, Hogan J, Mor V. (2002). A problem-solving approach to stress reduction among younger women with breast carcinoma: a randomized controlled trial. Cancer, 94, 3089-3100.
21. 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. AJR Am J Roentgenol.2006;186:1342-8.
22. Amant F, Deckers S, Van Calsteren K, et al. Breast cancer in pregnancy: Recommendations of an international consensus meeting. Eur J Cancer (2010), 46:3158-68.
23. Amant F, Van Calsteren K, Halaska MJ, et al. Gynecologic cancers in pregnancy: guidlines of an international consensus meeting. Cancer (2006);106:(2)237-46.
24. Amar s, McCullough A, Tan W et al. Prognosis and outcome of small (< 1 cm), node-negative breast cancer on the basis of hormonal and Her2 status. The oncologist 2010: 15: 1043-1049
25. American Association of clinical endocrinologists. Medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003. Endocrine Practice 2003; 9: 544.
26. American College of Radiology. Breast Imaging Reporting and Data System (BI-RADS). 4th ed.Reston: American College of Radiology; 2003 (www.acr.org)
27. Anderson BO, Petrek JA, Byrd DR, Senie RT, Borgen PI. Pregnancy influences breast cancer stage at diagnosis in women 30 years of age and younger. Ann Surg Oncol 1996;3:204-11
28. Anderson WF, Jatoi I, Tse J, Rosenberg PS. Male breast cancer: a population-based comparison with female breast cancer. J Clin Oncol 2010;28:232-9.
29. Andrieu N, Easton DF, Chang-Claude J et al. Effect of chest X-rays on the risk of breast cancer among BRCA1/2 mutation carriers in the international BRCA1/2 carrier cohort study: a report from the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS Collaborators' Group. J Clin Oncol 2006; 24: 3361-6.
30. Apestequia L, Pina L, Inchusta M, Mellado M, Franquet T, De Miquel C, et al. Nonpalpable, well-defined, probably defined benign breast nodule: management by fine-needle aspiration biopsy and long-interval follow-up mammography. Eur Radiol 1997; 7: 1235-9.
31. Arimidex, tamoxifen, alone or in combination (ATAC) trialists group. Effect of anastrozol and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-months analysis of the ATAC trial. Lancet Oncol. 2008; 9;45-53
32. Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res 2004; 6: R149-56.
33. Arriagada, R. et al. Results of two randomized trials evaluating adjuvant anthracycline-based chemotherapy in 1146 patients with early breast cancer. Acta Oncol 2005 44(5): 458-66.
34. Arriola E, Hui E, Dowsett M, Smith IE. Aromatase inhibitors and male breast cancer. Clin Transl Oncol. 2007 Mar;9(3):192-

4.
35. Auvinen A, Curtis RE, Ron E. Risk of subsequent cancer following breast cancer in men. J Natl Cancer Inst. 2002 Sep 4;94(17):1330-2.
36. Averette HE, Mirhashemi R, Moffat FL. Pregnancy after breast cancer: the ultimate medical challenge. Cancer 1999;85:2301-4
37. Aviles A, Neri N. Hematologic malignancies and pregnancy: a final report of 84 children who received chemotherapy in utero. Clin Lymphoma 2001;2:173-7
38. Ayers M, Symmans WF, Stec J, Damokosh AI, Clark E, Hess K, et al. Gene expression profiles predict complete pathologic response to neoadjuvant paclitaxel and fluorouracil, doxorubicin, and cyclophosphamide chemotherapy in breast cancer. J Clin Oncol 2004;22(12):2284-93.
39. Azambuja E de, McCaskill W, Francis P, Quinaux E, Crown JPA, Vicente M, Giuliani R, Nordenskjöld B, Gutiérez J, Andersson M, Vila MM, Jakesz R, Demol J, Dewar J, Santoro A, Lluch A, Olsen S, Gelber RD, Di Leo A, Piccart-Gebhart M. (2010). The effect of body mass index on overall and disease-free survival in node-positive breast cancer patients treated with docetaxel and doxorubicin-containing adjuvant chemotherapy: the experience of the BIG 02-98 trial. Breast Cancer Research and Treatment, 119, 145-153.
40. Azim HA Jr, Bellettini G, Gelber S, Peccatori FA. Breast-feeding after breast cancer: if you wish, madam. Breast Cancer Res Treat. 2009 ;114:7-12
41. Azim HA Jr, Bellettini G, Liptrott SJ, Armeni ME, Dell'Acqua V, Torti F, Di Nubila B, Galimberti V, Peccatori F. Breastfeeding in breast cancer survivors: pattern, behaviour and effect on breast cancer outcome. Breast. 2010;19:527-31
42. Bagchi S. Men with breast cancer have high risk of second cancer. Lancet Oncol. 2007 Mar;8(3):198.
43. Baldini E, Gardin G, Giannessi P, Brema F, Camorriano A, Carnino F, et al. A randomized trial of chemotherapy with or without estrogenic recruitment in locally advanced breast cancer. North-West Oncology Group (GONO) Study, Italy. Tumori 1997; 83: 829-33
44. Balduzzi A, leonardi M, Cardillo A et al. timing of adjuvantsystemic ttherapy and radiotherapy after breast-conserving surgery and mastectomy. Cancer Treat Rev 2010; 36: 443- 450
45. Banerjee s, Smith i. Management of small HER2-positive breast cancers. Lancet Oncol 2010, 11:1193-1199Literatuur triple negatives
46. Barlow WE, Lehman CD, Zheng Y, Ballard-Barbash R, Yankaskas BC, Cutter GR, et al. Performance of diagnostic mammography for women with signs or symptoms of breast cancer. J Natl Cancer Inst 2002 ;94: 1151-9.
47. Barrios CH, Liu MC, Lee SC, Vanlemmens L, Ferrero JM, Tabei T, Pivot X, Iwata H, Aogi K, Lugo-Quintana R, Harbeck N, Brickman MJ, Zhang K, Kern KA, Martin M. Phase III randomized trial of sunitinib versus capecitabine in patients with previously treated HER2-negative advanced breast cancer. Breast cancer Res Treatment 2010;121:121-31
48. Bartelink H, Horiot JC, Poortmans PM, Struikmans H, Van den Bogaert W, Fourquet A, Jager JJ, Hoogenraad WJ, Oei SB, Warlam-Rodenhuis CC, Pierart M, Collette L. 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;25:3259-65
49. Bartelink H, Rubens RD, van der Schueren E, Sylvester R. Hormonal therapy prolongs survival in irradiated locally advanced breast cancer: a European Organization for Research and Treatment of Cancer Randomized Phase III Trial. J Clin Oncol 1997; 15: 207-15
50. Barthelmes L, Gateley CA. Tamoxifen and pregnancy. Breast 2004;13:446-51
51. Barton MB, Elmore JG. Pointing the way to informed medical decision making: test characteristics of clinical breast examination. J Natl Cancer Inst. 2009;101(18):1223-5. Epub 2009 Aug 31.
52. Barton MB, Harris R, Fletcher SW. The rational clinical examination. Does the patient have breast cancer? The screening clinical breast examination: should it be done? How? JAMA 1999; 282: 1270-80.
53. Bartsch R, Wenzel C, Altorjai G, Pluschnig U, Rudas M, Mader RM Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer. J Clin Oncol. 2007 ;25: 3853-8.
54. Baselga J. Monoclonal antibodies directed at growth factor receptors. Ann Oncol 2000; 11: 187-90
55. Basen-Engquist K, Taylor CL, Rosenblum C, Smith MA, Shinn EH, Greisinger A, Gregg X, Massey P, Valero V, Rivera E. Randomized pilot test of a lifestyle physical activity intervention for breast cancer survivors. Patient Educ Couns. 2006 Dec;64(1-3):225-34.
56. Baum M, Buzdar A, Cuzick J Forbes J, Houghton J, Howell A. et al. The ATAC Trialist's Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: results of the ATAC trial efficacy and safety update analysis. Cancer 2003; 98: 1802-10
57. Baum M, Hackshaw A, Houghton J, Rutqvist T, Fornander T, Nordenskjold B, et al. Adjuvant goserelin in pre-menopausal patients with early breast cancer: Results from the ZIPP study. Eur J Cancer 2006; 42: 895-904.
58. Baum M, Houghton J, Odling-Smee W On behalf of the ZIPP Group. Adjuvant Zoladex in premenopausal patients with early breast cancer: results from the ZIPP trial. Breast 2001; S32-3.
59. Bear HD, Anderson S, Smith RE, Geyer CE Jr, Mamounas EP, Fisher B, Brown AM, Robidoux A, Margolese R, Kahlenberg MS, Paik S, Soran A, Wickerham DL, Wolmark N. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer:National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2006 May 1;24(13):2019-27
60. Beaver K, Tysver-Robinson D, Campbell M, et al. Comparing hospital and telephone follow-up after treatment for breast cancer: randomised equivalence trial. BMJ 2009, 338:a3147.
61. Beaver, K. and K. A. Luker. Follow-up in breast cancer clinics: reassuring for patients rather than detecting recurrence. Psychooncology 2005 14(2): 94-101.
62. BEIR VII. National Research Council, Committee on the Biological Effects of Ionizing Radiation. Health effects of exposure to low levels of ionizing radiation (BEIR VII Phase 2). National Academy Press, Washington DC, 2006.
63. Belli P, Costantini M, Romani M, Marano P, Pastore G. Magnetic Resonance imaging in breast cancer recurrence. Breast Cancer Res Treat 2002; 73: 223-35.
64. Bellon J.R. , S.E. Come, R.S. Gelman, et al. Sequencing of chemotherapy and radiation therapy in early stage breast cancer: updated results of a prospective randomized trial. J Clin Oncol. 2005; 23: 1934-40.
65. Berg WA, Blume JD, Cormack JB, Mendelson EB, Lehrer D, Böhm-Vélez et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA 2008 ;299: 2151-63..
66. Berg WA, Campassi CI, Ioffe OB. Cystic lesions of the breast: sonographic-pathologic correlation. Radiology 2003; 227: 183-91.
67. Berg WA, D'Orsi CJ, Jackson VP, Bassett LW, Beam CA, Lewis RS, et al. Does training in the breast imaging reporting

and data system improve biopsy recommendations or feature analysis agreement with expierienced breast imagers at mammography? Radiology 2002; 224: 871-80.
68. Berg WA, Gutierrez L, NessAiver MS, Carter WB, Bhargavan M, Lewis RS, et al. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. Radiology 2004; 233: 830-49.
69. Berg WA. Sonographically depicted breast clustered microcysts: is follow-up appropriate? Am J Roentgenol 2005; 185: 952-9.
70. Berg WA.Tailored supplemental screening for breast cancer: What now and what next? AJR Am J Roentgenol 2009;192:390-9.
71. Bernstein JL, Teraoka SN, John EM et al. The CHEK*1100delC allelic variant and risk of breast cancer: screening results from the breast cancer family registry. Cancer Epidemiol Biomarkers Prev 2006; 15: 348-52.
72. Bernstein L. Identifying population-based approaches to lower breast cancer risk. Oncogene 2009;27:S3-S8.
73. Bernstein, J. L., et al. Risk factors predicting the incidence of second primary breast cancer among women diagnosed with a first primary breast cancer. Am J Epi 1992 136(8): 925-36.
74. Berrington de Gonzalez A, Reeves G. Mammographic screening before age 50 years in the UK: comparison of the radiation risks with the mortality benefits. Br J Cancer 2005; 93: 590-6.
75. Berry D, Ueno NT, Johnson MM, et al. High-dose chemotherapy with autologous stem-cell support versus standard-dose chemotherapy: meta-analysis of individual patient data from 15 randomized adjuvant breast cancer trials. Breast Cancer Res Treat 2007; 106(Suppl 1):S5.
76. Berry DA, C. Cirrincione, I.C. Henderson, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. Jama, 2006;295:1658-67.
77. Berry DL, Theriault RL, Holmes F, et al. Management of breast cancer during pregnancy using a standarized protocol. J Clin Oncol 1999;17:855-61
78. Bertelsen L, Bernstein L, Olsen J et al Effect of systemic adjuvant treatment on risk for contralateral breast cancer in the Women's Environment, Cancer and Radiation Epidemiology Study. J Natl Cancer Inst 2008; 100: 32-40
79. Bezjak A, Adam J. Symptom response after palliative radiotherapy for patients with brain metastases. Eur J Cancer 2002;38(487):496.
80. Bick U, Diekmann F. Digital mammography: what do we and what don't we know? Eur Radiol 2007;17:1931-42.
81. BIG 1-98 Collaborative Group,Mouridsen H,Giobbie-Hurder,A et al:Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N.Engl J Med 2009;361:766-776,
82. Biganzoli L, Cufer T, Bruning P, et al: Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: the European Organization for Research and Treatment of Cancer 10961 multicenter phase III trial. J Clin Oncol 2002; 20: 3114-21.
83. Bigenwald, R.Z., et al., Is mammography adequate for screening women with inherited BRCA mutations and low breast density? Cancer Epidemiology, Biomarkers & Prevention, 2008;17(3):706-11.
84. Black D, Younger J, Martei Y et al. Recurrence risk in T1a-b, node-negative, HER2 positive breast cancer. Breast Cancer Res Treat 2006; 100: abstract 2037.
85. Blackwell KL; Burstein HJ; Storniolo AM; Rugo H; Sledge G; Koehler M; Ellis C; Casey M; Vukelja S; Bischoff J; Baselga J; O'Shaughnessy J. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol. 2010 Mar 1;28(7):1124-30.
86. Blakely LJ, Buzdar AU, Lozada JA, Shullaih SA, Hoy E, Smith TL et al. Effects of pregnancy after treatment for breast carcinoma on survival and risk of recurrence. Cancer 2004;100:465-9
87. Blanford AT, Murphy BE. In vitro metabolism of prednisolone, dexamethasone, betamethasone, and cortisol by the human placenta. Am J Obstet Gynecol 1977; 127 (3):264-7.
88. Bleicher BJ, Ciocca RM, Egleston BL, Sesa L, Evers K, Sigurdson ER et al. Association of routine pretreatment MRI with time to surgery, mastectomy rate and margin status. J Am Coll Surg 2009;209:180-7.
89. Bloom HJG, Richardson WW, Harries EJ. Natural history of untreated breast cancer (1805-1933); comparison of untreated and treated cases according to histological grade of malignancy. BMJ 1962;2:213.
90. Bloom JR, Stewart S, D'Onofrio, Luce J, Banks PJ. (2008). Addressing the needs of young breast cancer survivors at the 5 year milestone: can a short-term, low intensity intervention produce change? J Cancer Surviv, 2, 190-204.
91. Bloom JR, Stewart SL, Chang S, Banks PJ. (2004). Then and now: quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. Psychooncology, 13, 147-160.
92. Bluekens AM, Karssemeijer N, Beijerinck D, Deurenberg JJ, van Engen RE, Broeders MJ, den Heeten GJ. Consequences of digital mammography in population-based breast cancer screening: initial changes and long-term impact on referral rates. Eur Radiol 2010; 20: 2067-73.
93. Bluemke DA, Gatsonis CA, Chen MH, DeAngelis GA, DeBruhl N, Harms S, et al. Magnetic resonance imaging of the breast prior to biopsy. JAMA 2004; 292: 2735-42.
94. Blumenfeld Z. How to preserve fertility in young women exposed to chemotherapy? The role of GnRH agonist cotreatment in addition to cryopreservation of embrya, oocytes, or ovaries. Oncologist 2007;12:1044-54.
95. Bobo JK, Lee NC, Thames SF. Findings from 752.081 clinical breast examinations reported to a national screening program from 1995 through 1998. J Natl Cancer Inst 2000: 92: 971-6.
96. Boccardo F, Rubagotti A, puntoni M, Guglielmini P, Amoroso D, Fini A, et al. Switching to anastrozole versus continued tamoxifen treament of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. J Clin Oncol. 2005;23:5138-47
97. Bock de GH, Putter H, Bonnema J, van der Hage JA, Bartelink H, van de Velde CJ. The impact of loco-regional recurrences on metastatic progression in early-stage breast cancer. Breast Cancer Res Treat 2009;117:401-8.
98. Bock GH de, Beusmans GHMI, Hinloopen R, Corsten MC, Salden NMA, Scheele ME, Wiersma Tj. NHG-Standaard Diagnostiek van mammacarcinoom. Huisarts Wet 2008;51(12):598-609. http://nhg.artsennet.nl/upload/104/standaarden/MO7.
99. Body JJ, Diel IJ, Lichinitzer M, Lazarev A, Pecherstorfer M, Bell R, et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomized, placebo-controlled phase III studies. Br J Cancer. 2004;90:1133-7
100. Boer, R., H. J. de Koning, et al. In search of the best upper age limit for breast cancer screening. Eur J Cancer 1995 31A(12): 2040-3.
101. Boerner S, Fornage BD, Singletary E, Sneige N. Ultrasound-guided fine-needle aspiration (FNA) of nonpalpable breast lesions: a review of 1885 FNA cases using the National Cancer Institute-supported recommendations on the uniform approach to FNA. Cancer 1999; 87: 19-24.

102. Bonadonna G., M. Zambetti, A. Moliterni et al. Clinical relevance of different sequencing of doxorubicin and cyclophosphamide, methotrexate, and fluorouracil in operable breast cancer. J Clin Oncol 2004; 22:1614.
103. Bonneterre J, Thürliman B, Robertson JFR. Anastrozole vs tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopauzal women: results of the Tamoxifen or Arimidex randomised group efficacy and tolerability study. J Clin Oncol 2000; 18: 3748-57.
104. Bonneterre J., H. Roché and P. Kerbrat, et al. Epirubicin increases long-term survival in adjuvant chemotherapy of patients with poor-prognosis, node-positive, early breast cancer: 10-year follow-up results of the French adjuvant study group 05 randomized trial, J Clin Oncol 2005; 23:2686–2693.
105. Bonneterre J., H. Roche, P. Kerbrat, et al. Long-term cardiac follow-up in relapse-free patients after six courses of fluorouracil, epirubicin, and cyclophosphamide, with either 50 or 100 mg og epirubicin, as adjuvant therapy for node-positive breast cancer; French Adjuvant Study Group. J Clin Oncol 2004; 22;3070-79.
106. Bontenbal M, Creemers GJ, Braun HJ, de Boer AC, Janssen JT, Leys RB Phase II to III study comparing doxorubicin and docetaxel with fluorouracil, doxorubicin, and cyclophosphamide as first-line chemotherapy in patients with metastatic breast cancer: results of a Dutch Community Setting Trial for the Clinical Trial Group of the Comprehensive Cancer Centre. J Clin Oncol. 2005;23:7081-8
107. Bontenbal M, de Wit R, Klijn JGM, Seynaeve C. Chemotherapie bij het gemetastaseerde mammacarcinoom. Ned Tijdschr Geneeskd 1998; 30: 1709 13.
108. Borger JH, van Tienhoven G, Passchier DH, Hart AAM, van Dongen JA, Rutgers EJTh, et al. Primary radiotherapy for breast cancer. Treatment results in locally advanced breast cancer and in patients selected by positive axillary apex biopsy; Radiother Oncol 1992; 25: 1-11
109. Borner M, Bacchi M, Goldhirsch A, Greiner R, Harder F, Castiglione M, et al.First isolated locoregional recurrence following mastectomy for breast cancer: results of a phase III multicenter study comparing systemic treatment with observation after excision and radiation. Swiss Group for Clinical Cancer Research. J Clin Oncol. 1994; 12: 2071-7.
110. BorstkankerVereniging Nederland. Kwaliteitscriteria vanuit patiëntenperspectief voor onderzoek en behandeling van vrouwen en mannen met borstkanker. BVN, Utrecht, 2003.
111. Botelho F, Clark DA. How might pregnancy immunize against breast cancer? Am J Reprod Immunol 1998;39:279-83
112. Box RC, Reul-Hirche HM, Bullock-Saxton JE, Furnival CM. Shoulder movement after breast cancer surgery: results of a randomised controlled study of postoperative physiotherapy. Breast Cancer Res Treat 2002; 75: 35-50
113. Boyages J, Chua B, Taylor R, Bilous M, Salisbury E, Wilcken N, et al. Use of the St Gallen classification for patients with node-negative breast cancer may lead to overuse of adjuvant chemotherapy. Br J Surg 2002;89(6):789-96.
114. Boyages J, Taylor R, Chua B, Ung O, Bilous M, Salisbury E, et al. A risk index for early node-negative breast cancer. Br J Surg 2006;93(5):564-71.
115. Boyd NF, Martin LJ, Bronskill M, Yaffe MJ, Duric N, Minkin S. Breast tissue composition and susceptibility to breast cancer. Review. J Natl Cancer Inst 2010;102:1224-37.
116. Boyd NF, Martin LJ. Yaffe M, Minkin S. Mammographic density: a hormonally responsive risk factor for breast cancer. Menopause International 2006; 4: 186-93.
117. Braithwaite D, Sutton S, Mackay J, Stein J, Emery J. Development of a risk assessment tool for woman with family history of breast cancer. Cancer Detect Prev 2005; 29: 433-9.
118. Braun S, Cevatli BS, Assemi C, Janni W, Kentenich CR, Schindlbeck C, et al. Comparative analysis of micrometastasis to the bone marrow and lymph nodes of node-negative breast cancer patients receiving no adjuvant therapy. J Clin Oncol 2001;19(5):1468-75.
119. Braun S, Pantel K, Muller P, Janni W, Hepp F, Kentenich CR, et al. Cytokeratin-positive cells in the bone marrow and survival of patients with stage I, II, or III breast cancer. N Engl J Med 2000;342(8):525-33.
120. Breast cancer in randomised study: initial findings from the hotline study. BMJ 1997; 314(7075): 174.
121. Brekelmans CTM, Tilanus-Linthorst MMA, Alves C, Seynaeve C, Ouweland A van de, Menke-Pluymers M, et al. Tumour characteristics, survival and prognostic factors of hereditary breast cancer from BRCA2-, BRCA1-, and non-BRCA1/2 families as compared to sporadic breast cancer cases. Eur J Ca 2007; 43: 867-76.
122. Brennan ME, Houssami N, Lord S, Macaskill P, Irwing L, Dixon M 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):5640-49.
123. Brennan ME, Turner RM, Ciatto et al. Ductal Carcinoma in Situ: meta-analysis of underestimation and predictors of invasive breast cancer. Radiology 2011;260:119-8
124. Brennan SF, Cantwell MM, Cardwell CR, Velentzis LS, Woodside JV. Dietary patterns and breast cancer risk: a systematic review and meta-analysis. Am J Clin Nutr. 2010 May;91(5):1294-302.
125. Brief Min VWS, betreffende 32 123-XVI, nr 67-de motie Koser-Kaya, 2010.
126. Britton PD, Goud A, Godward S, Barter S, Freeman A, Gaskarth M. Use of US-guided axillary node core biopsy in staging early breast cancer. Eur Radiol 2009;19:561-69.
127. Broët P, Scholl SM, de la Rochefordière A, Fourquet A, Moreau T, De Rycke Y, Asselain B, Pouillart P. Short and long-term effects on survival in breast cancer patients treated by primary chemotherapy: an updated analysis of a randomized trial. Breast Cancer Res Treat. 1999 Nov;58(2):151-6
128. Broet, P., A. de la Rochefordiere, et al. Contralateral breast cancer: annual incidence and risk parameters. J Clin Oncol 1995 13(7): 1578-83.
129. Bruening W, Fontanarosa J, Tipton K, Treadwell JR, Launders J, Schoelles K. et al. Systematic review: comparative effectiveness of core-needle and open surgical biopsy to diagnose breast lesions. Ann Intern Med 2010;152:238-46.
130. Buchberger W, Niehoff A, Obrist P, DeKoekkoek-Doll P, Dunser M. Clinically and mammographically occult breast lesions: detection and classification with high resolution sonography. Semin Ultrasound CT MR 2000;21:325-36.
131. Buchholz TA, et al. Statement of the science concerning loco-regional treatments after preoperative chemotherapy for breast cancer: a National Cancer Institute Conference JCO (128) 2008
132. Buchholz TA, Hunt KK, Whitman GJ, Sahin AA, Hortobagyi GN. Neoadjuvant chemotherapy for breast carcinoma: multidisciplinary considerations of benefits and risks. Cancer. 2003 Sep 15;98(6):1150 60.
133. Buchholz, T. A. et al. Impact of systemic treatment on local control for patients with lymph node-negative breast cancer treated with breast-conservation therapy. J Clin Onc 2001;19(8): 2240-6.
134. Budette-radoux s, muss H. Optimizing the use of anthracyclines in the adjuvant treatment of early-stage breast cancer. Clin Breast Cancer 2003;4:264-272
135. Budman D.R., D.A. Berry and C.T. Cirrincione. et al. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. J Natl Cancer Inst 1998; 90:1205–1211.

136. Bueno-de_Mesquita JM, Linn SC, Keijzer R, Wesseling J, Nuyten DSA, van Krimpen C, Meijers C, de Graaf PW, Bos MMEM, Hart AAM, Rutgers EJT, Peterse JL, Halfwerk H, de Groot R, Pronk A, Floore AN, Glas AM, van 't Veer LJ, van de Vijver MJ. Validation of 70-gene prognosis signature in node-negative breast cancer. Breast Cancer Res Treat, 117:483-95, 2009.
137. Bueno-de-Mesquita JM, van Harten WH, Retel VP, van 't Veer LJ, van Dam FSAN, Karsenberg K, et al. Use of 70-gene signature to predict prognosis of patients with node-negative breast cancer: a prospective community-based feasibility study (RASTER). Lancet Oncol 2007;8: 1079-1087.
138. Buist DSM, Andersen ML, Haneuse SJ et al. Influence of annual interpretive volume on screening mammography performance in the US. Radiology 2011; 259 72-84
139. Bundred N, P Maguire, J Reynolds, J Grimshaw, J Morris, L Thomson, L Barr, A Baildam. Randomised controlled trial of effects of early discharge after surgery for breast cancer. Bmj 1998; 317: 1275-1279.
140. Burgerlijk Wetboek 7, titel 7, Afdeling 5 (art.446-68): De overeenkomst inzake geneeskundige behandeling (WGBO), 1994.
141. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. (2005). Depression and anxiety in women with early breast cancer: five year observational cohort study. BMJ,330,702.
142. Burnell M, Levine MN, Chapman JA et al Cyclophosphamide, epirubicin, and Fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by Paclitaxel versus Doxorubicin and cyclophosphamide followed by Paclitaxel in node-positive or high-risk node-negative breast cancer. J Clin Oncol. 2010 1;28(1):77-82
143. Burnet K, Chapman D, Wishart G, Purushotham A. Nurse specialists in breast care: a developing role. Nurs Stand 2004; 18: 38-42.
144. Burnside ES, Ochner JE, Fowler KJ, Fine JP, Salkowski LR, Rubin DL, et al. Use of microcalcification descriptors in BI-RADS 4th Edition to stratify risk of malignancy. Radiology 2007; 242: 388-95.
145. Burstein H, Winer E. Refining Therapy for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: T Stands for Trastuzumab, Tumor Size, and Treatment Strategy. J Clin Oncol 2009, 27;34: 5671-5673
146. Burstein H.J, Keshaviah A, Baron A.D., Hart R.D., Lambert-Falls R, Marcom K. Trastuzumab Plus Vinorelbine or Taxane Chemotherapy for HER2-overexpressing Metastatic Breast Cancer: The Trastuzumab and Vinorelbine or Taxane Study. Cancer 2007;110:965–72.
147. Burstein HJ, Kuter I, Campos SM, Gelmon RS, Tribou L, Parker LM et al. Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. J Clin Oncol 2001; 19: 2722-30
148. Buyse M, Loi S, van't Veer L, Viale G, Delorenzi M, Glas AM, et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J Natl Cancer Inst 2006;98(17):1183-92.
149. Buzdar A.U., S.E. Singletary, V. Valero, et al. Evaluation of paclitaxel in adjuvant chemotherapy for patients with operable breast cancer: preliminary data of a prospective randomized trial. Clin Cancer Res 2002; 8: 1073-9.
150. Buzdar AU, Valero V, Ibrahim NK, Francis D, Broglio KR, Theriault RL, Pusztai L, Green MC, Singletary SE, Hunt KK, Sahin AA, Esteva F, Symmans WF, Ewer MS, Buchholz TA, Hortobagyi GN. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. Clin Cancer Res. 2007;13:228-33
151. BVN, www.borstkanker.nl; Zenuwpijn na een operatie wegens borstkanker
152. Caplan LS, Blackman D, Nadel M, Monticciolo DL. Coding mammograms using the classification probably benign finding-short interval follow-up suggested. Am J Roentgenol 1999; 172: 339-42.
153. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. Lancet Oncol 2004;5:283-291
154. Cardoso F, Ferreira AF, Crown J, et al. Doxorubicin followed by docetaxel versus docetaxel followed by doxorubicin in the adjuvant treatment of node positive breast cancer: results of a feasibility study. Anticancer Res 2001; 21: 789–95.
155. Cardoso F, Senkus-Konefka E, Fallowfield L, Costa A, Castiglione M, ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v15-9.
156. Carrick S, Parker S, Wilcken N, Ghersi D, Marzo M, Simes J. Single agent versus combination chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev. 2005;(2):CD003372.
157. Carty NJ, Carter C, Rubin C, Ravichandran D, Royle GT, Taylor I. Management of fibroadenoma of the breast. Ann R Coll Surg Engl 1995; 77: 127-30.
158. Casper ES, Guidera CA, Bosl GJ, Hakes TB, Kaufman RJ, Shurgot B, et al. Combined modality treatment of locally advanced breast cancer: adjuvant combination chemotherapy with and without doxorubicin. Breast Cancer Res Treat 1987; 9: 39-44
159. Casper RF. Aromatase inhibitors in ovarian stimulation. J Ster Biochem Mol Biol 2007;106:71-5.
160. Casso D, Buist DS, Taplin S. Quality of life of 5–10 year breast cancer survivors diagnosed between age 40 and 49. Health Qual Life Outcome 2004; 2:25.
161. Cataliotti L, Buzdar AU, Noguchi S, Bines J, Takatsuka Y, Petrakova K, Dube P, de Oliveira CT. Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer: the Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) trial. Cancer. 2006 May 15;106(10):2095-103
162. Chamness GC, Bannayan LA, Landry JR. Abnormal reproductive development in rats after neonatally administered antiestrogen (tamoxifen). Biol Reprod 1979;21:1087–90
163. Chan A, Miles DW, Pivot X. Bevacizumab in combination with taxanes for the first-line treatment of metastatic breast cancer. Ann Oncol 2010;Mar Epub
164. Chan A. A review of the use of trastuzumab (Herceptin®) plus vinorelbine in metastatic breast cancer Ann Oncol. 2007; 18: 1152-8
165. Chan S, Romieu G, Huober J et al. Gemcitabine plus docetaxel (GD) versus capecitabine plus docetaxel (CD) for anthracycline-pretreated metastatic breast cancer (MBC) patients (pts): Results of a European phase III study. J Clin Oncol 2005:23 (suppl 16):581
166. Chang HR. Trastuzumab-based neoadjuvant therapy in patients with HER2-positive breast cancer. Cancer. 2010 Jun 15;116(12):2856-67
167. Chang JC, Wooten EC, Tsimelzon A, Hilsenbeck SG, Gutierrez MC, Elledge R, et al. Gene expression profiling for the prediction of therapeutic response to docetaxel in patients with breast cancer. Lancet 2003;362(9381):362-9.
168. Chen AM, Meric-Bernstam F, Hunt KK, Thames HD, Outlaw ED, Strom EA, McNeese MD, Kuerer HM, Ross MI, Singletary SE, Ames FC, Feig BW, Sahin AA, Perkins GH, Babiera G, Hortobagyi GN, Buchholz TA.. Breast conservation after neoadjuvant chemotherapy; A prognostic index for clinical decision-making. Cancer 2005;103:689–95
169. Chen L, Chantra PK, Larsen LH, Barton P, Rohitopakarn M, Zhu E, et al. Imaging characteristics of malignant lesions of

the male breast. Radiographics 2006; 26: 993-1006.
170. Chereau, E., et al., Characteristics, treatment, and outcome of breast cancers diagnosed in BRCA1 and BRCA2 gene mutation carriers in intensive screening programs including magnetic resonance imaging. Clinical Breast Cancer 2010; 10(2): 113-118.
171. Chetty U, Jack W, Prescott RJ, Tyler C, Rodger A. Management of the axilla in operable breast cancer treated by breast conservation: a randomized clinical trial. Brit J Surg 2000; 87: 163-9
172. Chia S, Norris B, Speers C et al. Human epidermal growth factor receptor 2 overexpression as a prognostic factor in a large tissue microarray series of nodenegative breast cancers. J Clin Oncol 2008; 26: 5697–5704.
173. Chiarelli AM, Majpruz V, Brown P, Thériault M, Shumak R, Mai V. The contribution of clinical breast examination to the accuracy of breast screening. J Natl Cancer Inst. 2009;101(18):1236-43. Epub 2009 Aug 31.
174. Chlebowski, R. T., S. L. Hendrix, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. Jama 2003 289(24): 3243-53.
175. Choueiri TK, Alenay CA, Abou-Jawde RM, Budd GT. Role of aromatase inbibitors in the treatment of breast cancer. Clin Ther 2004; 26: 1199-1214.
176. Chuo CB, Corder AP. Core biopsy vs fine needle aspiration cytology in a symptomatic breast clinic. Eur J Surg Oncol 2003; 29: 374-8.
177. Ciatto S, Pacini P, Azzini V, Neri A, Jannini A, Gosso P, et al. Preoperative staging of primary breast cancer. A multicentric study. Cancer 1988; 61: 1038-40
178. Cibula D, Gompel A, Mueck AO, La Vecchia C, Hannaford PC, Skouby SO, et al. Hormonal contraception and risk of cancer. Hum Reprod Update. 2010;16(6):631-50. Epub 2010 Jun 12.
179. Cid JA, Rampaul RS, Ellis IO, Wilson AR, Burrell HC, Evans AJ, et al. Woman feels breast lump--surgeon cannot: the role of ultrasound in arbitration. Eur J Cancer 2004; 40: 2053-5.
180. Citron M.L., D.A. Berry, C. Cirrincione, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003; 21:1431.
181. Clark GM, McGuire WL. Steroid receptors and other prognostic factors in primary breast cancer. Semin Oncol 1988; 15(suppl 1): 20-5.
182. Clark RM, Chua T. Breast caner and pregnancy: the ultimate challenge. Clin Oncol R Col Radiol 1989;1:11-18
183. Clarke M, Collins R, Darby S, Elphinstone P, Evans E, Godwin J et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet 2005;366:2087-106.
184. Clavarezza M., L Delmastro, M Venturini et al. Taxane-containing chemotherapy in the treatment of early breast cancer patients. Ann Oncol 2006;17 (suppl 7):22-
185. Clemons M, Danson S, Hamilton T, Goss P. Locoregionally recurrent breast cancer: incidence, risk factors and survival. Cancer Treat Rev. 2001 Apr;27(2):67-82
186. Cobb CJ, Raza AS. Obituary: 'Alas poor FNA of breast-we knew thee well!' Diagn Cytopathol 2004; 32: 1-4.
187. Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, Scholl S, Fehrenbacher L, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999; 17: 2639-48
188. Cocconi G, Bisagni G, Ceci G, Di Blasio B, De Lisi V, Passalacqua R, et al. Three new active cisplatin-containing combinations in the neoadjuvant treatment of locally advanced and locally recurrent breast carcinoma: a randomized phase II trial. Breast Cancer Res Treat 1999;56:125 32.
189. Cocconi G, di Blasio B, Bisagni G, Alberti G, Botti E, Anghinoni E. Neoadjuvant chemotherapy or chemotherapy and endocrine therapy in locally advanced breast carcinoma. A prospective, randomized study. Am J Clin Oncol 1990; 13: 226 32
190. Cognetti F et al. Sequential epirubicin-docetaxel-CMf as adjuvant therapy for node-positive early stage breast cancer: updated results of the TaxiT216 randomized trial Ann Oncol 2008, 19 (suppl) a 1820
191. Coleman EA, Coon SK, Fitzgerald AJ, Cantrell MJ. Breast cancer screening education: comparing outcome skills of nurse practitioners students and medical residents. Clin Excell Nurse Pract 2001; 5: 102-7.
192. Coleman RE, Thorpe HC, Cameron D, Dodwell D, Burkinshaw R, Keane M, Gil M, Houston SJ, Grieve RJ, Barrett-Lee PJ, Ritchie D, Davies C, Bell R. Adjuvant Treatment with Zoledronic Acid in Stage II/III Breast Cancer. The AZURE Trial (BIG 01/04). Cancer Res 2010;70(24 Suppl.): Abstract nr S4-5
193. Coleman RE. Adjuvant bisphosphonates in breast cancer: are we witnessing the emergence of a new therapeutic strategy? Eur J Cancer 2009; 45: 1909-1915.
194. Coleman RE. Effect of anastrozole on bone mineral density: 5-year results from the "Arimidex," Tamoxifen Alone or in Combination (ATAC) trial. J Clin Oncol. 2006;24:18S.
195. Colleoni M, Rotmensz N, Maisonneuve P, Sonzogni A, Pruneri G, Casadio C, et al. Prognostic role of the extent of peritumoral vascular invasion in operable breast cancer. Ann Oncol 2007;18;1632-40.
196. Colleoni M., S. Li, R. Gelber, et al. Timing of CMF chemotherapy in combination with tamoxifen in postmenopausal women with breast cancer : role of endocrine responsiveness of the tumor. Ann Oncol 2005; 16:716-25.
197. Colomer R, Vinas G, Beltran M, Izquierdo A, Lluch A, Llombart-Cussac A, et al. Validation of the 2001 St Gallen risk categories for node-negative breast cancer using a database from the Spanish Breast Cancer Research Group (GEICAM). J Clin Oncol 2004;22(5):961-2.
198. Conforti R, Boulet T, Tomasic G, Taranchon E, Arriagada R, Spielmann M, Ducourtieux M, Soria JC, Tursz T, Delaloge S, Michiels S, Andre F. Breast cancer molecular subclassification and estrogen receptor expression to predict efficacy of adjuvant anthracyclines-based chemotherapy: a biomarker study from two randomized trials. Ann Oncol. 2007;18(9):1477-83
199. Conte PF, Guarneri V, Bruzzi P, Prochilo T, Salvadori B, Bolognesi A, Concomitant versus sequential administration of epirubicin and paclitaxel as first-line therapy in metastatic breast carcinoma: results for the Gruppo Oncologico Nord Ovest randomized trial. Cancer. 2004;101:704-12
200. Coombes RC, Kilburn S, Snowdon C, et al. Survival and savety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): randomized controlled trial Lancet 2007;369:559-70
201. Coombes, RC, Howell, A, Emson, M, et al. High dose chemotherapy and autologous stem cell transplantation as adjuvant therapy for primary breast cancer patients with four or more lymph nodes involved: long-term results of an international randomised trial. Ann Oncol 2005; 16:726.
202. Coördinatiecommissie Borstkankeronderzoek, Ziekenfondsraad. Regeling Taken en Verantwoordelijkheden, 1998.

203. Costelloe CM, Rohren EM, Madewell JE, Hamaoka T, Theriault RL, Yu T-K, O Lewis V, Ma J, Stafford RJ, Tari AM, Hortobayi GN, Ueno NT. Imaging bone metastases in breast cancer: techniques and recommendations for diagnosis. Lancet Oncol 2009;10:606-14
204. Crew KD, Neugut AI, Wang X, Jacobson JS, Grann VR, Raptis G. Racial disparities in treatment and survival of male breast cancer. J Clin Oncol. 2007 Mar 20;25(9):1089-98.
205. Crowther CA, Doyle LW, Haslam RR, et al. Outcomes at 2 years of age after repeat doses of antenatal corticosteriods. New Engl J Med 2007;357 (12):1179-89.
206. Crystal P, Strano SD, Shcharynski S, Koretz MJ. Using sonography to screen women with mammographically dense breasts. AJR Am J Roentgenol 2003:181:177-82.
207. Cufer T. Which tools can I use in daily practice to improve tailoring of treatment for breast cancer? The 2007 St Gallen guidelines and/or Adjuvant! Online. Ann Oncol 2008: 19(suppl 7) vii41-vii45
208. Cullins SL, Pridjian G, Sutherland CM. Goldenhar's syndrome associated with tamoxifen given to the mother during gestation. J Am Med Assoc 1994;271:1905–6
209. Curigliano G, Viale G, Bagnardi V et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. J Clin Oncol 2009; 27: 5693–5699.
210. Cuzick J,Sestak I,Baum M et al:Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer:10-year analysis of the ATAC trial. Lancet Oncol 2010;11:1135-1141.
211. Dahl-Iversen E, Tobiassen T. Radical Mastectomy with parasternal and Supraclavicular Dissection for Mammary Carcinoma. Ann Surg 1963; 157: 170-3
212. Dalberg K, Mattsson A, Sandelin K, Rutqvist LE. Outcome of treatment for ipsilateral breast tumor recurrence in early-stage breast cancer. Breast Cancer Res Treat 1998; 49: 69-78.
213. Danish Breast Cancer Cooperative Group, Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies.J Clin Oncol. 2006;24:2268-75
214. Danoff BF, Coia LR, Cantor RI, Pajak TF, Kramer S. Locally recurrent breast carcinoma: the effect of adjuvant chemotherapy on prognosis. Radiology 1983; 147: 849-52.
215. Daveau C, Savignoni A, Abrous-Anane S, Pierga JY, Reyal F, Gautier C, Kirova YM, Dendale R, Campana F, Fourquet A, Bollet MA. Is Radiotherapy an Option for Early Breast Cancers With Complete Clinical Response After Neoadjuvant Chemotherapy? Int J Radiat Oncol Biol Phys. 2010 Jun 2. [Epub ahead of print]
216. Davidson N, O'Neill S, Vukov CK. Effect of chemo-hormonal therapy in premenopausal Node +, receptor +, breast cancer: an Eastern Cooperative Oncology Group Phase III Intergroup trial (INT 01-01). Breast 1999; 232-3.
217. Davidson NE. Ovarian ablation as adjuvant therapy for breast cancer. J. Natl Cancer Inst Monogr 2001; 30: 67-71.
218. Dawson I, Stam L, Heslinga JL, Kalsbeek HL. Effect of shoulder immobilization on wound seroma and shoulder dysfunction following modified radical mastectomy: a randomized prospective clinical trial. Brit J Surg 1989; 76: 311-2
219. de Bock GH, van der Hage JA, Putter H, Bonnema J, Bartelink H, van de Velde CJ. Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long-term results of European Organisation for Research and Treatment of Cancer studies. Eur J Cancer. 2006 Feb;42(3):351-356.
220. de Bock, G. H., J. Bonnema, et al. Patient's needs and preferences in routine follow-up after treatment for breast cancer. Br J Cancer 2004 90(6): 1144-50.
221. De Boer R, Hillen HF, Roumen RM, Rutten HJ, van der Sangen MJ, Voogd AC. Detection, treatment and outcome of axillary recurrence after axillary clearance for invasive breast cancer. Br J Surg 2001; 88: 118-22.
222. De Boer RH, Allum WH, Ebbs SR, Gui GP, Johnston SR, Sacks NP, et al. Multimodality therapy in inflammatory breast cancer: is there a place for surgery? Ann Oncol 2000; 11: 1147-53
223. De Bruin ML, Sparidans J, Van't Veer MB, Noordijk EM, Louwman MW, Zijlstra JM. et al. Breast Cancer Risk in Female Survivors of Hodgkin's Lymphoma: Lower Risk After Smaller Radiation Volumes. J Clin Clin Oncol. 2009;27:4239-46.
224. De Buck F, Deprest J, Van De Velde M. Anesthesia for fetal surgery. Curr Opin Anaestesiol 2008; 21: 293-7.
225. de Korte MA, EG de Vries, MN Lub-deHooge et al. (111)Indium-trastuzumab visualises myocardial human epidermal growth factor receptor 2 expression shortly after anthracycline treatment but not during heart failure: A clue to uncover the mechanisms of trastuzumab-related cardiotoxicity.Eur J cancer 2007; 14:2046-51
226. De Lena M, Varini M, Zucali R, Rovini D, Viganotti G, Valagussa P, et al. Multimodal treatment for locally advanced breast cancer. Result of chemotherapy-radiotherapy versus chemotherapy-surgery. Cancer Clin Trials 1981; 4: 229-36
227. De Wilde JP, Rivers AW, Price DL. A review of the current use of magnetic resonance imaging in pregnancy and safety implications for the fetus. Prog Biophys Mol Biol 2005;87:335-353
228. de Zeeuw S, Wildenberg F, Strobbe L, Wobbes T. Vaker een tweede operatie na borstsparende behandeling wegens invasief lobulair dan wegens invasief niet-lobulair carcinoom. NTVG 2009;153:A56 .
229. Del Mastro L, Boni L, Michelotti A, Gamucci T, Olmeo N, Gori S, Giordano M, Garrone O, Pronzato P, Bighin C, Levaggi A, Giraudi S, Cresti N, Magnolfi E, Scotto T, Vecchio C, Venturini M. Effect of the Gonadotropin-Releasing Hormone Analogue Triptorelin on the Occurrence of Chemotherapy-Induced Early Menopause in Premenopausal Women With Breast Cancer. JAMA. 2011 Jul 20;306(3):269-76.
230. Del Mastro L, Catzeddu T, Ventorini M. Infertility and pregnancy after breast cancer: current knowledge and future perspectives. Cancer Treat Reviews 2006; 32: 417-22.
231. Del Mastro L, Venturini M, Sertoli MR, Rosso R. Amenorrhea induced by adjuvant chemotherapy in early breast cancer: prognostic role and clinical implications. Breast Cancer Res Treat 1997; 43: 183-90.
232. Demark-Wahnefried W, Aziz NM, Rowland JH, Pinto BM. (2005). Riding the crest of the teachable moment: promoting long-term health after the diagnosis of cancer. Journal of Clinical Oncology, 23, 5814-5830.
233. Demark-Wahnefried, W., & Jones, L.W. (2008). Promoting a healthy lifestyle among cancer survivors. Hematology / Oncology Clinics of North America, 22, 319-342.
234. Demartini WB, Eby PR, Peacock S et al. Utility of targeted sonography for breast lesions that were suspicious on MRI. AJR Am J Roentgenol, 2009;192:1128-34.
235. Dennis MA, Parker S, Kaske TI et al. Incidental treatment of nipple discharge caused by benign intraductal papilloma through diagnostic mammotome biopsy. AJR Am J Roentgenol 2000;174:1263-8.
236. Dennis MA, Parker SH. Klaus AJ. Breast biopsy avoidance: the value of normal mammograms and normal sonograms in the setting of a palpable lump. Radiology 2001; 219: 186-91.
237. Derman DP, Browde S, Kessel IL, de Moor NG, Lange M, Dansey R, et al. Adjuvant chemotherapy (CMF) for stage III breast cancer: a randomized trial. Int J Radiat Oncol Biol Phys 1989; 17: 257-61.

238. Dershaw DD, McCormick B, Osborne MP Detection of local recurrence after conservative therapy for breast carcinoma. Cancer 1992; 70: 493-6.
239. Desmedt C, Piette F, Loi S, Wang Y, Lallemand F, Haibe-Kains B, et al. Strong time dependence of the 76-gene prognostic signature for node-negative breast cancer patients in the TRANSBIG multicenter independent validation series. Clin Cancer Res 2007;13(11):3207-14.
240. Destounis S, Arieno A, Somerville PA et al. Community-based practice experience of unsuspected breast MRI abnormalities evaluated with second-look ultrasound. J Ultrasound Med 2009;28:1337-46.
241. Deurloo EE, Klein Zeggelink WF. Teertstra HJ, Peterse JL, Rutgers EJTh, 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;16:692-701.
242. Deurloo EE, Peterse JL, Rutgers EJ, Besnard AP, Muller SH, Gilhuijs KG. Additional breast lesions in patients eligible for breast-conserving therapy by MRI: impact on preoperative management and potential benefit of computerised analysis. Eur J Cancer 2005; 41: 1393-401.
243. Deurloo EE, Tanis PJ, Gilhuijs KG, Muller SH, Kroger R, Peterse JL, et al. Reduction in the number of sentinel lymph node procedures by preoperative ultrasonography of the axilla in breast cancer. Eur J Cancer 2003; 39: 1068-73.
244. Deutsch M, Land S, Begovic M, Sharif S. The incidence of arm edema in women with breast cancer randomized on the National Surgical Adjuvant Breast and Bowel Project study B-04 to radical mastectomy versus total mastectomy and radiotherapy versus total mastectomy alone. Int J Radiat Oncol Biol Phys. 2008 Mar 15;70(4):1020-4
245. Deutsch M, Parsons JA, Mittal BB. Radiation therapy for local-regional recurrent breast carcinoma. Int J Radiat Oncol Biol Phys 1986; 12: 2061-5.
246. Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. J Clin Oncol. 2010;28:4594-600. Epub 2010 Sep 20.
247. Diaz LK, Wiley EL, Venta LA. Are malignant cells displaced by large-needle core biopsy of the breast? Am J Roentgenol 1999; 173: 1303-13.
248. Dickson RB, Lippman ME. Cancer of the breast; management of metastatic disease. In: Cancer Principles and practice of Oncology deVita VT et al eds. Lippincott Raven, Philadelphia/New York 5th edition, 2000; pp: 1602-6.
249. Diel IJ, Jaschke A, Solomayer EF, Gollan C, Bastert G, Sohn C, Schuetz F. Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow: a long-term follow-up. Ann Oncol. 2008; 19:2007-11.
250. Diel IJ, Kaufmann M, Costa SD, Holle R, von Minckwitz G, Solomayer EF, et al. Micrometastatic breast cancer cells in bone marrow at primary surgery: prognostic value in comparison with nodal status. J Natl Cancer Inst 1996;88(22):1652-8.
251. Diepenmaat LA, van der Sangen MJ, van de Poll-Franse LV, van Beek MW, van Berlo CL, Luiten EJ, Nieuwenhuijzen GA, Voogd AC. The impact of postmastectomy radiotherapy on local control in patients with invasive lobular breast cancer. Radiother Oncol. 2009 Apr;91(1):49-53.
252. Dillon MF, Hill AD, Fleming FJ, O'Doherty A, Quinn CM, McDermott EW et al. Identifying patients at risk of compromised margins following breast conservation for lobular carcinoma. Am J Surg 2006;191:201-5.
253. Diwan BA, Anderson LM, Ward JM. Proliferative lesions of oviduct and uterus in CD-1 mice exposed prenatally to tamoxifen, Carcinogenesis 1997;18:2009–20
254. Dixon JM, Dobie V, Lamb J, Walsh JS, Chetty U. Assessment of the acceptability of conservative treatment of fibroadenoma of the breast. Br J Surg 1996; 83: 264-5.
255. Djulbegovic B, Lyman GH. Screening mammography at 40-49 years: regret or no regret? Comment. Lancet 2006; 368: 2035-7.
256. Doll DC, Ringenberg QS, Yarbro JW. Antineoplastic agents and pregnancy. Semin Oncol 1989;16;337-46
257. Dombernowsky P, Brincker H, Hansen M, Mouridsen HT, Overgaard M, Panduro J, et al. Adjuvant therapy of premenopausal and menopausal high-risk breast cancer patients. Present status of the Danish Breast Cancer Cooperative Group Trials 77-B and 82-B. Acta Oncol 1988; 27: 691-7
258. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, Garber JE, Neuhausen SL, Matloff E, Eeles R, Pichert G, Van t'veer L, Tung N, Weitzel JN, Couch FJ, Rubinstein WS, Ganz PA, Daly MB, Olopade OI, Tomlinson G, Schildkraut J, Blum JL, Rebbeck TR. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010 Sep 1;304(9):967-75
259. Dominici LS, Negron Gonzalez VM, Buzdar AU, Lucci A, Mittendorf EA, Le-Petross HT, Babiera GV, Meric-Bernstam F, Hunt KK, Kuerer HM. Cytologically proven axillary lymph node metastases are eradicated in patients receiving preoperative chemotherapy with concurrent trastuzumab for HER2-positive breast cancer. Cancer 2010;116:2884-9
260. Dongen van JA, Voogd AC, Fentiman IS, Legrand C, Sylvester J, Tong D et al. Longterm results of a randomized trial comparing breast-conservation therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 Trial. J Natl Cancer Inst 2000:92;1143-50.
261. Donnez J, Martinez-Madrid B, Jadoul P, Van Langendonckt A, Demylle D, Dolmans MM: Ovarian tissue cryopreservation and transplantation: a review. Hum.Reprod.Update. 2006;12:519-35
262. Dor J, Lerner-Geva L, Rabinovici J, Chetrit A, Levran D, Lunenfeld B, et al. Cancer incidence in a cohort of infertile women who underwent in vitro fertilization. Fertil Steril 2002; 77: 324-7.
263. Dornfeld JM, Thompson SK, Shurbaji MS. Radiation-induced changes in the breast: a potential diagnostic pitfall on fine-needle aspiration. Diagn Cytopathol 1992; 8: 79-80.
264. Dowsett M, AllredDC , Relationship between quantitative ER and PgR expression and HER2 status with recurrence in the ATAC trial, Breast Cancer Research and Treatment 2006, vol 100 supplement 1; abstract 48
265. Dowsett M, Cuzick J, Wale C, Forbes J, Mallon EA, Salter J, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. J Clin Oncol 2010;28: 1829-1834.
266. Dowsett M,Cuzick J,Ingle JN et al:Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen 2010;28:509-518.
267. Drew PJ, Kerin MJ, Turnbull LW, Imrie M, Carleton PJ, Fox JN, et al. Routine screening for local recurrence following breast censerving therapy for cancer with dynamic contrast-enhanced MRI of the breast. Annals Surg Oncol 1998; 5: 265-70.
268. Dubey A., A. Recht, S.E. Come, et al. Concurrent CMF and radiation therapy for early stage breast cancer : results of a pilot study. Int J Radiat Oncol Biol Phys 1999; 45: 877-84.
269. Dumitrescu RG, Cotarla I. Understanding breast cancer risk - where do we stand in 2005? J Cell Mol Med 2005; 9: 208-21.

270. Earl H M, Vallier A, Hiller L, et al. Neo-Tango: a neoadjuvant randomized phase III trial of epirubicin/cyclophosphamide and paclitaxel +/- gemcitabine in the treatment of women with high-risk early breast cancer (EBC): fi rst report of the primary endpoint, pathological complete response (pCR). Proc Am Soc Clin Oncol 2009; 27 (suppl): abstr 522.
271. 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(9472):1687-717.
272. Early Breast Cancer Trialists' Group (EBCTCG). Adjuvant chemotherapy in estrogen-receptor-poor breast cancer: patient-level meta-analysis of randomized trials. Lancet 2008; 371: 29-40
273. Early Breast Cancer Triallists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Lancet 2000; 355: 1757-70
274. EBCN: European guidelines for quality assurance in breast cancer screening and diagnosis", 4th Edition, European Communities, 2006 ISBN 92-79-01258-4
275. EBCTCG: Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998 351(9114): 1451-67.
276. Ebert U, Loeffler H, Kirch W. Cytotoxic therapy and pregnancy. Pharmacol Ther 74:207-20, 1997
277. Eekhoff EMW, Pinedo HM, Lips P. Osteoporose bij patiënten die worden behandeld wegens kanker en de mogelijkheden voor preventie en behandeling. Ned Tijdschr Geneesk 2007; 151: 1388-92
278. Eidtmann H, de Boer R, Bundred N, Llombart-Cussac A, Davidson N, Neven P, von Minckwitz G, Miller J, Schenk N, Coleman R. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. Ann Oncol 2010;21:2188-94.
279. Eiermann W et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. Ann Oncol 2001; 12: 1527-32
280. Eiermann W, Pienkowski T, Crown J et al. BCIRG 005 efficacy analysis: a phase III randomized trail cmparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus doxorubicin and cyclophosphamide followed bij docetaxel (AC?T) in women with Her-2/neu negatieve, axillary lymph node positive breast cancer. SABCC 2008 abstract……..
281. Eisen A, Trudeau M, Shelley W, Messersmith H, Pritchard K. Aromatase inhibitors in adjuvant therapy for hormone receptor positive breast cancer: A systematic review. Cancer Treat Rev 2008:34(2)157-74
282. Ejlertsen B, Mouridsen HT, Langkjer ST, Andersen J, Sjöström J, Kjaer M; Scandinavian Breast Group Trial (SBG9403. Phase III study of intravenous vinorelbine in combination with epirubicin versus epirubicin alone in patients with advanced breast cancer: a Scandinavian Breast Group Trial (SBG9403). J Clin Oncol. 2004;22: 2313-20.
283. Elkhuizen PH, Hermans J, Leer JW, van de Vijver MJ. Isolated late local recurrences with high mitotic count and early local recurrences following breast-conserving therapy are associated with increased risk on distant metastasis. Int J Radiat Oncol Biol Phys 2001; 50: 387 96.
284. Elkhuizen, P. H., M. J. van de Vijver, et al. Local recurrence after breast-conserving therapy for invasive breast cancer: high incidence in young patients and association with poor survival. Int J Radiat Oncol Biol Phys 1998 40(4): 859-67.
285. Ellis MJ, Coop A, Singh B, Mauriac L, Llombert-Cussac A, Jänicke F, Miller WR, Evans DB, Dugan M, Brady C, Quebe-Fehling E, Borgs M. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol. 2001;19:3808-16
286. Ellis MJ, Hayes DF, Lippman ME. Treatment of metastatic breast cancer. In: Diseases of the breast, eds Harris J et al. Lippincott, Williams and Wilkins, Philadelphia, 2nd Ed., 2000; 749-97.
287. Elmore JG, Armstrong K, Lehman CD, Fletcher SW. Screening for breast cancer. JAMA 2005; 293: 1245-58.
288. Elmore JG, Barton MB, Moceri VM, Polk S, Arena PJ, Fletcher SW. Ten-year risk of false positive screening mammograms and clinical breast examinations. N Engl J Med 1998; 338; 1089-96.
289. Elmore JG, Gigerenzer G. Benign breast disease. The risks of communicating risk. N Engl J Med 2005;353:297-9.
290. Elshof LE, Rutgers EJ, Deurloo EE, Loo CE, Wesseling J, Pengel KE et al. A practical approach to manage additional lesions at preoperative breast MRI in patients eligible for breast conserving therapy: results. Breast Cancer Res Treat 2010 Jul.22. Epub.
291. Eltahir A, Heys SD, Hutcheon AW, Sarkar TK, Smith I, Walker LG, et al. Treatment of large and locally advanced breast cancers using neoadjuvant chemotherapy. Am J Surg 1998; 175: 127-32
292. Engeland van S, Snoeren PR, Huisman H, Boetes C, Karssemeijer N. Volumetric breast density estimation from full-field digital mammograms. IEEE Trans Med Imaging 2006;25:273-82.
293. EORTC Breast Cancer Cooperative Group; EORTC Radiotherapy Group, Bijker N, Meijnen P, Peterse JL, Bogaerts J, Van Hoorebeeck I, Julien JP, Gennaro M, Rouanet P, Avril A, Fentiman IS, Bartelink H, Rutgers EJ. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853-a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group.J Clin Oncol 2006;20:3381-7
294. Epstein RJ. Adjuvant breast cancer chemotherapy during late-trimester pregnancy: not quite a standard of care. BMC Cancer 2007;7:92
295. Estevez LG, Seidman a. HER2-positive breast cancer. Incidence, prognosis, and treatment options. Am J. Cancer 2003; 2:169-79.
296. European Commission. Radiation protection 100; Guidance for protection of unborn children and infants irradiated due to parental medical exposures. Directorate General Environment, Nuclear Safety and Civil Protection, 1998
297. European guidelines for quality assurance in breast cancer screening and diagnosis (EUREF) ed. Perry N, Broeders M, de Wolf C et al. European Communities 2006, http://europa.eu.int/comm/dgs/health_consumer/index_en.htm
298. Ewer MS; Vooletich MT; Durand JB; Woods ML; Davis JR; Valero V; Lenihan DJ. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. J Clin Oncol 2005 Nov 1;23(31):7820-6.
299. Faddy MJ. Follicle dynamics during ovarian aging. Mol Cell Endocrinol. 2000 May 25;163(1-2):43-8.
300. Fahrbach K, Sledge I, Cella C, Linz H, Ross SD. A comparison of the accuracy of two minimally invasive breast biopsy methods: a systematic literature review and meta-analysis. Arch Gynecol Obstet 2006; 274: 63-73.
301. Fajardo LL, Pisano ED, Caudry DJ, Gatsonis CA, Berg WA, Connolly J, et al; Radiologist Investigators of the Radiologic Diagnostic Oncology Group V. Stereotactic and sonographic large-core biopsy of nonpalpable breast lesions: results of the Radiologic Diagnostic Oncology Group V study. Acad Radiol 2004; 11: 293-308.
302. Falkson G, Gelman R, Falkson CI, Glick J, Harris J. Factors predicticy for response, time to treatment failure and survival in women with metastatic breast cancer treated with DAVTH a prospective ECOG study. J Clin Oncol 1991; 9: 2153-61.
303. Falkson G, Gelman RS, Leone L, Falkson CL. Survival of premenopausal women with metastatic breast cancer. Longterm

follow up of Eastern Cooperative group and Cancer Leukemia Group B studies. Cancer 1990; 66: 1621-9.
304. Fargeot P., J. Bonneterre, H. Roché, et al. Disease-free survival advantage of weekly Epirubicin plus Tamoxifen versus Tamoxifen alone as adjuvant treatment of operable, node-positive, elderly breast cancer patients: 6-year follow-up results of the French Adjuvant Study Group 08 trial. J Clin Oncol 2004; 22:4622-30.
305. Farooq A, Walker LJ, Bowling J, Audisio RA. Cowden Syndrome. Cancer Treatment Reviews 2010;36:577-83.
306. Farquhar C, Marjoribanks J, Lethaby A, et al High dose chemotherapy for poor prognosis breast cancers: systematic review and meta-analysis. Cancer Treat Rev 2007; 33:325–337.
307. Feigin KN, Keating DM, Telford PM, Cohen MA. Clinical Breast examination in a comprehensive breast cancer screening program: Contribution and Cost. Radiology 2006; 240: 650-5.
308. Fenig E, Mishaeli M, Kalish Lishner M. Pregnancy and radiation. Cancer treatment reviews 2001;27:1-7
309. Fetting J.H., R. Gray, D.L. Fairclough, et al. Sixteen-week multidrug regimen versus cyclophosphamide , doxorubicin, and fluorouracil as adjuvant therapy for node-positive, receptor-negative breast cancer: an Intergroup study. J Clin Oncol 1998; 16:2382.
310. Fiets W.E., R.P. van Helvoirt, J.W. Nortier, et al. Acute toxicity of concurrent adjuvant radiotherapy and chemotherapy (CMF or AC) in breast cancer patients; a prospective, comparative, non-randomised study. Eur J Cancer 2003; 39: 1081-8.
311. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomised trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002; 347: 1233-41.
312. Fisher B, Anderson S, DeCillis A, Dimitrov N, Atkins JN, Fehrenbacher L, Henry PH, Romond EH, Lanier KS, Davila E, Kardinal CG, Laufman L, Pierce HI, Abramson N, Keller AM, Hamm JT, Wickerham DL, Begovic M, Tan-Chiu E, Tian W, Wolmark N. Further evaluation of intensified and increased total dose of cyclophosphamide for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-25. J Clin Oncol. 1999 Nov;17(11):3374-88.
313. Fisher B, Anderson S, Fisher ER, Redmond C, Wickerham DL, Wolmark N, et al. Significance of ipsilateral breast tumour recurrence after lumpectomy. Lancet 1991; 338: 327 31.
314. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N.Twenty-five-year follow-up of a randomized trial comparing radical mastectomy,total mastectomy, and total mastectomy followed by irradiation. N Engl J Med. 2002 Aug 22;347(8):567-75
315. Fisher B, Land S, Mamounas E, Dignam J, Fisher ER, Wolmark N. 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
316. Fisher B, Redmond C, Fisher ER, Bauer M, Wolmark N, Wickerham DL, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med 1985; 312: 674 81
317. Fisher B., A.M. Brown, N.V. Dimitrov, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol 1990; 8:1483.
318. Fisher B., J. Dignam and N. Womark, et al., Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer, J Natl Cancer Inst 1997; 89:1673–82.
319. Fisher B., J. Jeong, J. Bryant, 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.
320. Fisher B., S. Anderson and D.L. Wickerham, et al. Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-22. J Clin Oncol 1997;15:1858–1869.
321. Fisher B., S. Anderson, E. Tan-Chiu, et al. Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-23. J Clin Oncol 2001; 19:931.
322. Fishman JE, Milikowski C, Ramsinghani R, Velasquez MV, Aviram G. US-guided core-needle biopsy of the breast: how many specimens are necessary? Radiology 2003; 226: 779-82.
323. Fleissig A, Fallowfield LJ, Langridge CI, Johnson L, Newcombe RG, Dixon JM. Post-operative arm morbidity and quality of life: Results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. Breast Cancer Research and Treatment, 2006. 95:279-293.
324. Flobbe K, Bosch AM, Kessels AG, Beets GL, Nelemans PJ, von-Meyenfeldt MF, et al. The additional diagnostic value of ultrasonography in the diagnosis of breast cancer. Arch Intern Med 2003; 163: 1194-9.
325. Foekens JA, Atkins D, Zhang Y, et al. Multicenter validation of a gene expression-based prognostic signature in lymph node-negative primary breast cancer. J Clin Oncol 2006;24(11):1665-71.
326. Fossati R, Confalonieri C, Torri V, Ghislandi E, Penna A, Pistotti V et al. Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomised trials involving 31510 women. J Clin Oncol 1998; 16: 3439-60
327. Fountzilas G, Skarlos D, Dafni U et alPostoperative dose-dense sequential chemotherapy with epirubicin, followed by CMF with or without paclitaxel, in patients with high-risk operable breast cancer: a randomized phase III study conducted by the Hellenic Cooperative Oncology Group. Ann Oncol. 2005 16(11):1762-71.
328. Fountzilas G; Razis E; Tsavdaridis D; Karina M; Labropoulos S; Christodoulou C; Mavroudis D; Gogas H; Georgoulias V; Skarlos D. Continuation of trastuzumab beyond disease progression is feasible and safe in patients with metastatic breast cancer: a retrospective analysis of 80 cases by the hellenic cooperative oncology group. Clin Breast Cancer 2003 Jun;4(2):120-5.
329. Fourquet A, Campana F, Zafrani B, Mosseri V, Vielh P, Durand J-C, et al. Prognostic factors of breast recurrence in the conservative management of early breast cancer: a 25 year follow up. Int J Radiat Oncol Biol Phys 1989; 17: 719-25.
330. Fowble B. et al. Breast recurrence following conservative surgery and radiation: patterns of failure, prognosis, and pathologic findings from mastectomy specimens with implications for treatment. Int J Radiat Oncol Biol Phys 1990; 19: 833-42.
331. Foxcroft L, Evans E, Hirst C. Newly arising fibroadenomas in women aged 35 and over. Aust N Z J Surg 1998, 68: 419-22.
332. Fracheboud J, Groenewoud JH, Boer R, Draisma G, de Bruijn AE, Verbeek AL, et al. Seventy-five years is an appropriate upper limit for population-based mammographic screening. Int J Cancer 2006; 118: 2020-5.
333. Francis P, Crown J, Di Leo A, et al. Adjuvant chemotherapy with sequential or concurrent anthracycline and docetaxel: Breast International Group 02-98 randomized trial. J Natl Cancer Inst. 2008 100(2):121-33.
334. Frederick MG, Paulson EK, Nelson RC. Helical CT for detecting focal liver lesions in patients with breast carcinoma:

comparison of noncontrast phase, hepatic arterial phase, and portal venous phase. J Comput Assist Tomogr 1997; 21: 229-35.
335. Freedman GM, Fowble BL, Nicolaou N, Sigurdson ER, Torosian MH, Boraas MC, Hoffman JP. Should internal mammary lymph nodes in breast cancer be a target for the radiation oncologist? Int J Radiat Oncol Biol Phys. 2000 Mar 1;46(4):805-14
336. French Adjuvant Study Group, Benefit of a high dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French adjuvant study group 05 randomized trial. J Clin Oncol 2001; 19: 602–611.
337. Freund C, Mirabel L, Annane K, Mathelin C. [Breastfeeding and breast cancer]. Gynecol Obstet Fertil. 2005 ;33:739-44 (French)
338. Fumoleau P., P. Kerbrat, P. Romestaing, et al. Randomized trial comparing six versus three cycles of epirubicin-based adjuvant chemotherapy in premenopausal, node-positive breast cancer patients: 10-year follow-up results of the French Adjuvant Study Group 01 Trial. J Clin Oncol 2003; 21:298.
339. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989; 81: 1879-86.
340. Galea MH, Blamey RW, Elston CE, Ellis IO. The Nottingham Prognostic Index in primary breast cancer. Breast Cancer Res Treat 1992;22(3):207-19.
341. Galligioni E. , G. Cetto, D. Crivellari, et al. High dose epirubicin and cyclophosphamide (EC) vs cyclophosphamide , methotrexate, fluorouracil (CMF) in high risk premenopausal breast cancer patients; 5-year results of a prospective randomised trial. Breast Cancer Res Treat 2000; 60: 63. abstr 230.
342. Gallowitsch HJ, Kresnik E, Gasser J, Kumnig G, Igerc I, Mikosch P, Lind P. F-18 fluorodeoxyglucose positron-emission tomography in the diagnosis of tumor recurrence and metastases in the follow-up of patients with breast carcinoma: a comparison to conventional imaging. Invest Radiol. 2003;38:250-6
343. Galper S, Blood E, Gelman R, Abner A, Recht A, Kohli A, Wong JS, Smith D, Bellon J, Connolly J, Schnitt S, Winer E, Silver B, Harris JR. Prognosis after local recurrence after conservative surgery and radiation for early-stage breast cancer. Int J Radiat Oncol Biol Phys. 2005;61:348 57
344. Ganz PA, Coscarelli A, Fred C, Kahn B, Polinsky ML, Petersen L: Breast cancer survivors: psychosocial concerns and quality of life. Breast cancer research and treatment 1996, 38(2):183-199.
345. Ganz PA, Desmond KA, Leedham B, et al. Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. J Natl Cancer Ins 2002; 94:39–49.
346. Ganz PA, Greendale GA, Petersen L, et al. Breast cancer in younger women: reproductive and late health effects of treatment. J Clin Oncol 2003; 21:4184–93.
347. Ganz: The 'three Ps' of cancer survivorship care. BMC Medicine 2011 9:14.
348. Garcia-Etienne CA, Barile M, Gentilini OD, Botteri E, Rotmensz N, Sagona A, Farante G, Galimberti V, Luini A, Veronesi P, Bonanni B. Breast-conserving surgery in BRCA1/2 mutation carriers: are we approaching an answer? Ann Surg Oncol. 2009;16:3380-7
349. Garcia-Ortega MJ, Benito MA, Vahamonde EF, Torres PR, Velasco AB, Paredes MM. Pretreatment axillary ultrasonography and core biopsy in patients with suspected breast cancer: Diagnostic accuracy and impact on management. Eur J Radiol 2009; doi:10.1016/j.ejrad.2009.12.011
350. Garg AK, Oh JL, Oswald MJ, Huang E, Strom EA, Perkins GH, Woodward WA, Yu TK, Tereffe W, Meric-Bernstam F, Hahn K, Buchholz TA. Effect of postmastectomy radiotherapy in patients <35 years old with stage II-III breast cancer treated with doxorubicin-based neoadjuvant chemotherapy and mastectomy. Int J Radiat Oncol Biol Phys. 2007 Dec 1;69(5):1478-83. Epub 2007 Sep 12.)
351. Garg AK, Strom EA, McNeese MD, Buzdar AU, Hortobagyi GN, Kuerer HM, Perkins GH, Singletary SE, Hunt KK, Sahin A, Schechter N, Valero V, Tucker SL, Buchholz TA; T3 disease at presentation or pathologic involvement of four or more lymph nodes predict for locoregional recurrence in stage II breast cancer treated with neoadjuvant chemotherapy and mastectomy without radiotherapy; Int J Radiat Oncol Biol Phys. 2004 May 1;59(1):138-45
352. Gazendam-Donofrio SM, Hoekstra HJ, van der Graaf WT, van de Wiel HB, Visser A, Huizinga GA, Hoekstra-Weebers JE. (2011). Adolescents' emotional reactions to parental cancer: effect on emotional and behavioral problems. J Pediatr Psychol,36, 346-359.
353. Gazet JC, Ford HT, Coombes RC. Randomised trial of chemotherapy versus endocrine therapy in patients presenting with locally advanced breast cancer (a pilot study). Br J Cancer 1991; 63: 279 82
354. Gazet JC, Ford HT, Gray R, McConkey C, Sutcliffe R, Quilliam J, Makinde V, Lowndes S, Coombes RC. Estrogen-receptor-directed neoadjuvant therapy for breast cancer: results of a randomised trial using formestane and methotrexate, mitozantrone and mitomycin C (MMM) chemotherapy. Ann Oncol. 2001;12:685-91
355. Gelber S, Coates AS, Goldhirsch A, Castiglione-Gertsch M, Marini G, Lindtner J, Edelmann DZ, Gudgeon A, Harvey V, Gelber RD; International Breast Cancer Study Group. Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer. J Clin Oncol. 2001;19:1671-5
356. Gelmon KA; Mackey J; Verma S; Gertler SZ; Bangemann N; Klimo P; Schneeweiss A; Bremer K; Soulieres D; Tonkin K; Bell R; Heinrich B; Grenier D; Dias R. Use of trastuzumab beyond disease progression: observations from a retrospective review of case histories. Clin Breast Cancer 2004 Apr;5(1):52-8.
357. Gemignani ML, Petrek JA. Breast cancer during pregnancy: diagnostic and therapeutic dilemma's. Advances in Surgery 2000;34: 273-286
358. Gentilini O, Chagas E, Zurrida S, Intra M, De Cicco C, Gatti G, Silva L, Renne G, Cassano E, Veronesi U. Sentinel lymph node biopsy in male patients with early breast cancer. Oncologist. 2007 May;12(5):512-5
359. Gentilini O, Cremonesi M, Trifiro G et al. Safety of sentinel node biopsy in pregnant patients with breast cancer. Ann Oncol 2004;15:1348-51
360. Gerber B, Dieterich M, Muller H, Reimer T. Controversies in preservation of ovary function and fertility in patients with breast cancer. Breast Cancer Res Treat 2008;108:1-7.
361. Gerber B, von Minckwitz G, Stehle H, Reimer T, Felberbaum R, Maass N, Fischer D, Sommer HL, Conrad B, Ortmann O, Fehm T, Rezai M, Mehta K, Loibl S; German Breast Group Investigators. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. J Clin Oncol. 2011 Jun 10;29(17):2334-41.
362. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006;355 (26): 2733-43
363. Gezondheidsraad. Nacontrole in de oncologie. Doelen onderscheiden, inhoud onderbouwen. Den Haag: Gezondheidsraad

2007; publicatienummer 2007/10.
364. Ghersi D, Wilcken N, Simes J, Donoghue E. Taxane containing regimens for metastatic breast cancer. Cochrane Database Syst Rev. 2005 CD003366.
365. Giacalone Pl, Laffargue F, Benos P. Chemotherapy for breast carcinoma during pregnancy: A French national survey. Cancer 1999;86:2266-72
366. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, Zambetti M, Vazquez F, Byakhow M, Lichinitser M, Climent MA, Ciruelos E, Ojeda B, Mansutti M, Bozhok A, Baronio R, Feyereislova A, Barton C, Valagussa P, Baselga J.Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet. 2010;375:377-84
367. Gibbs P, Liney GP, Lowry M, Kneeshaw PJ, Turnbull LW. Differentiation of benign and malignant sub-1 cm breast lesions using dynamic contrast enhanced MRI. Breast 2004; 13: 115-21.
368. Gibson LJ, Dawson CK, Lawrence DH, Bliss JM. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database Syst Rev. 2007;(1): CD003370
369. Gielissen MF, Verhagen S, Witjes F, Bleijenberg G. (2006). Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: A randomized controlled trial. J Clin Oncol 24, 4882-4887.
370. Giordano SH, Buzdar AU, Smith TL, Kau SW, Yang Y, Hortobagyi GN. Is breast cancer survival improving? Cancer. 2004; 100(1):44-52.
371. Giordano SH, Valero V, Buzdar AU, Hortobagyi GN. Efficacy of anastrozole in male breast cancer. Am J Clin Oncol. 2002; 25:235-7
372. Giordano SH. A review of the diagnosis and management of male breast cancer. The Oncologist 2005; 10: 471-9.
373. GIVIO. Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. The GIVIO Investigators. Jama 1994;271(20):1587-92.
374. Gnant M,Mlineritsch B,Schippinger W, et al: Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009;360:679-691.
375. Goldfrank D, Chuai S, Bernstein JL et al. Effect of mammography on breast cancer risk in women with mutations in BRCA1 or BRCA2. Cancer Epidemiol Biomarkers Prev 2006; 15: 2311-3.
376. Goldhirsch A, Coates AS, Gelber RD, Glick JH, Thurlimann B, Senn HJ. First--select the target: better choice of adjuvant treatments for breast cancer patients. Ann Oncol 2006;17(12):1772-6.
377. Goldhirsch A, Gelber RD. Life with consequences of breast cancer: pregnancy during and after endocrine therapies. Breast, 2004;13:443-5
378. Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn HJ, et al. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Ann Oncol 2009;20:1319-29.
379. Goldhirsch A, M. Castiglione and R.D. Gelber, Adjuvant chemo-endocrine therapy in postmenopausal women with breast cancer and axillary-node metastases (letter). Lancet 1990; 335: 1099–1100.
380. Goldhirsch A, Wood WC, Gelber RD, et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 2007;18:1133-44.
381. Goldstein L., A. O'Neill, E. Sparano, et al. E 2197; phase III AT vs AC in the adjuvant treatment of node positive and high-risk node negative breast cancer. Proc Am Soc Clin Oncol 2005;23 (suppl 16):abstr 512.
382. Gonzalez-Angulo AM, Litton JK, Broglio KR et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol 2009; 27: 5700–5706.
383. Gordon PB, Goldenberg SL. Malignant breast masses detected only by ultrasound: a retrospective review. Cancer 1995:76:626-30.
384. Gordon PB. Gagnon FA, Lanzkowsky L. Solid breast masses diagnosed as fibroadenomas at FNAB: acceptable rates of growth at long-term follow-up. Radiology 2003; 229: 233-8.
385. Gorechlad JW, McCabe EB et al. Screening for recurrences in patients with breast conserving surgery: Is there a role for MRI?. Ann Surg Oncol 2008;15(16): 1703-09.
386. Goss P, Ingl J, Martino S, Robert N, Muss H, Piccart M et al A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early stage breast cancer. N Engl J Med 2003;349:1793-1802
387. Goss PE, Ingle JN, Pater JL, Martino S, Robert NJ, Muss HB, Piccart MJ, Castiglione M, Shepherd LE, Pritchard KI, Livingston RB, Davidson NE, Norton L, Perez EA, Abrams JS, Cameron DA, Palmer MJ, Tu D. Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. J Clin Oncol. 2008 Apr 20;26(12):1948-55.
388. Goss PE, Reid C, Pintilie M, Lim R, Miller N. Male breast carcinoma; a review of 229 patients who presented to the Princess Margaret Hospital during 40 yrs: 1955-1996. Cancer 1999; 85: 629-39.
389. Gottlieb BH, Cachala ED. (2007). Cancer support groups: a critical review of empirical studies. Psychooncology, 16, 379-400.
390. Grabiak BR, Bender CM, Puskar KR. (2007). The impact of parental cancer on the adolescent: an analysis of the literature. Psychooncology,16, 127-137.
391. Grady I, Gorsuch H, Wilburn-Bailey S. Long-term outcome of benign fibroadenomas treated by US-guided percutaneous excision. Breast J. 2008;14:275-8.
392. Graeser MK, Engel C, Rhiem K, Gadzicki D, Bick U, Kast K, Froster UG, Schlehe B, Bechtold A, Arnold N, Preisler-Adams S, Nestle-Kraemling C, Zaino M, Loeffler M, Kiechle M, Meindl A, Varga D, Schmutzler RK. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. 2009 Dec 10;27(35):5887-92
393. Graf O, Helbich TH, Fuchsjaeger MH, Hopf G, Morgun M, Graf C, et al. Follow-up of palpable circumscribed noncalcified solid breast masses at mammography and US: can biopsy be overted? Radiology 2004; 233: 850-6.
394. Gralla RJ, Osoba D, Kris MG, et al. Recommendations for the use of antiemetics: evidence based, clinical practice guidelines. American society of clinical oncology. J Clin Oncol 1999; 17 (9):2971-94.
395. Granader, E.J., B. Dwamena, and R.C. Carlos, MRI and Mammography Surveillance of Women at Increased Risk for Breast Cancer. Recommendations Using an Evidence-based Approach. Academic Radiology, 2008;15(12):1590-5.
396. Green JR. Bisphosphonates: Preclinical review. The Oncologist 2004; 9 (suppl 4): 3-13.
397. Greenberg P, Hortobagyi G, Smith T, Ziegler L, Frye K, Buzdar A. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. J Clin Oncol 1996;14: 2197-205.
398. Grobmeyr SR, Mortellaro VE, Marshall J, Moore Higgs G, Hochwald SN, Mendenhall NP et al. Is there a role for routine use of MRI in selection of patients for breast-conserving cancer therapy? J Am Coll Surg 2008;206:1045-52.

399. Groenewoud JH, Otten JD, Fracheboud J, Draisma G, van Ineveld BM, Holland R. Cost-effectiveness of different reading and referral strategies in mammographic screening in The Netherlands. Breast Cancer Res Treat 2007;102(2):211-8
400. Gross SW. A Practical Treatise on Tumors of the Mammary Gland. London: Lewis HK., 1880
401. Grosse A, Schreer I, Frischbier HJ, Maass H, Loening T, Bahnsen J. Results of breast conserving therapy for early breast cancer and the role of mammographic follow-up. Int J Radiat Oncol Biol Phys. 1997 Jul 1;38(4):761-7.
402. Grunfeld E, Levine MN, Julian JA, Coyle D, Szechtman B, Mirsky D, et al. Randomized trial of long-term follow-up for early-stage breast cancer: a comparison of family physician versus specialist care. J Clin Oncol 2006;24(6):848-55.
403. Grunfeld E, Mant D, Yudkin P, Adewuyi-Dalton R, Cole D, Stewart J, et al. Routine follow up of breast cancer in primary ca re: randomised trial. Bmj 1996;313(7058):665-9.
404. Guarneri V; Lenihan DJ; Valero V; Durand JB; Broglio K; Hess KR; Michaud LB; Gonzalez-Angulo AM; Hortobagyi GN; Esteva FJ. Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. J Clin Oncol. 2006 Sep 1;24(25):4107-15.
405. Gufler H, Buitrago-Tellez CH, Madjar H, Allmann KH, Uhl M, Rohr-Reyes A. Ultrasound demonstration of mammographically detected microcalcifications. Acta Radiol 2000; 41: 217-21.
406. Gulliford T, Opomu M, Wilson E, Hanham I, Epstein R. Popularity of less frequent follow up for
407. Gulliford T, Opomu M, Wilson E, Hanham I, Epstein R. Popularity of less frequent follow up for breast cancer in randomised study: initial findings from the hotline study. Bmj 1997;314(7075):174-7.
408. Gwyn K, Theriault RL. Breast cancer during pregnancy. Oncology 2001;15:39-45
409. Gwyn K. Children exposed to chemotherapy in utero. J Natl Cancer Inst Monogr 2005;34:69-71
410. Haagensen CD, Cooley E, Kennedy CS, et al. Treatment of Early Mammary Carcinoma, a Cooperative International Study. Ann Surg 1963; 157, 157-79.
411. Haagensen CD, Stout AP. Carcinoma of the breast: criteria for operability. Ann Surg 1943;118:859-870
412. Haagensen CD. Results with Halsted's Radical Mastectomy. In: Haagensen CD. Ed. Diseases of the breast, pp 663-667. Third ed. WB Saunders Company, New York, 1986.
413. Habel LA, Shak S, Jacobs MK, Capra A, Alexander C, Pho M, et al. A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients. Breast Cancer Res 2006;8:R25.
414. Haffty BG, Fischer D, Beinfield M, McKhann C. Prognosis following local recurrence in the conservatively treated breast cancer patient. Int J Radiat Oncol Biol Phys 1991; 21: 293-8.
415. Haffty BG, Fischer D, Rose M, Beinfield M, McKhann C. Prognostic factors for local recurrence in the conservatively treated breast cancer patient: a cautious interpretation of the data. J Clin Oncol. 1991 Jun;9(6):997-1003.
416. Haffty, B. G. et al. Adjuvant systemic chemotherapy and hormonal therapy. Effect on local recurrence in the conservatively treated breast cancer patiënt. Cancer 1994 73(10): 2543-8.
417. Hagedoorn M, Sanderman R, Bolks HN, Tuinstra J, Coyne JC. (2008). Distress in couples coping with cancer: a meta-analysis and critical review of role and gender effects. Psychol Bull, 134, 1-30.
418. Hahn KM, Johnson PH, Gordon N, et al. Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. Cancer 2006;107(6):1219–26
419. Hamaoka T, Madewell JE, Podoloff DA, Hortobagyi GN, Ueno NT. Bone imaging in metastatic breast cancer.J Clin Oncol. 2004 ;22:2942-53.
420. Han BK, Schnall MD, Orel SG, Rosen M. Outcome of MRI-guided breast biopsy. AJR Am J Roentgenol 2008;191:1798-804.
421. Hanrahan, EO, Broglio, K, Frye, D, et al. Randomized trial of high-dose chemotherapy and autologous hematopoietic stem cell support for high-risk primary breast carcinoma: follow-up at 12 years. Cancer 2006; 106:2327.
422. Hargaden GC, Yeh ED, Georgian-Smith D, Moore RH, Rafferty EA, Halpern EF et al. Analysis of the mammographic and sonographic features of pseudoangiomatous stromal hyperplasia. AJR Am J Roentgenol 2008;191:359-63.
423. Harmonisatie Kwaliteitsbeoordeling in de Zorgsectoer (HKZ): Bevolkingsonderzoek naar Borstkanker. Certificatieschema versie 2006.
424. Harris E.E. , V.J. Christensen, W.T. Hwang, et al. Impact of concurrent versus sequential tamoxifen with radiation therapy in early-stage breast cancer patients undergoing breast conservation treatment. J Clin Oncol. 2005; 23:11-6.
425. Harris L, Fritsche H, Mennel R Norton R, Ravdin P, Taube S et al. American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer J Clin Oncol 2007, 33: 5287-312
426. Harris, J. R. and S. Hellman. Observations on survival curve analysis with particular reference to breast cancer treatment. Cancer 1986 57(5): 925-8.
427. Hartmann LC, Sellers TA, Frost MH, Lingle WL, Degnim AC, Ghosh et al. Benign Breast Disease and the Risk of Breast Cancer. N Engl J Med 2005;353:229-37.
428. Haward R, Amir Z, Borrill C, et al. Breast cancer teams: the impact of constitution, new cancer workload, and methods of operation on their effectiveness. Br JCancer 2003; 89: 15-22.
429. Hayes DF, Henderson IC, Shapiro CL. Treatment of metastatic breast cancer: present and future prospects. Semin Oncol 1995; 22: 5-19.
430. Hayes DF. Clinical practice. Follow-up of patients with early breast cancer. N Engl J Med. 2007 Jun 14;356(24):2505-13.
431. Hayes, D. F. Clinical practice. Follow-up of patients with early breast cancer. N Engl J Med 2007 356(24): 2505-13.
432. Haylock BJ, Coppin CM, Jackson J, Basco VE, Wilson KS. Locoregional first recurrence after mastectomy: prospective cohort studies with and without immediate chemotherapy. Int J Radiat Oncol Biol Phys 2000; 46: 355 62.
433. Hehr T, Lamprecht U, Glocker S, Classen J, Paulsen F, Budach W, Bamberg M. Thermoradiotherapy for locally recurrent breast cancer with skin involvement. Int J Hyperthermia. 2001;17:291 301
434. Helbich TH, Matzek W, Fuchsjager MH. Stereotactic and ultrasound-guided breast biopsy. Eur Radiol 2004; 14: 383-93.
435. Helgeson, V. S., S. Cohen, et al. Education and peer discussion group interventions and adjustment to breast cancer. Arch Gen Psychiatry 1999 56(4): 340-7.
436. Henderson I.C , D.A. Berry and G.D. Demetri, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003; 21: 976–983
437. Hennequin C, Romestaing P, Maylin C. [Irradiation of lymph nodes areas in breast cancer]. Cancer Radiother. 2008 Nov;12(6-7):559-64
438. Hermsen BB, Olivier RI, Verheijen RH, Beurden M van, Hullu JA de, Massuger LF, et al. No efficacy of annual gynaecological screening in BRCA1/2 mutation carriers; an observational follow-up study. Br J Cancer. 2007; 96: 1335-42.
439. Heron DE, KomarnickyLT, Hyslop T, Schwartz GF, Mansfield CM. Bilateral breast carcinoma. Cancer 2000; 88: 2739-50.
440. Hershman, A.I. Neugut, J.S. Jacobson. Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte

colony-stimulating factors during breast cancer adjuvant chemotherapy, J. Natl. Cancer Inst. 2007, 99: 196–205.
441. Heywang-Kobrunner SH, Sinnatamby R, Lebeau A, Lebrecht A, Brittin PD, Schreer I, Consensus Group. Interdisciplinary consensus on the uses and technique of MR-guided vacuum-assisted breast biopsy (VAB): Results of a European consensus meeting. Eur J Radiol 2009;72:289-94.
442. Hickey B. , D. Francis, M. lehmann. Sequencing of chemotherapy and radiation therapy for early breast cancer. Cochrane Database of Systematic Reviews 2006, Oct 18;(4):CD005212.
443. Hillner BE, Ingle JN, Chlebowski T, Gralow J, Yee GC, Janjan NA et al. American Society of Clinical Oncology 2003 Update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 2003; 21: 4042-57.
444. Hinnen C, Ranchor AV, Sanderman R, Snijders TA, Hagedoorn M, Coyne JC. (2008). Course of distress in breast cancer patients, their partners, and matched control couples. Ann Behav Med, 36, 141-148.
445. Hladiuk M, Huchcroft S, Temple W, Schnurr BE. Arm function after axillary dissection for breast cancer. J Surg Oncol 1992; 50: 47-52
446. Holland H, Solke HJ, Veling J, Mravunac M, Hendriks JHCL. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. Cancer 1985;56:979-90.
447. Holland R, Connolly JL, Gelman R, Mravunac M, Hendriks JH, Verbeek AL et al. The presence of an extensive intraductal component following a limited excision correlates with prominent residual disease in the remainder of the breast.J Clin Oncol 1990;8:113-8.
448. Holland R, Hendriks JHCL, Verbeek ALM, Mravunac M, Schuurmans Stekhoven JH. Extent, distribution, and mammographic/histologic correlations of breast ductal carcinoma in situ. Lancet 1990;335:519-22
449. Holmberg, L. and H. Anderson. HABITS (hormonal replacement therapy after breast cancer--is it safe?), a randomised comparison: trial stopped. Lancet 2004 363(9407): 453-5.
450. Hoogerbrugge, N., et al., The impact of a false-positive MRI on the choice for mastectomy in BRCA mutation carriers is limited. Annals of Oncology, 2008;19(4): 655-9.
451. Hooning MJ, Aleman BMO, Rosmalen AJM et al. Cause specific mortality in long term survivors of breast cancer: a 25-year follow-up study. Int J Cancer Radiat Oncol Biol Phys 2006; 64: 1081 91.)
452. Hortobagyi GN, Buzdar AU, Theriault RL, Valero V, Frye D, Booser DJ, et al. Randomized trial of high-dose chemotherapy and blood cell autografts for high-risk primary breast carcinoma. J Natl Cancer Inst 2000; 92: 225-33
453. Hortobagyi GN, Singletary SE, Strom EA. Treatment of locally advanced and inflammatory breast cancer. In: Harris JR, Lippman ME, Morrow M, Osborne CK, Ed. Diseases of the breast. Second ed. Lippincott Williams & Wilkins, Philadelphia, p 645-67; 2000
454. Houssami N, Ciatto S, Ambrogetti D, Catarzi S, Risso G, Bonardi R, et al. Florence-Sydney Breast Biopsy Study: sensitivity of ultrasound-guided versus freehand fine needle biopsy of palpable breast cancer. Breast Cancer Res Treat 2005; 89: 55-9.
455. Houssami N, Ciatto S, Macaskill P, Lord SJ, Warren RM, Dixon M et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: a systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol 2008;26 :3248-58.
456. "Houssami N, Ciatto S, Turner RM et al. Preoperative US-guided needle biopsy of axillary nodes in invasive breast cancer. Meta-analysis of its accuracy and utility in staging the axilla.
457. Ann Surg 2011;254:243-251
458. "
459. Houssami N, Irwig L, Simpson JM, McKessar M, Blome S, Noakes J. Sydney Breast Imaging Accuracy Study: Comparative sensitivity and specificity of mammography and sonography in young women with symptoms. Am J Roentgenol 2003; 180: 935-40.
460. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, Hoctin-Boes G, Houghton J, Locker GY, Tobias JS; ATAC Trialists' Group Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer Lancet. 2005 Jan 1-7;365(9453):60-2.
461. Howell A, Robertson JF, Abram P, Lichinitser MR, Elledge R, Bajetta E, et al. Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomised trial. J Clin Oncol 2004; 22: 1605-13.
462. Hrung JM, Sonnad SS, Schwartz JS, Langlotz CP. Accuracy of MR imaging in the work-up of suspicious breast lesions: a diagnostic meta-analysis. Acad Radiol 1999; 6: 387-97.
463. Hsi RA, et al. Radiation therapy for chest wall recurrence of breast cancer after mastectomy in a favorable subgroup of patients. Int J Radiat Oncol Biol Phys 1998; 42: 495-9.
464. HT Mouridsen, SW Langer, J Buter, H Eidtmann, G Rosti, M de Wit: Treatment of anthracycline extravasation with Savene (dexrazoxane): results from two prospective clinical multicentre studies Ann Oncol. 2007; 18: 546-50
465. Huang E, Cheng SH, Dressman H, Pittman J, Tsou MH, Horng CF, et al. Gene expression predictors of breast cancer outcomes. Lancet 2003;361(9369):1590-6.
466. Huang EH, Strom EA, Perkins GH, Oh JL, Chen AM, Meric-Bernstam F, Hunt KK, Sahin AA, Hortobagyi GN, Buchholz TA. Comparison of risk of local-regional recurrence after mastectomy or breast conservation therapy for patients treated with neoadjuvant chemotherapy and radiation stratified according to a prognostic index score. Int J Radiat Oncol Biol Phys. 2006 Oct 1;66(2):352-7
467. Huang EH, Tucker SL, Strom EA, McNeese MD, Kuerer HM, Buzdar AU Meric-Bernstam F, Hunt KK, Thames HD, Outlaw ED, Strom EA, McNeese MD, Kuerer HM, Ross MI, Singletary SE, Ames FC, Feig BW, Sahin AA, Perkins GH, Babiera G, Hortobagyi GN, Buchholz TA. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. J Clin Oncol 2004; 22(23):4691-4699
468. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. J Clin Oncol 2003;21:555-63
469. Huang JY, Chian RC, Gilbert L, et al. Retrieval of immature oocytes from unstimulated ovaries followed by in vitro maturation and vitrification: A novel strategy of fertilitypreservation for breast cancer patients. Am J Surg 2010;200: 177-83.
470. Hudis C.A. . Trastuzumab-mechanism of action and use in clinical practice. NEJM 2007;357;39-51.
471. Hugh J, Hanson J, Cheang MC et al .Breast cancer subtypes and response to docetaxel in node-positive breast cancer: use of an immunohistochemical definition in the BCIRG 001trial. J Clin Oncol 2009 27(8):1168–1176
472. Huizinga GA, Visser A, van der Graaf WT, Hoekstra HJ, Gazendam-Donofrio SM, Hoekstra-Weebers JE. (2010). Stress response symptoms in adolescents during the first year after a parent's cancer diagnosis. Support Care Cancer, 18, 1421-

1428.
473. Huizinga GA, Visser A, van der Graaf WT, Hoekstra HJ, Klip EC, Pras E, Hoekstra-Weebers JE. (2005). Stress response symptoms in adolescent and young adult children of parents diagnosed with cancer. Eur J Cancer, 41, 288-295
474. Hunt KK, Ames FC, Singletary SE, Buzdar AU, Hortobagyi GN. Locally advanced noninflammatory breast cancer. Surg Clin North Am 1996; 76: 393-410.
475. Hurria, A., G. Somlo, et al. Renaming "chemobrain". Cancer Invest 2007 25(6): 373-7.
476. Hwang ES, Kinkel K, Esserman LJ, Lu Y, weidner N, Hylton NM. Magnetic resonance imaging in patients diagnosed with DCIS: value in the diagnosis of residual disease, occult invasion, and multicentricity. Ann Surg Oncol 2003;10:381-8.
477. Ignatiadou E, Ziogas D, Lykoudis E et al. Screening for or prevention of local ipsilateral recurrence and contralateral breast cancer after breast-conserving therapy? Annal Surg Oncol 2008;15:3617-9.
478. IGZ. Zorgketen voor kankerpatienten moet verbeteren. Den Haag, maart 2009.
479. Ingle JN, Suman VJ, Rowland KM, Mirchandani D, Bernath AM, Camoriano JK, Fishkin PA, Nikcevich DA, Perez EA; North Central Cancer Treatment Group Trial N0032 Fulvestrant in women with advanced breast cancer after progression on prior aromatase inhibitor therapy: North Central Cancer Treatment Group Trial N0032 J Clin Oncol. 2006 Mar 1;24(7):1052-6
480. International Breast Cancer Study Group (IBCSG). Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: A randomized trial. J Clin Oncol 2003; 95: 1833-46.
481. International Commission on Radiological Protection. Doses to the embryo and fetus from intakes of radionuclides by the mother. Ann ICRP 2001;31:19-515
482. Ioannidis JP. Is molecular profiling ready for use in clinical decision making? Oncologist 2007;12(3):301-11.
483. Irwig L, Macaskill P, Walter SD, Houssami N. New methods give better estimates of changes in diagnostic accuracy when prior information is provided. J Clin Epidemiol 2006; 59: 299-307.
484. Isaacs RJ, Hunter W, Clark K. Tamoxifen as systemic treatment of advanced breast cancer during pregnancy -- case report and literature review. Gynecol Oncol 2001;80:405-8
485. Isasi CR, Moadel RM, Blaufox MD A meta-analysis of FDG-PET for the evaluation of breast cancer recurrence and metastases. . Breast Cancer Res Treat. 2005;90:105 12
486. Ivens D, Hoe AL, Podd TJ, Hamilton CR, Taylor I, Royle GT. Assessment of morbidity from complete axillary dissection. Br J Cancer 1992; 66: 136-8
487. Iwata H. Neoadjuvant endocrine therapy for postmenopausal patients with hormone receptor-positive early breast cancer: a new concept. Breast Cancer. 2010 Dec 8. [Epub ahead of print]
488. Jackman RJ. False-negative diagnoses at stereotactic vacuum-assisted needle breast biopsy: long-term follow-up of 1280 lesions and review of the literature. AJR Am J Roentgenol. 2009;192:341-51.
489. Jacobs TW, Connolly JL, Schnitt SJ. Nonmalignant lesions in breast core needle biopsies. Ann J Surg Pathol. 2006;26:1095-110.
490. Jacquillat C, Weil M, Baillet F, Borel C, Auclerc G, de Maublanc MA, et al. Results of neoadjuvant chemotherapy and radiation therapy in the breast-conserving treatment of 250 patients with all stages of infiltrative breast cancer. Cancer 1990; 66: 119-29
491. Jager JJ, Volovics L, Schouten LJ, de Jong JM, Hupperets PS, von Meyenfeldt MF, et al. Loco-regional recurrences after mastectomy in breast cancer: prognostic factors and implications for postoperative irradiation. Radiother Oncol 1999; 50: 267 75.
492. Jager JJ, Volovics L, Schouten LJ, de Jong JM, Hupperets PS, von Meyenfeldt MF, et al. Loco-regional recurrences after mastectomy in breast cancer: Treatment results and prognostic factors, Thesis (ch. 6) University of Utrecht, 1998.
493. Jager, J. J. et al. Loco-regional recurrences after mastectomy in breast cancer: prognostic factors and implications for postoperative irradiation. Radiother Oncol 1999 50(3): 267-75.
494. Jagsi R, Raad RA, Goldberg S, Sullivan T, Michaelson J, et al. Locoregional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy: implications for postmastectomy radiation. Int J Radiat Oncol Biol Phys 2005; 62: 1035-9.
495. Jakesz R, Gnant M, Griel R et al: Tamoxifen and anastrozole as a sequencing strategy in postmenopausal women with hormone responsive early breast cancer: Updated data from the Austrian breast and colorectal cancer study Group 8, SABCS 2008, abstract 14
496. Jakesz R, Greil R, Gnant M, Kwasny W, Kubista E, Mlineeritsch B et al. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Caner study Group Trial 6a. J Natl Cancer Inst 2007; 99:1825-1827
497. Jakesz R, Jonat W, Gnant M, Mittlboeck M, Greil R, Tausch C, et al. ABCSG and the GABG. Switching op postmenopauzal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet. 2005;366:455-62
498. Janicke F, Prechtl A, Thomssen C, Harbeck N, Meisner C, Untch M, et al. Randomized adjuvant chemotherapy trial in high-risk, lymph node-negative breast cancer patients identified by urokinase-type plasminogen activator and plasminogen activator inhibitor type 1. J Natl Cancer Inst 2001;93(12):913-20.
499. Jansen R, Geel A van, Groot H de, Rottier A, Olthuis G, Putten W van. Immediate versus delayed shoulder exercises after axillary lymph node dissection. Am J Surg 1990; 160: 481-4
500. Jansen SJT, Kievit J, Nooij MA, de Haes JCJM, Overpelt E, van Slooten H. Patients preferences for adjuvant chemotherapy in early-stage breast cancer: is treatment worthwhile. Br J Cancer 2001; 84: 1577-85.
501. Jansen-van der Weide MC, Greuter MJW, Jansen L, Oosterwijk JC, Pijnappel R, De Bock GH. Exposure to low-dose radiation and the risk of breast cancer among women with a familial or genetic predisposition: A meta-analysis. Eur Radiol 2010, 20:2547-56.
502. 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.
503. Jenninga E, Hilders CG, Louwe LA, Peeters AA. Female fertility preservation: practical and ethical considerations of an underused procedure. Cancer J 2008;14(5):333-9.
504. Jensen B.V. . Cardiotoxic consequences of anthracycline-containing therapy in patients with breast cancer. Semin Oncol 2006; 33:s15-21.
505. Jepson AS, Fentiman IS. Male breast cancer. Int J Clin Pract 1998; 52: 571-6.
506. Jimenez-Gordo AM, Espinosa E, Zamora P, Feliu J, Rodrigues-Salas N, Gonzalez-Baron. Pregnancy in a breast cancer patient treated with a LHRH analogue at ablative doses. Breast 2000;9:110-2
507. Joensuu H, Isola J, Lundin M et al. Amplification of erbB2 and erbB2 expression are superior to estrogen receptor status

as risk factors for distant recurrence in pT1N0M0 breast cancer: a nationwide population-based study. Clin Cancer Res 2003; 9: 923–930.
508. Joensuu H. , P.L. Kellokumpu-lehtinen, P. Bono, R et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. NEJM 2006, 354:809-20.
509. Joerger M, Thurlimann b, Huober j. Small HER2-positive, node-negative breast cancer: who should receive systemic adjuvant therapy? Ann Oncol 2011, 22:17-23
510. John EM, Phipps AI, Knight JA et al. Medical radiation and breast cancer risk: findings from the breast cancer family registry. Int J Cancer 2007;121:386-94.
511. Johnson NB, Collins LC. Update on percutaneous needle biopsy of nonmalignant breast lesions. Review. Adv Anat Pathol 2009;16:183-195.
512. Johnson S.A. . Anthracycline-induced cardiotoxicity in adult hematologic malignancies.Semin Oncol 2006; 33:s22-27.
513. Johnston S, Pippen J Jr, Pivot X, Lichinitser M, Sadeghi S, Dieras V, Gomez HL, Romieu G, Manikhas A, Kennedy MJ, Press MF, Maltzman J, Florance A, O'Rourke L, Oliva C, Stein S, Pegram M. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol. 2009 ;27:5538-46.
514. Jones D, Ghersi D, Wilcken N Addition of drug/s to a chemo-therapy regimen for metastatic breast cancer. Cochrane Database Syst Rev. 2006 Jul 19;3:CD003368.
515. Jones EL, Marks LB, Prosnitz LR. Point: Hyperthermia with radiation for chest wall recurrences. J Natl Compr Canc Netw. 2007;5:339-44
516. Jones S.E. , M.A. Savin, F.A. Holmes, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol 2006; 24:5381–5387.
517. Jones SE, Erban J, Overmoyer B et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 2005; 23:5542–5551.
518. Jørgensen KJ, Gøtzsche PC. Content of invitations for publicly funded screening mammography. BMJ 2006; 332: 538-41.
519. Joseph, E., M. Hyacinthe, et al. Evaluation of an intensive strategy for follow-up and surveillance of primary breast cancer. Ann Surg Oncol 1998 5(6): 522-8.
520. Kaas, R., A. A. Hart, et al. Impact of mammographic interval on stage and survival after the diagnosis of contralateral breast cancer. Br J Surg 2001 88(1): 123-7.
521. Kal HB, Struikmans H. Radiotherapy during pregnancy: fact and fiction. Lancet Oncol 2005;6:328-333
522. Kamby C, Sengelov L. Pattern of dissemination and survival following isolated locoregional recurrence of breast cancer. A prospective study with more than 10 years of follow up. Breast Cancer Res Treat 1997; 45: 181-92.
523. Kamila C, Jenny B, Per H, Jonas B. How to treat male breast cancer. Breast 2007 Nov 2;16(2S):147-154.
524. Kaplan SS. Clinical utility of bilateral whole-breast US in the evaluation of women with dense breast tissue. Radiology 2001;221:641-9.
525. Kapp DS, Cox RS, Barnett TA, Ben-Yosef R. Thermoradiotherapy for residual microscopic cancer: elective or post-excisional hyperthermia and radiation therapy in the management of local-regional recurrent breast cancer. Int J Radiat Oncol Biol Phys. 1992;24:261-77..
526. Karssemeijer N, Bluekens AM, Beijerinck D, Deurenberg JJ, Beekman M, Visser R et al. Breast cancer screening results 5 years after introduction of digital mammography in a population-based screening program. Radiology 2009;253:353-8.
527. Kase KR, Svensson GK, Wolbarst AB, Marks MA, Measurements of dose from secondary radiation outside a treatment field. Int J Radiat Oncol Biol Phys 1983;9:1177-1183
528. Kaufman B, Mackey JR, Clemens MR, Bapsy PP, Vaid A, Wardley A, Tjulandin S, Jahn M, Lehle M, Feyereislova A, Révil C, Jones A. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study.J Clin Oncol. 2009 ;27:5529-37.
529. Kaufman CS, Bachman B, Littrup PJ, Freeman-Gibb LA, White M, Carolin K, et al. Cryoablation treatment of benign breast lesions with 12 month follow-up. Am J of Surg 2004; 188: 340-8.
530. Kaufman CS, Littrup PJ, Freeman-Gibb LA, Smith JS, Franscescatti D, et al. Office-based cryoablation of breast fibroadenomas with long-term follow-up. Breast J 2005; 11: 344-50.
531. Kaufmann M et al Benefit From Exemestane As Extended Adjuvant Therapy After 5 Years of Adjuvant Tamoxifen: Intention-to-Treat Analysis of the National Surgical Adjuvant Breast and Bowel Project B-33 Trial Journal of Clinical Oncology, Vol 26, No 12 (April 20), 2008: pp. 1965-1971
532. Kaufmann M, Jonat W, Hilfrich J 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 Study. J Clin Oncol 2007;25:2664-2670.
533. Kavanagh AM, Giles GG, Mitchell H, Cawson JN. The sensitivity, specificity, and positive predictive value of screening mammography and symptomatic status. J Med Screen 2000; 7: 105-10.
534. Keleher A, Wendtt R, III, Delpassand E, Stachowiak AM, Kuerer HM. The safety of lymphatic mapping in pregnant breast cancer patients using Tc-99m sulfer colloid. Breast J. 2004;10(6): 492-5.
535. 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 2001;194:54-64
536. Kellen E, Vansant G, Christiaens MR, Neven P, Limbergen E van (2009). Lifestyle changes and breast cancer prognosis: a review. Breast Cancer Research and Treatment, 114, 13-21.
537. Keller AM, Mennel RG, Georgoulias VA, Nabholtz JM, Erazo A, Lluch A randomized phase III trial of pegylated liposomal doxorubicin versus vinorelbine or mitomycin C plus vinblastine in women with taxane-refractory advanced breast cancer. J Clin Oncol. 2004;22: 3893-901.
538. Kerbrat P, Roche H, Bonneterre J, Veyret C, Lortholary A, Monnier A,; French adjuvant Study Group. Epirubicin-vinorelbine vs FEC100 for node-positive, early breast cancer: French Adjuvant Study Group 09 trial. Br J Cancer. 2007;96: 1633-8.
539. Kerlikowske K, Salzmann P, Phillips KA, Cauley JA, Cummings SR. Continuing screening mammography in women aged 70 to 79 years: impact on life expectancy and cost-effectiveness. JAMA 1999; 282:2156-63.
540. Kerlikowske K, Smith-Bindman R, Ljung BM, Grady D. Evaluation of abnormal mammography results and palpabel breast abnormalities. Ann Intern Med 2003; 139: 274-84.
541. Kettritz U, Rotter K, Schreer I, Murauer M, Schulz-Wendtland R, Peter D, et al. Stereotactic vacuum-assisted breast biopsy in 2874 patients. A multicenter study. Cancer 2004; 100: 245-51.
542. Key J, Hodgson S, Omar RZ, Jensen TK, Thompson SG, Boobis AR, et al. Meta-analysis of studies of alcohol and breast

cancer with consideration of the methodological issues. Cancer Causes Control. 2006;17:759-70.
543. Khatcheressian JL, Wolff AC, Smith ThJ et al. American Society of Clinical Oncology 2006 Update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol 2006;24:5091-7
544. Khatcheressian JL, Wolff AC, Smith ThJ et al. American Society of Clinical Oncology 2006 Update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol 2006;24:5091-7.
545. Khera SY, Kiluk JV, Hasson DM, et al. Pregnancy-associated breast cancer patients can safely undergo lymphatic mapping. Breast J 2008;14(3):250–4.
546. Kim SS: Fertility preservation in female cancer patients: current developments and future directions. Fertility and Sterility 2006;85:1-11
547. Kimman ML Bloebaum MMF, Dirksen CD et al. Patiënt satisfaction with nurse-led telephone follow-up after curative treatment for breast cancer. BMC Cancer 30;10:174, 2010.
548. Kimman ML, Dirksen CD, Voogd AC, et al. An economic evaluation of four follow-up strategies after curative treatment for breast cancer: results of an RCT. Eur J Cancer 2011b, Jan 21. [Epub ahead of print].
549. Kimman ML, Dirksen CD, Voogd AC, et al. Nurse-led telephone follow-up and an educational group programme after breast cancer treatment: results of a 2x2 randomised controlled trial. Eur J Cancer 2011a, Jan 13. [Epub ahead of print].
550. Klijn JGM, Blamey RW, Boccardo F, Tominaga T, Duchateau L, Sylvester R on behalf of the Combined Hormone Agents Trialists' Group. Combined tamoxifen and LHRH-agonist versus LHRH-agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomised trials. J Clin Oncol 2001; 19: 343-53.
551. Knauer MS, Mook S, Rutgers EJT, Bender RA, Hauptmann M, van de Vijver MJ, et al. The predictive value of the 70-gene signature for adjuvant chemotherapy in early breast cancer. Breast Cancer Res Treat 2010;120: 655-661Knauer M, Cardoso F, Wesseling J, Bedard PL, Linn SC, Rutgers EJ, van 't Veer LJ. Identification of a low-risk subgroup of HER-2-positive breast cancer by the 70-gene prognosis signature. Br J Cancer 2010;103(12):1788-93.
552. Knols R, Aaronson NK, Uebelhart D, et al. Physical exercise in cancer patients during and after medical treatment: a systematic review of randomized and controlled clinical trials. J Clin Oncol. 2005;23(16):3830-42
553. Knuistingh Neven A, Bock GH de. Pijnlijke borsten/mastopathie in: Kleine kwalen in de huisartsenpraktijk, ed. Eekhof JAH et al. 5e druk, 2007. Elsevier, Maarssen
554. Koca T, Akgun Z, Baskaya Yucel S, Zerman Dag N, Teomete M. Pregnancy a short time after multimodal therapy for bilateral breast cancer: a case report and review of literature. J Oncol Pharm Pract. 2010 Sep 21. [Epub ahead of print] PubMed PMID: 20858636
555. Koelliker SL, Chung MA, Mainiero MB, Steinhoff MM, Cady B. Axillary lymph nodes: US-guided fine-needle aspiration for initial staging of breast cancer-correlation with primary tumor size. Radiology 2008;246:81-9
556. Koelliker SL, Chung MA, Mainiero MB, Steinhoff MM, Cady B. Axillary lymph nodes: US-guided fine-needle aspiration for initial staging of breast cancer-correlation with primary tumor size. Radiology 2008;246:81-9.
557. Kohno N, Aogi K, Minami H, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: A randomized, placebo-controlled trial. J Clin Oncol 2005; 23:3314-21.
558. Koinberg IL, Fridlund B, Engholm GB, Holmberg L. Nurse-led follow-up on demand or by a physician after breast cancer surgery: a randomised study. Eur J Oncol Nurs 2004;8(2):109-17; discussion 118-20
559. Koizumi K, Aono T. Pregnancy after combined treatment with bromocriptine and tamoxifen in two patients with pituitary prolactinomas. Fertil Steril 1986;46:312–4
560. Kok M de , CD Dirksen, AGH Kessels, T van der Weijden, CJH van de Velde, JA Roukema, AVRJ Bell, FW van der Ent and MF von Meyenfeldt. Cost-effectiveness of a short stay admission programme for breast cancer surgery. Acta Oncol 2010; 49: 338-346
561. Kok M de , CD Dirksen, AGH Kessels, T van der Weijden, CJH van de Velde, JA Roukema, AVRJ Bell, FW van der Ent and MF von Meyenfeldt. Cost-effectiveness of a short stay admission programme for breast cancer surgery. Acta Oncol 2010; 49: 338-346.
562. Kok M de , CNA Frotscher, T van der Weijden, AGH Kessels, CD Dirksen, CJH van de Velde, JA Roukema, AVRJ Bell, FW van der Ent and MF von Meyenfeldt. Introduction of a breast cancer care programme including ultra short hospital stay in 4 early adopter centres: framework for an implementation study. BMC Cancer 2007; 7:117-126.
563. Kok M de , T van der Weijden, AC Voogd, CD Dirksen, CJH van de Velde, JA Roukema, C Finaly-Marais, FW van der Ent and MF von Meyenfeldt . Implementation of a short-stay programme after breast cancer surgery. Br J Surg. 2010; 97: 189-194.
564. Kok M de , T van der Weijden, AGH Kessels, CD Dirksen, HJM Sixma, CJH van de Velde, JA Roukema, C Finaly-Marais, FWC van der Ent, MF von Meyenfeldt. Patients' opinions on quality of care before and after implementation of a short stay programme following breast cancer surgery et al. The Breast 2010; 19: 404-409.
565. Kok RD, de Vries MM, Heerschap A, van den Berg PP. Absence of harmful effects of magnetic resonance exposure at 1.5 T in utero during the third trimester of pregnancy: a follow-up study. Magn reson imaging 2004;22:851-4
566. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27.825 patient evaluations. Radiology 2002; 225: 165-75.
567. Koning C, Hart G. Long-term follow-up of a randomized trial on adjuvant chemotherapy and hormonal therapy in locally advanced breast cancer. Int J Radiat Oncol Biol Phys 1998;41:397 400
568. Koning de HJ. Mammographic screening: evidence from randomised controlled trials. Review. Ann Oncol 2003;14:1185-9.
569. Kootstra JJ, Hoekstra-Weebers JEHM, Rietman H, Vries J de, Baas P, Geertzen JHB, Hoekstra HJ (2008). Quality of life after Sentinel Lymph Node Biopsy or Axillary Lymph Node Dissection in Stage I/II Breast Cancer Patients: A Prospective Longitudinal Study. Annals of Surgical Oncology, 15(9), 2533-2541
570. Korde LA, Zujewski JA, Kamin L, Giordano S, Domchek S, Anderson WF, et al. Multidisciplinary meeting on male breast cancer: summary and research recommendations. J Clin Oncol 2010;28:2114-22.
571. Korstjens I, May AM, van Weert E, Mesters I, Tan F, Ros WJ, Hoekstra-Weebers JE, van der Schans CP, van den Borne B. (2008). Quality of life after self-management cancer rehabilitation: a randomized controlled trial comparing physical and cognitive-behavioral training versus physical training. Psychosom Med, 70, 422-429.
572. Kösters JP, Gøtzsche PC. Regular self-examination or clinical examination for early detection of breast cancer. Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.: CD003373. DOI: 10.1002/14651858.CD003373.
573. Koswig S, Budach V. (Remineralization and pain relief in bone metastases after different radiotherapy fractions (10 x 3 Gy vs. 1 x 8 Gy). A prospective study). Strahlenther Onkol 1999;175 :500-8.
574. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, Ashikaga T, Weaver DL, Mamounas EP, Jalovec

LM, Frazier TG, Noyes RD, Robidoux A, Scarth HM, Wolmark N. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010 Oct;11(10):927-33
575. Krainick-Strobel U, Huber B, Bergmann A, Gall C, Gruber I, Hoffmann J et al. Complete extirpation of benign breast lesions with an ultrasound-guided vacuum biopsy system. Ultrasound Obstet Gynecol. 2007; 29:342-6.
576. Kramer, S., R. Schulz-Wendtland, et al. Magnetic resonance imaging in the diagnosis of local recurrences in breast cancer. Anticancer Res 1998 18(3C): 2159-61.
577. Kriege M, Brekelmans CT, Obdeijn IM, Boetes C, Zonderland HM, Muller SH, et al. Factors affecting sensitivity and specificity of screening mammography and MRI in women with an inherited risk for breast cancer. Breast Cancer Res Treat 2006; 100: 109-19.
578. Kriege, M., et al., Differences between first and subsequent rounds of the MRISC breast cancer screening program for women with a familial or genetic predisposition. Cancer, 2006; 106(11): 2318-26.
579. Kriege, M., et al., Tumor characteristics and detection method in the MRISC screening program for the early detection of hereditary breast cancer. Breast Cancer Research & Treatment, 2007;102(3): p. 357-63.
580. Kroman N, Holtveg H, Wohlfahrt J, Jensen MB, Mouridsen HT, Blichert-Toft M, Melbye M. Effect of breast-conserving therapy versus radical mastectomy on prognosis for young women with breast carcinoma. Cancer. 2004;100:688-93
581. Kronemer KA, Rhee K, Siegel MJ, Sievert L, Hildeboldt CF. Gray scale sonography of breast masses in adolescent girls. J Ultrasound Med 2001, 20: 491-6.
582. Kuerer HM, Newman LA, Fornage BD, Dhingra K, Hunt KK, Buzdar AU, et al. Role of axillary lymph node dissection after tumor downstaging with induction chemotherapy for locally advanced breast cancer Ann Surg Oncol 1998; 5: 673-80.
583. Kuerer HM, Sahin AA, Hunt KK, Newman LA, Breslin TM, Ames FC, et al. Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy. Ann Surg 1999; 230: 72-8
584. Kuhl CK, Schrading S, Bieling HB, Wardelmann E, Leutner CC, Koenig R et al. MRI for diagnosis of pure ductal carcinoma in situ: a prospective observational study. Lancet 2007: 370:485-92.
585. Kuhl CK, Schrading S, Leutner CC, Morakkabati-Spitz N, Wardelmann E, Fimmers R, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol 2005; 23: 8469-76.
586. Kuhl CK. MRI of the breast. Review article. Eur Radiol 2000; 10: 46-58.
587. Kuhl, C., et al., Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. Journal of Clinical Oncology 2010; 28(9) : 1450-57.
588. Kuijper A, Mommers ECM, Wall van der E, Diest van PJ. Histopathology of fibroadenoma of the breast. Am J Clin Pathol 2001;115:736-42
589. Kunju LP, Kleer CG. Significance of flat epithelial atypia on mammotome core needle biopsy: should it be excised? Human Pathol 2007; 38: 35-41.
590. Kurtz JM, Amalric R, Brandone H, Ayme Y, Jaquemier J, Pietra J-C, et al. Local recurrence after breast conserving surgery and radiotherapy; frequency, time course, and prognosis. Cancer 1989; 63: 1912 7.
591. Kurtz JM, Spitalier J-M, Amalric R, Brandone H, Ayme Y, Jaquemier J, et al. The prognostic significance of late local recurrence after breast-conserving therapy. Int J Radiat Oncol Biol Phys 1990; 18: 87 93.
592. Kuukasjarvi T, Kononen J, Helin H, Holli K, Isola J. Loss of estrogen receptor in recurrent breast cancer is associated with poor response to endocrine therapy. J Clin Oncol. 1996;14:2584-2589.
593. Kwon JS, Guttierrez-Barrere AM, Young D et al. Expanding the criteria for BRCA mutation testing in breast cancer survivors. J Clin Oncol 2010;28:4214-20. Epub 2010 Aug 23.
594. Landelijk Referentiecentrum voor Bevolkingsonderzoek op Borstkanker (LRCB) Typekeuring Lorad Selenia (uitvoering met W-anode) t.b.v. het Nederlandse Bevolkingsonderzoek op Borstkanker, LRCB 2008, Nijmegen
595. Langley RE, Carmichael J, Jones AL, Cameron DA, Qian W, Uscinska B, Phase III trial of epirubicin plus paclitaxel compared with epirubicin plus cyclophosphamide as first-line chemotherapy for metastatic breast cancer: United Kingdom National Cancer Research Institute trial AB01. J Clin Oncol. 2005;23 :8322-30
596. LaTrenta LR, Menell JH, Morris EA, Abramson AF, Dershaw DD, Liberman L. Breast lesions detected with MRImaging: utility and histopathologic importance of identification with US. Radiology 2003; 227: 856-61.
597. Lauridsen MC, Christiansen P, Hessov I. The effect of physiotherapy on shoulder function in patients surgically treated for breast cancer: a randomized study. Acta Oncol. 2005;44(5):449-57.
598. Lawrenz B, Jauckus J, Kupka MS et al. Fertility preservation in > 1000 patients: patients characteristics, spectrum, efficacy and risks of applied preservations techniques. Arch Gynecol Obstet, published online: 1 December 2010.
599. Layer G, Steudel A, Schuller H, van Kaick G, Grunwald F, Reiser M, et al. MRI to detect bone marrow metastases in the initial staging of small cell lung carcinoma and breast carcinoma. Cancer 1999; 85: 1004-910.
600. Lazarus E, Mainiero MB, Schepps B, Koeliker SL, Livingston LS. BI-RADS lexicon for US and mammography: interobserver variability and positive predictive value. Radiology 2006; 239: 385-91.
601. Leconte I, Feger C, Galant C, Berlière M, Berg BV, D'Hoore W et al. Mammography and subsequent whole-breast sonography of nonpalpable breast cancers: the importance of radiologic breast density. AJR Am J Roentgenol 2003:180:1675-9.
602. Lee CH, Philpotts LE, Horvath LJ, Tocino I. Follow-up of breast lesions diagnosed as benign with stereotactic core-needle biopsy: frequency of mammographic change and false negative rate. Radiology 1999; 212: 189-94.
603. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, Beck LN, Brennan LV, Oktay K: American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 2006;24:2917-31
604. Leeuwen FE van, Klokman WJ, Stovall M, Dahler EC, van't Veer MB, Noordijk EM, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst. 2003;95:971-80.
605. Lehman C, Holt S, Peacock S, White E, Urban N. Use of the American College of Radiology BI-RADS guidelines by community radiologists: concordance of assessments and recommendations assigned to screening mammograms. Am J Roentgenol 2002; 179: 15-20.
606. Lehman CD, Gatsonis C, Kuhl CK, Hendrick RE, et al. MRI Evaluation of the contralateral breast in women with recently diagnosed breast cancer. N Engl J Med 2007; 356: 1295-303.
607. Lehman CD, Isaacs C, Schnall MD, Pisano ED, Ascher SM, Weatherall PT et al. Cancer yield of mammography, MR and US in high-risk women: prospective multi-institution breast cancer screening study. Radiology 2007;244:381-8.
608. Leonard, RC, Lind, M, Twelves, C, et al. Conventional adjuvant chemotherapy versus single-cycle, autograft-supported, high-dose, late-intensification chemotherapy in high-risk breast cancer patients: a randomized trial. J Natl Cancer Inst

2004; 96:1076.
609. Lepore SJ, Coyne JC. Psychological interventions for distress in cancer patients: A review of reviews. (2006). Ann Behav Med, 32, 85-92
610. Lepore SJ, Coyne JC. Psychological interventions for distress in cancer patients: A review of reviews. (2006). Ann Behav Med, 32, 85-92.
611. LETB XII. Landelijke evaluatie van bevolkingsonderzoek naar borstkanker in Nederland. Rotterdam NETB 2010. www.erasmusmc.nl/mage.
612. Levine M.N., K.L. Pritchard, V.H. Bramwell, 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. J Clin Oncol 2005;23:5166.
613. Levine, M. N., V. Bramwell, et al. The effect of systemic adjuvant chemotherapy on local breast recurrence in node positive breast cancer patients treated by lumpectomy without radiation. Br J Cancer 1992 65(1): 130-2
614. LHRH-agonists in Early Breast Cancer Overview Group. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatmentin premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised trials. Lancet. 2007;369:1711-1723
615. Li CI, Anderson BO, Daling JR, Moe RE. Trends in incidence rate of invasive lobular and ductal breast carcinoma. JAMA 2003; 289: 1421-4.
616. Li CI, Chlebowski RT, Freiberg M, Johnson KC, Kuller L, Lane D, et al. Alcohol consumption and risk of postmenopausal breast cancer by subtype: the women's health initiative observational study. JNCI 2010;102:1422-31
617. Li J, Dershaw DD, Lee Ch, Kaplan J, Morris EA. MRI follow-up after concordant, histologically benign diagnosis of breast lesions sampled by MRI-guided biopsy. AJR Am J Roentgenol 2009;193:850-5.
618. Liao J, Davey DD, Warren G, Davis J, Moore AR, Samayoa LM. Ultrasound-guided fine-needle aspiration biopsy remains a valid approach in the evaluation of nonpalpable breast lesions. Diagn Cytopathol 2004; 30: 325-31.
619. Liberman L, Bonaccio E, Hamele-Bena D, Abramson AF, Cohen MA, Dershaw DD. Benign and malignant phyllodes tumors: mammographic and sonographic findings. Radiology 1996; 198: 121-4.
620. Liberman L, Morris EA, Lee MJ, Kaplan JB, LaTrenta LR, Menell JH, et al. Breast lesions detected on MR imaging: features and positive predictive value. Am J Roentgenol 2002; 179: 171-8.Morrow M, Schmidt RA, Bucci C. Breast Conservation for mammographically occult carcinoma. Ann Surg 1998; 227: 502-6.
621. Liebens FP, Carly B, Pastijn A, Rozenberg S. Management of BRCA1/2 associated breast cancer: a systematic qualitative review of the state of knowledge in 2006. Eur J Cancer 2007;43:238-57.
622. Liedtke C, Mazouni C, Hess KR et al Response to neoadjuvant therapy and long-term survival in patients with triple negative breast cancer. J Clin Oncol 2008 26(8):1275–1281
623. Linda A, Zuiani C, Londero V et al. Outcome of initially only MRmammography detected findings with and without correlate at second-look sonography: distribution according to patient history of breast cancer and lesion size. Breast 2008;17:51-7.
624. Linden H.M., C.M. Haskell, et al. Sequenced compared with simultaneous anthracycline and cyclophosphamide in high-risk stage I and II breast cancer: final analysis from INT-0137 (S9313). J Clin Oncol 2007; 25:656.
625. Lister D, Evans AJ, Burrell HC, Blamey RW, Wilson AR, Pinder SE, et al. The accuracy of breast ultrasound in the evaluation of clinically benign discrete, symptomatic breast lumps. Clin Radiol 1998; 53: 490-2.
626. Ljung B-M, Drejet A, Chiampi N, Jeffrey J, Goodson III W, Chew K, et al. Diagnostic accuracy of fine needle aspiration biopsy is determined by physician training in sampling technique. Cancer (Cancer Cytopathol) 2001; 93: 263-8.
627. Lohrisch C, Paltiel C, Gelmon K, et al. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. J Clin Oncol 2006;24:4888–4894.
628. Lokate MA, Kallenberg MG, Karssemeijer N, Bosch van den MA, Peeters PH, Gils van CH. Volumetric breast density from full-field digital mammograms and its association with breast cancer risk factors: a comparison with a threshold method. Cancer Epidemiol Biomarkers Prev. 2010; 19:3096-105. Epub 2010 Oct 4.
629. Lønning E, Lien EA Mechanisms of action of endocrine treatment in breast cancer. Crit Rev Oncol Hematol. 1995;21:158-93.
630. Lonning PE, Bajetta E, Murray R, Tubania-Hulin M, Eisenberg PD, Mickiewicz E, et al. Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatise inhibitors: a phase II trial. J Clin Oncol 2000; 18: 2234-44
631. Look MP, van Putten WL, Duffy MJ, Harbeck N, Christensen IJ, Thomssen C, et al. Pooled analysis of prognostic impact of urokinase-type plasminogen activator and its inhibitor PAI-1 in 8377 breast cancer patients. J Natl Cancer Inst 2002;94(2):116-28.
632. Lord, S.J., et al., A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer. European Journal of Cancer, 2007;43(13):1905-17.
633. Lorenzen J, Welger J, Lisboa BW, Riethof L, Grzyska B, Adam G. Percutaneous core needle biopsy of palpable breast tumors. Do we need US guidance? Rofo 2002; 174: 1142-6.
634. Louis-Sylvestre C, Clough K, Asselain B, Vilcoq JR, Salmon RJ, Campana F, Fourquet A. Axillary treatment in conservative management of operable breast cancer: dissection or radiotherapy? Results of a randomized study with 15 years of follow-up. J Clin Oncol. 2004 Jan 1;22(1):97-101
635. Lu W, de Bock GH, Schaapveld M, Baas PC, Wiggers T, Jansen L. The value of routine physical examination in the follow up of women with a history of early breast cancer. Eur J Cancer 2010 Dec 2. [Epub ahead of print]
636. Lu WL, Jansen L, Post WJ, Bonnema J, Van de Velde JC, De Bock G. Impact on survival of early detection of isolated breast recurrences after the primary treatment for breast cancer: a meta-analysis. Breast Cancer Res Treat. 2009; 114 (3): 403-412.
637. Lück HJ, Thomssen C, Untch, et al: Multicentric phase III study in first line treatment of advanced metastatic breast cancer (ABC): epirubicin/paclitaxel (ET) vs epirubicin/cyclophosphamide (EC): A study of the AGO Breast Cancer Group. Proc Am Soc Clin Oncol 19:73a, 2000 (abstr 280)
638. Ludwig Breast Cancer Study Group. Randomised trial of chemo-endocrine therapy, endocrine therapy, and mastectomy alone in postmenopausal patients with operable breast cancer and axillary node metastasis. Lancet 1984; 1:1256–60.
639. Lumachi F, Ermani M, Brandes AA, Boccagni P, Polistina F, Basso SM, et al. Breast complaints and risk of breast cancer. Population-based study of 2,879 self-selected women and long-term follow-up. Biomed Pharmacother 2002; 56: 88-92.
640. Lundin J, Lehtimaki T, Lundin M, Holli K, Elomaa L, Turpeenniemi-Hujanen T, et al. Generalisability of survival estimates for patients with breast cancer--a comparison across two population-based series. Eur J Cancer 2006;42(18):3228-35.
641. M.J.C. van der Sangen, A.C. Voogd, L.V. van de Poll-Franse, V.C.G. Tjan-Heijnen.Mammacarcinoom bij jonge vrouwen: epidemiologie en dilemma's in de behandeling. Ned Tijdschr Geneeskd 2008; 152: 2495-500.

642. Ma H, Hill CK, Bernstein L, Ursin G . Low-dose medical radiation exposure and breast cancer risk in women under age 50 years overall and by estrogen and progesterone receptor status: results from a case-control and case-case comparison. Breast Cancer Res Treat 2008;109:77-90.
643. Machiavelli MR, Romero AO, Perez JE, Lacava JA, Dominguez ME, Rodriguez R, et al. Prognostic significance of pathological response of primary tumor and metastatic axillary lymph nodes after neoadjuvant chemotherapy for locally advanced breast carcinoma. Cancer J Sci Am 1998; 4: 125-31
644. Mackey JR, Paterson A, Dirix LY, et al: Final results of the phase III randomized trialcomparing docetaxel (T), doxorubicin (A) and cyclophosphamide (C) to FAC as first-line chemotherapy (CT) for patients (pts) with metastatic breast cancer (MBC). Proc Am Soc Clin Oncol 21:35a, 2002
645. Madalinska JB, Hollenstein J, Bleiker E, van Beurden M, Valdimarsdottir HB, Massuger LF, et al. Quality-of-life effects of prophylactic salpingo-oophorectomy versus gynecologic screening among women at increased risk of hereditary ovarian cancer. J Clin Oncol 2005; 23: 6890-8.
646. Madalinska JB, van Beurden M, Bleiker EM, Valdimarsdottir HB, Hollenstein J, Massuger LF, et al. The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy. J Clin Oncol 2006; 24: 3576-82.
647. Malhaire C, El Khoury C, Thibault F Athanasiou A, Petrow P, Ollivier L, et al. Vacuum-assisted biopsies under MR-guidance: results of 72 procedures. Eur Radiol 2010;20:1554-62.
648. Malik et al, External-beam radiotherapy in the management of liver metastases,Semin Oncol 2002, 29:196-201)
649. Malmstrom P, Bendahl PO, Boiesen P, Brunner N, Idvall I, Ferno M. S-phase fraction and urokinase plasminogen activator are better markers for distant recurrences than Nottingham Prognostic Index and histologic grade in a prospective study of premenopausal lymph node-negative breast cancer. J Clin Oncol 2001;19(7):2010-9.
650. Malone KE, Begg CB, Haile RW, Borg A, Concannon P, Tellhed L, et al. Population-based study of the risk of second primary contralateral breast cancer associated with carrying a mutation in BRCA1 or BRCA2. J Clin Oncol. 2010; 28(14):2404-10.
651. Malone KE, Begg CB, Haile RW, Borg A, Concannon P, Tellhed L, Xue S, Teraoka S, Bernstein L, Capanu M, Reiner AS, Riedel ER, Thomas DC, Mellemkjaer L, Lynch CF, Boice JD Jr, Anton-Culver H, Bernstein JL. Population-based study of the risk of second primary contralateral breast cancer associated with carrying a mutation in BRCA1 or BRCA2. J Clin Oncol. 2010 May 10;28(14):2404-10.
652. Mamounas E et al Breast Cancer Research and Treatment 2006, vol 100, suppl 1 abstract 49.
653. Mamounas E.P., J. Bryant, B.C. Lembersky, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28. J Clin Oncol 2005;23:3686-96.
654. Mamounas EP, Brown A, Anderson S, Smith R, Julian T, Miller B, Bear HD, Caldwell CB, Walker AP, Mikkelson WM, Stauffer JS, Robidoux A, Theoret H, Soran A, Fisher B, Wickerham DL, Wolmark N. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2005 Apr 20;23(12):2694-702
655. Mandelblatt JS, Cronin KA, Bailey S, Berry DA, Koning de HJ, Draisma G et al. Effects of mammography under different screening schedules: model estimates of potential benefits and harms. Ann Intern Med 2009;151:738-747
656. Mann RM, Hoogeveen YL, Blickman JG, Boetes C. MRI compared to conventional diagnostic work-up in the detection and evaluation of invasive lobular carcinoma of the breast: a review of existing literature. Breast Cancer Res Treat 2008;107:1-14.
657. Mann RM, Loo CE, Wobbes T, Bult P, Barentsz Jo, Gilhuis KGA et al. The impact of preoperative MRI on the re-excision rate in invasive lobular carcinoma of the breast. Breast Cancer Res Treat 2010;119:415-22.
658. Mann RM, Veltman J, Barentsz JO, Wobbes T, Blickman JG, Boetes C. The value of MRI compared to mammography in the assesment of tumour extent in invasive lobular carcinoma of the breast. Eur J Surg Oncol 2008;34:135-42.
659. Marchionni L, Wilson RF, Marinopoulos SS, Wolff AC, Parmigiani G, Bass EB, Goodman SN. Impact of gene expression profiling tests on breast cancer outcomes. Evid Rep Technol Assess (Full Rep) 2008;160:1-105.
660. Margaria E, Chiusa L, Ferrari L, Dal Canton O, Pich A. Therapy and survival in male breast carcinoma: A retrospective analysis of 50 cases. Oncol Rep 2000; 7: 1035-9.
661. Margolin FR, Kaufman L, Jacobs RP, Denny SR, Schrumpf JD. Stereotactic core breast biopsy of malignant microcalcifications: diagnostic yield of cores with and cores without calcifications on specimen radiographs. Radiology 2004; 233: 251-4.
662. Markes M, Brockow T, Resch KL. Exercise for women receiving adjuvant therapy for breast cancer (Review), The Cochrane Library 2007, Issue 1
663. Markiewicz D.A. , K.R. Fox, D.J. Schultz, et al. Concurrent chemotherapy and radiation for breast conservation treatmentr of early-stage breast cancer. The Cancer Journal from Scientific American. 1998; 3: 185-93.
664. Martín M, Ruiz A, Muñoz M, Balil A, García-Mata J, Calvo L Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. Lancet Oncol. 2007; 8: 219-25.
665. Martin M, Seguí, M, Antón A, et al. Adjuvant docetaxel for high-risk node-negative breast cancer. N Engl J Med, 2010, 363:2200-2210.
666. Martin M., A. Rodrigues-Lescure, A. Ruiz, et al.Multicenter, randomized phase II study of adjuvant chemotherapy for node positive breast cancercomparing six cycles of FEC90 versus 4 cycles of FEC90 followed by 8 weekly paclitaxel administrations: interim efficacy analysis of GEICAM 9906 trial. Breast Cancer Res Treat 2005; S20 (abstr 39)
667. Martin M., T. Pienkowski, J. Mackey, et al. Adjuvant docetaxel for node-positive breast cancer., N Engl J Med. 2005;352(22):2302-13.
668. 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. J Clin Oncol. 2005; 23:4265-74
669. Mary C. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive Heart Failure in Older Women Treated With Adjuvant Anthracycline Chemotherapy for Breast Cancer J Clin Oncol, 2007, 25,: 3808-3815
670. Mass-trial: http://www.lrcb.nl/onderzoek/ebh/mass-trial.
671. Matthew J, Crawford DJ, Lwin M, Barwick C, Gash A. Ultrasound-guided, vacuum-assisted excision in the diagnosis and treatment of clinically benign breast lesions. Ann R Coll Surg Engl. 2007;89:494-6.
672. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 2005; 97(3):188-194
673. Mauri D, Pavlidis N, Polyzos NP, Ioannidis JP Survival with aromatase inhibitors and inactivators versus standard

hormonal therapy in advanced breast cancer: meta-analysis. J Natl Cancer Inst. 2006;98:1285-91.
674. Mauriac L , Keshavia A, Debled et al. Predictors of early relapse in postmenopausal women with hormone receptor-positive breast cancer in the BIG 1-98 trial. Ann Oncol 2007;18:859-867
675. Mauriac L, MacGrogan G, Avril A, Durand M, Floquet A, Debled M, Dilhuydy JM, Bonichon F. Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: a unicentre randomized trial with a 124-month median follow-up. Institut Bergonié Bordeaux Groupe Sein (IBBGS). Ann Oncol. 1999;10:47-52
676. May AM, Korstjens I, van Weert E, van den Borne B, Hoekstra-Weebers JE, van der Schans CP, Mesters I, Passchier J, Grobbee DE, Ros WJ. (2009). Long-term effects on cancer survivors' quality of life of physical training versus physical training combined with cognitive-behavioral therapy: results from a randomized trial. Support Care Cancer, 17, 653-663
677. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2006; 15: 1159-69.
678. McCready, T., D. Littlewood, et al. Breast self-examination and breast awareness: a literature review. J Clin Nurs 2005 14(5): 570-8.
679. McGuire SE, Gonzalez-Angulo AM, Huang EH, Tucker SL, Kau SW, Yu TK Strom EA, Oh JL, Woodward WA, Tereffe W, Hunt KK, Kuerer HM, Sahin AA, Hortobagyi GN, Buchholz TA.. Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys 2007; 68(4):1004-1009
680. McNeely ML, Campbell KL, Rowe BH, et al. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. CMAJ 2006; 175(1): 34-41
681. McNeely ML, Campbell KL, Rowe BH, et al. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. CMAJ 2006; 175(1): 34-41McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. BMJ 20
682. McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. BMJ 2000; 321: 624-8.
683. McTiernan A, Irwin M, VonGruenigen V. (2010). Weight, physical activity, diet, and prognosis in breast and gynecologic cancers. Journal of Clinical Oncology, 28, 4074-4080.
684. Meeuwissen PA, Seynaeve C, Brekelmans CT, Meijers-Heijboer HJ, Klijn JG, Burger CW. Outcome of surveillance and prophylactic salpingo-oophorectomy in asymptomatic women at high risk for ovarian cancer. Gynecol Oncol 2005; 97: 476-82.
685. Meinardi M..T, W.T. van der Graaf, et al. Evaluation of long term cardiotoxiciy after epirubicin containing adjuvant chemotherapy and locoregional radiotherapy for breast cancer using various detection techniques. Heart. 2002l; 88:81-2.
686. Meissnitzer M, Dershaw DD, Lee CH et al. Targeted ultrasound of the breast in women with abnormal MRI findings for whom biopsy has been recommended. AJR Am J Roentgenol, 2009;193:1025-9.
687. Mellink, W. A., R. Holland, et al. The contribution of routine follow-up mammography to an early detection of asynchronous contralateral breast cancer. Cancer 1991 67(7): 1844-8.
688. Mendelson EB, Berg WA, Merritt CR. Toward a standardized breast US lexicon. Semin Roentgenol 2001; 36: 217-25.
689. Mendenhall NP, Devine JW, Mendenhall WM, Bland KI, Million RR, Copeland EM. Isolated local-regional recurrence following mastectomy for adenocarcinoma of the breast treated with radiation therapy alone or combined with surgery and/or chemotherapy. Radiother Oncol 1988; 12: 177 85.
690. Merajver SD, Weber BL, Cody R, Zhang D, Strawderman M, Calzone KA, et al. Breast conservation and prolonged chemotherapy for locally advanced breast cancer: the University of Michigan experience. J Clin Oncol 1997; 15: 2873 81.
691. Merajver, S. D. et al. Breast conservation and prolonged chemotherapy for locally advanced breast cancer: the University of Michigan experience. J Clin Oncol 1997 15(8): 2873-81.
692. Metcalfe K, Gershman S, Lynch HT, Ghadirian P, Tung N, Kim-Sing C, Olopade OI, Domchek S, McLennan J, Eisen A, Foulkes WD, Rosen B, Sun P, Narod SA. Metcalfe K, Gershman S, Lynch HT, Ghadirian P, Tung N, Kim-Sing C, Olopade OI, Domchek S, McLennan J, Eisen A, Foulkes WD, Rosen B, Sun P, Narod SA. Predictors of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. British Journal of Cancer , (12 April 2011) | doi:10.1038/bjc.2011.120
693. Meyer, T. J. and M. M. Mark. Effects of psychosocial interventions with adult cancer patients: a meta-analysis of randomized experiments. Health Psychol 1995 14(2): 101-8.
694. Mieog JS, van der Hage JA, van de Velde CJ. Preoperative chemotherapy for women with operable breast cancer. Cochrane Database Syst Rev. 2007;CD005002
695. Miles, D., G. von Minckwitz, and A. D. Seidman. Combination versus sequential single-agent therapy in metastatic breast cancer. Oncologist. 2002; 7: 13-9
696. Miller AB, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50-59 years. J Natl Cancer Inst 2000; 92: 1490-9.
697. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007; 357: 26: 2666-2676.
698. Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbachr et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in pts with previously treated metastatic breast cancer. J Clin Oncol 2005; 23, 792-9
699. Miller KD, Soule SE, Calley C, et al. Randomized phase II trial of the antiangiogenic potential of doxorubicin and docetaxel; primary chemotherapy as Biomarker Discovery Laboratory. Breast Cancer Res Treat 2005; 89: 187–97.Literatuur
700. Millikan RC, Player JS, Decotret AR et al. Polymorphisms in DNA repair genes, medical exposure to ionizing radiation, and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2005; 14: 2326-34.
701. Minckwitz von G; du Bois A; Schmidt M; Maass N; Cufer T; de Jongh FE; Maartense E; Zielinski C; Kaufmann M; Bauer W; Baumann KH; Clemens MR; Duerr R; Uleer C; Andersson M; Stein RC; Nekljudova V; Loibl S. 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. J Clin Oncol. 2009 ;27:1999-2006.
702. Mir O, Berveiller P, Ropert S, Goffinet F, Pons G, Treluyer JM, Goldwasser F. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. Ann Oncol. 2007 Oct 5; (Epub ahead of print)
703. Mitre BK, Kanbour AI, Mauser N. Fine needle aspiration biopsy of breast carcinoma in pregnancy and lactation. Acta Cytol. 1997;41:1121-30
704. Mittendorf EA, Wu Y, Scaltriti M, Meric-Bernstam F, Hunt KK, Dawood S, Esteva FJ, Buzdar AU, Chen H, Eksambi S, Hortobagyi GN, Baselga J, Gonzalez-Angulo AM. Loss of HER2 amplification following trastuzumab-based neoadjuvant systemic therapy and survival outcomes. Clin Cancer Res. 2009;15:7381-8
705. Mlineritsch B, Tausch C, Singer C, Luschin-Ebengreuth G, Jakesz R, Ploner F,Stierer M, Melbinger E, Menzel C, Urbania

A, Fridrik M, Steger G, Wohlmuth P,Gnant M, Greil R; Austrian Breast, Colorectal Cancer Study Group (ABCSG).Exemestane as primary systemic treatment for hormone receptor positive post-menopausal breast cancer patients: a phase II trial of the Austrian Breast and Colorectal Cancer Study Group (ABCSG-17). Breast Cancer Res Treat. 2008 Nov;112(1):203-13
706. Moebus V, Jackisch C, Lueck HJ, Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. J J. Clin Oncol. 2010 10;28(17):2874-80.
707. Mols F, Vingerhoets AJJM, Coebergh JWW, Poll-Franse van de (2009). Well-being, posttraumatic growth and benefit finding in long-term breast cancer survivors. Psychol Health, 24, 583-595.
708. Montgomery DA, Krupa K, Cooke Tg Follow-up inbreast cancer: does routine clinical examination improve outcome? A systematic review of the literature. Br J Cancer 2007 97(12): 1632-41
709. Monticciolo DL, Caplan LS. The American College of Radiology's BI-RADS 3 Classification in a Nationwide Screening Program: current assessment and comparison with earlier use. Breast J 2004; 10: 106-10.
710. Mook S, Knauer M, Bueno-de-Mesquita JM, Retel VP, Wesseling J, Linn SC, Van't Veer LJ, Rutgers EJ. Metastatic potential of T1 breast cancer can be predicted by the 70-gene MammaPrint signature. Ann Surg Oncol. 2010;17(5):1406-13.
711. Mook S, Schmidt MK, Rutgers EJ, van de Velde AO, Visser O, Rutgers SM, Armstrong N, van 't Veer LJ, Ravdin PM. Calibration and discriminatory accuracy of prognosis calculation for breast cancer with the online Adjuvant! program: a hospital-based retrospective cohort study. Lancet Oncol 2009;10:1070-6.
712. Mook S, Schmidt MK, Viale G, Pruneri G, Eekhout I, Floore A, et al. The 70-gene prognosis-signature predicts disease outcome in breast cancer patients with 1-3 positive lymph nodes in an independent validation study. Breast Cancer Res Treat 2009;116: 295-302.
713. Mook S, Schmidt MK, Weigelt B, Kreike B, Eekhout I, van de Vijver MJ, et al. (2010). The 70-gene prognosis signature predicts early metastasis in breast cancer patients between 55 and 70 years of age. Ann Oncol 2010;21: 717-722.
714. Moore HC, Foster RS. Breast cancer and pregnancy. Semin Oncol 2000;27:646-653
715. Moore, HC, Green, SJ, Gralow, JR, et al. Intensive dose-dense compared with high-dose adjuvant chemotherapy for high-risk operable breast cancer: Southwest oncology Group/Intergroup study 9623. J Clin Oncol 2007; 25:1677.
716. Mora EM, et al. Aggressive therapy for locoregional recurrence after mastectomy in stage II and III breast cancer patients. Ann Surg Oncol 1996; 3: 162-8.
717. Morakkabati-Spitz N, Leutner C, Schild H, Traeber F, Kuhl C. Diagnostic usefulness of segmental and linear enhancement in dynamic breast MRI. Eur Radiol 2005;15(9):2010-2017.
718. Moran BJ, Yano H, Al Zahir N, et al. Conflicting priorities in surgical intervention for cancer in pregnancy. Lancet Oncol. 2007; 8: 536-544.
719. Moreno-Aspitia A, Morton RF, Hillman DW, Lingle WL, Rowland KM Jr, Wiesenfeld M, Flynn PJ, Fitch TR, Perez EA. Phase II trial of sorafenib in patients with metastatic breast cancer previously exposed to anthracyclines or taxanes: North Central Cancer Treatment Group and Mayo Clinic Trial N0336. J Clin Oncol 2009;27:11-5
720. Morris, A. D., R. D. Morris, et al. Breast-conserving therapy vs mastectomy in early-stage breast cancer: a meta-analysis of 10-year survival. Cancer J Sci Am 1997 3(1): 6-12.
721. Morrow M, Freedman G. A clinical oncology perspective on the use of breast MR. MRI Clin North Am 2006;14:363-78.
722. Morrow M. Identification of the woman at risk for breast cancer: problem solved? Recent Results Cancer Res 1999; 151: 85-95.
723. Morrow M. Magnetic Resonance Imaging in Breast Cancer. One step forward, two steps back? JAMA 2004; 292:2779-80.
724. Moss HA, Britton PD, Flower CD, Freeman AH, Lomas DJ, Warren RM. How reliable is modern breast imaging in differentiating benign from malignant breast lesions in the symptomatic population? Clin Radiol 1999, 54: 676-82.
725. Moss S, Waller M, Anderson TJ, Cuckle H. Trial Management Group. Randomised controlled trial of mammographic screening in women from age 40: predicted mortality based on surrogate outcome measures. Br J Cancer 2005; 92: 955-60.
726. Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial . Lancet 2006; 368: 2053-60.NABON nota 2008
727. Mouridsen H, Gershanovich M, Sun Y, Perez-Carrion R, Boni C, Monnier A et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer. Results of a phase III study of the international letrozole Breast Cancer Group. J Clin Oncol 2001; 19: 2596-606.
728. Moy L, Slanetz PJ, Moore R, Satija S, Yeh ED, et al. Specificity of mammography and US in the evaluation of a palpable abnormality: retrospective review. Radiology 2002; 225: 176-81.
729. Mueller BA, Simon MS, Deapen D, Kamineni A, Malone KE, Daling JR. Child bearing and survival after breast carcinoma in young women. Cancer 2003;98:131-40
730. Mullen EE, Deutsch M, Bloomer WD. Salvage radiotherapy for local failures of lumpectomy and breast irradiation Radiother Oncol 1997; 42: 25-9.
731. Muller-Schimpfle M, Ohmenhauser K, Stoll P, Dietz K, Claussen CD. Menstrual cycle and age: influence on parenchymal contrast medium enhancement in MR Imaging of the breast. Radiology 1997; 203: 145-9.
732. Muraca L, Leung D, Clark A, Beduz MA, Goodwin P. (2010). Breast cancer survivors: Taking charge of lifestyle choices after treatment. European Journal of Oncology Nursing, Jan 21. [Epub ahead of print].
733. Muss HB, Case LD, Atkins JN, Bearden JD, Cooper MR, Cruz JM, et al. Tamoxifen versus high-dose oral medroxyprogesterone acetate as initial endocrine therapy for patients with metastatic breast cancer: a Piedmont Oncology Association study. J Clin Oncol 1994; 12: 1630-8.
734. N Yamamoto, T Watanabe, N Katsumata, Y Omuro, M Ando, H Fukuda, et al. Construction and validation of a practical prognostic index for patients with metastatic breast cancer J Clin Oncol 1998, 14; 2401-08
735. Nabholtz JM, Buzdar A, Pollak M, Harwin W, Burton G, Mangalik A, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. J Clin Oncol 2000; 18: 3758-3767.
736. Nabholtz JM, Falkson C, Campos D, et al: Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter phase III trial. J Clin Oncol 21:968-975, 2003
737. Nadeem R, Chagla LS, Harris O, Desmond S, Thind R, Flavin A, Audisio RA. Tumour localisation with a metal coil before the administration of neo-adjuvant chemotherapy Breast. 2005;14:403-7
738. Nahleh ZA, Srikantiah R, Safa M, Jazieh AR, Muhleman A, Komrokji R. Male breast cancer in the veterans affairs

population: a comparative analysis. Cancer. 2007 Apr 15;109(8):1471-7.
739. Naik AM, Fey J, Gemignani M, et al: The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: a follow-up study of 4008 procedures. Ann Surg 240:462-468, 2004
740. Namer M, Soler-Michel P, Turpin F, Chinet-Charrot P, de Gislain C, Pouillart P, et al. Results of a phase III prospective, randomised trial, comparing mitoxantrone and vinorelbine (MV) in combination with standard FAC/FEC in front-line therapy of metastatic breast cancer. Eur J Cancer. 2001;37: 1132-40
741. Namer M., P. Fargeot, H. Roché, et al. Improved disease-free survival with epirubicin-based chemoendocrine adjuvant therapy compared with tamoxifen alone in one to three node-positive, estrogen-receptor-positive, postmenopausal breast cancer patients: results of French Adjuvant Study Group 02 and 07 trials. Ann Oncol 2006; 17:65-73
742. Narod SA, Lubinski J, Ghadirian P, Lynch HT, Moller P, Foulkes WD, et al. Hereditary Breast Cancer Clinical Study Group. Screening mammography and risk of breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Lancet Oncol 2006;7:402-6.
743. National Comprehensive Cancer Network (NCCN). NCCN Clini¬cal Practice Guidelines in Oncology: Breast Cancer V.2.2010. Fort Washington, PA: NCCN; 2010.
744. National Institute of Clinical Excellence (NICE) guideline CG 104 Metastatic malignant disease of unknown primary origin (2010). www.nice.org.uk/guidance/CG104.
745. National Institute of Clinical Excellence (NICE) guideline CG41 Familial Breast Cancer 2004 met update in 2006; www.nice.org.uk/CG041.
746. Navrozoglou I, Vrekoussis T, Kontostolis E, et al. Breast cancer during pregnancy: a mini-review. Eur J Surg Oncol 2008; 34 (8):837-43.
747. NCCN clinical practice guidelines in clinical oncology. v.2.2010;2010. Available from: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf.
748. NCCN Clinical Practice Guidelines, breast cancer, chemotherapy, breast-conserving therapy, adjuvant therapy, mastectomy, endocrine therapy, radiation, therapy, lobular carcinoma in situ, ductal carcinoma in situ.JNCCN 2009;7:122–192
749. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the US preventive Task Force. Ann Intern Med 2009; 151: 727-37.
750. Newell SA, Sanson-Fisher RW, Savolainen NJ. (2002). Systematic review of psychological therapies for cancer patients: overview and recommendations for future research.J Natl Cancer Inst, 94, 558-584.
751. Newman EA,Cimmino VM, Sabel, MS et al. Lymphatic mapping and sentinellymph node biopsy for patients with local recurrence after breast-conservation therapy Ann Surg Oncol 2006;13: 52-7
752. Newman L, Hunt K, Buchholz T, Kuerer H, Vlastos G, Mirza N, et al. Presentation, management and outcome of axillary recurrence from breast cancer. Am J Surg 2000; 180: 252 6.
753. Newman LA, Hunt KK, Buchholz T, Kuerer HM, Vlastos G, Mirza N, Ames FC, Ross MI, Singletary SE. Presentation, management and outcome of axillary recurrence from breast cancer. Am J Surg. 2000 Oct;180(4):252-6
754. NHSBSP Publication No 54. Review of Radiation Risk in Breast Screening. 2003. www.cancerscreening.nhs.uk.
755. Ni Mhuireachtaigh R, O'Gorman DA. Anesthesia in pregnant patients for nonobstectric surgery. J Clin Anesth. 2006; 18: 60-66.
756. Nicklas A, Baker M. Imaging strategies in pregnant patients. Semin Oncol 2000 ;27:623-632
757. Nieto Y, Shpall E. High-dose chemotherapy fot high-risk primary and metastatic breast cancer: Is another look warranted? Curr opin Oncol 2009, 21: 150-157
758. Nishimura R, Nagao K, Miyayama H, Yasunaga T, Asao C, Matsuda Y, et al. Diagnostic problems of evaluating vertebral metastasis from breast cancer with a higher degree of malignancy. Cancer 1999; 85: 1782-8
759. Nitz U.A., S. Mohrmann, J. Fischer, et al. Comparison of rapidly cycled tandem high-dose chemotherapy plus peripheral-blood stem-cell support versus dose-dense conventional chemotherapy for adjuvant treatment of high-risk breast cancer: results of a multicentre phase III trial. Lancet 2005; 366:1935.
760. Noroozian M, Gombos EC, Chikarmane S, Georgian-Smith D, Raza S, Denison CM et al. Factors that impact the duration of MRI-guided core needle biopsy. AJR Am J Roentgenol 2010;194:W150-57.
761. Norum J, Andreassen T. Screening for metastatic disease in newly diagnosed breast cancer patients. What is cost-effective? Anticancer Res 2000; 20: 2193-6
762. Nowak A.K. , N.R. Wilcken, Stockler, et al. Systematic review of taxane-containing versus non-taxane-containing regimens for adjuvant and neoadjuvant treatment of early breast cancer. Lancet Oncol 2004; 5: 372-80.
763. Nunes LW, Schnall MD, Orel SG. Update of breast MR imaging architectural interpretation model. Radiology 2001; 219: 484-94.
764. 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;20:2812–2823.
765. O'Shaugnessy JA, Brufsky AM. RiBBON 1 and RiBBON 2: phase III trials of bevacizumab with standard chemotherapy for metastatic breast cancer. Clin Breast Cancer 2008;8:373.O'Shaughnessy JA, Osborne C, Pippen JE, Yoffe M, Patt D, Rocha C,Iniparib plus chemotherapy in metastatic triple-negative breast cancer. N Engl J Med. 2011 ;364:205-14. Epub 2011 Jan 5.
766. Oakman c, Sapino a, Marchio c et al. Chemotherapy with or without trastuzumab. Ann Oncol 2010: 21 (suppl 21) 112-119
767. Obdeijn IM, Brouwers-Kuyper EM, Tilanus-Linthorst MM, Wiggers T, Oudkerk M. MR imaging-guided sonography followed by fine-needle aspiration cytology in occult carcinoma of the breast. Am J Roentgenol 2000; 174: 1079-84.
768. Obedian E., et al. Second malignancies after treatment of early-stage breast cancer: lumpectomy and radiation therapy versus mastectomy. J Clin Oncol 2000 18(12): 2406-12.
769. O'Brien ME, Wigler N, Inbar M, Rosso R, Grischke E, Santoro A Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol. 2004;15: 440-9
770. Oei AL, Massuger LF, Bulten J, Ligtenberg MJ, Hoogerbrugge N, de Hullu JA. Surveillance of women at high risk for hereditary ovarian cancer is inefficient. Br J Cancer 2006; 94: 814-9.
771. Oestreicher N, Lehman CD, Seger DJ, Buist DS, White E. The incremental contribution of clinical breast examination to invasive cancer detection in a mammography screening program. Am J Roentgenol 2005; 184: 428-32.
772. Oh JL, Nguyen G, Whitman GJ, Hunt KK, Yu TK, Woodward WA, Tereffe W, Strom EA, Perkins GH, Buchholz TA. Placement of radiopaque clips for tumor localization in patients undergoing neoadjuvant chemotherapy and breast conservation therapy. Cancer. 2007; 110:2420-7
773. Oktay K, Cil AP, Bang H: Efficiency of oocyte cryopreservation: a meta-analysis. Fertility and Sterility 2006;86:70-80

774. Oktay K, Sonmezer M, Oktem O, Fox K, Emons GBang H. Absence of conclusive evidence for the safety and efficacy of gonadotropin-releasing hormone analogue treatment in protecting against chemotherapy-induced gonadal injury. Oncologist 2007;12:1055-66.
775. Oktay K: Further evidence on the safety and success of ovarian stimulation with letrozole and tamoxifen in breast cancer patients undergoing in vitro fertilization to cryopreserve their embryos for fertility preservation. J Clin Oncol 2005;23:3858-9
776. Ökzüzoglu B, Güler N, An infertile patient with breast cancer who delivered a healthy child under adjuvant tamoxifen therapy. Eur J Obstet Gynecol Reprod Biol 2002;104:79
777. Olivotto IA, Bajdik CD, Ravdin PM, Speers CH, Coldman AJ, Norris BD, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. J Clin Oncol 2005;23(12):2716-25.
778. Olson JA Jr, Morris EA, Van Zee KJ, Linehan DC, Borgen PI. MRI facilitates breast conservation for occult breast cancer. Ann Surg Oncol 2000; 7: 411-5.
779. Olson JE, Neuberg D, Pandya KJ, Richter MP, Solin LJ, Gilchrist KW, et al. The role of radiotherapy in the management of operable locally advanced breast carcinoma: results of a randomized trial by the Eastern Cooperative Oncology Group. Cancer 1997; 79: 1138-49
780. Osborn RL, Demoncada AC, Feuerstein M. (2006). Psychosocial interventions for depression and anxiety, and quality of life in cancer survivors: Meta-analyses. Int J Psych Med, 36, 13-34.
781. Osborne CK, Pippen J, Jones SE, Parker LM, Ellis M, Come S, et al. Double-blind, randomised trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol 2002; 20: 3386-95.
782. Osborne MP, Simmons RM, Salvage surgery for recurrence after breast conservation. World J Surg 1994; 18: 93-7.
783. Osteen RT. Risk factors and management of local recurrence following breast conservation surgery. World J Surg 1994; 18: 76-80.
784. Osteoporose.Tweede herziene richtlijn. Utrecht: Kwaliteitsinstituut voor de Gezondheidszorg CBO; van Zuiden Communications, Alphen aan den Rijn, 2002.
785. Otten JDM, Broeders MJM, Fracheboud J, Otto SJ, Koning de HJ, Verbeek ALM. Impressive time-related influence of the Dutch screening programme on breast cancer incidence and mortality 1076-2006. Int J Cancer 2008;123:1929-34.
786. Otten JDM, Broeders MJM, Heeten den GJ, Holland R, Fracheboud J, Koning de HJ et al. Life expectancy of screen-detected invasive breast cancer patients compared with women invited to the Nijmegen screening program. Cancer 2010,116:586-91.
787. Ottini L, Palli D, Rizzo S, Federico M, bazan V, Russo A. Male breast cancer. Crit Rev Oncology Hematology 2010;73:141-55.
788. Otto SJ, Fracheboud J, Looman CW, Broeders MJ, Boer R, Hendriks JH, et al. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 2003;361:1411-7.
789. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997; 337: 949 55.
790. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant Tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999; 353: 1641-8
791. Paap E, Verbeek AL, Puliti D, Paci E, Broeders MJ. Breast cancer screening case-control study design: impact on breast cancer mortality. Ann Oncol 2010 Epub Oct 5.
792. Pagani O, O'Neill A, Castiglione M, Gelber RD, Goldhirsch A, Rudenstam CM. et al. Prognostic impact of amenorrhea after adjuvant chemotherapy in premenopausal breast cancer patients with axillary node involvement: results of the IBCSG trial VI. Eur J Cancer 1998; 34: 632-40.
793. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351(27):2817-26.
794. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006;24(23):3726-34.
795. Pant S, Landon MB, Blumenfeld M et al. Treatment of breast cancer with trastuzumab during pregnancy. J Clin Oncol 2008; 26(9):1567-9;
796. Papaioannou A, Lissaios B, Vasilaros S, Miligos S, Papadimitriou G, Kondilis D, et al. Pre- and postoperative chemoendocrine treatment with or without postoperative radiotherapy for locally advanced breast cancer. Cancer 1983; 51: 1284-90
797. Paredes JP, Puente JL, Potel J. Variations in sensitivity after sectioning the intercostalbrachial nerve. Am J Surg 1990;5:525-8
798. Paridaens R, Therasse P, Dirix L, Beex L, Piccart M, Cameron D. First-line hormonal treatment for metastatic breast cancer with exemestane or tamoxifen in postmenopausal patients- A randomized phase III trial of the EORTC Group. J Clin Oncol 2008; 26: 4883-90
799. Paridaens RJ, Gelber S, Cole BF Adjuvant! Online estimation of chemotherapy effectiveness when added to ovarian function suppression plus tamoxifen for premenopausal women with estrogen-receptor-positive breast cancer. Breast Cancer Res Treat. 2010;123:303-10.
800. Park YH, Kim ST, Cho EY et al. A risk stratification by hormonal receptors (ER, PgR) and HER-2 status in small (< or = 1 cm) invasive breast cancer: who might be possible candidates for adjuvant treatment? Breast Cancer Res Treat 2010;
801. Park, C. C., M. Mitsumori, et al. Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: influence of margin status and systemic therapy on local recurrence. J Clin Oncol 2000 18(8): 1668-75.Pennery E, Mallet J: A preliminary study of patients' perceptions of routine follow-up after treatment for breast Cancer. Eur J Oncol Nurs 2000, 4(3):138-145; discussion 146-137.
802. Parker JS, Mullins M, Cheang MC et al Supervised risk predictor of breast cancer based on intrinsic subtypes. J Clin Oncol 2009 27(8):1160–1167
803. Partridge AH, Gelber S, Peppercorn J, Sampson E, Knudsen K, Laufer M, Rosenberg R, Przypyszny M, Rein A, Winer EP: Web-based survey of fertility issues in young women with breast cancer. J Clin Oncol 2004;22:4174-83
804. Paskett, ED, Herndon JE, Day JM, Stark NN, Winer EP, Grubbs SS, Pavy MD, Shapiro CL, List MA, Hensley ML, Naughton MA, Kornblith AB, Habin KR, Fleming GF, Bittoni MA. (2008). Applying a conceptual model for examining health-related quality of life in long-term breast cancer survivors: CALGB study 79804. Psychooncology, 17, 1108-1120.
805. Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, Mohiuddin M, Young B Direct decompressive surgical

resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet. 2005 26; 366 :643-8.
806. Patterson RE, Cadmus LA, Emond JA, Pierce JP. Physical activity, diet, adiposity and female breast cancer prognosis: a review of the epidemiologic literature. Maturitas. 2010;66:5-15
807. Pavlakis N, Schmidt RL, Stockler M. Bisphosphonates for breast cancer. The Cochrane Database of Systematic Reviews 2005, Issue 3. CD003474.pub2. DOI: 10.1002/ 14651858. CD003474.
808. Pavlides N, Pentheroudakis G. The pregnant mother with breast cancer: Diagnostic and therapeutic management. Cancer Treat Rev 2005;31:439-47
809. Pengel KE, Loo CE, Teertstra HJ, Muller SH, Wesseling, Peterse JL et al.The impact of preoperative MRI on breast-conserving surgery of invasive cancer: a comparive cohort study. Breast Cancer Res Treat 2009;116:161-9.
810. Peralta EA, Ellenhorn JD, Wagman LD, Dagis A, Andersen JS, Chu DZ. Contralateral prophylactic mastectomy improves the outcome of selected patients undergoing mastectomy for breast cancer. Am J Surg 2000; 180: 439-45.
811. Perez E, Moreno-Aspitia, Thompson E et al. Adjuvant therapy of triple negative breast cancer. Breast Cancer Res treat. 2010, 120:285-291
812. Perlet C, Heywang-Kobrunner SH, Heinig A, Sittek H, Casselman J, Anderson I, et al. Magnetic Resonance-Guided, Vacuum-assisted breast biopsy. Cancer 2006; 106: 982-90.
813. Perloff M, Lesnick GJ, Korzun A, Chu F, Holland JF, Thirlwell MP, et al. Combination chemotherapy with mastectomy or radiotherapy for stage III breast carcinoma: a Cancer and Leukemia Group B study. J Clin Oncol 1988; 6: 261-9
814. Perre CI, Hoefnagel CA, Kroon BB, Zoetmulder FA, Rutgers EJ. Altered lymphatic drainage after lymphadenectomy or radiotherapy of the axilla in patients with breast cancer. Br J Surg 1996; 83: 1258.
815. Peter Kenemans, Nigel J Bundred, Jean-Michel Foidart, Ernst Kubista, Bo von Schoultz, Piero Sismondi, Rena Vassilopoulou-Sellin, Cheng Har Yip, Jan Egberts, Mirjam Mol-Arts, Roel Mulder, Steve van Os, Matthias W Beckmann and on behalf of the LIBERATE Study Group. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. The Lancet Oncology, Volume 10, Issue 2, February 2009, Pages 135-146.
816. Peters NH, Borel Rinkes IH, Zuithoff NP, Mali WP, Moons KG, Peeters PH. Meta-analysis of MR-imaging in the diagnosis of breast lesions. Radiology 2008;246:116-24.
817. Peters NH, Meeuwis C, Bakker CJ, Mali WP, Fernandez-Gallardo AM, van Hillegersberg R, et al. Feasibility of MRI-guided large-core-needle biopsy of suspicious breast lesions at 3T. Eur Radiol 2009;19:1639-44.
818. Peters W.P. , G. Rosner, J. Vredenburgh, et al. Updated results of a prospective, randomised comparison of two doses of combination alkylating agents (AA) as consolidation after CAF in high-risk primary breast cancer involving ten or more axillary lymphnodes (LN): CALGB 9082/SWOG 9114/NCIC Ma-13. Proc Am Soc Clin Oncol 2001; 20: 81.
819. Peters, WP, Rosner, GL, Vredenburgh, JJ, et al. Prospective, randomized comparison of high-dose chemotherapy with stem-cell support versus intermediate-dose chemotherapy after surgery and adjuvant chemotherapy in women with high-risk primary breast cancer: a report of CALGB 9082, SWOG 9114, and NCIC MA-13. J Clin Oncol 2005; 23:2191.
820. Petrek JA, Moore A. Breast cancer treatment in pregnant or postpartum women and subsequent pregnancy in breast cancer survivors. In: Harris JR, Lippman ME, Morrow M, Osborne CK eds. Diseases of the Breast. 3rd ed. Lippincott: Williams and Wilkins, Philadelphia, USA, 2004, pp. 691-701
821. Petrek JA, Naughton MJ, Case LD, Paskett ED, Naftalis EZ, Singletary SE, et al. Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study. J Clin Oncol 2006;24:1045-51.
822. Piccart M., A. Di Leo, A. Beauduin A, et al. Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide , methotrexate and fluorouracil in node-positive breast cancer, J Clin Oncol 2001;19: 3103–3110.
823. Piccart MJ, de Valeriola D, Paridaens R, Balikdjian D, Mattheiem WH, et al. Six-year results of a multimodality treatment strategy for locally advanced breast cancer. Cancer 1988; 62: 2501-6.
824. Piccart-Gebhart MJ, Burzykowski T, Buyse M, Sledge G, Carmichael J, Luck HJ et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. J Clin Oncol 2008, 26: 1980-6.
825. Piedbois P, Serin D, Priou F, et al. Dose-dense adjuvant chemotherapy in node-positive breast cancer: docetaxel followed by epirubicin/cyclophosphamide (T/EC), or the reverse sequence (EC/T), every 2 weeks, versus docetaxel, epirubicin and cyclophosphamide (TEC) every 3 weeks. AERO B03 randomized phase II study. Ann Oncol 2007; 18: 52–57.
826. Pierce L.J., L.F. Hutchins, S.R. Green, et al. Sequencing of tamoxifen and radiotherapy after breast-conserving surgery in early-stage breast cancer. J Clin Oncol. 2005 Jan 1;23(1):24-9.
827. Pierce LJ, Lippman M, Ben-Baruch N, Swain S, O'Shaughnessy J, Bader JL, et al. The effect of systemic therapy on local-regional control in locally advanced breast cancer. Int J Radiat Oncol Biol Phys 1992; 23: 949-60
828. Pisani P, Parkin DM, Ngelangel C, Esteban D, Gibson L, Munson M, et al. Outcome of screening by clinical examination of the breast in a trial in the Philippines. Int J Cancer 2006; 118: 149-54.
829. Pitceathly C, Maguire P. (2003). The psychological impact of cancer on patients' partners and other key relatives: a review. Eur J Cancer, 39, 1517-1524.
830. Poggi MM, Danforth DN, Sciuto LC, Smith SL, Steinberg SM, Liewehr DJ, Menard C, Lippman ME, Lichter AS, Altemus RM. Eighteen year results in the treatment of early breast carcinoma with mastectomy versus breast conservation therapy: the National Cancer Institute Randomized Trial. Cancer. 2003 Aug 15;98(4):697-702
831. Powles T, Paterson A, McCloskey E, Schein P, Scheffler B, Tidy A, Ashley S, Smith I, Ottestad L, Kanis J. Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026]. Breast Cancer Res. 2006;8(2):R13.
832. Praga C., J. Bergh, et al. Risk of acute myeloid leukaemia and myelodysplastic syndrome in trials of adjuvant epirubicin for early breast cancer: correlation with doses of epirubicin and cyclophosphamide. J Clin Onc 2005; 23;4179-91.
833. Preda L, Villa G et al. MRI in the evaluation of recurrence at the prior lump site after conservative surgery and radiotherapy. Breast Cancer Res 2006;8(5)
834. Press MF, Cordon-Cardo C, Slamon DJ, Expression of the HER-2/neu proto-oncogene in normal human adult and fetal tissues. Oncogene 1990;5(7):953-62.
835. Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD Jr. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. Radiat Res 2002; 158: 220-35. Erratum in: Radiat Res 2002; 158: 666.
836. Pritchard K.L., A. H. Paterson, S.Fine, et al. Randomized trial of cyclophosphamide, methotrexate, and fluorouracil chemotherapy added to tamoxifen as adjuvant therapy in postmenopausal women with node-positive estrogen and/or progesterone receptor-positive breast cancer: a report of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1997; 15: 2302–11.

837. Prochazka M, Hall P, Granath F, Czene K. Family history of breast cancer and young age at diagnosis of breast cancer increase risk of second primary malignancies in women: a population-base cohort study. Brit J Cancer 2006; 95: 1291-5
838. Puhalla S, Mrozek E, Young D, et al. Randomized phase II adjuvant trial of dose-dense docetaxel before or after doxorubicin plus cyclophosphamide in axillary node-positive breast cancer. J Clin Oncol 2008; 26: 1691–97.
839. Qaseem A, Snow V, Sherif K, Aronson M, Weiss KB, Owens DK. Screening mammography in women 40-49 years of age: a clinical practice guideline form the American College of Physicians. Ann Intern Med 2007; 146: 511-5.
840. Raatgever M. De meerwaarde van de nurse practitioner Oncologica 2002; 1: 26-8.
841. Rabin C. (2009). Promoting Lifestyle Change Among Cancer Survivors: When Is the Teachable Moment? American Journal of Lifestyle Magazine, 3, 369-378
842. Rades D, Bohlen G, Pluemer A, Veninga T, Hanssens P, Dunst J, et al. Stereotactic radiosurgery alone versus resection plus whole-brain radiotherapy for 1 or 2 brain metastases in recursive partitioning analysis class 1 and 2 patients. Cancer 2007;109(12):2515-21.
843. Rades D, Heidenreich F, Karstens JH. Final results of a prospective study of the prognostic value of the time to develop motor deficits before irradiation in metastatic spinal cord compression. Int J Radiat Oncol Biol Phys 2002;53:975-9.
844. Rades D, Veninga T, Stalpers LJ, Schulte R, Hoskin PJ, Poortmans P, et al. Prognostic factors predicting functional outcomes, recurrence-free survival, and overall survival after radiotherapy for metastatic spinal cord compression in breast cancer patients. Int J Radiat Oncol Biol Phys 2006;64:182-8.
845. Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, Knowling MA, Coppin CM, Weir L, Gelmon K, Le N, Durand R, Coldman AJ, Manji M. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst. 2005 Jan 19;97(2):116-26
846. Rakkhit R, Broglio K, Peintinger F et al. Significant increased recurrence rates among breast cancer patients with HER2-positive, T1a,bN0M0 tumors. Cancer Res 2009; 69: abstract 701.
847. Rangan, A. M., V. Ahern, et al. Local recurrence after mastectomy and adjuvant CMF: implications for adjuvant radiation therapy. Aust N Z J Surg 2000 70(9): 649-55.
848. Rao R, Lilley L, Andrews V, Radford L, Ulissey M.Axillary staging by percutaneous biopsy: sensitivity of FNA versus core needle biopsy. Ann Surg Oncol 2009;16:1170-5.
849. Rauschecker H, Clarke M, Gatzemeier W, Recht A. Systemic therapy for treating locoregional recurrence in women with breast cancer, Cochrane Database Syst Rev. 2001;(4):CD002195
850. Ravardi-Kashani F, Hayers TG. Male breast cancer: a review of the literature. Eur J Cancer 1998; 34: 1341 7.
851. Ravdin PM, Siminoff LA, Davis GJ, Mercer MB, Hewlett J, Gerson N, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol 2001;19(4):980-91.
852. Rayan G, Dawson LA, Bezjak A, Lau A, Fyles AW, Yi QL, et al. Prospective comparison of breast pain in patients participating in a randomized trial of breast-conserving surgery and tamoxifen with or without radiotherapy. Int J Radiat Oncol Biol Phys 2003; 55: 154-61
853. Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. 2005;23(31):7804-10. Epub 2005 Oct 11.
854. Rebbeck TR, Kauff, ND, Domcheck SM. Meta-analysis of Risk Reduction Estimates Associated Risk-Reducing Salpingo-oophorectomy in BRCA1 or BRCA2 Mutation Carriers. J Natl Cancer Inst 2009; 101;80-87
855. Recht A, Silen W, Schnitt SJ, Conolly JL, Gelman RS, Rose MA, et al. Time course of local recurrence following conservative surgery and radiotherapy for early stage breast cancer. Int J Radiat Oncol Biol Phys 1988; 15: 255-61.
856. Recht A. Locally advanced breast cancer and postmastectomy radiotherapy. Surg Oncol Clin N 2000; 9: 603-20
857. Recht, A., W. Silen, et al. Time-course of local recurrence following conservative surgery and radiotherapy for early stage breast cancer. Int J Radiat Oncol Biol Phys 1988 15(2): 255-61.
858. Reynolds HY. Diagnostic and management strategies for diffuse interstitial lung disease. Review. Chest 1998; 113: 192-202.
859. Rieber A, Merkle E, Zeitler H, Gorich J, Kreienberg R, Brambs HJ, et al. Value of MR Mammography in the detection and exclusion of recurrent breast carcinoma. J Comput Assist Tomogr 1997; 21: 780-4.
860. Rieber A, Schramm K et al. Breast conserving surgery and autogenous tissue reconstruction in patients with breast cancer: efficacy of MRI of the breast in the detection of recurrent disease. Eur Radiol 2003;13(4):780-7.
861. Rijnsburger AJ, Obdeijn IM, Kaas R, Tilanus-Linthorst MM, Boetes C, Loo CE, et al. BRCA1-Associated Breast Cancers Present Differently From BRCA2-Associated and Familial Cases: Long-Term Follow-Up of the Dutch MRISC Screening Study. J Clin Oncol. 2010 Epub Nov 15.
862. Rijnsburger, A.J., et al., Impact of screening for breast cancer in high-risk women on health-related quality of life. British Journal of Cancer, 2004; 91(1): 69-76.
863. Ring AE, Smith IE, Ellis PA. Breast cancer and pregnancy. Ann Oncol Ann Oncol 2005;16:1855-60
864. Ring AE, Smith IE, Jones A, Shannon C, Galani E, Ellis P. Chemotherapy for breast cancer during pregnancy. An 18-year experience from five London teaching hospitals. J Clin Oncol 2005;23:4192-7
865. Rivera CM, Grossardt BR, Rhodes DJ, Brown RD Jr, Roger VL, Melton LJ 3rd, Rocca WA. Increased cardiovascular mortality after early bilateral oophorectomy. Menopause. 2009 Jan-Feb;16(1):15-23.
866. RIVM Beleidskader Bevolkingsonderzoek Borstkanker. RIVM Briefrapport 225111001/2008, RIVM-Bilthoven-the Netherlands: www.rivm.nl
867. RIVM rapport 86102002/2003, Ionizing radiation exposure in the Netherlands. RIVM-Bilthoven-the Netherlands 2003: www.rivm.nl
868. Robinson E, Rennert G, Bar-Deroma R, Dori DL, Neugut AI. The pattern of diagnosis of a second primary tumor in the breast. Breast Cancer Res Treat. 1993;25(3):211-5
869. Roche H., P. Fumoleau, M. Spielmann, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positieve breast cancer patients: the FNCLCC PACS 01 trial. J Clin Oncol 2006; 24:5664-71.
870. Roche H., P. Viens, P. Biron, et al. High-dose chemotherapy for breast cancer: the French PEGASE experience. Cancer Control. 2003; 10: 42-7.
871. Rodenhuis S, Richel DJ, van der Wall E, Schornagel JH, Baars JW, Koning CC, et al. Randomised trial of high-dose chemotherapy and haemopoietic progenitor-cell support in operable breast cancer with extensive axillary lymph-node involvement. Lancet 1998; 352: 515-21.
872. Rodenhuis S., M. Bontenbal, L.V. Beex, et al. On behalf of the Netherlands Working Party on Autologous Transplantation in Solid Tumors. High-dose chemotherapy with hematopoietic stem-cell rescue for high-risk breast cancer. N Engl J Med 2003; 349: 7-16.

873. Rodenhuis S., M. Bontenbal, O.G. van Hoesel, et al. Efficacy of high-dose alkylating chemotherapy in HER2/neu-negative breast cancer. Ann Oncol 2006; 17;588-96.
874. Rodger A, Jack WJ, Hardman PD, Kerr GR, Chetty U, Leonard RC. Locally advanced breast cancer: report of phase II study and subsequent phase III trial. Br J Cancer 1992; 65: 761-5
875. Rodriguez-Wallberg KA, Oktay K. Fertility preservation in women with breast cancer. Clin Obstet Gynecol 2010;53: 753-62.
876. Rojas MP, et al. Follow-up strategies for women treated for early breast cancer (Cochrane Review). In: The Cochrane Library, 2005.
877. Romond E., E.A. Perez, J. Bryant, et al. Doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab as adjuvant therapy for patients with HER-2 positive operable breast cancer: combined analysis of NSABP-B31/NCCTG-N9831. N Engl J Med 2005 353:1673-84.
878. Roodman GD. Mechanisms of bone metastasis. N Engl J Med 2004; 350: 1655-64.
879. Rose, M. A., I. C. Henderson, et al. Premenopausal breast cancer patients treated with conservative surgery, radiotherapy and adjuvant chemotherapy have a low risk of local failure. Int J Radiat Oncol Biol Phys 1989 17(4): 711-7.
880. Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer 2003; 98:1735-44
881. Rosselli Del Turco M, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. Jama 1994;271(20):1593-7.
882. Roumen RMH, Kuijt GP, Liem IH. Lymphatic mapping and sentinel node harvesting in patients with recurrent breast cancer Eur J Surg Oncol 2006;
883. Rowland JH, Meyerowitz BE, Crespi CM, Leedham B, Desmond K, Belin TR, Ganz PA. (2009). Addressing intimacy and partner communication after breast cancer: a randomized controlled group intervention. Breast Cancer Res Treat., 118, 99-111.
884. Rubens RD, Bartelink H, Engelsman E, Hayward JL, Rotmensz N, Sylvester R, et al. Locally advanced breast cancer: the contribution of cytotoxic and endocrine treatment to radiotherapy. An EORTC Breast Cancer Cooperative Group Trial (10792). Eur J Cancer Clin Oncol 1989; 25: 667 78
885. Russell JR, Stabin MG, Sparks RB, Watson E. Radiation absorbed dose to the embryo/fetus from radiopharmaceuticals. Health Phys 1997;73:756-769
886. Rutgers EJ, van Rossum AB, Peterse JL, Cohen P, Borger JH, Kemperman HW Breast-conserving therapy for invasive carcinoma: diagnosis of local recurrence. Neth J Surg 1991; 43: 110-3.
887. Rutgers EJTh, van Slooten EA, Kluck HH. Follow-up after treatment of primary breast cancer. Br J Surg 1989(2); 76: 187-90.
888. Ryberg M, Nielsen DL, Cortese G, Nielsen P, Andersen PK, Skovsgaard T et al. Epirubicin cardiac toxicity: A retrospective analysis of 1097 pts treated for metastatic breast cancer. Proceedings of Am Soc Clin Oncol 2007, 25, 18S, A1029.
889. Ryttov N, Holm NV, Ovist N, Blichert-Toft M. Influence of adjuvant irradiation on the development of late arm lymphedema and impaired shoulder mobility after mastectomy for carcinoma of the breast. Acta Oncol 1988; 27: 667-70
890. Saarto 2004
891. Salhab M, Al Sarakbi W, Mokbel K. In vitro fertilization and breast cancer risk: a review. Int J Fertil Womens Med 2005; 50: 259-66.
892. Salvadori B, Marubini E, Miceli R, Conti AR, Cusumano F, Andreola S, et al. Reoperation for locally recurrent breast cancer in patients previously treated with conservative surgery. Br J Surg 1999; 86: 84-7.
893. Samant R, Ganguly P. Staging investigations in patients with breast cancer: the role of bone scans and liver imaging. Arch Surg 1999; 134: 551-3
894. Samarel, N., J. Fawcett, et al. Effect of support groups with coaching on adaptation to early stage breast cancer. Res Nurs Health 1997 20(1): 15-26.
895. Santen RJ, Mansel R. Benign breast disorders. N Engl J med 2005;353:275-85.
896. Sardanelli F, Giuseppetti GM, Panizza P, Bazzocchi M, Fausto A, Simonetti G, et al. Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in fatty and dense breasts using the whole-breast pathologic examination as a gold standard. Am J Roentgenol 2004; 183: 1149-57.
897. Sardanelli F, Podo F, D'Agnolo G, Verdecchia A, Santaquilani M, Musumeci R et al. Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT study): interim results. Radiology 2007;242:698-715
898. Sardi A, Eckholdt G, McKinnon WM, Bolton JS The significance of mammographic findings after breast-conserving therapy for carcinoma of the breast. Surg Gynecol Obstet 1991; 173: 309-12.
899. Satram-Hoang S, Ziogas A, Anton-Culver H. Risk of second primary cancer in men with breast cancer. Breast Cancer Res. 2007;9(1):R10.
900. Saunders CM, Baum M. Breast cancer and pregnancy. J R Soc Med, 1993;86:162-5
901. Schaake-Koning CCE, Hamersma-Van der Linden EH, Hart AAM, Engelsman E. Adjuvant chemo- and hormonal therapy in locally advanced breast cancer: a randomised clinical study. Int J Radiat Oncol Biol Phys 1985; 11: 1759-63
902. Schaapveld M, Visser O, Louwman M et al. Risk of new primary nonbreast cancers after breast cancer treatment: a Dutch population-based study. J Clin Oncol. 2008 2008,10;26(8):1239-46
903. Schinkelshoek M, Guinee N, Hohner S, Zandveld C, Wagenaar RC. Vroege versus late start van fysiotherapie na een mammaprocedure met OKD. Research synthese en landelijke enquête. Ned T Fysiother 1998; 108: 120-7
904. Schlooz-Vries, M.S., M. Raatgever, J.P. Versluis, A. Hennipman, I.H.M. Borel Rinkes (2000). Patiënten tevreden over nurse practitioner. Duidelijke verbeteringen op chirurgische mammapolikliniek.;Medisch contact 55: 48 – 50.
905. Schnall MD, Blume J, Bleumke 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. J Sug Oncol 2005;92:32-8.
906. Schopper D, de Wolf C. How effective are breast cancer screening programmes by mammography? Review of current evidence. Eur J Cancer 2009;45:1916-23.
907. Schouten van der Velden AP, Schlooz-Vries MS, Boetes C, Wobbes T Magnetic resonance imaging of ductal carcinoma in situ: what is its clinical application? A review. Am J Surg 2009;198:262-9.
908. Schrading S, Simon B, Braun M, Wardelmann E, Schild HH, Kuhl CK. MRI-guided breast biopsy: influence of choice of vacuum biopsy system on the mode of biopsy of MRI-only suspicious breast lesions. AJR Am J Roentgenol 2010 194:1650-7.
909. Schrama J, Faneyte,I Schornagel, J al. Randomized trial of high-dose chemotherapy and hematopoietic progenitor cell

support in operable breast cancer with extensive lymph node involvement : final analysis with 7 years of follow-up. Ann Oncol 2002; 13: 689-98.
910. Schroevers MJ, Ranchor AV, Sanderman R. (2004). The role of age at the onset of cancer in relation to survivor's long-term adjustment: a controlled comparison over an eight-year period. Psychooncology, 13, 740-752.
911. Schwaibold F, Fowble BL, Solin LJ, Schultz DJ, Goodman RL. The results of radiation therapy for isolated local regional recurrence after mastectomy. Int J Rad Oncol Biol Phys 1991; 21: 299 310.
912. Schwartz AL, Winters-Stone K, Galluci B. Exercise effects on bone mineral density in women with breast cancer receiving adjuvant chemotherapy. Oncol Nurs Forum 2007; 34: 627-33.
913. Seidman AD, Berry D, Cirrincione C et al. CALGB 9840: phase III study of weekly paclitaxel via 1-hour infusion versus standard 3h infusion every third week intreatment of metastatic breast cancer, with trastuzumab for HER2-positive metastatic breast cancer and randomized for trastuzumab in HER2 normal metastatic breast cancer. Proc Am Soc Clin Onc 2004;22 (Sup 14S)
914. Seidman AD, O'Shaughnessy J, Misset JL Single-agent capecitabine: a reference treatment for taxane-pretreated metastatic breast cancer? Oncologist. 2002;7 Suppl 6:20-8
915. Semiglazov VF, Semiglazov VV, Dashyan GA, Ziltsova EK, Ivanov VG, Bozhok AA, et al. Phase II randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer 2007;110:244–54
916. Shah AJ, Parsons B, Pope I, Callaway M, Finch-Jones MD, Thomas MG. The clinical impact of magnetic resonance imaging in diagnosing focal hepatic lesions and suspected cancer. Clinical imaging 2009;33:209-212
917. Shah VI, Raju U, Chitale D, Deshpande V, Gregory N, Strand V. False-negative core needle biopsies of the breast. Cancer 2003; 97: 1824-31.
918. Shan K. , A.M. Linkoff, J.B. Young. Adriamycine-induced cardiotoxicity. Ann Intern Med 1996; 125:47-58.
919. Sheafor DH, Frederick MG, Paulson EK, Keogan MT, DeLong DM, Nelson RC. Comparison of unenhanced, hepatic arterial-dominant, and portal venous-dominant phase helical CT for the detection of liver metastases in women with breast carcinoma. AJR 1999; 172: 961-8.
920. Shen J, Gilcrease MZ, Babiera GV, Ross MI, Meric-Bernstam F, Feig BW, Kuerer HM, Francis A, Ames FC, Hunt KK. Feasibility and accuracy of sentinel lymph node biopsy after preoperative chemotherapy in breast cancer patients with documented axillary metastases. Cancer. 2007 Apr 1;109(7):1255-63
921. Shetty MK, Shah YP. Prospective evaluation of the value of negative sonographic and mammographic findings in patients with palpable abnormalities of the breast. J Ultrasound Med 2002; 21: 1211-6.
922. Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. Premature menopause or early menopause: long-term health consequences. Maturitas. 2010;65(2):161-6. Epub 2009 Sep 5.
923. Sideras K, et al. Coprescription of tamoxifen and medications that Inhibit CYP2D6. J Clin Oncol 2010 May 10. [Epub ahead of print]. PMID: 20439629
924. Sim LS, Hendriks JH, Bult P et al. US correlation for MRI-detected breast lesions in women with familial risk of breast cancer. Clin Radiol. 2005;60:801-6.
925. Simmons C, Miller N, Geddie W, et al. Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases? Ann Oncol. 2009;20:1499-1504.
926. Simon R. Development and evaluation of therapeutically relevant predictive classifiers using gene expression profiling. J Natl Cancer Inst 2006;98(17):1169-71
927. Skaane P, Engedal K. Analysis of sonographic features in the differentiation of fibroadenoma and invasive ductal carcinoma. Am J Roentgenol 1998; 171: 1159-60.
928. Slamon D., W. Eiermann, N. Robert, et al. Phase III trial comparing AC-T with AC-TH and with TCH the adjuvant treatment of HER2 positive early breast cancer patients: second interim efficacy analysis. Breast Cancer Research & Treatment 2007; vol 1206, suppl 1
929. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Pharm D et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpress HER2. N Engl J Med 2001; 344: 783-92.
930. Sledge GW, Neuberg D, 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 21 (4): 588-92, 2003.
931. Smith DN, Kaelin CM, Korbin CD, Ko W, Meyer JE, Carter GR. Impalpable breast cysts: utility of cytologic examination of fluid obtained with radiologically guided aspiration. Radiology 1997; 204: 149-51.
932. Smith IE et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005; 23: 5108-16
933. Smith L., M. Procter, R. Gelber, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 2007; 369:29-36.
934. Smith R., J. Bryant, A. DeCellis, et al. Acute myeloid leukaemia and myelodysplastic syndrome after doxorubicin-cyclophosphamide adjuvant therapy for operable breast cancer: the National Surgical adjuvant Breast and Bowel Project experience. J Clin Oncol 2003; 21:1195-120.
935. Son EJ, Oh KK, Kim EK, Cho N, Lee JD, Kim SH et al. Characteristic imaging features of breast fibroadenomas in women given cyclosporine A after renal transplantation. J Clin Ultrasound 2004;32:69-77.
936. Soo MS, Rosen EL, Baker JA, Vo TT, Boyd BA.. Negative Predictive Value of sonography with mammography in patients with palpable breast lesions. Am J Roentgenol 2001; 177: 1167-70.
937. Sorlie T Introducing molecular subtyping of breast cancer into the clinic? J Clin Oncol 2009 27(8):1153–1154
938. Sotiriou C, Neo SY, McShane LM, Korn EL, Long PM, Jazaeri A, et al. Breast cancer classification and prognosis based on gene expression profiles from a population-based study. Proc Natl Acad Sci U S A 2003;100(18):10393-8.
939. Sparano JA, Makhson AN, Semiglazov VF, Tjulandin SA, Balashova OI, Bondarenko IN, Pegylated liposomal doxorubicin plus docetaxel significantly improves time to progression without additive cardiotoxicity compared with docetaxel monotherapy in patients with advanced breast cancer previously treated with neoadjuvant-adjuvant anthracycline therapy: results from a randomized phase III study. J Clin Oncol. 2009;27: 4522-9. Epub 2009 Aug 17.
940. Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T, Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med. 2008;358:1663-71.
941. Sperber F, Blank A, Metser U, Flusser G, Klausner JM, Lev-Chelouche D. Diagnosis and treatment of breast fibroadenomas by US-guided vacuum-assisted biopsy. Arch Surg 2003; 138: 796-800.
942. Sprundel TC van, Schmidt MK, Rookus MA, Brohet R, Asperen CJ van, Rutgers EJ, et al. Risk reduction of contralateral

breast cancer and survival after contralateral prophylactic mastectomy in BRCA1 or BRCA2 mutation carriers. Br J Cancer 2005; 93: 287-92.
943. Stavros AT, Thickman D, Rapp CL, Dennis MA, Parker SH, Sisney GA. Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. Radiology 1995; 196: 123-34.
944. Stirling D, Evans DG, Pichert G, Shenton A, Kirk EN, et al. Screening for familial ovarian cancer: failure of current protocols to detect ovarian cancer at an early stage according to the international Federation of gynecology and obstetrics system. J Clin Oncol 2005; 23: 5588-96.
945. STOET. Erfelijke tumoren. Richtlijnen voor diagnostiek en preventie. Vereniging Klinische Genetica Nederland. 4e druk, 2010. www.stoet.nl/uploads/richtlijnenboekje.pdf
946. Stomper PC, Recht A, Berenberg AL, Jochelson MS, Harris JR Mammographic detection of recurrent cancer in the irradiated breast. Am J Roentgenol 1987; 148: 39-43.
947. Storm, H. H. and O. M. Jensen Risk of contralateral breast cancer in Denmark 1943-80. Br J Cancer 1986 54(3): 483-92.
948. Stovall et al: Stovall M, Blackwell CR, Cundiff J, Novak DH, Palta JR, Wagner LK, Webster EW, Shalek RJ, Fetal dose from radiotherapy with photon beams: report of AAPM Radiation Therapy Committee Task Group no 36, Medical Physics, 1995 (22-1): 63-82
949. Streford C, Shore R, One-man G, Meadows A, Yuma Devil P, Preston Withers J, Holm LE, Sather J, Mabuchi K, H R. Biological effects after prenatal irradiation (embryo and fetus). A report of the International Commission on Radiological Protection. Annals of the ICRP 2003:33:5 -206
950. Stull VB, Snyder DC, Demark-Wahnefried W. (2007). Lifestyle interventions in cancer survivors: designing programs that meet the needs of this vulnerable and growing population. The Journal of Nutrition, 137, 243-248
951. Sung, JS, Lee CH, Morris EA et al. Screening breast MRI in women with a history of chest irradiation. Radiology 2011;259:65-71.
952. Suter T., M Procter, D van Veldhuisen et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. J Clin Oncol 2007; 25;3859-65
953. Swain S.M , F.S. Whaley, M.S. Ewer. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003; 97:2869-79.
954. Swartz GF, Guliano AE, Veronesi U, Consensus Conference Committee, Proccedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast, April 19-22, 2001, Philadelphia, PA. Cancer 2002;94:2542-51
955. Tabar L, Fagerberg G, Chen HH, Duffy SW, Gad A. Screening for breast cancer in women aged under 50: mode of detection, incidence, fatality, and histology. J Med Screen. 1995:2:94-8.
956. Tabernero J, Climent MA, Lluch A et al. A multicenter, randomised phase II study of weekly or 3-weekly docetaxel in patients with metastatic breast cancer. Ann Oncol 2004; 15: 1358–1365
957. Takatsuka Y, Yayoi E, Kobayashi T, Aikawa T, Kotsuma Y. Neoadjuvant intra-arterial chemotherapy in locally advanced breast cancer: a prospective randomized study. Osaka Breast Cancer Study Group. Jpn J Clin Oncol 1994; 24: 20-5
958. Takei H, Suemasu K, Inoue K, Saito T, Okubo K, Koh J, Sato K, Tsuda H, Kurosumi M, Tabei T; Saitama Breast Cancer Clinical Study Group. Multicenter phase II trial of neoadjuvant exemestane for postmenopausal patients with hormone receptor-positive, operable breast cancer: Saitama Breast Cancer Clinical Study Group (SBCCSG-03). Breast Cancer Res Treat. 2008 Jan;107(1):87-94
959. Talele AC, Slanetz PJ, Edmister WB, Yeh ED, Kopans DB. The lactating breast: MRI findings and literature review. Breast J 2003;9:237-40
960. Tallman M..S , R. Gray, N.J. Robert, et al. Conventional adjuvant chemotherapy with or without high-dose chemotherapy and autologous stem-cell transplantation in high-risk breast cancer. N Engl J Med 2003; 349: 17-26.
961. Tan AR, Swain SM Therapeutic strategies for triplenegative breast cancer. Cancer J 2008 14(6):343–351
962. Tan DS, Marchio C, Jones RL et al Triple negative breast cancer: molecular profiling and prognostic impact in adjuvant anthracycline-treated patients. Breast Cancer Res Treat 2008 111(1): 27–44
963. Tan VK, Goh BK, Fook-Chong S, Khin LW, Wong WK, Yong WS. The feasibility and accuracy of sentinel lymph node biopsy in clinically node-negative patients after neoadjuvant chemotherapy for breast cancer--a systematic review and meta-analysis. J Surg Oncol. 2011 Jul 1;104(1):97-103.
964. Taylor SE. (2003). Health Psychology (5th Ed.). Boston: McGraw-Hill.
965. Teifke A, Lehr HA, Vomweg TW, Hlawatsch A, Thelen M. Outcome analysis and rational management of enhancing lesions incidentally detected on contrast-enhanced MRI of the breast. Am J Roentgenol 2003; 181: 655-62.
966. Telli M., S. Hunt, R. Carlson, et al. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. J Clin Oncol 2007; 25:3525-33.
967. Telli ML, Horst KC, Guardino AE et al. Phyllodes tumors of the breast: natural history, diagnosis and treatment. J Natl Compr Canc Netw 2007;5:324-30
968. Tewari K, Bonebrake RG, Asrat T, Shanberg AM. Ambiguous genitalia in infant exposed to tamoxifen in utero. Lancet 1997;350:183
969. Tham YL, Sexton K, Weiss H, Elledge R, Friedman LC, Kramer R. The rates of chemotherapy-induced amenorrhea in patients treated with adjuvant doxorubicin and cyclophosphamide followed by a taxane. Am J Clin Oncol. 2007;30:126-32
970. The Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenpausal women with early breast cancer. N Engl J Med.2005; 353: 2747-57
971. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer . Clinical practice guidelines for the care and treatment of breast cancer. CMAJ 1998; 158: 1-83
972. Therasse P Mauriac L, Welnicka-Jaskiewicz M Final results of a randomized phase III trial comparing cyclophosphamide, epirubicin, and fluorouracil with a dose-intensified epirubicin and cyclophosphamide + filgrastim as neoadjuvant treatment in locally advanced breast cancer: an EORTC-NCIC-SAKK multicenter study. J Clin Oncol. 2003 Mar 1;21(5):843-50.
973. Theriault RL, Lipton A, Hortobagyi GN, Leff R, Gluck S, Stewart JF, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled tial. J Clin Oncol 1999; 17: 846-54.
974. Thomas DB, Gao DL, Ray RM, Wang WW, Allison CJ, Chen FL, et al. Randomized trial of breast self-examination in Shanghai: final results. J Natl Cancer Inst 2002; 94: 1445-57. US Preventive Services Task Force. Screening for Breast Cancer: US Preventive Services Task Force Recommendation Statement. Ann Intern Med 2009; 151: 716-26.
975. Thomas E, et al. The Use of Alternate, Non–Cross-Resistant Adjuvant Chemotherapy on the Basis of Pathologic Response to a Neoadjuvant Doxorubicin-Based Regimen in Women With Operable Breast Cancer: Long-Term Results From a Prospective Randomized Trial. Journal of Clinical Oncology, 2004;22:2294-2302

976. Thompson AM, Jordan LB, Quinlon P et al. Prospective comparison of switches in biomarker status between primary and recurrent breast cancer: the breast recurrence in tissue study. Breast Cancer Res Treatment 2010; 12: epub nov 2010.
977. Thull DL, Vogel VG. Recognition and management of hereditary breast cancer syndromes. The Oncologist 2004;9:13-24.
978. Thurfjell E. Mammographically-guided FNA in differential diagnosis of cystic versus solid rounded masses smaller than 2 cm detected at mammographic screening. Breast Cancer Res Treat 2002; 75: 221-6.
979. Tilanus-Linthorst MM, Obdeijn IM, Hop WC, Causer PA, Leach MO, Warner E et al. BRCA1 mutation and young age predict fast breast cancer growth in the Dutch, United Kingdom, and Canadian magnetic resonance imqging screening trials. Clin Cancer Res 2007;13:7357-62.
980. Tilanus-Linthorst MM. Breast density as indicator for thr use of mammography or MRI to screen women with familial risk for breast cancer: a RCT. KWF EMCR 2009-4491, ZonMw 200320002.
981. Tokuda Y., T. Tajima, M. Narabayashi, et al. Randomized phase III study of high-dose chemotherapy with autologous stem cell support as consolidation in high-risk postoperative breast cancer: Japan Clinical Oncology Group (JCOG9208). Proc Am Soc Clin Oncol 2001; 20: 38a (abstr. 148).
982. Toles M, Demark-Wahnefried W. (2008). Nutrition and the cancer survivor: evidence to guide oncology nursing practice. Seminars in Oncology Nursing, 24, 171-179.
983. Torrenga H, et al: Omitting axillary lymph node dissection in sentinel node negative breast cancer patients is safe: a long term follow-up analysis. J Surg Oncol 2004 88:4-7
984. Tovey SM, Brown S, Doughty JC et al. Poor survival outcomes in HER2-positive breast cancer patients with low-grade, node-negative tumours. Br J Cancer 2009; 100: 680–683.
985. Townsend PW, Smalley SR, Cozad SC, Rosenthal HG, Hassanein RE. Role of postoperative radiation therapy after stabilization of fractures caused by metastatic disease. Int J Radiat Oncol Biol Phys 1995 Jan 1;31(1):43-9.
986. Trijsburg, R. W., F. C. van Knippenberg, et al. Effects of psychological treatment on cancer patients: a critical review. Psychosom Med 1992 54(4): 489-517.
987. Tripathy D; Slamon DJ; Cobleigh M; Arnold A; Saleh M; Mortimer JE; Murphy M; Stewart SJ. Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. J Clin Oncol 2004 ;22:1063-70.
988. Tsao MN, et al. Radiotherapeutic management of brain metastases: a systematic review and meta-analysis. Cancer Treat Rev 2005;31(4):256-73.
989. Tubiana M, Bonneterre J, Dieras V, Tubiana-Hulin M, Bougnoux P, Bonneterre ME, 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.
990. Turnbull L, Brown S, Harvey I, Olivier C, Drew P, Napp V et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. Lancet 2010;375:563-71.
991. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 2004; 23: 1111-30.
992. UICC , Sobin LH, Gospodarowicz MK Wittekind Ch (eds) TNM Classification of malignant tumors, seventh edition edition, Wiley Blackwell, Sussex, ISBN 978-1-4443-3241-4, 2009
993. UICC , Sobin LH, Wittekind Ch (eds) TNM Classification of malignant tumors, sixth edition, Wiley Liss, New York, 2002
994. Untch M, Rezai M, Loibl S, Fasching PA, Huober J, Tesch H, Bauerfeind I, Hilfrich J, Eidtmann H, Gerber B, Hanusch C, Kühn T, du Bois A, Blohmer JU, Thomssen C, Dan Costa S, Jackisch C, Kaufmann M, Mehta K, von Minckwitz G. Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. J Clin Oncol. 2010 Apr 20;28(12):2024-31
995. Upponi SS, Ahmad F, Whitaker IS, Purushotham AD. Pregnancy after breast cancer. Review. Eur J Cancer 2003;39:736-41
996. USPSTF. Screening for breast cancer: US Preventive Services Task Force Recommendation Statement. Ann Intern Med 2009;151:716-26
997. Vaittinen P, Hemminki K. Risk factors and age-incidence relationships for contralateral breast cancer. Int J Cancer. 2000 Dec 15;88(6):998-1002.
998. Valachis A, Polyzos NP, Patsopoulos NA, Georgoulias V, Mavroudis D, Mauri D. Bevacizumab in metastatic breast cancer: a meta-analysis of randomized controlled trials. Breast Cancer Res Treat. 2010; 122: 1-7.
999. Valagussa P, Zambetti M, Bonadonna G, Zucali R, Mezzanotte G, Veronesi U. Prognostic factors in locally advanced noninflammatory breast cancer. Long-term results following primary chemotherapy. Breast Cancer Res Treat 1990; 15: 137-47
1000. Valentin J (ed). International Commission on Radiological Protection. Biological effects after prenatal irradiation. Ann ICRP; ICRP publication 90, ISBN 008 044 265X, 2003
1001. Valero V, Buzdar AU, Hortobagyi GN. Locally Advanced Breast Cancer. Oncologist 1996; 1: 8-17
1002. Vallance JKH, Courneya SK, Plotnikoff CR, Mackey JR. (2008). Analyzing theoretical mechanisms of physical activity in breast cancer survivors: results from the activity promotion (ACTION) trial. Annals of Behavioral Medicine, 35, 150-158.
1003. van Belle V, Van Calster B, Brouckaert O, Vanden Bempt I, Pintens S, Harvey V, et al. Qualitative assessment of the progesterone receptor and HER2 improves the Nottingham Prognostic Index up to 5 years after breast cancer diagnosis. J Clin Oncol 2010;28:4129-34.
1004. Van Calsteren K, Berteloot P, Hanssens M, et al. In utero exposure to chemotherapy: effect on cardiac and neurologic outcome. J Clin Oncol 2006;24(12):e16–7.c
1005. van de Vijver MJ, He YD, van't Veer LJ, Dai H, Hart AA, Voskuil DW, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002;347(25):1999-2009.
1006. Van der Giessen PH. A simple and generally applicable method to estimate the peripheral dose in radiation teletherapy with high energy x-rays or gamma radiation. Int J Radiat Oncol Biol Phys 1996;35:1059-68
1007. Van der Giessen PH. Peridose, a software program to calculate the dose outside the primary beam in radiation therapy. Radiother Oncol. 2001;58:209-13
1008. van der Hage, J. A., H. Putter, et al. Impact of locoregional treatment on the early-stage breast cancer patients: a retrospective analysis" Eur J Cancer 2003 39(15): 2192-9.
1009. van der Kolk DM, de Bock GH, Leegte BK, Schaapveld M, Mourits MJ, de Vries J, et al. Penetrance of breast cancer, ovarian cancer and contralateral breast cancer in BRCA1 and BRCA2 families: high cancer incidence at older age. Breast Cancer Res Treat. 2010;124(3):643-51.
1010. van der Leest, M., L. Evers, et al. The safety of breast-conserving therapy in patients with breast cancer aged < or = 40 years. Cancer 2007 109(10): 1957-64.
1011. Van der Linden YM, et al. Patients with a favourable prognosis are equally palliated with single and multiple fraction

radiotherapy: results on survival in the Dutch Bone Metastasis Study. Radiother Oncol 2006;48:245-53.
1012. van der Linden YM, Kroon HM, Dijkstra PD, Lok JJ, Noordijk EM, Leer JWH, et al. Simple radiographic parameter predicts fracturing in metastatic femoral bone lesions: results from a randomized trial. Radiother Oncol 2003;69:21-31.
1013. Van der Linden YM, Lok JJ, Steenland E, Martijn H, Houwelingen JC, Leer JWH, et al. Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. Int J Radiat Oncol Biol Phys 2004;59(2):528-37.
1014. Van der Sangen MJ, Coebergh JW, Roumen RM, Rutten HJ, Vreugdenhil G, Voogd AC. Detection, treatment, and outcome of isolated supraclavicular recurrence in 42 patients with invasive breast carcinoma. Cancer. 2003 Jul 1;98(1):11-7
1015. Van der Sangen MJ, van de Poll-Franse LV, Roumen RM, Rutten HJ, Coebergh JW,Vreugdenhil G, Voogd AC. The prognosis of patients with local recurrence more than five years after breast conservation therapy for invasive breast carcinoma. Eur J Surg Oncol. 2006;32:34-8
1016. van der Sangen, M et al. Are breast conservation and mastectomy equally effective in the treatment of young women with early breast cancer? Long-term results of a population-based cohort of 1,451 patients aged </=40 years; Breast Cancer Res Treat 2010 Aug 12. [Epub ahead of print].
1017. van der Sangen, M., et al. The prognosis of patients with local recurrence more than five years after breast conservation therapy for invasive breast carcinoma. Eur J Surg Oncol. 2006; 32(1):34-8.
1018. Van der Zee J, Rhoon GC van, Wijnmaalen AJ, Koper PC, van Putten WL. Reirradiatie met hyperthermie bij patiënten met een recidief mammacarcinoom. Ned Tijd Gen 1999; 143: 80 4.
1019. van Deurzen HM et al: Accuracy of sentinel node biopsy after neoadjuvant chemotherapy in breast cancer patients: A systematic review EUROPEAN JOURNAL OF CANCER 45 (2009) 3124 –3130
1020. van Goethem M, Schelfhout K, Dijckmans L, Van der Auwera JC, Weyler J, Verslegers I et al. MR-mammography in the pre-operative staging of breast cancer patients with dense breast tissue: comparison with mammography and ultrasound. Eur Radiol 2004;14:809-16.
1021. Van Limbergen E, van der Schueren E, Van den Bogaert W, Wing J van. Local control of operable breast cancer after radiotherapy alone. Eur J Cancer 1990; 26: 674 9
1022. van 't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002;415(6871):530-6.
1023. Van Tienhoven G, Borger JH, Hart AAM, Rutgers EJTh, van Dongen JA, Bartelink H. The prognostic significance of the axillary apex biopsy in clinically operable breast cancer. Eur J Cancer 1995; 31A: 1965-8
1024. Van Tienhoven G, Voogd AC, Peterse JL, Nielsen M, Mignolet F, West Andersen K, et al on behalf of the EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group. Prognosis after salvage treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomized trials (EORTC 10801 and DBCG-82TM). Eur J Cancer 1999; 35: 32-8.
1025. van Tienhoven, G., A. C. Voogd, et al. Prognosis after treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomised trials (EORTC 10801 and DBCG-82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group. Eur J Cancer 1999 35(1): 32-8.
1026. Varas X, Leborgne JH, Leborgne F, Mezzera J, Jaumandreu S, Leborgne F. Revisiting the Mammographic follow-up of BI-RADS Category 3 lesions. Am J Roentgenol 2002; 179: 691-5.
1027. Vargas HI, Vargas MP, Eldrageely K, Gonzalez KD, Burla ML, Venegas R, et al. Outcomes of surgical and sonographic assessment of breast masses in women younger than 30. Am Surg 2005; 71: 716-9.
1028. Vargas HI, Vargas MP, Gonzalez KD, Eldrageely K, Khalkhali I. Outcomes of sonography-based management of breast cysts. Am J Surg 2004; 188: 443-7.
1029. Vasen HF, Tesfay E, Boonstra H, Mourits MJ, Rutgers E, Verheyen R, et al. Early detection of breast and ovarian cancer in families with BRCA mutations. Eur J Cancer 2005; 41: 549-54.
1030. VBOC (maart 2009) Toekomstige behoefte verpleegkundig specialisten bij somatische aandoeningen, een zoektocht in onontgonnen gebied. Utrecht STG / Health Management Forumin opdracht van Stuurgroep VBOC-project “Implementatie verpleegkundig specialist” MArij VBulto, Gerjanne Vianene
1031. Velde vd CJH, results of TEAM trial, Lancet 2011(in press)
1032. Venta LA, Kim JP, Pelloski CE, Morrow M. Management of complex breast cysts. Am J Roentgenol 1999; 173: 1331-6.
1033. Venturini M., L. Del Mastro, E. Aitini, et al. Dose-dense adjuvant chemotherapy in early breast cancer patients: results from a randomized trial. J Natl Cancer Inst 2005; 97:1724.
1034. Verhagen EH, Taphoorn MJ. Richtlijn hersenmetastasen. Utrecht, VIKC; 2006. www.oncoline.nl
1035. Verkooijen HM; Core Biopsy After Radiological Localisation (COBRA) Study Group. Diagnostic accuracy of stereotactic large-core needle biopsy for nonpalpable breast disease: results of a multicenter prospective study with 95% surgical confirmation. Int J Cancer 2002; 99: 853-9.
1036. Verma S, Lavasani S, Mackey J Optimizing the management of her2-positive early breast cancer: the clinical reality. Curr Oncol. 2010 Aug;17(4):20-33.
1037. Vernon CC, Hand JW, Field SB, Machin D, Whaley JB, van der Zee J, et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. Int J Radiat Oncol Biol Phys 1996; 35: 731-44.
1038. Veronesi U, Arnone P, Veronesi P, Galimberti V, Luini A, Rotmensz N, Botteri E, Ivaldi GB, Leonardi MC, Viale G, Sagona A, Paganelli G, Panzeri R, Orecchia R. The value of radiotherapy on metastatic internal mammary nodes in breast cancer. Results on a large series. Ann Oncol. 2008 Sep;19(9):1553-60
1039. Veronesi U, Marubini E, Mariani L, Valagussa P, Zucali R. The dissection of internal mammary nodes does not improve the survival of breast cancer patients. 30-year results of a randomised trial. Eur J Cancer. 1999;35:1320-5
1040. VIKC: Concept richtlijn herstel na kanker 2010.
1041. Visser A, Huizinga GA, Graaf WTA van der, Hoekstra HJ, Hoekstra-Weebers JEHM. (2004).The impact of parental cancer on children: a review of the literature. Cancer Treatment Reviews, 30, 683-694
1042. Visser A, Huizinga GA, Hoekstra HJ, van der Graaf WT, Gazendam-Donofrio SM, Hoekstra-Weebers JE. (2007). Emotional and behavioral problems in children of parents recently diagnosed with cancer: a longitudinal study. Acta Oncol, 46, 67-76.
1043. Visser A, Huizinga GA, Hoekstra HJ, van der Graaf WT, Klip EC, Pras E, Hoekstra-Weebers JE. (2005). Emotional and behavioural functioning of children of a parent diagnosed with cancer: a cross-informant perspective. Psychooncology, 14, 746-758.

1044. Vizcaino I, Gadea L, Andreo L, Salas D, Ruiz-Perales F, Cuevas D, et al. Short-term follow-up results in 795 nonpalpable probably benign lesions detected at screening mammography. Radiology 2001; 219: 475-83.
1045. Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002; 20: 719-26.
1046. Vollebergh MA, Lips EH, Nederlof PM, Wessels LF, Schmidt MK, van Beers EH, Cornelissen S, Holtkamp M, Froklage FE, de Vries EG, Schrama JG, Wesseling J, van de Vijver MJ, van Tinteren H, de Bruin M, Hauptmann M, Rodenhuis S, Linn SC. An aCGH classifier derived from BRCA1-mutated breast cancer and benefit of high-dose platinum-based chemotherapy in HER2-negative breast cancer patients. Ann Oncol. 2010 Dec 6. [Epub ahead of print]
1047. Volm MD. Male breast cancer. Current Treatment Options in Oncology. 2003; 4:159-64
1048. Von Minckwitz G, Blohmer JU, Raab G, Löhr A, Gerber B, Heinrich G, et al. German Breast Group. In vivo chemosensitivity-adapted preoperative chemotherapy in patients with early-stage breast cancer: the GEPARTRIO pilot study. Ann Oncol 2005; 16: 56-63
1049. Voogd AC, de Boer R, van der Sangen MJ, Roumen RM, Rutten HJ, Coebergh JW. Determinants of axillary recurrence after axillary lymph node dissection for invasive breast cancer. Eur J Surg Oncol 2001;27:250–5
1050. Voogd AC, Rodrigus PT, Crommelin MA, Repelaer, van Driel OJ, Roukema JA et al. Lokaal recidief na borstsparende behandeling wegens mammacarcinoom; behandeling en prognose bij 82 patiënten. Ned Tijdschr Geneesk 1995; 139: 2422-7.
1051. Voogd AC, van Oost FJ, Rutgers EJ, Elkhuizen PH, van Geel AN, Scheijmans LJ, van der Sangen MJ, Botke G, Hoekstra CJ, Jobsen JJ, van de Velde CJ, von Meyenfeldt MF, Tabak JM, Peterse JL, van de Vijver MJ, Coebergh JW, van Tienhoven G; Dutch Study Group on Local Recurrence after Breast Conservation (BORST Group). Long-term prognosis of patients with local recurrence after conservative surgery and radiotherapy for early breast cancer.Eur J Cancer. 2005;41:2637 44
1052. Voogd AC, van Oost FJ, Rutgers EJ, Elkhuizen PH, van Geel AN,Scheijmans LJ et al. Long-term prognosis of patients with local recurrence after conservative surgery and radiotherapy for early breast cancer. Eur J Cancer 2005; 41: 2637-44.
1053. Voogd, A. C., M. Nielsen, et al. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. J Clin Oncol 2001 19(6): 1688-97.
1054. Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot J-C, Jager JJ et al. Can patient-, treatment- and pathology-related characteristics explain the high local recurrence rate following breast-conserving surgery therapy in young patients? Eur J Cancer 2003;39:932-44.
1055. Wai Man Sze, Mike S, Ines H, Malcolm M. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy - a systematic review of the randomised trials. Cochrane Database Syst Rev 2004; CD004721.
1056. Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int.J.Radiat.Oncol.Biol.Phys. 2005;62:738-44.
1057. Wallack MK, Wolf JA, Bedwinek J et al. Gestational carcinoma of the female breast. Curr Probl Cancer, 1983;7:1-58
1058. Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, Lindtner J, Thürlimann B, Fey M, Werner ID, Forbes JF, Price K, Coates AS, Collins J; International Breast Cancer Study Group Trials I through VII. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol. 2003 Apr 1;21(7):1205-13
1059. Wallis M, Tardivon A, Helbich T, Schreer I. Guidelines from the European Society of Breast Imaging for diagnostic interventional breast procedures. Eur Radiol 2007; 17: 581-8.
1060. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. J Clin Oncol 2006;24:5769-79.
1061. Wang S, Yang H, Tong F et al. Response to neoadjuvant therapy and disease free survival in patients with triple-negative breast cancer. Gan To Kagaku Ryoho 2009 36(2):255–258
1062. Wang WJ, Wang Q, Cai QP, Zhang JQ. Ultrasonographically guided vacuum-assisted excision for multiple breast masses: non-randomized comparison with conventional open excision. J Surg Oncol 2009;100:675-80.
1063. Wang Y, Klijn JG, Zhang Y, Sieuwerts AM, Look MP, Yang F, et al. Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer. Lancet 2005;365(9460):671-9.
1064. Warner E, Plewes DB, Hill KA, Causer PA, Zubovits JT, Jong RA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 2004; 292: 1317-25.
1065. Warner, E., et al., Systematic review: Using magnetic resonance imaging to screen women at high risk for breast cancer. Annals of Internal Medicine, 2008;148(9):671-9.
1066. Warren RM, Pointon L, Caines R, Hayes C, Thompson D, Leach MO (MARIBS). What is the recall rate of breast MRI when used for screening asymptomatic women at high risk? Magn Reson Imaging 2002; 20: 557-65.
1067. Webb JA, Thomsen HS, Morcos SK; Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). The use of iodinated and gadolinium contrast media during pregnancy and lactation. Eur Radiol. 2005;15:1234-40
1068. Weert E van, May AM, Korstjens I, Post WJ, van der Schans CP, van den Borne B, Mesters I, Ros WJ, Hoekstra-Weebers JEHM. (2010). Cancer-related fatigue and rehabilitation: a randomized controlled multicenter trial comparing physical training combined with cognitive-behavioral therapy with physical training only and with no intervention. Phys Ther, 90, 1413-1425.
1069. Weiner JG, Jordan TR, Thompson AJ, Fink BN. (2010). Analysis of the relationship between diet and exercise beliefs and actual behaviors among breast cancer survivors in northwest Ohio. Breast Cancer: Basic and Clinical Research, 4, 5-13.
1070. Weinstein, S.P., et al., Multimodality screening of high-risk women: a prospective cohort study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2009:27(36):6124-8.
1071. Weiss NS. Breast cancer mortality in relation to clinical breast examination and breast self-examination. Breast J 2003; 9: S86-9.
1072. Wely van B, Strobbe LJA, Smidt M et al: False negative sentinel lymph node biopsy: follow up of 391 node-negative patients with breastcancer.Nederlands Tijdschrift voor Heelkunde 2006
1073. Werkgroep Indicatoren. Interne indicatoren voor de radiologie, 9-11, april 2007. Nederlandse Vereniging voor Radiologie, april 2007, Utrecht
1074. Westenend PJ, Sever AR, Beekman-De Volder HJ, Liem SJ. A comparison of aspiration cytology and core needle

biopsy in the evaluation of breast lesions. Cancer 2001; 93: 146-50.
1075. Whelan, T, R. Clark, et al. Ipsilateral breast tumor recurrence postlumpectomy is predictive of subsequent mortality: results from a randomized trial. Investigators of the Ontario Clinical Oncology Group. Int J Radiat Oncol Biol Phys 1994 30(1): 11-6.
1076. Whitehouse PA, Baber Y, Brown G, Moskovic E, King DM, Gui GP. The use of ultrasound by breast surgeons in outpatients: an accurate extension of clinical diagnosis. Eur J Surg Oncol 2001; 27: 611-6.
1077. Wiedswang G, Borgen E, Karesen R, Kvalheim G, Nesland JM, Qvist H, et al. Detection of isolated tumor cells in bone marrow is an independent prognostic factor in breast cancer. J Clin Oncol 2003;21(18):3469-78.
1078. Wiegel T Bottke D, Kreusel KM, Schmidt S, Bornfeld N, Foerster MH, et al. External beam radiotherapy of choroidal metastases – final results of a prospective study of the German Cancer Society (ARO 95–08). Radiother Oncol 200; 64: 13–18
1079. Wildiers H, Forceville K, Paridaens R et al Taxanes and anthracyclines in early breast cancer: which first? Lancet oncol 2010, 11, 219-220
1080. Wildiers H, Dirix L, Neven P, et al. Delivery of adjuvant sequential dose-dense FEC-Doc to patients with breast cancer is feasible, but dose reductions and toxicity are dependent on treatment sequence. Breast Cancer Res Treat 2009; 114: 103–12.
1081. Wilke LG, McCall LM, Posther KE, Withworth PW, Reintgen DS, Leitch AM et al. Surgical complications associated with sentinel lymph node biopsy: results from a prospective international cooperative group trial. Annals of surgical Oncology,2006. 13:491-500.
1082. Wilking, N, Lidbrink, E, Wiklund, T, et al. Long-term follow-up of the SBG 9401 study comparing tailored FEC-based therapy versus marrow-supported high-dose therapy. Ann Oncol 2007; 18:694.
1083. Wilkins E, Head J, Burke J. Pulmonary resection for metastatic neoplasms in the lung. Experience at the Massachusetts general hospital. Am J Surg 1978; 135: 480-3.
1084. Willner J, Kiricuta IC, Kolbl O. Locoregional recurrence of breast cancer following mastectomy: always a fatal event? Results of univariate and multivariate analysis. Int J Radiat Oncol Biol Phys 1997; 37: 853-63.
1085. Wils J.A., J.M. Bliss and M. Marty, et al, Epirubicin plus tamoxifen versus tamoxifen alone in node positive postmenopausal patients with breast cancer: a randomized trial of International Collaborative Cancer group, J Clin Oncol 1999; 17: 1988–1998.
1086. Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. Int.J.Radiat.Oncol.Biol.Phys. 2009;73:1304-12.
1087. Woo S-B, Hellstein JW, Kalmar JR. Systematic review: Bisphosphonates and osteonecrosis of the jaws. Ann Int Med 2006; 144:753-61.
1088. Wood WC, Muss HB, Solin LJ, Olopade OI. Malignant tumors of the breast. In: DeVita VT Jr, Hellman S, Rosenberg SA. Cancer Principles and Practice of Oncology, 7th ed, 2005; 1415-1478
1089. Xing Y, Foy M, Cox DD, Kuerer HM, Hunt KK, Cormier JN. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. Br J Surg 2006; 93(5):539 546
1090. Yang CH and Cristofanilli M. Systemic Treatments for Inflammatory Breast Cancer. Breast Disease 2006;22:55 65
1091. Yang WT, Tse GM. Sonographic, mammographic, and histopathologic correlation of symptomatic ductal carcinoma in situ. Am J Roentgenol 2004; 182: 101-10.
1092. Yilmaz E, Sal S, Lebe B. Differentiation of phyllodes tumors versus fibroadenomas. Acta Radiol 2002; 43: 34-9.
1093. Yoshioka H. Rehabilitation for the terminal cancer patient. Am J Phys Med Reh 1994; 73: 199-206
1094. Youk JH, Kim EK, Kim MJ, Lee JY, Oh KK. Missed breast cancers at US-guided core needle biopsy: how to reduce them. Radiographics 2007; 27: 79-94.
1095. Zabora J, Brintzenhofeszoc K, Curbow B, Hooker C, Piantadosi S. (2001). The prevalence of psychological distress by cancer site. Psycho-Oncol., 10, 19-28.
1096. Zander, AR, Kroger, N, Schmoor, C, et al. High-dose chemotherapy with autologous hematopoietic stem-cell support compared with standard-dose chemotherapy in breast cancer patients with 10 or more positive lymph nodes: first results of a randomized trial. J Clin Oncol 2004; 22:2273.
1097. Zonderland HM, Coerkamp EG, Hermans J, van de Vijver MJ, van Voorthuisen AE. Diagnosis of breast cancer: contribution of US as an adjunct to mammography. Radiology 1999; 213: 413-22.
1098. Zonderland HM, Pope TL, Nieborg AJ. The Positive Predictive Value of the Breast Imaging Reporting and Data System (BI-RADS) as a method of quality assessment in breast imaging in a hospital population. Eur Radiol 2004; 14: 1743-50.
1099. Zreik TG, Mazloom A, Chen Y, Vannucci M, Pinnix CC, Fulton S, et al. Fertility drugs and the risk of breast cancer: a meta-analysis and review. Breast Cancer Res Treat. 2010;124(1):13-26. Epub 2010 Aug 31.