

Interdisciplinary GoR level III Guidelines for the Diagnosis, Therapy and Follow-up Care of Breast Cancer

Short version – AWMF Registry No.: 032-045OL

Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms

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1 Information about this Guideline

1.1 Editor

Guideline Program in Oncology of the AWMF (Association of the Scientific Medical Societies of Germany), the German Cancer Society (Deutsche Krebsgesellschaft e.V.) and German Cancer Aid (Deutsche Krebshilfe e.V.)

1.2 Funding of this guideline

These guidelines were funded by the German Cancer Aid (Deutsche Krebshilfe e.V.) within the scope of the Guideline Program in Oncology of the AWMF (Association of Medical Scientific Societies).

1.3 Lead professional associations

German Cancer Society (DKG)
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1.5 Additional documents relating to these guidelines

The topics of this version are the same as in the long version of the S3 Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer which can be accessed via the links listed below:

- ▶ <http://www.leitlinienprogramm-onkologie.de/OL/leitlinien.html>
- ▶ <http://www.awmf.org/leitlinien/aktuelle-leitlinien.html>
- ▶ http://www.krebsgesellschaft.de/wub_llevidenzbasiert,120884.html
- ▶ <http://www.krebshilfe.de>
- ▶ <http://www.dggg.de>
- ▶ <http://www.senologie.org>

In addition to this short version, the following supplementary documents are available:

- ▶ Comprehensive version
- ▶ Guideline report
- ▶ Patient guide on the early detection of breast cancer
- ▶ Patient guide on breast cancer 1: Initial disease and DCIS – A guide for patients
- ▶ Patient guide on breast cancer 2: Advanced disease, recurrence and metastasis
- ▶ Gartlehner G et al. Comparative efficacy and safety of sentinel lymph node biopsy alone or complete axillary dissection for sentinel-positive breast cancer: A systematic review. 2011
- ▶ Agency for Quality in Medicine (ÄZQ). Synopsis of evidence-based guideline recommendations for diagnosis, therapy and follow-up care of breast cancer. Berlin: 2011
- ▶ A guideline app called “Leitlinien Onkologie” (in German) can be downloaded at <http://itunes.apple.com/de/app/leitlinien-onkologie/id453786520?mt=8> or https://play.google.com/store/apps/details?id=de.dkg.app&feature=apps_topselling_free?t=W251bGwsMSWylG51bGwslmRlLmRrZy5hcHAiXQ. The contents of these guidelines are anticipated to be published this year.

Bibliography

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3.3	Women at increased risk of developing breast cancer	Schmutzler, (Bick) , Albert, Hahne, Lebeau, Madjar, Meindl, Rhiem, Schreer
Chapter 4 Locoregional primary disease		
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4.2	Pretherapeutic diagnosis in patients with abnormal or suspicious breast findings	Kühn, (Albert) , Bick, Degenhardt, Kreienberg, Kreipe, Lebeau, Madjar, Schreer
4.3	Preinvasive neoplasms	Kreipe/Beckmann, (Lebeau/Dietel) , Albert, Harbeck, Kühn, Marx, Schlake, Schreer, Souchon
4.4	Surgical treatment of invasive carcinoma	Bloher, (Kühn) , Angele, Budach, Dietel, Engel, Kreienberg, Lebeau, Marx, Scharl, Souchon, Wagner
4.5	Pathomorphological study	Lebeau, (Kreipe/Dietel) , Harbeck, Janni, Schlake, Thomssen
4.6	Adjuvant radiotherapy of breast cancer	Souchon/Dunst, (Thomssen) , Bloher, Budach, Hölzel, Kühn, Untch
4.7	Systemic adjuvant therapy (endocrine therapy, chemotherapy and antibody therapy)	
4.7.1	Choice of adjuvant therapy and risk assessment	Kreienberg , Gerber, Harbeck, Possinger, Thomssen
4.7.2	Endocrine therapy	Possinger, (Maass) , Emons, Scharl
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4.7.4	Neoadjuvant (primary systemic) therapy (NACT or PST)	Gerber, (v. Minckwitz) , Marschner, Untch
4.7.5	Antibody therapy	Thomssen, (Schneeweiss) , Jackisch
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Chapter 5 Recurrent or metastatic breast cancer		
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5.3	Treatment of local/locoregional recurrence	Dunst, (Kühn) , Angele, Bloher, Dietel, Heitmann, Marx, Gerber
5.4	Distant metastases	Marschner, (Emons) , Angele, Dunst, Harbeck, Possinger, Thomssen
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1.7 Abbreviations used

Abbreviation	Explanation
ACR	American College of Radiology
ADH	Atypical (intra-)ductal hyperplasia
AI	Aromatase inhibitor
APBI	Accelerated partial breast irradiation
ASCO	American Society of Clinical Oncology
BCT	Breast-conserving therapy
BI-RADS	Breast imaging reporting and data system
CAD	Computer-aided detection
CAP	College of American Pathologists
CISH	Chromogenic in-situ hybridization
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
DGS	Deutsche Gesellschaft für Senologie – German Society of Senology
DKG	Deutsche Krebsgesellschaft – German Cancer Society
EBM	Evidence-based medicine
EORTC	European Organisation for Research and Treatment of Cancer
FISH	Fluorescence in-situ hybridization
FN	Febrile neutropenia
HER2	Human epidermal growth factor receptor 2
ITC	Isolated tumor cells
IORT	Intraoperative radiotherapy
CE-MRI	Contrast-enhanced magnetic resonance imaging
LCIS	Lobular carcinoma in situ
LIN	Lobular intraepithelial neoplasia
LOE	Level of evidence
MRM	Modified radical mastectomy
MRI	Magnetic resonance imaging
NACT	Neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NHSBSP	National Coordinating Group for Breast Screening Pathology
NICE	National Institute for Health and Clinical Excellence
NOS	Not otherwise specified
NZGG	New Zealand Guidelines Group
OS	Overall survival
PBI	Partial breast irradiation
pCR	Pathological complete remission
PCR	polymerase chain reaction
SLNB	Sentinel lymph node biopsy
RT	Radiotherapy
UDH	Intraductal hyperplasia
UICC	Union internationale contre le cancer
WHO	World Health Organization

2 Notices

2.1 Special notice

Health care is in a continuous process of evolution, so that all information, particularly about diagnostic and therapeutic procedures, is only as good as the state of knowledge at the time the guidelines are printed. The greatest possible care has been taken over the recommendations given for treatment and the choice and dosage of medications. Nevertheless, users are asked to consider the manufacturer's package leaflet and summary of product characteristics and consult a specialist in case of any doubt. In our general interest, please notify the GGPO editors of any inconsistencies or discrepancies you may find.

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3 General

3.1 Patient information and education

Info-1	Information material
	The provision of qualified and useful information material (printed or Internet material) should meet defined quality criteria for health information and should provide the patient with easily understood risk information (e.g. specification of absolute risk reductions) to help her arrive at a self-determined decision for or against medical procedures.
GCP	(Albert US et al. 2003; Albert US et al. 2008; Klemperer D et al. 2010)

Info-2	Basic principles of patient-centered communication
Grade of recommendation A	When conveying information to the patient, doctors should observe the following basic principles of patient-centered communication, allowing the patient to participate in the decision-making process: <ul style="list-style-type: none"> ▶ Display empathy and listen actively ▶ Address difficult topics directly and with empathy ▶ Whenever possible, avoid medical terminology, and if medical terms cannot be avoided, they should be explained ▶ Employ strategies that improve understanding (e.g. repeating, summarizing the salient points, using graphics, etc.) ▶ Encourage the patient to ask questions. ▶ Allow and encourage the expression of feelings. ▶ Offer further assistance (Cf. Psychooncology)
Level of evidence 1b	(Bruera E et al. 2002; Butow P et al. 2007; Elkin EB et al. 2007; Ford S et al. 2006; NICE 2009a; Politi MC et al. 2007)

Info-3	Consultation to inform the patient about treatment
	The consultation to inform the patient about the treatment should cover the following points at least: <ul style="list-style-type: none"> ▶ Surgical therapy: possibilities for breast-conserving therapy with mandatory radiotherapy as equivalent to mastectomy with different variants of primary and secondary reconstruction or the provision of an external prosthesis ▶ Systemic therapy: principles and desired treatment targets of adjuvant or palliative therapy, duration and mode of administration of therapy, its side effects and possible late sequelae, and the treatment options for side effects ▶ Radiotherapy: principles and desired treatment targets, duration and follow-up surveillance, possible acute and late sequelae, treatment options for side effects ▶ Participation in clinical studies, principles behind the treatment and treatment targets, duration and mode of administration of the therapy, effects and side-effects known to date, special features (e.g. monitoring, additional measures, cooperation, data storage and processing) ▶ Other: possibilities for prevention and treatment of therapy-related side effects (e.g. emesis, osteoporosis, lymphedema, etc.), necessity for follow-up care, possibilities for rehabilitation and psycho-oncological support as well as services offered by self-help groups, aspects that are the responsibility of the patient and cooperation (e.g. reporting symptoms and problems, treatment compliance)
GCP	(NZGG 2009)

3.2 Early detection, mammographic screening

Early-1	Early detection
	a. Early breast cancer detection is a cross-sectoral task. There should be a quality-assured, interdisciplinary combination of clinical examination, instrument-based diagnosis, surgical exploration and pathomorphological evaluation.
GCP	(Albert US et al. 2008)
	b. The care chain requires complex and quality-assured medical documentation to unify the whole quality management process.
GCP	(Albert US et al. 2008)
	c. Cancer registries are as important as they are necessary for the evaluation and quality assurance of early breast cancer detection. All patients diagnosed with breast cancer should therefore be reported to a cancer registry including the relevant details on primary findings and primary therapy. Cancer registries contribute to evaluation and quality assurance through population-related and regionally based analyses of tumor stages and long-term follow-up (recurrences and survival). When an early detection program is instituted or adapted, baseline data should be available for the preceding period.
GCP	(Albert US et al. 2008)
	d. Examinations for early detection can cause physical and mental stress. This situation must be urgently addressed by careful information and an effective communication strategy.
GCP	(Albert US et al. 2008)
Grade of recommendation A	e. In the context of early breast cancer detection, information should not just be confined to preformulated texts, but necessitates an informational discussion with the doctor that takes account of the woman's preferences, needs, worries and anxieties and allows joint decision-making for informed consent. In the case of mammography screening, information and explanations should be provided to the woman in the first place in writing, with the additional mention of the possibility of a consultation with the doctor in the invitation letter.
	(Albert US et al. 2008)
	f. Health outcome and quality of life should be recorded and evaluated in the long term with particular regard to any false-positive and false-negative findings in the diagnostic chain.
GCP	(Albert US et al. 2008)
	g. Women should be offered the possibility of discussing their medical history and possible risk factors as part of the statutory early cancer screening.
GCP	(Albert US et al. 2008)
Grade of recommendation A	h. The main population-related risk factor for the development of breast cancer is advanced age.
Level of evidence 2a	(Albert US et al. 2008)
Grade of recommendation B	i. Next to the BRCA1/2 mutation, high mammographic density (ARC3 and 4) is the greatest individual risk factor, so that the limited sensitivity of mammography in this context should be enhanced by an additional ultrasound scan.
Level of evidence 3b	(Albert US et al. 2008)

Early-1	Early detection (<i>continuation</i>)
	j. Women aged 70 years and over can be invited to participate in early detection measures, with due regard to the individual risk profile, health status and life expectancy.
GCP	(Albert US et al. 2008)
	k. Women with a BRCA1 or BRCA2 gene mutation, or with a high risk defined as a heterozygous risk > 20% or a permanent lifelong risk of developing the disease > 30%, should seek advice in specialist centers for hereditary breast and ovarian cancer and be counseled about an individual early detection strategy.
GCP	(Albert US et al. 2008)
Grade of recommendation A	l. Quality-assured mammographic screening at 2-year intervals in women aged between 50 and 70 years old is suited for detecting breast cancer early. At present, it is the only method generally recognized to be effective in detecting early stages of breast cancer or early tumor stages.
Level of evidence 1a	(Albert US et al. 2008)
Grade of recommendation A	m. Self-examination of the breasts, even with regular application and training, is not sufficient as a method on its own for reducing breast cancer mortality.
Level of evidence 1a	(Albert US et al. 2008)
	n. Women should be encouraged through qualified information to familiarize themselves with the normal changes of their own body. These include the appearance and feel of the breast so that the woman can identify any abnormalities herself.
GCP	(Albert US et al. 2008)
	o. The clinical breast examination, in other words palpation, breast inspection and evaluation of lymphatic flow, should be offered annually as part of the statutory early screening tests for women aged 30 years and over.
GCP	(Albert US et al. 2008)
	p. Ultrasound on its own is not suitable as a method of early detection.
GCP	(Albert US et al. 2008)
B	q. CE-MRI should be utilized as a supplementary method in the presence of a familial increased risk (BRCA1 or BRCA2 mutation carriers, or with a high risk defined as a heterozygous risk > 20% or a permanent lifelong risk of developing the disease > 30%).
Level of evidence 2a	(Albert US et al. 2008)

Early-2	Mammography
Grade of recommendation B	a. A reduction in breast cancer mortality is also documented for women aged between 40 and 49 years and outweighs the risks resulting from radiation exposure. However, the figure is lower in the age group of women between 50 and 69 years, in whom relatively more false-positive and false-negative findings are obtained. Consequently, the decision should be taken on the basis of an individual risk analysis and a risk-benefit evaluation, as well as with due regard to the woman's preferences and objections.
Level of evidence 1b	(Albert US et al. 2008)
Grade of recommendation B	b. Second opinions on screening mammograms increase the sensitivity of carcinoma detection by 2.9–13.7% (median 7.8%). Depending on the decision-making process following a second opinion, the specificity may be reduced (up to 2.1%) or increased (up to 2.8%).
Level of evidence 2b	(Albert US et al. 2008)
Grade of recommendation 0	c. It is not possible on the basis of the currently available study data to determine unequivocally whether the use of CAD systems can replace second opinions.
Level of evidence 3b	(Albert US et al. 2008)
	d. The structural, process and outcome quality is regulated for mammography in conjunction with the mammographic screening of women aged between 50 and 69 years.
GCP	(Albert US et al. 2008)
Grade of recommendation A	e. Structural, process and outcome quality should also be used to the appropriate extent for so-called curative mammography.
Level of evidence 2b	(Albert US et al. 2008)
	f. If a mammographic finding of BI-RADS0, III, IV or V is obtained, further investigations should be performed within 5 working days to minimize the mental burden on the woman as far as possible.
GCP	(Albert US et al. 2008; Madjar H et al. 2003)

Early-3	Biopsies
Grade of recommendation B	a. With interventional, and preferably ultrasound-guided, biopsies, > 3 specimens should be taken using a 16 G needle.
Level of evidence 3b	(Albert US et al. 2008)
	b. Stereotactic vacuum-assisted biopsy should be performed in a standardized way. The access route and needle positioning (stroke margin) must be documented.
GCP	(Albert US et al. 2008)
Grade of recommendation A	c. The excision of findings detected only on ultrasound should be monitored by intraoperative specimen ultrasound.
Level of evidence 3b	(Albert US et al. 2008)

3.3 Women at increased risk of developing breast cancer

Risk-1	Counseling and genetic testing
	Multidisciplinary counseling and genetic testing should be carried out at special centers if one line of the family includes: <ul style="list-style-type: none"> ▶ at least three women who developed breast cancer ▶ at least two women (including one below age 50) who developed breast cancer ▶ at least one woman who developed breast cancer and one woman who developed ovarian cancer ▶ at least two women who developed ovarian cancer ▶ at least one woman who developed breast and ovarian cancer ▶ at least one woman who developed breast cancer before age 36 ▶ at least one woman who developed cancer in both breasts before age 51 ▶ at least one man who developed breast cancer and one woman who developed breast or ovarian cancer.
GCP	

Risk-2	Pathology of BRCA1-associated carcinoma of the breast
	a. BRCA1-associated carcinomas of the breast frequently exhibit a characteristic histopathological and immunohistochemical phenotype: <ul style="list-style-type: none"> ▶ invasive carcinoma (NOS) with a growth pattern similar to that of medullary carcinoma ▶ G3 morphology ▶ negativity for estrogen receptors, progesterone receptors and HER2/neu (triple negative)
Level of evidence 2a	(Honrado E et al. 2006; Lakhani SR et al. 1998; Lakhani SR et al. 2005)
	b. In cases where these characteristics are present, the pathologist should draw attention to the possibility of an inherited susceptibility.
GCP	(Honrado E et al. 2006; Lakhani SR et al. 1998; Lakhani SR et al. 2005)

Risk-3	Intensified early detection
	Early detection measures in patients with a high* familial risk include: <ul style="list-style-type: none"> ▶ Palpation of the breast by the doctor (every 6 months; from the age of 25 or 5 years before the earliest age of onset of the disease in the family) ▶ Ultrasound examination of the breast (every 6 months; from the age of 25 or 5 years before the earliest age of onset of the disease in the family) ▶ Mammography of the breast (every 12 months; from the age of 30, for subjects with a high mammary gland density (ACR4) from the age of 35) ▶ MRI of the breast (every 12 months; from the age of 25 or 5 years before the earliest age of onset of the disease in the family, usually only up to age 55 or until involution of the glandular parenchyma (ACRI-II), cycle-dependently in premenopausal women).
GCP	(Consortium of familial breast and ovarian cancer)

* i.e. confirmed pathogenic BRCA1 or BRCA2 mutation, or a permanent risk of developing the disease of 30% or more, or a heterozygous risk of 20% or more.

Risk-4	Treatment of BRCA-associated carcinoma of the breast
	The treatment of BRCA-associated carcinoma of the breast is based on the guideline recommendations for sporadic carcinoma of the breast.
GCP	

Risk-5	Primary prevention
Grade of recommendation B	Women with pathogenic BRCA1 or BRCA2 should be offered a bilateral prophylactic mastectomy. Bilateral prophylactic salpingo-oophorectomy (usually around the age of 40) is recommended.
Level of evidence 3a	(Bermejo-Perez MJ et al. 2007; Calderon-Margalit R et al. 2004; Christiaens M et al. 2007; Cochrane: Lostumbo L et al. 2010; Domchek SM et al. 2006; Evans DG et al. 2009a; NZGG 2009)

4 Locoregional Primary Disease

4.1 General diagnostic and therapeutic concepts (no statements)

4.2 Pretherapeutic diagnosis in patients with abnormal or suspicious breast findings

4.2.1 Basic diagnostic workup

Stag-1	Basic diagnostic workup
Grade of recommendation A	a. Necessary baseline examinations include: <ul style="list-style-type: none"> ▶ clinical breast examination: Breast inspection and palpation of breast and lymphatic drainage areas ▶ Mammography ▶ Ultrasound If the clinical breast examination produces abnormal findings, diagnostic imaging and histological examination should be performed to complete the diagnostic workup.
Level of evidence 1a	(NICE 2009b; NZGG 2009)
Grade of recommendation A	b. For the investigation of symptomatic findings in women under age 40, sonography is the imaging method of first choice.
Level of evidence 3b	(Nothacker M et al. 2007)
Grade of recommendation B	c. The effects of endogenous and exogenous hormones should be taken into account during the performance and interpretation of diagnostic procedures.
Level of evidence 2b	(Albert US et al. 2008; Houssami N et al. 2009)

4.2.2 Imaging methods

Stag-2	Mammography
Grade of recommendation A	a. For the investigation of abnormal clinical findings in women under age 40, mammography is the imaging method of first choice.
Level of evidence 1a	(NICE 2009b; NZGG 2009)
Grade of recommendation A	b. In high mammographic density (ARC3 and 4), the sensitivity of mammography is limited and should be enhanced by an additional ultrasound scan.
Level of evidence 3b	(Nothacker M et al. 2007; Nothacker M et al. 2009)

Stag-3	Ultrasonography
	a. Sonography is a supplementary study performed to investigate indeterminate lesions. (clinical/mammographic).
Level of evidence 1a	(Albert US et al. 2008; NICE 2009b; NZGG 2009)
Grade of recommendation A	b. Sonography should be used to especially to investigate clinically non-palpable mammographic lesions with the classifications BI-RADS0, III, IV and V.
Level of evidence 2b	(NICE 2009b; Nothacker M et al. 2007)
Grade of recommendation A	c. The aim of standardized breast sonography is the systematic and reproducible examination of both breasts and the axilla. The findings must be documented in a reproducible manner.
Level of evidence 2b	(Albert US et al. 2008; Madjar H et al. 2006; Madjar H 2010; NCCN 2011)
	d. Structural and process quality, as well as quality of outcomes, should also be demonstrated as a prerequisite for the use of breast sonography.
GCP	(Albert US et al. 2008; Madjar H et al. 2006)

Stag-4	MRI with contrast medium
Grade of recommendation A	a. A contrast-enhanced MRI of the breasts should not be routinely performed for pretherapeutic diagnosis.
Level of evidence 1a	(Houssami N et al. 2008; NICE 2009b; NZGG 2009; Turnbull L et al. 2010)
	b. A CE-MRI should only be performed if an MRI-guided intervention is a possible option.
GCP	

4.2.3 Diagnostic confirmation

Stag-5	Imaging-guided minimally invasive biopsy
Grade of recommendation A	a. The histological diagnostic investigation of unclear findings should be carried out via core biopsy, vacuum-assisted biopsy or excision biopsy. Core biopsy and vacuum-assisted biopsy can be performed mammographically and guided by ultrasound. Any interventions should be performed taking current quality recommendations into consideration.
Level of evidence 3a	(Albert US et al. 2008; NICE 2009b)
Grade of recommendation A	b. Fine-needle biopsy should not be employed as the standard method for diagnostic confirmation of solid breast tumors.
Level of evidence 2b	(Albert US et al. 2008; NCCN 2011; NICE 2009b)
Grade of recommendation A	c. In mammographic classification BI-RADS IV and V, intervention-guided tissue biopsy for histopathological confirmation of the diagnosis and for therapeutic planning should be performed using the imaging procedure which best represents the findings and is the least invasive.
Level of evidence 3a	(Albert US et al. 2008; NICE 2009b)
Grade of recommendation A	d. In the presence of microcalcifications without an accompanying focal lesion, stereotactically guided vacuum-assisted biopsy should preferably be performed.
Level of evidence 2b	(Nothacker M et al. 2007)

Stag-5	Imaging-guided minimally invasive biopsy (continuation)
	e. Vacuum-assisted biopsy should also be used for MRI-guided tissue sampling.
GCP	
	f. Following minimally invasive imaging-guided tissue sampling, the results should be verified by correlating the results of the imaging diagnostic studies with the histopathological findings.
GCP	(Albert US et al. 2008; Del Turco MR et al. 2010)
	g. If the histopathological examination reveals a benign lesion according to BI-RADS classification IV or V, a follow-up imaging study should be performed with the appropriate imaging method in 6–12 months' time. The quality requirements set down in the Stage 3 Guidelines for Early Breast Cancer Detection in Germany must be observed.
GCP	(Albert US et al. 2008)
Grade of recommendation 0	h. When primary clinical and/or radiological findings suggest that axillary lymph nodes are involved, an imaging-guided core biopsy can be performed as a minimally invasive procedure for cytohistological diagnostics to avoid superfluous axillary surgeries.
Level of evidence 3a	(NICE 2009b)

Stag-6	Open excisional biopsy
	a. Primary, open diagnostic excision biopsy should only be performed in exceptional cases, as when an imaging-guided intervention is not possible or too risky.
GCP	(Albert US et al. 2008; Gruber R et al. 2008)
Grade of recommendation A	b. In the case of non-palpable changes, it is always important to perform preoperative marking. Adequate resection via imaging methods must also be demonstrated.
Level of evidence 3b	(Albert US et al. 2008)
Grade of recommendation A	c. During the preoperative wire marking of non-palpable lesions, the wire should penetrate the focal lesion and project beyond the lesion by less than 1 cm. In cases where the wire does not penetrate the focal lesion, the distance between the wire and the margin of the lesion should be ≤ 1 cm. In non-space-occupying processes, marking of the surgically relevant target volume may be useful.
Level of evidence 3b	(Albert US et al. 2008)
	d. The material collected during the operation should be clearly marked and sent to the pathologists without any incision of the tissue material obtained.
GCP	(Albert US et al. 2008)
	e. An intraoperative decision as to whether a lesion is benign or malignant on the basis of a frozen section should be made only in exceptional cases. Prerequisites for a frozen section of surgical specimens are: <ul style="list-style-type: none"> ▶ The lesion is palpable intraoperatively and in the specimen ▶ The lesion is sufficiently large (generally > 10 mm)
GCP	(Albert US et al. 2008)

4.2.4 Staging

Stag-7	Staging
Grade of recommendation A	In patients with locally advanced carcinomas and in cases where metastasis is suspected, the following individual studies should be performed for staging prior to the institution of treatment: <ul style="list-style-type: none"> ▶ chest x-ray ▶ ultrasound examination of the liver ▶ bone scan
Level of evidence 5	(Alderson PO et al. 1983; Crump M et al. 1996; NICE 2009b; NZGG 2009)

4.3 Preinvasive neoplasms

Preinv-1	Therapeutic concept for preinvasive lesions
	Once a histological finding has been established from a core/vacuum-assisted biopsy, the therapeutic strategy for preinvasive neoplasms should be elaborated by an interdisciplinary team consisting of a specialist in diagnostic radiology, a surgeon and a pathologist.
GCP	(NCCN 2011)

Preinv-2	Therapeutic concept for preinvasive lesions
	An individualized treatment strategy should be elaborated for and offered to every patient with ductal carcinoma in situ (DCIS) without invasive portions. The patient must be briefed on the arguments for and against the particular therapies and combinations of these therapies, as well as on the advantages with respect to the likelihood of local recurrence and the absence of an effect on the probability of survival.
GCP	(NICE 2009; NZGG 2009)

Preinv-3	Operation
Grade of recommendation A	a. The resection margin is an important prognostic factor in DCIS. The tumor-free distance to the excision margin should be at least 2 mm whenever postoperative radiation therapy is planned.
Level of evidence 2b	(Dunne C et al. 2009; NICE 2009; NZGG 2009)
Grade of recommendation A	b. In DCIS, axillary dissection should not be performed. A sentinel node biopsy should only be performed when a secondary sentinel node biopsy is not possible for technical reasons.
Level of evidence 1b	(Christiaens M et al. 2007; NZGG 2009)

Preinv-4	Radiotherapy
Grade of recommendation A	a. Postoperative radiotherapy after breast-conserving surgery for DCIS lowers the rate of invasive and non-invasive local recurrences without any demonstrable effect on overall survival.
Level of evidence 1a	(Bijker N et al. 2006; Clarke M et al. 2005; Cochrane: Goodwin A et al. 2009; Cutuli B et al. 2002; Cuzick J et al. 2011; EBCTCG: Correa C et al. 2010; Emdin SO et al. 2006; Holmberg L et al. 2008)
Grade of recommendation A	b. The absolute risk reduction in the local recurrence rate by radiotherapy after breast-conserving surgery for DCIS depends on individual factors.
Level of evidence 1b	(Baxter NN et al. 2005; Boyages J et al. 1999; Cochrane: Goodwin A et al. 2009; Cuzick J et al. 2011; EBCTCG: Correa C et al. 2010; Houghton J et al. 2003; Omlin A et al. 2006; Shelley W et al. 2006; Smith BD et al. 2006)

Preinv-5	Pharmacotherapy
	Tamoxifen can lower the risk for an ipsilateral and contralateral recurrence of a DCIS. There is no effect on survival. The decision for the adjuvant use of tamoxifen should be made individually after weighing the benefits and side-effects.
GCP	(Fisher B et al. 1999; Fisher B et al. 2001b; Houghton J et al. 2003)

4.4 Surgical treatment of invasive carcinoma

4.4.1 General recommendation

Surg-1	Tumor resection
	a. Tumor excision with a negative resection margin (R0 status) is the basis of therapy for all non-advanced breast carcinomas.
GCP	(Blichert-Toft M et al. 1998; Renton SC et al. 1996)
	b. The resection margin status has a prognostic effect in invasive breast carcinoma. There is a significant relationship between the resection margin status (positive vs. close vs. negative) and the local recurrence rate.
Level of evidence 3a	(Houssami N et al. 2010)

Surg-2	Minimum safety distance
Grade of recommendation A	For this reason, the minimum safety distance in invasive breast carcinoma between the tumor (invasive carcinoma and associated DCIS) and the resection margin should be at least 1 mm.
Level of evidence 3a	(Houssami N et al. 2010; NZGG 2009)

4.4.2 Breast-conserving treatment

Surg-3	Breast-conserving treatment
	a. The objective of surgical treatment is removal of the tumor. Breast-conserving treatment (BCT) followed by radiotherapy of the whole breast is equivalent in terms of survival to modified radical mastectomy (MRM) alone.
Level of evidence 1a	(EBCTCG 1995; Fisher B et al. 2001; Veronesi U et al. 2002; Wald NJ et al. 1995; Weaver DL et al. 2000)
	b. For this reason, all patients should be briefed on the options of breast-conserving treatment (BCT) and modified radical mastectomy (MRM) with the possibility of primary or secondary reconstruction.
GCP	(NZGG 2009)

4.4.3 Mastectomy

Surg-4	Modified radical mastectomy
Grade of recommendation A	The following constitute indications for modified radical mastectomy: <ul style="list-style-type: none"> ▶ diffuse, extensive calcifications of the malignant type ▶ multicentricity ▶ incomplete removal of the tumor (including the intraductal component), even after repeat excision ▶ inflammatory carcinoma of the breast, (including following neoadjuvant treatment) ▶ likelihood of an unsatisfactory cosmetic result with breast-conserving treatment ▶ postoperative radiotherapy clinically contraindicated after breast-conserving treatment ▶ patient's informed preference
Level of evidence 2b	(Fisher B et al. 1994; NZGG 2009; Voogd AC et al. 2001)

4.4.4 Plastic reconstructive procedures

Surg-5	Breast reconstruction
Grade of recommendation A	Every patient due to undergo a mastectomy should be informed about the possibility of immediate or later breast reconstruction or of not having any reconstructive procedure at all; contact with other patients or self-help groups or organizations should also be offered.
Level of evidence 2b	(Lanitis S et al. 2010; NICE 2009; Potter S et al. 2011)

4.4.5 Surgical treatment of the axilla

Surg-6	Surgical treatment of the axilla
	a. Determination of the histological node status (pN status) is part of the surgical treatment of invasive breast cancer. This should be done by means of sentinel lymph node biopsy (SLNB).
GCP	(Kuehn T et al. 2005; Lyman GH et al. 2005; NICE 2009; NZGG 2009)
Level of evidence 1b	b. SLNB is equivalent to axillary dissection in terms of local control in SLN-negative patients. (Krag DN et al. 2010; NZGG 2009)
Level of evidence 1a	c. Morbidity after SLNB is significantly reduced compared with axillary dissection. (Fleissig A et al. 2006; Mansel RE et al. 2006; NICE 2009; Veronesi U et al. 2003)
	d. Axillary dissection must be performed in patients in whom no SLN is detected.
GCP	
Grade of recommendation A	e. In patients who exhibit a positive SLN (macrometastasis), axillary dissection with removal of at least 10 lymph nodes from levels I and II is indicated.
Level of evidence 1b	(NZGG 2009)
	f. For patients with pT1-pT2/cN0 tumors undergoing breast-conserving surgery followed by tangential field irradiation and who exhibit one or two positive sentinel lymph nodes, there is the option of refraining from axillary dissection.
GCP	(Giuliano AE et al. 2010)
	g. This procedure requires extensive preliminary information and briefing of the patient. The process and outcome quality must be evaluated prospectively in conjunction with quality assuring measures.
GCP	
	h. Axillary dissection is not necessary if only micrometastases are present.
GCP	

Surg-7	Removal of sentinel lymph nodes
	If the sentinel lymph node is removed, the quality criteria of the medical associations must be met.
GCP	(Kuehn T et al. 2005; Lyman GH et al. 2005; NICE 2009)

4.5 Pathomorphological examination

4.5.1 Preliminary remarks

(no statements)

4.5.2 General principles

Patho-1	General principles for surgical material
	The surgical material should be identified with unambiguous topographical markings and sent to the pathologist without the prior removal of any tissue by the clinician or surgeon (or others).
GCP	(Amendoeira I 2006b; NCCN 2011)

Patho-2	Histological classification of invasive carcinomas
	All invasive carcinomas must be classified histologically (according to WHO 2003).
GCP	(Amendoeira I 2006b; NCCN 2011; NHMRC2001; The Association of Breast Surgery at BASO RCoSoE 2005; WHO 2003)

Patho-3	Grading of invasive carcinomas
	All invasive carcinomas are to be graded according to the WHO system (Elston and Ellis modification of the Bloom and Richardson grading (Elston CW et al. 1991)).
GCP	

Patho-4	Hormone receptor (ER/PgR) and HER2 status of invasive carcinomas
Grade of recommendation A	a. In patients with invasive breast carcinoma, the primary diagnostic procedures should include determination of the estrogen and progesterone receptor status and of the HER2 status, preferably directly on the core biopsy.
Level of evidence 2a	(Hammond ME et al. 2010; ICSI 2005; NCCN 2011; NHMRC2001; NICE 2009; NZGG 2009; Wolff AC et al. 2007a)
	b. The estrogen and progesterone receptor status should be determined by immunohistochemistry assay. The percentages of positive tumor cell nuclei and the mean color intensity should be stated for each receptor type. In addition, scores can be calculated, in which case the procedure used should be specified (Allred (Quick) Score, Immunoreactive Score of Remmele and Stegner). At least 1 % positive tumor cell nuclei are required for classification as ER- or PgR-positive.
GCP	(Hammond ME et al. 2010; NCCN 2011; NICE 2009; NZGG 2009)
Grade of recommendation A	c. HER2 positivity as a precondition for trastuzumab therapy is defined as protein overexpression with a score of 3+ demonstrated by immunohistochemistry assay, or gene amplification demonstrated preferably by fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH).
Level of evidence 1b	(Carlson RW et al. 2006; Crump M 2005; NCCN 2011; NCRI 2005; Nothacker M et al. 2007; Wolff AC et al. 2007a)
	d. It must be ensured that the detection method used to determine the hormone receptor and HER2 status is reliable. This involves internal test validation, the use of standardized protocols and internal controls, and regular successful participation in external quality assurance measures.
GCP	(Carlson RW et al. 2006; Hammond ME et al. 2010; NCCN 2011; NICE 2009; NZGG 2009; Wolff AC et al. 2007a)

Patho-5.1	Prognosis and prediction
	The tumor characteristics and the patient's situation must be documented in order to be able to assess the course of the disease (prognosis) and the expected effect of systemic therapies (prediction). The following should be documented as prognostic factors:
Grade of recommendation A	a. pTNM status (tumor size, axillary lymph node involvement, distant metastasis)
Level of evidence 1a	(Bundred NJ 2001; Carter CL et al. 1989; NCCN 2011; NZGG 2009; Page DL et al. 1992; Page DL et al. 1998; Rosen PP et al. 1991; Rosen PP et al. 1993)
Grade of recommendation A	b. Resection margin (R classification) and safety distances
Level of evidence 1b	(Bundred NJ 2001; Kurtz JM et al. 1989; NCCN 2011; NICE 2009; NZGG 2009; Park CC et al. 2000)
Grade of recommendation A	c. histological type
Level of evidence 2b	(Fisher ER et al. 1990; NCCN 2011; NZGG 2009)
Grade of recommendation A	d. tumor grade
Level of evidence 2a	(Elston CW et al. 1991; NCCN 2011; NZGG 2009)
	The following should be documented as prognostic factors:
Level of evidence 2b	e. Lymphatic and vascular invasion (Lx, Vx) (Colleoni M et al. 2007; Gasparini G et al. 1994; Kato T et al. 2003; NCCN 2011; NZGG 2009)
	f. Age
GCP	
Grade of recommendation 0	g. In the case of node-negative breast cancers, the determination of tumor concentrations of uPA and PAI-1 by ELISA can provide additional prognostic information.
Level of evidence 1a	(Harbeck N et al. 2009; Harris L et al. 2007; Janicke F et al. 2001; Look MP et al. 2002)
	The following predictive factors for adjuvant therapy should be documented:
Grade of recommendation A	h. Estrogen/progesterone receptor status for hormone therapy
Level of evidence 1a	(Bundred NJ 2001; EBCTCG 1992; EBCTCG 1998; NCCN 2011; Osborne CK 1998)
Grade of recommendation A	i. HER2/neu status for targeted anti-HER2 treatment
Level of evidence 1b	(NCCN 2011; NICE 2009; Nothacker M et al. 2007; NZGG 2009)
Grade of recommendation A	j. Menopausal status for use of antiestrogen therapy.
Level of evidence 1c	(EBCTCG 2000; NCCN 2011)
	k. The prognostic and predictive value of the proliferation marker Ki-67 is not sufficiently documented. Outside of studies, therefore, it cannot be used clinically for subtyping ER-positive breast cancers (e.g. Ki-67 < 14%: luminal A; Ki-67 ≥ 14%: luminal B) as a basis for deciding on the use of systemic treatment.
GCP	(de Azambuja E et al. 2007; Dowsett M et al. 2011; Stuart-Harris R et al. 2008; Yerushalmi R et al. 2010)
	l. The use of gene expression analyses – PCR-based or by microarray – for evaluation of the prognosis or response to treatment (prediction) is not sufficiently validated for routine use and can therefore not be recommended.
GCP	(EGAPP Working Group 2009; Marchionni L et al. 2008; Paik S et al. 2004; Paik S et al. 2006)

Patho-5.2	Predictive factors in connection with neoadjuvant systemic treatment
Grade of recommendation A	Predictive factors that should be taken into account before administering neoadjuvant systemic treatment because they hold significant predictive value for the occurrence of a pathological complete remission (pCR)§: <ul style="list-style-type: none"> ▶ Age ▶ cT ▶ cN ▶ histological type ▶ histological grading ▶ ER and PgR status ▶ HER2 status
Level of evidence 1a	(von Minckwitz G et al. 2011)

Patho-6	Frozen section examination
	An intraoperative decision as to whether a lesion is benign or malignant on the basis of a frozen section should be made only in exceptional cases. Prerequisites for a frozen section of surgical specimens are: <ul style="list-style-type: none"> ▶ The lesion is palpable intraoperatively and in the specimen ▶ The lesion is sufficiently large (generally > 10 mm)
GCP	(Amendoeira I 2006b; NHMRC2001; NZGG 2009; O'Higgins N et al. 1998)

4.5.3 Percutaneous biopsies used in connection with interventional diagnostic procedures

(no statements)

4.5.4 Excisional biopsies

(no statements)

4.5.5 Mastectomy specimens

(no statements)

4.5.6 Lymph nodes

Patho-7	Lymph node status
	The lymph node status is determined on the basis of histological examination of all the lymph nodes removed. Documentation of the following is mandatory: number of lymph nodes removed and involved, capsule penetration, pN category (according to TNM classification, 76th Edition, UICC20 022010).
GCP	(ICSI 2005; NHMRC2001; NZGG 2009; The Association of Breast Surgery at BASO RCoSoE 2005; UICC2010)

4.6 Adjuvant radiotherapy of breast cancer

4.6.1 Radiotherapy after breast-conserving surgical treatment

RT-1	Radiotherapy after breast-conserving surgical treatment (general)
Grade of recommendation A	In patients with invasive carcinoma, irradiation of the affected breast is indicated after breast-conserving surgery.
Level of evidence 1a	(Clarke M et al. 2005; EBCTCG 2011; Darby S et al. 2011; EBMG 2006; Harnett A et al. 2009; NZGG 2009; Peto R 2006)

RT-2	Administration of radiotherapy after breast-conserving therapy (BCT)
Grade of recommendation A	a. The target volume of percutaneous adjuvant radiotherapy should encompass the entire residual breast and the adjoining chest wall.
Level of evidence 1a	(EBCTCG 2011; Darby S et al. 2011; EBMG 2006; NCCN 2007; NHMRC2001; NICE 2009; NZGG 2009; SIGN 2005)
Grade of recommendation A	b. The dose should be approx. 50 Gy in conventional fractionation (5×1.8 – 2.0 Gy/week).
Level of evidence 1a	(Clarke M et al. 2005; EBCTCG 2011; Darby S et al. 2011; EBMG 2006; NCCN 2011; NHMRC2001; Peto R 2006; SIGN 2005)
Grade of recommendation B	c. In older patients without locoregional lymph node involvement and with tumors < 5 cm who do not require chemotherapy, hypofractionated regimens can also be used as an alternative to conventionally fractionated radiotherapy for percutaneous homogeneous irradiation of the breast (e.g., 5×2.666 Gy per week up to 40 Gy).
Level of evidence 1a	(Goldhirsch A et al. 2011; Harnett A 2010; NCCN 2011; NICE 2009; Smith BD et al. 2011a; Whelan TJ et al. 2010)
Grade of recommendation A	d. The application of a local booster dose (boost irradiation) to the tumor bed reduces the rate of local recurrence in the breast without conferring an advantage in terms of survival. Boost irradiation is generally indicated. The recommended boost dose is (10–)16 Gy in conventional fractionation (5×1.8 – 2.0 Gy/week).
Level of evidence 1a	(Antonini N et al. 2007; Bartelink H et al. 2007; Jones HA et al. 2009; Livi L et al. 2009; Poortmans P 2007; Poortmans PM et al. 2008; Poortmans PM et al. 2009; Romestaing P et al. 1997; Romestaing P et al. 2009; Sautter-Bihl ML et al. 2007; SIGN 2005)
Grade of recommendation C	e. In postmenopausal patients with a very low risk of local recurrence (in particular, age > 60 years, small tumors and favorable prognostic factors), the absolute advantage conferred by boost irradiation is small. In this subgroup, the administration of boost irradiation may be omitted if necessary.
Level of evidence 2a	(EBCTCG 2011; Darby S et al. 2011; NZGG 2009)

4.6.2 Partial breast irradiation

RT-3	Radiotherapy confined to parts of the breast (partial breast irradiation, PBI) as the sole form of irradiation, including intraoperative radiotherapy (IORT) alone
	Partial breast irradiation as the sole form of intraoperative or postoperative radiation treatment is not standard therapy
Level of evidence 3b	(NCCN 2006; NCCN 2007)

4.6.3 Radiotherapy of the chest wall after mastectomy

RT-4	Radiotherapy of the chest wall after mastectomy
	a. Postoperative radiotherapy of the chest wall after mastectomy reduces the risk of locoregional recurrence.
Level of evidence 1a	(Clarke M et al. 2005; EBMG 2006; NCCN 2011; NHMRC2001; NICE 2009; NZGG 2009; Peto R 2006; Shafiq J et al. 2007; SIGN 2005; Whelan T et al. 2007)
	b. In patients with a high risk of a local recurrence, overall survival is also improved.
Level of evidence 1a	(Clarke M et al. 2005; Darby S et al. 2009; Fernando SA et al. 2007; GebSKI V et al. 2006; Harris EE 2008; JagSI R et al. 2009; Kyndi M et al. 2008b; Kyndi M et al. 2008a; NCCN 2011; NICE 2009; Nielsen HM et al. 2006a; Nielsen HM et al. 2006b; NZGG 2009; Overgaard M et al. 2007; Peto R 2006; Poortmans P 2007; Rowell NP 2009; Rowell NP 2010; Voordeckers M et al. 2009; Whelan T et al. 2007)
	c. Postoperative radiotherapy of the chest wall after mastectomy is therefore indicated in the following situations:
Grade of recommendation A	▶ T3/T4
Level of evidence 1a	(NCCN 2011; NICE 2009; NZGG 2009)
Grade of recommendation B	▶ pT3 pN0 R0 only in the presence of other risk factors (lymphatic vessel invasion, G3 grade, close resection margin, premenopausal status, age < 50 years)
Level of evidence 2b	(Floyd SR et al. 2009; Kunkler I 2010; McCammon R et al. 2008; Rowell NP 2009; Russell NS et al. 2009)
Grade of recommendation A	▶ R1-/R2 resection and no possibility of a complete repeat resection
Level of evidence 1a	(NCCN 2011; NICE 2009; NZGG 2009)
Grade of recommendation A	▶ pN+ (> 3 lymph nodes)
Level of evidence 1a	(NCCN 2011; NICE 2009; NZGG 2009)
Grade of recommendation A	d. After primary (neoadjuvant) systemic therapy, the indication for radiotherapy should be based on the pretherapeutic T and N category, regardless of the degree of response to the primary systemic therapy.
Level of evidence 2a	(Buchholz TA et al. 2002; Buchholz TA et al. 2008; Buchholz TA 2009; Garg AK et al. 2007; Goldhirsch A et al. 2009; Huang EH et al. 2006; Kaufmann M et al. 2003; Kaufmann M et al. 2010; NCCN 2007; NCCN 2011)

4.6.4 Radiotherapy of the regional lymphatic drainage system

RT-5	Radiotherapy of the regional lymphatic drainage system
Grade of recommendation A	a. In a pN0 situation, the regional lymphatic drainage areas should not undergo adjuvant irradiation.
Level of evidence 3b	(NCCN 2011; NICE 2009)
Grade of recommendation A	b. Radiotherapy of the axilla is recommended only in the following situations: ▶ residual tumor in the axilla
Level of evidence 2b	(NCCN 2011; NICE 2009; NZGG 2009; SIGN 2005; Truong PT et al. 2004; Truong PT et al. 2005b)
Grade of recommendation A	▶ unequivocal clinical involvement and in the absence of axillary dissection.
Level of evidence 3b	(NCCN 2011; NICE 2009; NZGG 2009)
Grade of recommendation A	c. The benefit of radiotherapy of the regional lymphatic drainage channels following detection of isolated tumor cells or micrometastases in regional lymph nodes (pNm1c) is not substantiated and therefore it should not be performed.
Level of evidence 3b	(de Boer M et al. 2009; de Boer M et al. 2010; Lupe K et al. 2011; Tjan-Heijnen VC et al. 2009; Truong PT et al. 2008)
GCP	d. Radiotherapy of the internal mammary lymph node drainage region should not be performed. (NICE 2009; NZGG 2009)
Grade of recommendation B	e. Radiotherapy of the supraclavicular and infraclavicular lymphatic drainage channels is recommended in the following situations: ▶ patients with > 3 positive axillary lymph nodes (> pN2a)
Level of evidence 1b	(NICE 2009; NZGG 2009)
Grade of recommendation B	▶ level III axillary involvement
Level of evidence 3b	(NZGG 2009; SIGN 2005)
Grade of recommendation B	▶ where irradiation of the axilla is indicated (residual tumor in the axilla)
Level of evidence 3b	(NZGG 2009; SIGN 2005)
Level of evidence 3b	f. The indication for radiotherapy of the regional lymph drainage channels following primary systemic therapy should be dependent on the pretherapeutic baseline situation and independent of the response of the tumor manifestations to systemic therapy.
Level of evidence 3b	(Buchholz TA et al. 2002; Garg AK et al. 2007; Huang EH et al. 2006; Kaufmann M et al. 2010; McGuire SE et al. 2007; NCCN 2011)
GCP	g. Where irradiation of lymphatic drainage areas is indicated, radiotherapy is administered with approx. 50 Gy in conventional fractionation (5 × 1.8–2.0 Gy/week). For irradiation of the supraclavicular lymphatic drainage region, a single dose of 1.8 Gy should be preferred.

4.6.5 Radiotherapy of advanced or inoperable tumors

RT-6	Radiotherapy for locally very advanced tumors and primary inoperability
Grade of recommendation A	a. Primary systemic therapy followed by surgery and postoperative radiotherapy is recommended for patients with primarily inoperable or inflammatory carcinomas.
Level of evidence 1b	(Kaufmann M et al. 2003; Kaufmann M et al. 2010; NCCN 2011; NICE 2009)
GCP	b. If systemic therapy fails to achieve operability, radiotherapy – possibly in combination with simultaneous systemic therapy – is indicated. (Kaufmann M et al. 2003; Kaufmann M et al. 2010; NCCN 2007; NCCN 2011; Shenker T et al. 2004; Truong PT et al. 2004)

4.6.6 Sequencing of chemotherapy, antibody therapy, systemic endocrine therapy and hormonal therapy

RT-7	Sequencing of chemotherapy and radiotherapy
Grade of recommendation B	The superiority of a particular chronological sequence of chemotherapy and radiotherapy has not been sufficiently established. As a basic rule, the postoperative sequence depends on the type of recurrence most likely to occur, especially since the optimal time is not sufficiently substantiated.
Level of evidence 1a	(Cochrane: Hickey BE et al. 2006; Kaufmann M et al. 2010; NCCN 2011; NICE 2009; Poortmans P 2007; Recht A 2003; Recht A 2010; Rouesse J et al. 2006; Tsoutsou PG et al. 2010)

RT-8	Sequencing of antibody therapy and radiotherapy
GCP	The concurrent administration of trastuzumab and radiotherapy can be justified as long as no irradiation of the internal mammary lymph nodes is planned. (Azria D et al. 2010b; Balduzzi A et al. 2010; Belkacemi Y et al. 2008; Chargari C et al. 2011a; Chargari C et al. 2011b; Halyard MY et al. 2009; Kirova YM et al. 2009; Romond EH et al. 2005; Shaffer R et al. 2009)

RT-9	Sequencing systemic endocrine therapy and radiotherapy
Level of evidence 1a	Endocrine treatment modalities can be performed concurrently or sequentially with radiotherapy. (Ahn PH et al. 2005; Harris EE et al. 2005; Hoeller U et al. 2007; Pierce LJ et al. 2005; Whelan T et al. 2005)

4.7 Systemic adjuvant therapy (endocrine therapy, chemotherapy and antibody therapy)

Adj-1	Diagnostic procedures before the start of chemotherapy
	A sentinel node biopsy should be performed before the beginning of neoadjuvant chemotherapy in patients with cN0; in those with cN1, the diagnosis can also be made by core biopsy or fine-needle biopsy.
GCP	

Adj-2	Pharmacotherapy of the primary disease
Grade of recommendation A	Pharmacotherapy of the primary disease is undertaken before or after surgery in the form of chemotherapy, endocrine therapy, anti-HER2 antibody therapy or a combination or sequence of these different forms.
Level of evidence 1a	(EBCTCG 2005; NCCN 2006)

Adj-3	Recurrence rate and mortality
	The recurrence rate and mortality can be reduced by systemic therapy. This applies to polychemotherapy, in particular the administration of anthracyclines and taxanes, pharmacological suppression of ovarian function, tamoxifen, aromatase inhibitors and trastuzumab. The extent of this effect in absolute terms depends on the disease risk.
Level of evidence 1a	(Cochrane: Ferguson T et al. 2007; EBCTCG 1998; EBCTCG 2005; EBCTCG 2011; NIH 2001)

Adj-4	Supportive therapy
	Optimal supportive therapy (e.g., stimulation of granulopoiesis, anti-emetic medication, provision of wigs, etc.) is an integral part of all systemic therapies. All patients should be briefed on possible side effects and late sequelae and offered prophylactic measures.
GCP	(NICE 2009)

Adj-5	Systemic therapy in older patients
Grade of recommendation B	Older* patients should receive similar systemic adjuvant therapy to that given to younger patients. Changes in organ function and comorbidities should be taken into account when establishing the indication for and implementing adjuvant treatment measures.
Level of evidence 1a	(EBCTCG 2011)

* "Older" patients are deemed to be all patients > 65 years. The deciding factors in the choice of adjuvant therapy are organ function and comorbidities.

4.7.1 Endocrine therapy

Adj-6	Indications for endocrine therapy
Grade of recommendation A	a. Endocrine therapy is indicated in patients with estrogen and/or progesterone receptor-positive tumors.
Level of evidence 1a	(EBCTCG 1998; EBCTCG: Davies C et al. 2011; Fisher B et al. 1997; NICE 2009; Thuerlimann B et al. 2001)
Grade of recommendation A	b. This should not be initiated until after chemotherapy has been completed.
Level of evidence 1a	(EBCTCG 1998; EBCTCG: Davies C et al. 2011; Fisher B et al. 1997; NICE 2009; Thuerlimann B et al. 2001)

Adj-7	Therapy in premenopausal patients
Grade of recommendation A	In premenopausal patients, tamoxifen is the endocrine therapy of choice. Antihormonal therapy with tamoxifen 20 mg per day should be given over a period of 5 years or until recurrence.
Level of evidence 1a	(EBCTCG 1998; EBCTCG: Davies C et al. 2011)

Adj-8	Therapy in postmenopausal patients
	a. In women who are definitely postmenopausal, third-generation aromatase inhibitors are superior to tamoxifen in terms of disease-free survival.
Level of evidence 1b	(Burstein HJ et al. 2010; NZGG 2009)
	b. The following endocrine treatment regimens can be used: <ul style="list-style-type: none"> ▶ tamoxifen for 5 years ▶ aromatase inhibitors for 5 years ▶ tamoxifen for 2–3 years followed by aromatase inhibitors, up to a total treatment duration of 5 years ▶ aromatase inhibitors for 2–3 years followed by tamoxifen, up to a total treatment duration of 5 years ▶ tamoxifen for 5 years followed by aromatase inhibitors for 5 years
GCP	

4.7.2 Chemotherapy

Adj-9	Adjuvant chemotherapy in receptor-negative tumors
Grade of recommendation A	a. All patients with receptor-negative tumors (pN0 and pN+) should receive adjuvant chemotherapy.
Level of evidence 1a	(EBCTCG 2011; NICE 2009; NZGG 2009)
Grade of recommendation A	b. Chemotherapy should be administered at the recommended dosages.
Level of evidence 1a	(Budman DR et al. 1998; EBCTCG 2011; Fisher B et al. 1997; French Adjuvant Study Group 2001; Fumoleau P et al. 2003)
	c. Underdosing or a reduction in the number of cycles is liable to cause a loss of effectiveness.
Level of evidence 1a	(Bonadonna G et al. 1995; Budman DR et al. 1998; Cady B et al. 1993; Fisher B et al. 1990; French Adjuvant Study Group 2001)

Adj-10	Administration of cytostatics
Grade of recommendation A	Cytotoxic agents should be administered concurrently or sequentially. Dose-dense treatments should be used in patients with an increased risk of recurrence.
Level of evidence 1b	(Bonadonna G et al. 1995; Citron ML et al. 2003; Eiermann W et al. 2011; Francis P et al. 2008; Moebus V et al. 2010; NIH 2001)

Adj-11	Indications for adjuvant chemotherapy
Grade of recommendation B	An indication for adjuvant chemotherapy should be established in the case of: <ul style="list-style-type: none"> ▶ HER2-positive tumors ▶ Tumors that are not sensitive to endocrine therapy (ER- and PR-negative). ▶ node-positive tumors or node-negative tumors with a high risk of recurrence ▶ G III ▶ young age of disease onset (< 35 years)
Level of evidence 1a	(Cochrane: Ferguson T et al. 2007; EBCTCG 2005; EBCTCG 2011; EBM Reviews 2003; NIH 2001; NZGG 2009)

Adj-12	Taxane-containing adjuvant standard chemotherapy
Grade of recommendation B	Adjuvant chemotherapy should include a taxane. Anthracycline- and taxane-containing adjuvant standard chemotherapy lasts 18–24 weeks.
Level of evidence 1b	(Bria E et al. 2006; Citron ML et al. 2003; Clavarezza M et al. 2006; Cochrane: Ferguson T et al. 2007; Estevez LG et al. 2007; Henderson IC et al. 2003; Mamounas EP et al. 2005; Roche H et al. 2006)

4.7.3 Neoadjuvant (primary systemic) therapy (NACT or PST)

Adj-13	Neoadjuvant systemic therapy
	Neoadjuvant (primary, preoperative) systemic therapy is now deemed the standard treatment for patients with locally advanced, primarily inoperable or inflammatory breast carcinoma within the context of a multimodal therapeutic strategy.
GCP	(Brito RA et al. 2001; Fisher B et al. 1997; Kaufmann M et al. 2006; von Minckwitz G et al. 2011)

Adj-14	Neoadjuvant or adjuvant chemotherapy
Grade of recommendation 0	a. If chemotherapy is indicated, this can be undertaken preoperatively (neoadjuvant) or postoperatively (adjuvant). The two procedures are equivalent in terms of overall survival. Neoadjuvant therapy can result in a higher rate of breast-conserving treatments.
Level of evidence 1a	(Kaufmann M et al. 2006; von Minckwitz G et al. 2011)
Level of evidence 1a	b. The effect is greatest on hormone receptor-negative carcinomas.
Level of evidence 1a	(Bear HD et al. 2006; von Minckwitz G et al. 2005; von Minckwitz G et al. 2011)
Level of evidence 1a	c. Resection within the new tumor margins is possible if R0 resection with a sufficient safety distance can be achieved.
Level of evidence 1a	(Kaufmann M et al. 2003; von Minckwitz G et al. 2011)

Adj-15	Primary hormonal therapy in postmenopausal patients
	Primary hormonal therapy represents an option for postmenopausal patients with receptor-positive and HER2-negative tumors in cases where surgery is contraindicated or refused.
GCP	

Adj-16	Neoadjuvant chemotherapeutic combination
	If a chemotherapeutic combination is used as neoadjuvant therapy, this should include an anthracycline and a taxane (trastuzumab if HER2-positive). The duration of preoperative therapy should be 6–8 cycles (equivalent to 18–24 weeks).
GCP	(von Minckwitz G et al. 2011)

4.7.4 Antibody therapy

Adj-17	Indications for antibody therapy
Grade of recommendation A	a. Patients with HER2-overexpressing tumors with a diameter ≥ 1 cm (immunohistochemical score 3+ and/or ISH-positive) should receive (neo-)adjuvant treatment with trastuzumab for one year.
Level of evidence 1b	(NICE 2009; NZGG 2009)
Grade of recommendation B	b. Adjuvant treatment with trastuzumab should preferably be started simultaneously with the taxane phase of adjuvant chemotherapy.
Level of evidence 2a	(Petrelli F et al. 2011)
	c. If there is an indication for chemotherapy in tumors < 10 mm, trastuzumab should be given additionally.
GCP	

4.7.5 Bisphosphonates

(no statements)

5 Recurrent or Metastatic Breast Cancer

5.1 Definition and prognosis

(no statements)

5.2 Diagnostic procedures for local or locoregional recurrence

(no statements)

5.3 Treatment of local/locoregional recurrence

5.3.1 Local (in-breast) recurrence

Rec-1	Local (in-breast) recurrence
	a. In patients with an in-breast recurrence (DCIS or invasive carcinoma), the best local tumor control is achieved by secondary mastectomy.
GCP	(Borner M et al. 1994; Dalberg K et al. 1998)
Grade of recommendation 0	b. In patients with a favorable baseline situation, e.g. patients with DCIS or invasive carcinoma with a long recurrence-free interval and no skin involvement, an organ-conserving surgical procedure can be performed in cases where this is deemed justified.
Level of evidence 4a	(Deutsch M 2002; Haffty BG et al. 1996; Kurtz JM et al. 1991; Whelan T et al. 1994)
	c. The possibility of re-irradiation (partial breast irradiation) must be investigated in the case of breast-conserving surgery.
GCP	
	d. Patients who undergo organ-conserving surgery must be advised of the higher risk of a repeat in-breast recurrence.
GCP	

5.3.2 Local recurrence after mastectomy

Rec-2	Local recurrence after mastectomy
	An isolated recurrence in the chest wall should be removed completely by surgery (R0) where possible.
GCP	(Schmoor C et al. 2000)

5.3.3 Locoregional recurrences and isolated supraclavicular lymph node recurrences

Rec-3	Isolated regional recurrence
	In patients with an isolated regional recurrence, the aim should be to achieve local control of the disease by surgery and/or radiotherapy.
GCP	

5.3.4 Pharmacotherapy

Rec-4	Postoperative systemic therapy
	The value of postoperative systemic therapy following surgical resection of a locoregional recurrence in terms of improved overall survival has not been sufficiently substantiated. There is evidence that the disease-free interval can be prolonged by systemic therapy.
GCP	(Cochrane: Rauschecker H et al. 2001; Cochrane: Rauschecker HHF et al. 2008; Haffty BG et al. 1996)

5.3.5 Radiotherapy

Rec-5	Radiotherapy after surgery for recurrence
	a. The need for radiotherapy after surgery for a recurrence should be discussed and decided upon within an interdisciplinary team. Postoperative radiotherapy can be performed if radiotherapy was not administered previously or radical surgical excision of the local recurrence was not performed (R1–2).
GCP	(Aberizk WJ et al. 1986)
	b. In patients with an inoperable local recurrence, palliative radiotherapy may be beneficial.
GCP	(Jones EL et al. 2005; Karasawa K et al. 2003; Semrau S et al. 2006; Sherar M et al. 1997)

5.4 Distant metastases

5.4.1 General principles

Met-1	Patient briefing on therapeutic options
	A patient with demonstrated distant metastases of breast cancer should be briefed in particular detail about the therapeutic options and involved in the decision-making process. The patient's request for information about all the relevant available measures, including supportive and complementary treatment options, should be satisfied.
GCP	(NICE 2009)

Met-2	Criteria of choice of treatment
	The choice of treatment should be adapted to the disease and individually tailored to the patient's expectations, values and preferences, as well as her symptoms, comorbidities, age and general state of health, the aggressiveness of the disease and location of the metastases, the type of prior adjuvant and palliative treatment, HER-2 status, hormone-receptor status and menopausal status.
GCP	

Met-3	Prognostic and predictive factors
Grade of recommendation A	The following prognostic and predictive factors should be determined before instituting treatment of metastatic breast cancer: <ul style="list-style-type: none"> ▶ hormone receptor status for hormonal therapy ▶ HER-2 status for treatment with anti-HER2 active substances ▶ bone metastases for the administration of bisphosphonates, or where applicable a RANK ligand inhibitor ▶ the previous response to chemoendocrine therapy for further systemic and local therapies ▶ the performance status for the effect and usefulness of chemotherapy
Level of evidence 1a	(Andersson M et al. 1999; Cheung KL et al. 1997; Hortobagyi GN et al. 1996; NICE 2009)

5.4.2 Diagnostic procedures in patients with distant metastases

(no statements)

5.4.3 Systemic therapy of metastatic breast cancer

5.4.3.1 Systemic endocrine therapy

Met-4	Systemic endocrine therapy
Grade of recommendation A	Endocrine therapy is the treatment of choice for patients with a positive hormone receptor status.
Level of evidence 1b	(Fossati R et al. 1998; NICE 2009; Stockler M et al. 1997; Stockler M et al. 2000)

Met-5	Contraindications to endocrine therapy
Grade of recommendation A	Endocrine therapy is not indicated in the following cases: <ul style="list-style-type: none"> ▶ need to achieve rapid remission to prevent severe symptoms in the affected organ ▶ negative hormone receptor status ▶ brain metastases (no adequate/sufficient therapy).
Level of evidence 1b	(Fossati R et al. 1998; NICE 2009; Stockler M et al. 1997; Stockler M et al. 2000)

Met-6	Combined chemoendocrine therapy
Grade of recommendation A	Combined chemoendocrine therapy is not recommended. Although it can improve remission rates, it causes increased toxicity without prolonging either the progression-free interval or overall survival.
Level of evidence 1a	(Cochrane: Carrick S et al. 2005; Sledge Jr. GW et al. 2000)

5.4.3.2 Endocrine therapy in premenopausal patients

Met-7	Ovarian suppression and tamoxifen in premenopausal patients
Grade of recommendation A	Suppression of ovarian function (GnRH analogs, oophorectomy, and ovarian ablation by radiotherapy) in combination with tamoxifen is the first-choice therapy in premenopausal patients.
Level of evidence 1b	(Klijn JG et al. 2001; NBOCC2010; NICE 2009)

Met-8	Other treatments in premenopausal patients
Grade of recommendation 0	In premenopausal patients, ovarian suppression can be used subsequently in combination with an aromatase inhibitor. Treatment with high-dose progestins (MA/MPA) represents a further step.
Level of evidence 2c	(NICE 2009; Taylor CW et al. 1998; von Minckwitz G et al. 1991)

5.4.3.3 Endocrine therapy in postmenopausal patients

Met-9	Aromatase inhibitors in postmenopausal patients
Grade of recommendation A	In postmenopausal patients with metastases, the first step in endocrine treatment following adjuvant therapy with tamoxifen or no adjuvant endocrine therapy is the administration of an aromatase inhibitor.
Level of evidence 1a	(Cochrane: Gibson L et al. 2009; Ellis MJ et al. 2000; Fossati R et al. 1998; Hayes DF et al. 1995; Mouridsen H et al. 2001a; Mouridsen H et al. 2001b; NICE 2009)

Met-10	Treatment cascade in postmenopausal patients
	Depending on the prior treatment, further steps in the cascade of endocrine therapy in postmenopausal women are the administration of antiestrogens, estrogen receptor antagonists, switch from a steroidal to a non-steroidal aromatase inhibitor (or vice versa), or the use of high-dose progestins.
GCP	(Fossati R et al. 1998; Robertson JF et al. 2003)

5.4.4 Chemotherapy of metastatic breast cancer

Met-11	Criteria for chemotherapy
	The patient's general condition and comorbidities must be established and compliance must be assessed before chemotherapy is administered.
GCP	

Met-12	Assessment of toxicity
	Toxicity must be assessed both objectively and subjectively at regular intervals during therapy. The doses administered, as well as the intended time intervals, must conform to generally accepted standard or currently published therapeutic regimens. After a suitable and representative measurement parameter has been selected prior to the institution of therapy (e.g., symptoms, tumor markers, indicator metastasis), the therapeutic effect should be evaluated at least every 6–12 weeks, depending on the clinical requirements/studies. Cytotoxic maintenance therapy increases toxicity without improving survival. For this reason, cytotoxic therapy is recommended only in the event of progression (increased symptoms and/or progression of the tumor process).
GCP	

Met-13	End of chemotherapy
	Treatment should be stopped immediately if progression or intolerable toxicity occurs.
GCP	

Met-14	Combination chemotherapy
	a. The administration of combination, as opposed to single-agent, chemotherapy may confer a slight advantage in terms of survival, but is often associated with a higher rate of toxicity.
Level of evidence 1a	(Cochrane: Carrick S et al. 2005; Cochrane: Carrick S et al. 2009; Fossati R et al. 1998)
Grade of recommendation B	b. In patients with mild symptoms and slow tumor growth, as well as cases where endocrine therapy is ineffective, single-agent chemotherapy is useful.
	In patients with severe symptoms and rapidly growing or aggressive tumors (i.e. where there is a strong pressure to achieve remission), combination chemotherapy should be administered.
Level of evidence 1a	(Cochrane: Carrick S et al. 2005; Fossati R et al. 1998)

Met-15	Monotherapy
	The following substances, for example, may be used for single-agent chemotherapy: Anthracyclines (including those in liposomal form), alkylating agents, anthraquinones, taxanes, vinorelbine fluoropyrimidine, platinum complexes and halichondrin. In combination chemotherapy, these cytotoxic agents can be combined with each other or with other substances. The highest remission rates are achieved with a taxane in combination with an anthracycline or antimetabolite.
	Patients should be checked to see whether they are eligible for inclusion in studies.
GCP	(Cochrane: Carrick S et al. 2005; Fossati R et al. 1998)

Met-16	Further chemotherapies
Grade of recommendation B	After the benefits of anthracycline and taxane treatments have been exhausted, patients should not be denied further chemotherapies, e.g., to stabilize the disease or alleviate symptoms.
Level of evidence 2b	(Feher O et al. 2002; NBOCC2010; Vogel C et al. 1999)

Met-17	Dose-intensified and high-dose therapies
Grade of recommendation A	Dose-intensified and high-dose therapies do not exhibit any improvement in survival and should therefore not be used.
Level of evidence 1b	(Cochrane: Farquhar C et al. 2005; Stadtmauer EA et al. 2000)

5.4.5 Targeted therapies

5.4.5.1 HER2 inhibitors (trastuzumab, lapatinib)

Met-18	Hormone receptor status and HER2 status
	The histology of the suspected metastatic lesion should be determined in advance of any therapy, if possible, to reassess the benign or malignant nature of the tumor and, where applicable, the hormone receptor and HER2 status.
GCP	(NICE 2009)

Met-19	Anti-HER2 therapy
	a. Treatment with HER-2 inhibitors is indicated in patients with HER-2-overexpressing tumors in combination with chemotherapy, or after remission induction as single-agent therapy, or after previous treatment with taxanes or anthracyclines with a non-cross-resistant chemotherapeutic agent.
GCP	(Burstein HJ et al. 2001; NBOCC2010; Seidman AD et al. 2001; Slamon DJ et al. 2001)
	b. Any secondary therapy following progression during trastuzumab therapy should continue to include anti-HER2-directed therapy.
Level of evidence 2b	(NBOCC2010)

Met-20	Monitoring of cardiac function
	It is essential to monitor cardiac function before and during therapy with potentially cardiotoxic substances.
GCP	

5.4.5.2 Antiangiogenesis: VEGF inhibitors (bevacizumab)

Met-21	Use of bevacizumab
	In patients with metastatic breast cancer receiving paclitaxel or capecitabine as first-line cytostatic therapy, bevacizumab can be administered additionally to improve the therapeutic outcome.
GCP	(NBOCC2010; Robert NJ et al. 2011)

5.4.6 Specific treatment of skeletal metastases

5.4.6.1 Indications for radiotherapy

Met-22	Indications for radiotherapy
Grade of recommendation A	Radiotherapy should be used for local therapy in patients with symptomatic bone metastases, or those posing a risk of fracture. The following constitute indications for radiotherapy: <ul style="list-style-type: none"> ▶ local pain symptoms ▶ risk to stability (if necessary in combination with surgical stabilization) ▶ impairment of mobility and/or function, in particular neurological symptoms (spinal cord compression is an emergency) ▶ pathological fractures that cannot be surgically treated ▶ postoperatively following the surgical treatment of bone metastases if R0 resection was not possible
Level of evidence 1a	(Hoskin PJ et al. 2001; NICE 2009; Roos DE et al. 2000; Steenland E et al. 1999)

5.4.6.2 Surgical therapy

Met-23	Surgical therapy
	Surgical therapy of skeletal metastases is undertaken for pain management and to restore or preserve function and stability, as well as quality of life. The decision to operate is made on the basis of the urgency and the therapeutic objective of this surgery, where necessary by an interdisciplinary team including the surgeon (general surgeon, orthopedic surgeon or neurosurgeon), radiation oncologist, medical specialist with oncological expertise, and pain therapist.
GCP	(Ali SM et al. 2003; Wunder JS et al. 2003)

Met-24	Indications for surgical therapy
	The following constitute indications for surgical therapy: <ul style="list-style-type: none"> ▶ pathological fractures (especially in the lower extremities and the acetabulum) ▶ unstable pathological vertebral fractures ▶ progressive spinal or radicular compression (the option of radiotherapy should be considered) ▶ impending fractures of the lower extremities
GCP	(Ali SM et al. 2003; Brown JE et al. 2003; Clohisy DR 2003; Fourny DE et al. 2003; Kelly CM et al. 2003; Koizumi M et al. 2003; Walker MP et al. 2003; Wunder JS et al. 2003)

5.4.6.3 Bisphosphonates/RANK ligand inhibitor therapy

Met-25	Bisphosphonates/RANK ligand inhibitor therapy
	The following constitute indications for bisphosphonate therapy: hypercalcemia, bone pain related to metastases, osteolytic metastases, and manifest osteoporosis induced by cancer therapy. Alternatively, RANK ligand inhibitor therapy can also be used.
GCP	(Conte PF et al. 1996; Hortobagyi GN et al. 1998; NICE 2009; O'Rourke N et al. 1995; Rosen LS et al. 2001; Stopeck AT et al. 2010; Theriault RL et al. 1999)

5.4.6.4 Specific treatment of brain metastases

Met-26	Treatment of brain metastases
Grade of recommendation 0	An isolated brain metastasis can be treated by surgery, by single-session stereotactic irradiation (RS), or by fractionated radiotherapy (SFRT), especially if the extracerebral disease is under control.
Level of evidence 2a	(NICE 2009)

Met-27	Multiple brain metastases
Grade of recommendation A	In patients with multiple brain metastases, percutaneous irradiation of the entire cranium (whole brain radiotherapy), supported by steroid medication in patients with perifocal edema, is indicated for the control of existing neurological symptoms.
Level of evidence 2a	(Cochrane: Hart MG et al. 2004; Kondziolka D et al. 1999)

5.4.7 Special treatments of visceral metastases

Met-28	Treatment of visceral metastases
	In individual cases that satisfy the following criteria, local therapy may be indicated for patients with visceral metastases (liver, lungs or other organs): <ul style="list-style-type: none"> ▶ no disseminated metastases ▶ metastases in only one lobe of the lungs or liver; if both lobes are affected, surgery is not indicated ▶ the metastasis did not occur during the first year after primary treatment.
GCP	(Bathe OF et al. 1999; Vogl TJ et al. 1999)

5.4.7.1 Hepatic metastases

(no statements)

5.4.7.2 Pulmonary metastases

(no statements)

5.4.7.3 Malignant pleural effusion

Met-29	Malignant pleural effusion
	In cases where pleural carcinosis occurs with symptomatic effusion, pleurodesis may be indicated.
GCP	(Cardillo G et al. 2002)

5.4.7.4 Cutaneous and soft tissue metastases

(no statements)

6 Treatment, Care and Support

6.1 General concept

(no statements)

6.2 Psychosocial aspects and psycho-oncology

6.2.1 Basic principles of psycho-oncological care

Psych-1	Psycho-oncological assistance
	a. Psycho-oncological measures are an integral part of the overall strategy of cancer therapy.
Level of evidence 1b	(Cochrane: Edwards AG et al. 2004; NICE 2009b; Sheard T et al. 1999)
Grade of recommendation A	b. All patients and their relatives should be informed at an early stage of the possibilities of psycho-oncological assistance.
Level of evidence 1b	(NICE 2009b)

6.2.2 Psycho-oncological care strategies and interventions

Psych-2	Psycho-oncological interventions
Grade of recommendation A	The following psycho-oncological interventions should be offered, tailored to the patients' individual requirement: <ul style="list-style-type: none"> ▶ relaxation techniques ▶ psychoeducative interventions ▶ individual psychotherapeutic interventions ▶ group psychotherapeutic interventions ▶ couple psychotherapeutic interventions
Level of evidence 1a	(Faller H et al. Metaanalysis in press)

Psych-3	Continuity of psycho-oncological care
	To ensure the continuity of psycho-oncological care after inpatient treatment, the patient should be informed about continuing outpatient and aftercare options from professional helpers and self-help groups.
GCP	(NICE 2009a)

Psych-4	Recommendation
Grade of recommendation B	The patient's quality of life should be assessed regularly in the course of the disease.
Level of evidence 2a	(Lemieux J et al. 2011; Velikova G et al. 1999; Velikova G et al. 2004)

6.3 Supportive therapy

Supp-1	Physical activity
Grade of recommendation A	The patient should be made aware of the need for physical activity during chemotherapy and radiotherapy, as this can have a positive effect on patients' physical fitness and thus help them to carry out activities of daily living (ADL).
Level of evidence 1a	(Cochrane: Markes M et al. 2006)

6.4 Rehabilitation

Rehab-1	Rehabilitation measures
	The tumor and its treatment by surgery, radiotherapy and systemic therapy can cause sequelae of varying degrees of severity that require targeted somatic and psychosocial rehabilitation measures. Patients should be informed at an early stage about the options for outpatient and inpatient rehabilitation measures and about additional claims arising under German social law. The patient's preferences should be taken into consideration when establishing the need for, and recommending, a particular type of rehabilitation.
GCP	(DRV Bund 2009)

Rehab-2	Strength and endurance training
	Strength training, alone or in combination with endurance training, in the rehabilitation phase is a suitable way of improving the state of health and quality of life.
Level of evidence 1a	(Cheema B et al. 2008)

Rehab-3	Movement programs
	Movement programs are suitable for reducing fatigue (tiredness) due to cancer.
Level of evidence 1a	(Cochrane: Cramp F et al. 2008)

Rehab-4	Physiotherapy
Grade of recommendation A	Postoperative physiotherapy to mobilize the shoulder joint should start at an early stage.
Level of evidence 1a	(Chan DN et al. 2010; Cochrane: McNeely ML et al. 2010)

Rehab-5	Lymphedema
	In patients with lymphedema, combined physiotherapy (skin care, manual lymph drainage, movement therapy, and compression bandages) is a suitable treatment method.
GCP	(Devoogdt N et al. 2010)

6.5 Follow-up care including diagnostic workup of recurrences and metastases and support during therapy

6.5.1 Objectives

FU-1	Follow-up care for breast cancer
	Follow-up care for breast cancer begins when locoregional primary treatment is completed. It consists of history-taking, a physical examination, medical advice, support and continuing care, as well as diagnostic imaging procedures to detect locoregional recurrences. In the event of abnormal findings, follow-up care should be designed so as to be symptom-oriented.
GCP	(Cochrane: Rojas MP et al. 2005; Grunfeld E et al. 2005; Gulliford T et al. 1997; Hurria A et al. 2003; Khatcheressian JL et al. 2006; NBOCC2010; Palli D et al. 1999; Pestalozzi BC et al. 2005; Rosselli DT et al. 1994)

FU-2	Interdisciplinary support and continuing care
	As part of her follow-up care, the breast cancer patient requires intensive interdisciplinary support and continuing care. Oncology specialists and also other healthcare professionals such as psycho-oncologists, physiotherapists, oncological nursing staff, breast care nurses, etc., should be involved as needed. The patient should be given information appropriate to her individual needs about the options for further treatment and support.
GCP	(NBOCC2010; Selby P et al. 1996)

6.5.2 Examinations to detect locoregional and in-breast recurrences, or contralateral breast cancer

FU-3	Instrumental diagnostic procedures after BCT
	In asymptomatic women who have undergone breast-conserving therapy, regular instrumental diagnostic procedures (mammography and ultrasonography) in the area of the ipsilateral breast are indispensable.
GCP	(Grunfeld E et al. 2002; Khatcheressian JL et al. 2006; Loprinzi CL2004)

FU-4	Follow-up mammograms
	All patients should undergo annual follow-up mammograms (where necessary supplemented by ultrasonography) of the contralateral breast.
GCP	(Geller BM et al. 2003; Johnson RC et al. 2000; Jubelirer SJ 1998; Kollias J et al. 2000)

6.5.3 Examination for metastases

FU-5	Intensified instrumental and technical laboratory diagnostic procedures
Grade of recommendation A	Intensified instrumental and technical laboratory diagnostic procedures, including chest X-ray, bone scan, CT, PET or MRI, as well as blood counts, serum biochemistry or tumor marker determination, are used for the diagnostic workup of metastases and not for standard follow-up care, and are only indicated in the event of clinical abnormalities.
Level of evidence 1a	(Aguilar-Bujanda D et al. 2004; Bornhak S et al. 2007; Cochrane: Rojas MP et al. 2000; Cochrane: Rojas MP et al. 2005; GIVIO Investigators 1994; Hayes DF 2007; NBOCC2010)

6.5.4 Diagnostic workup and treatment of side effects and sequelae of primary and long-term treatments

FU-6	Briefing about lymphedema
Grade of recommendation A	All patients who have undergone axillary lymphadenectomy must be briefed about the options for detection, prophylaxis and treatment of postoperative lymphedema.
Level of evidence 1b	(Armer J et al. 2004; Bani HA et al. 2007; Francis WVP et al. 2006; Golshan M et al. 2003; Hamner JB et al. 2007; Harris SR et al. 2001; Hayes S et al. 2005; Moseley AL et al. 2007; NICE 2009; Sanjuan A et al. 2005; Torrenza H et al. 2004)

6.5.5 Frequency of follow-up examinations

FU-7	Follow-up intervals
	Follow-up visits should be scheduled four times a year during the first three years after local primary therapy, twice a year during the fourth and fifth years, and annually from the sixth year onwards. These visits should incorporate screening for early detection.
GCP	(Khatcheressian JL et al. 2006)

FU-8	Physical activity
	Patients should be encouraged to undertake physical activity (> 2–3 hours/week) and to normalize their bodyweight (if they have an increased BMI) as part of their follow-up care. Assistance should be provided.
GCP	(Grunfeld E et al. 2005; Hauner D. et al. 2011; Voskuil DW et al. 2010)

FU-9	Patient motivation
	An essential part of follow-up care is the constant motivation of the patient to regularly take the medications prescribed for adjuvant therapy, particularly endocrine therapy (e.g., tamoxifen or aromatase inhibitors). The patient should be questioned in detail about tolerability and/or side effects. Appropriate measures must be used to treat the symptoms.
GCP	

6.6 Palliative medicine

Pall-1	Palliative medicine measures
	Palliative medical measures are part of the overall strategy of oncological care.
GCP	

Pall-2	Briefing of the patient and her relatives
	The patient and her relatives should be informed about the possibilities of palliative medical measures and care structures.
GCP	

6.7 Complementary therapy

Compl-1	Complementary and alternative therapies
	All patients should be asked whether they employ complementary and/or alternative therapies. Patients who use such procedures should be briefed about the possible risks and, where applicable, about interactions with standard treatments.
GCP	

6.7.1 Diagnostic workup

Compl-2	Diagnostic measures for complementary treatment strategies
	The diagnostic measures based on scientifically unproven concepts and/or incorrect interpretations of the relationships between the different functions of the body that are offered in conjunction with complementary and alternative treatment strategies should not be recommended.
GCP	

Compl-3	Food supplements
	During chemotherapy, hormone therapy, or radiotherapy, food supplements such as vitamins and trace elements should be supplied, where possible, through the natural diet and according to physiological requirements.
GCP	(S3 Leitlinie Magenkarzinom 2011)

6.7.2 Mistletoe therapy

Compl-4	Mistletoe therapy
	Mistletoe therapy does not prolong the survival of patients with breast cancer and an improvement in the quality of life is doubtful on the basis of current data.
Level of evidence 1a	(Cochrane: Horneber MA et al. 2008)

6.7.3 Traditional Chinese medicine (TCM)

(no statements)

6.7.4 Cimicifuga (black cohosh)

(no statements)

6.7.5 Homeopathy

(no statements)

6.7.6 Meditation and mindfulness-based stress reduction

(no statements)

6.7.7 Alternative methods

Compl-5	Alternative treatment procedures
	Alternative treatment procedures should not be recommended to patients. In a sympathetic counseling situation, the patient should be informed about the harm and benefit of this treatment in a value-neutral, competent and comprehensive way.
GCP	

6.8 Documentation

Docu-1	Documentation of findings, treatments and outcomes
	Findings, treatments, both primary and during the course of the disease, and relevant outcome events should be documented by hospitals, office-based physicians, and institutes responsible for care, used as needed at any time, and analyzed regularly.
GCP	

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8 References

- Aberizk WJ, Silver B, Henderson IC et al. The use of radiotherapy for treatment of isolated locoregional recurrence of breast carcinoma after mastectomy. *Cancer* 1986; 58: 1214–1218
- Aguiar-Bujanda D, Bohn-Sarmiento U, Aguiar-Morales J. False elevation of serum CA 15–3 levels in patients under follow-up for breast cancer. *Breast J* 2004; 10: 375–376
- Ahn PH, Vu HT, Lannin D 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
- Albert US, Schulz K, Alt D et al. Eine Leitlinie für Leitlinien: methodische Erstellung und Anwendung der Leitlinie Fraueninformation. *Zentralbl Gynaekol* 2003; 125: 484–493
- Albert US und die Mitglieder der Planungskommission und Arbeitsgruppenleiter der Konzierten Aktion Brustkrebs-Früherkennung in Deutschland. Stufe-3-Leitlinie Brustkrebs-Früherkennung in Deutschland, 1. Aktualisierung 2008. München: Zuckschwerdt Verlag; 2008
- Alderson PO, Adams DF, McNeil BJ et al. Computed tomography, ultrasound, and scintigraphy of the liver in patients with colon or breast carcinoma: a prospective comparison. *Radiology* 1983; 149: 225–230
- Ali SM, Harvey HA, Lipton A. Metastatic breast cancer: overview of treatment. *Clin Orthop Relat Res* 2003; 1 (415 Suppl.): S132–S137
- Amendoeira I. Quality Assurance Guidelines for Pathology: Open Biopsy and Resection Specimens. In: Perry NM, ed. *European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis*. Luxembourg: Office for Official Publications of the European Communities; 2006: 256–311
- Andersson M, Madsen EL, Overgaard M et al. Doxorubicin versus methotrexate both combined with cyclophosphamide, 5-fluorouracil and tamoxifen in postmenopausal patients with advanced breast cancer – a randomised study with more than 10 years follow-up from the Danish Breast Cancer Cooperative Group. *Danish Breast Cancer Cooperative Group (DBCG). Eur J Cancer* 1999; 35: 39–46
- Antonini N, Jones H, Horiot JC et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881–10882. *Radiother Oncol* 2007; 82: 265–271
- Armer J, Fu MR, Wainstock JM et al. Lymphedema following breast cancer treatment, including sentinel lymph node biopsy. *Lymphology* 2004; 37: 73–91
- Azria D, Betz M, Bourcier C et al. Identifying patients at risk for late radiation-induced toxicity. *Crit Rev Oncol Hematol* 2012; 84 (Suppl. 1): e35–e41
- Balduzzi A, Leonardi MC, Cardillo A et al. Timing of adjuvant systemic therapy and radiotherapy after breast-conserving surgery and mastectomy. *Cancer Treat Rev* 2010; 36: 443–450
- Bani HA, Fasching PA, Lux MM et al. Lymphedema in breast cancer survivors: assessment and information provision in a specialized breast unit. *Patient Educ Couns* 2007; 66: 311–318

- 15 Bartelink H, Horiot JC, Poortmans PM *et al.* Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC22881-10882 trial. *J Clin Oncol* 2007; 25: 3259-3265
- 16 Bathe OF, Kaklamanos IG, Moffat FL *et al.* Metastectomy as a cytoreductive strategy for treatment of isolated pulmonary and hepatic metastases from breast cancer. *Surg Oncol* 1999; 8: 35-42
- 17 Baxter NN, Virnig BA, Durham SB *et al.* Radiation after lumpectomy for DCIS to reduce the risk of invasive breast cancer: a population-based study [Meeting Abstracts]. *J Clin Oncol* 2005; 23 (16 Suppl.): 516
- 18 Belkacemi Y, Fourquet A, Cutuli B *et al.* Radiotherapy for invasive breast cancer: guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence. *Crit Rev Oncol Hematol* 2011; 79: 91-102
- 19 Belkacemi Y, Gligorov J, Ozsahin M *et al.* Concurrent trastuzumab with adjuvant radiotherapy in HER2-positive breast cancer patients: acute toxicity analyses from the French multicentric study. *Ann Oncol* 2008; 19: 1110-1116
- 20 Bermejo-Perez MJ, Marquez-Calderon S, Llanos-Mendez A. Effectiveness of preventive interventions in BRCA1/2 gene mutation carriers: a systematic review. *Int J Cancer* 2007; 121: 225-231
- 21 Bijker N, Meijnen P, Peterse JL *et al.* 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; 24: 3381-3387
- 22 Blichert-Toft M, Smola MG, Cataliotti L *et al.* Principles and guidelines for surgeons - management of symptomatic breast cancer. On behalf of the European Society of Surgical Oncology. *Ann Chir Gynaecol* 1998; 87: 101-109
- 23 Bonadonna G, Zambetti M, Valagussa P. Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes. Ten-year results. *JAMA* 1995; 273: 542-547
- 24 Borner M, Bacchi M, Goldhirsch A *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: 2071-2077
- 25 Bornhak S, Heidemann E, Herschlein HJ *et al.* Symptom-oriented follow-up of early breast cancer is not inferior to conventional control. Results of a prospective multicentre study. *Onkologie* 2007; 30: 443-449
- 26 Boyages J, Delaney G, Taylor R. Predictors of local recurrence after treatment of ductal carcinoma in situ: a meta-analysis. *Cancer* 1999; 85: 616-628
- 27 Bria E, Nistico C, Cuppone F *et al.* Benefit of taxanes as adjuvant chemotherapy for early breast cancer: pooled analysis of 15,500 patients. *Cancer* 2006; 106: 2337-2344
- 28 Brito RA, Valero V, Buzdar AU *et al.* Long-term results of combined-modality therapy for locally advanced breast cancer with ipsilateral supraclavicular metastases: The University of Texas M.D. Anderson Cancer Center experience. *J Clin Oncol* 2001; 19: 628-633
- 29 Brown JE, Coleman RE. Metastatic bone disease: developing strategies to optimize management. [DKG-R]. *Am J Cancer* 2003; 2: 269-281
- 30 Bruera E, Willey JS, Palmer JL *et al.* Treatment decisions for breast carcinoma: patient preferences and physician perceptions. *Cancer* 2002; 94: 2076-2080
- 31 Buchholz TA. Radiation therapy for early-stage breast cancer after breast-conserving surgery. *N Engl J Med* 2009; 360: 63-70
- 32 Buchholz TA, Lehman CD, Harris JR *et al.* Statement of the science concerning locoregional treatments after preoperative chemotherapy for breast cancer: a National Cancer Institute conference. *J Clin Oncol* 2008; 26: 791-797
- 33 Buchholz TA, Tucker SL, Masullo L *et al.* Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. *J Clin Oncol* 2002; 20: 17-23
- 34 Budman DR, Berry DA, Cirincione CT *et al.* Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. *J Natl Cancer Inst* 1998; 90: 1205-1211
- 35 Bundred NJ. Prognostic and predictive factors in breast cancer. *Cancer Treat Rev* 2001; 27: 137-142
- 36 Burstein HJ, Kuter I, Campos SM *et al.* Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2001; 19: 2722-2730
- 37 Burstein HJ, Prestrud AA, Seidenfeld J *et al.* American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncol* 2010; 28: 3784-3796
- 38 Butow P, Harrison JD, Choy ET *et al.* Health professional and consumer views on involving breast cancer patients in the multidisciplinary discussion of their disease and treatment plan. *Cancer* 2007; 110: 1937-1944
- 39 Cady B, Stone MD, Wayne J. New therapeutic possibilities in primary invasive breast cancer. *Ann Surg* 1993; 218: 338-347
- 40 Calderon-Margalit R, Paltiel O. Prevention of breast cancer in women who carry BRCA1 or BRCA2 mutations: a critical review of the literature. *Int J Cancer* 2004; 112: 357-364
- 41 Cardillo G, Facciolo F, Carbone L *et al.* Long-term follow-up of video-assisted talc pleurodesis in malignant recurrent pleural effusions. *Eur J Cardiothorac Surg* 2002; 21: 302-305
- 42 Carlson RW, Moench SJ, Hammond ME *et al.* HER2 testing in breast cancer: NCCN Task Force report and recommendations. *J Natl Compr Canc Netw* 2006; 4 (Suppl. 3): S1-S22
- 43 Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer* 1989; 63: 181-187
- 44 Chan DN, Lui LY, So WK. Effectiveness of exercise programmes on shoulder mobility and lymphoedema after axillary lymph node dissection for breast cancer: systematic review. *J Adv Nurs* 2010; 66: 1902-1914
- 45 Chargarri C, Kirov KM, Bollet MA *et al.* Cardiac toxicity in breast cancer patients: from a fractional point of view to a global assessment. *Cancer Treat Rev* 2011a; 37: 321-330
- 46 Chargarri C, Levy A, Vadrine L *et al.* Current trials of cytotoxic and targeted agents in breast cancer: the caveat of radiotherapy. *Ann Oncol* 2011b; 22: 1243-1244
- 47 Cheema B, Gaul CA, Lane K *et al.* Progressive resistance training in breast cancer: a systematic review of clinical trials. *Breast Cancer Res Treat* 2008; 109: 9-26
- 48 Cheung KL, Willsher PC, Pinder SE *et al.* Predictors of response to second-line endocrine therapy for breast cancer. *Breast Cancer Res Treat* 1997; 45: 219-224
- 49 Christiaens M, Vlayen J, Gailly J. Scientific Support of the College of Oncology: a national clinical Practice Guideline for Breast Cancer. KCE Report 63A. Brussels: Belgian Health Care Knowledge Centre (KCE); 2007
- 50 Citron ML, Berry DA, Cirincione C *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: 1431-1439
- 51 Clarke M, Collins R, Darby S *et al.* Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 366: 2087-2106
- 52 Clavarezza M, Del Mastro L, Venturini M. Taxane-containing chemotherapy in the treatment of early breast cancer patients. *Ann Oncol* 2006; 17 (Suppl. 7): vii22-vii26
- 53 Clohisy DR. Metastatic bone disease: future directions. *Clin Orthop Relat Res* 2003; 1 (415 Suppl.): 1-5
- 54 Carrick S, Parker S, Thornton CE *et al.* Single agent versus combination chemotherapy for metastatic breast cancer. *Cochrane Database Syst Rev* 2009; (2): CD003372
- 55 Carrick S, Parker S, Wilcken N *et al.* Single agent versus combination chemotherapy for metastatic breast cancer. *Cochrane Database Syst Rev* 2005; (2): CD003372
- 56 Cramp F, Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev* 2008; (2): CD006145
- 57 Edwards AG, Hailey S, Maxwell M. Psychological interventions for women with metastatic breast cancer. *Cochrane Database Syst Rev* 2004; (2): CD004253
- 58 Farquhar C, Marjoribanks J, Bassar R *et al.* High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer. *Cochrane Database Syst Rev* 2005; (3): CD003142
- 59 Ferguson T, Wilcken N, Vagg R *et al.* Taxanes for adjuvant treatment of early breast cancer. *Cochrane Database Syst Rev* 2007; (4): CD004421

- 60 Gibson L, Lawrence D, Dawson C et al. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. *Cochrane Database Syst Rev* 2009; (4): CD003370
- 61 Goodwin A, Parker S, Ghera D et al. Post-operative radiotherapy for ductal carcinoma in situ of the breast. *Cochrane Database Syst Rev* 2009; (4): CD000563
- 62 Hart MG, Grant R, Walker M et al. Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases. *Cochrane Database of Systematic Review* 2004; (4): CD003292
- 63 Hickey BE, Francis D, Lehman MH. Sequencing of chemotherapy and radiation therapy for early breast cancer. *Cochrane Database Syst Rev* 2006; (4): CD005212
- 64 Horneber MA, Bueschel G, Huber R et al. Rostock M. Mistletoe therapy in oncology. *Cochrane Database Syst Rev* 2008; (2): CD003297
- 65 Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. *Cochrane Database Syst Rev* 2010; CD002748
- 66 Markes M, Brockow T, Resch KL. Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database Syst Rev* 2006; (4): CD005001
- 67 McNeely ML, Campbell K, Ospina M et al. Exercise interventions for upper-limb dysfunction due to breast cancer treatment. *Cochrane Database Syst Rev* 2010; (6): CD005211
- 68 Rauschecker H, Clarke M, Gatzemeier W et al. Systemic therapy for treating locoregional recurrence in women with breast cancer. *Cochrane Database Syst Rev* 2001; (4): CD002195
- 69 Rauschecker HHF, Clarke MJ, Gatzemeier W et al. Systemic therapy for treating locoregional recurrence in women with breast cancer. *Cochrane Database Syst Rev* 2008; 5: CD002195
- 70 Rojas MP, Telaro E, Russo A et al. Follow-up strategies for women treated for early breast cancer. *Cochrane Database Syst Rev* 2000; (4): CD001768
- 71 Rojas MP, Telaro E, Russo A, Moschetti I, Coe L, Fossati R, Palli D, del Roselli TM, Liberati A. Follow-up strategies for women treated for early breast cancer. *Cochrane Database Syst Rev* 2005; (1): CD001768
- 72 Colleoni M, Rotmensz N, Maisonneuve P et al. Prognostic role of the extent of peritumoral vascular invasion in operable breast cancer. *Ann Oncol* 2007; 18: 1632–1640.
- 73 Conte PF, Latreille J, Mauriac L et al. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. The Aredia Multinational Cooperative Group. *J Clin Oncol* 1996; 14: 2552–2559
- 74 Crump M. The role of trastuzumab (Herceptin) in the treatment of women with HER2/neu – overexpressing metastatic breast cancer. Toronto (ON): Practice Guideline Report no. 1–15 (Version 2.2004). Cancer Care Ontario; 2005
- 75 Crump M, Goss PE, Prince M et al. Outcome of extensive evaluation before adjuvant therapy in women with breast cancer and 10 or more positive axillary lymph nodes. *J Clin Oncol* 1996; 14: 66–69
- 76 Cutuli B, Cohen-Solal-le Nir C, de Lafontan B et al. Breast-conserving therapy for ductal carcinoma in situ of the breast: the French Cancer Centers' experience. *Int J Radiat Oncol Biol Phys* 2002; 53: 868–879
- 77 Cuzick J, Sestak I, Pinder SE et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. *Lancet Oncol* 2011; 12: 21–29
- 78 Dalberg K, Mattsson A, Sandelin K et al. Outcome of treatment for ipsilateral breast tumor recurrence in early-stage breast cancer. *Breast Cancer Res Treat* 1998; 49: 69–78
- 79 Darby S; on Behalf of the Early Breast Cancer Trialists' Collaborative Group, University of Oxford, GB. Overview of the randomised trials of radiotherapy in early breast cancer. SABCS2009; Minisymposium 3, 1. [MS3–1], Slides of the oral presentation at the 32nd Annual SABCS2009: www.sabcs.org/
- 80 de Azambuja E, Cardoso F, de Castro Jr. G et al. Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12,155 patients. *Br J Cancer* 2007; 96: 1504–1513
- 81 de Boer M, van Deurzen CH, van Dijck JA et al. Micrometastases or isolated tumor cells and the outcome of breast cancer. *N Engl J Med* 2009; 361: 653–663
- 82 de Boer M, van Dijck JA, Bult P et al. Breast cancer prognosis and occult lymph node metastases, isolated tumor cells, and micrometastases. *J Natl Cancer Inst* 2010; 102: 410–425
- 83 Del Turco MR, Ponti A, Bick U et al. Quality indicators in breast cancer care. *Eur J Cancer* 2010; 46: 2344–2356
- 84 Deutsch M. Repeat high-dose external beam irradiation for in-breast tumor recurrence after previous lumpectomy and whole breast irradiation. *Int J Radiat Oncol Biol Phys* 2002; 53: 687–691
- 85 Devoogdt N, Van Kampen M, Geraerts I et al. Different physical treatment modalities for lymphoedema developing after axillary lymph node dissection for breast cancer: a review. *Eur J Obstet Gynecol Reprod Biol* 2010; 149: 3–9
- 86 Domchek SM, Friebel TM, Neuhausen SL et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. *Lancet Oncol* 2006; 7: 223–229
- 87 Dowsett M, Nielsen TO, A'hern R et al. Assessment of ki67 in breast cancer: recommendations from the international ki67 in breast cancer working group. *J Natl Cancer Inst* 2011; 103: 1656–1664
- 88 DRV Bund. Deutsche Rentenversicherung Bund. Reha-Therapiestandards Brustkrebs. Leitlinie für die medizinische Rehabilitation der Rentenversicherung. 2009. deutsche-rentenversicherung.de
- 89 Dunne C, Burke JP, Morrow M et al. Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ. *J Clin Oncol* 2009; 27: 1615–1620
- 90 EBCTCG. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *N Engl J Med* 1995; 333: 1444–1455
- 91 EBCTCG. Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1998; 352: 930–942
- 92 EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 2005; 365: 1687–1717
- 93 EBCTCG. Comparisons between different polychemotherapy regimes for early breast cancer: meta-analysis of long-term outcome among 100000 women in 123 randomised trials. *Lancet* 2011; Published online December 6, 2011
- 94 Darby S, McGale P, Correa C et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011; 378: 1707–1716
- 95 Correa C, McGale P, Taylor C et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. *J Natl Cancer Inst Monogr* 2010; 2010: 162–177
- 96 Davies C, Godwin J, Gray R et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011; 378: 771–784
- 97 Early Breast Cancer Trialists' Collaborative Group. Multi-agent chemotherapy for early breast cancer. [DKG-R]. *Cochrane Database Syst Rev* 2003; 3: CD00487
- 98 EBMG. Evidence-based medicine guidelines 2006. Article ID: evd02580 (025.023). 2006. www.awmf.org
- 99 EGAPP Working Group. Recommendations from the EGAPP Working Group: can tumor gene expression profiling improve outcomes in patients with breast cancer? *Genet Med* 2009; 11: 66–73
- 100 Eiermann W, Pienkowski T, Crown J et al. Phase III study of doxorubicin/cyclophosphamide with concomitant versus sequential docetaxel as adjuvant treatment in patients with human epidermal growth factor receptor 2-normal, node-positive breast cancer: BCIRG-005 trial. *J Clin Oncol* 2011; 29: 3877–3884
- 101 Elkin EB, Kim SH, Casper ES et al. Desire for information and involvement in treatment decisions: elderly cancer patients' preferences and their physicians' perceptions. *J Clin Oncol* 2007; 25: 5275–5280
- 102 Ellis MJ, Hayes DF, Lippman ME. Treatment of metastatic breast cancer. [AGO]. *Cancer* 2000; 749–797
- 103 Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* 1991; 19: 403–410
- 104 Emdin SO, Granstrand B, Ringberg A et al. SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. *Acta Oncol* 2006; 45: 536–543
- 105 Estevez LG, Munoz M, Alvarez I et al. Evidence-based use of taxanes in the adjuvant setting of breast cancer. A review of randomized phase III trials. *Cancer Treat Rev* 2007; 33: 474–483
- 106 Evans DG, Baildam AD, Anderson E et al. Risk reducing mastectomy: outcomes in 10 European centres. *J Med Genet* 2009; 46: 254–258

- 107 *Feher O, Vadvorka P, Jassem J et al.* Randomized phase III study of epirubicin (E) versus gemcitabine (G) chemotherapy in elderly females with metastatic breast cancer (MBC). *Jk 3* 2002; EBCC, Barcelona. [AGO]
- 108 *Fernando SA, Edge SB.* Evidence and controversies in the use of post-mastectomy radiation. *J Natl Compr Canc Netw* 2007; 5: 331–338
- 109 *Fisher B, Anderson S.* Conservative surgery for the management of invasive and noninvasive carcinoma of the breast: NSABP trials. National Surgical Adjuvant Breast and Bowel Project. *World J Surg* 1994; 18: 63–69
- 110 *Fisher B, Anderson S, Wickerham DL 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* 1997a; 15: 1858–1869
- 111 *Fisher B, Brown A, Mamounas E et al.* Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 1997b; 15: 2483–2493
- 112 *Fisher B, Brown AM, Dimitrov NV 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-non-responsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *J Clin Oncol* 1990; 8: 1483–1496
- 113 *Fisher B, Dignam J, Wolmark N et al.* Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. *J Natl Cancer Inst* 1997c; 89: 1673–1682
- 114 *Fisher B, Dignam J, Wolmark N et al.* Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet* 1999; 353: 1993–2000
- 115 *Fisher B, Land S, Mamounas E et al.* Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the national surgical adjuvant breast and bowel project experience. *Semin Oncol* 2001; 28: 400–418
- 116 *Fleissig A, Fallowfield LJ, Langridge CI et al.* 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 Res Treat* 2006; 95: 279–293
- 117 *Floyd SR, Taghian AG.* Post-mastectomy radiation in large node-negative breast tumors: does size really matter? *Radiother Oncol* 2009; 91: 33–37
- 118 *Ford S, Schofield T, Hope T.* Observing decision-making in the general practice consultation: who makes which decisions? *Health Expect* 2006; 9: 130–137
- 119 *Fossati R, Confalonieri C, Torri V et al.* Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. *J Clin Oncol* 1998; 16: 3439–3460
- 120 *Fourney DR, Gokaslan ZL.* Thoracolumbar spine: surgical treatment of metastatic disease. [DKG-R]. *Current Opinion in Orthopedics* 2003; 14: 144–152
- 121 *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: 121–133
- 122 *Francis WP, Abghari P, Du W et al.* Improving surgical outcomes: standardizing the reporting of incidence and severity of acute lymphedema after sentinel lymph node biopsy and axillary lymph node dissection. *Am J Surg* 2006; 192: 636–639
- 123 *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. [CANADA]. *J Clin Oncol* 2001; 19: 602–611
- 124 *Fumoleau P, Kerbrat P, Romestaing P 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: 298–305
- 125 *Garg AK, Oh JL, Oswald MJ et al.* 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; 69: 1478–1483
- 126 *Gasparini G, Weidner N, Bevilacqua P et al.* Tumor microvessel density, p53 expression, tumor size, and peritumoral lymphatic vessel invasion are relevant prognostic markers in node-negative breast carcinoma. *J Clin Oncol* 1994; 12: 454–466
- 127 *Gebski V, Lagleva M, Keech A et al.* Survival effects of postmastectomy adjuvant radiation therapy using biologically equivalent doses: a clinical perspective. *J Natl Cancer Inst* 2006; 98: 26–38
- 128 *Geller BM, Kerlikowske K, Carney PA et al.* Mammography surveillance following breast cancer. *Breast Cancer Res Treat* 2003; 81: 107–115
- 129 *GIVIO Investigators.* 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: 1587–1592
- 130 *Goldhirsch A, Ingle JN, Gelber RD 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: 1319–1329
- 131 *Goldhirsch A, Wood WC, Coates AS et al.* Strategies for subtypes – dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol* 2011; 22: 1736–1747
- 132 *Golshan M, Martin WJ, Dowlatshahi K.* Sentinel lymph node biopsy lowers the rate of lymphedema when compared with standard axillary lymph node dissection. *Am Surg* 2003; 69: 209–211
- 133 *Gruber R, Bernt R, Helbich TH.* [Cost-effectiveness of percutaneous core needle breast biopsy (CNBB) versus open surgical biopsy (OSB) of nonpalpable breast lesions: metaanalysis and cost evaluation for German-speaking countries]. *Rofo* 2008; 180: 134–142
- 134 *Grunfeld E, Dhesy-Thind S, Levine M.* Clinical practice guidelines for the care and treatment of breast cancer: follow-up after treatment for breast cancer (summary of the 2005 update). *CMAJ* 2005; 172: 1319–1320
- 135 *Grunfeld E, Noorani H, McGahan L et al.* Surveillance mammography after treatment of primary breast cancer: a systematic review. *Breast* 2002; 11: 228–235
- 136 *Gulliford T, Opomu M, Wilson E et al.* Popularity of less frequent follow up for breast cancer in randomised study: initial findings from the hotline study. *BMJ* 1997; 314: 174–177
- 137 *Haffty BG, Reiss M, Beinfeld M et al.* Ipsilateral breast tumor recurrence as a predictor of distant disease: implications for systemic therapy at the time of local relapse. *J Clin Oncol* 1996; 14: 52–57
- 138 *Harbeck N, Schmitt M, Meisner C et al.* Final 10-year analysis of prospective multicenter Chemo N0 trial for validation of ASCO-recommended biomarkers uPA/PAI-1 for therapy decision making in node-negative breast cancer. *J Clin Oncol* 2009; 27 (15 Suppl.): Abstr. 511
- 139 *Halyard MY, Pisansky TM, Dueck AC et al.* Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCTG Phase III Trial N9831. *J Clin Oncol* 2009; 27: 2638–2644
- 140 *Hammond ME, Hayes DF, Dowsett M et al.* American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol* 2010; 28: 2784–2795
- 141 *Hammer JB, Fleming MD.* Lymphedema therapy reduces the volume of edema and pain in patients with breast cancer. *Ann Surg Oncol* 2007; 14: 1904–1908
- 142 *Harnett A.* Fewer fractions of adjuvant external beam radiotherapy for early breast cancer are safe and effective and can now be the standard of care. Why the UK's NICE accepts fewer fractions as the standard of care for adjuvant radiotherapy in early breast cancer. *Breast* 2010; 19: 159–162
- 143 *Harnett A, Smallwood J, Titshall V et al.* Diagnosis and treatment of early breast cancer, including locally advanced disease – summary of NICE guidance. *BMJ* 2009; 338: b438
- 144 *Harris EE.* Cardiac mortality and morbidity after breast cancer treatment. *Cancer Control* 2008; 15: 120–129
- 145 *Harris EE, Christensen VJ, Hwang WT 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: 11–16
- 146 *Harris L, Fritsche H, Mennel R et al.* American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 2007; 25: 5287–5312
- 147 *Harris SR, Hugi MR, Olivetto IA et al.* Clinical practice guidelines for the care and treatment of breast cancer: 11. Lymphedema. *CMAJ* 2001; 164: 191–199

- 148 Hauner D, Janni W, Rack B *et al.* The effect of overweight and nutrition on prognosis in breast cancer. *Dtsch Arztebl Int* 2011; 108: 795–801
- 149 Hayes DF. Clinical practice. Follow-up of patients with early breast cancer. *N Engl J Med* 2007; 356: 2505–2513
- 150 Hayes DF, Henderson IC, Shapiro CL. Treatment of metastatic breast cancer: present and future prospects. *Semin Oncol* 1995; 22 (2 Suppl. 5): 5–19
- 151 Hayes S, Cornish B, Newman B. Comparison of methods to diagnose lymphoedema among breast cancer survivors: 6-month follow-up. *Breast Cancer Res Treat* 2005; 89: 221–226
- 152 Henderson IC, Berry DA, Demetri GD *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
- 153 Hoeller U, Borgmann K, Feyer P *et al.* [On the interaction of adjuvant radiotherapy and tamoxifen treatment for breast cancer]. *Strahlenther Onkol* 2007; 183: 535–544
- 154 Holmberg L, Garmo H, Granstrand B *et al.* Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast. *J Clin Oncol* 2008; 26: 1247–1252
- 155 Honrado E, Osorio A, Palacios J *et al.* Pathology and gene expression of hereditary breast tumors associated with BRCA1, BRCA2 and CHEK2 gene mutations. *Oncogene* 2006; 25: 5837–5845
- 156 Hortobagyi GN, Piccart-Gebhart MJ. Current management of advanced breast cancer. *Semin Oncol* 1996; 23 (5 Suppl. 11): 1–5
- 157 Hortobagyi GN, Theriault RL, Lipton A *et al.* Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. *J Clin Oncol* 1998; 16: 2038–2044
- 158 Hoskin PJ, Yarnold JR, Roos DR *et al.* Second workshop on palliative radiotherapy and symptom control: radiotherapy for bone metastases. [DKG-N]. *Clin Oncol (R Coll Radiol)*. *Clin Oncol* 2001; 13: 88–90
- 159 Houghton J, George WD, Cuzick J *et al.* Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. *Lancet* 2003; 362: 95–102
- 160 Houssami N, Ciatto S, Macaskill P *et al.* Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. *J Clin Oncol* 2008; 26: 3248–3258
- 161 Houssami N, Hayes DF. Review of preoperative magnetic resonance imaging (MRI) in breast cancer: should MRI be performed on all women with newly diagnosed, early stage breast cancer? *CA Cancer J Clin* 2009; 59: 290–302
- 162 Houssami N, Macaskill P, Marinovich ML *et al.* Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. *Eur J Cancer* 2010; 46: 3219–3232
- 163 Huang EH, Strom EA, Perkins GH *et al.* 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; 66: 352–357
- 164 Hurria A, Hudis C. Follow-up care of breast cancer survivors. *Crit Rev Oncol Hematol* 2003; 48: 89–99
- 165 ICSI. Health care guideline: breast cancer treatment. 2005. www.guideline.gov
- 166 Jagsi R, Pierce L. Postmastectomy radiation therapy for patients with locally advanced breast cancer. *Semin Radiat Oncol* 2009; 19: 236–243
- 167 Janicke F, Prechtl A, Thomssen C *et al.*; German NO Study Group. Randomized adjuvant therapy trial in high-risk lymph node-negative breast cancer patients identified by urokinase-type plasminogen activator and plasminogen activator inhibitor type I. *J Natl Cancer Inst* 2001; 93: 913–920
- 168 Johnson RC, Banerjee D, Webster DJ. Mastectomy follow-up by biennial mammograms: is it worthwhile? *Breast* 2000; 9: 93–95
- 169 Jones HA, Antonini N, Hart AA *et al.* Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial. *J Clin Oncol* 2009; 27: 4939–4947
- 170 Jones EL, Oleson JR, Prosnitz LR *et al.* Randomized trial of hyperthermia and radiation for superficial tumors. *J Clin Oncol* 2005; 23: 3079–3085
- 171 Jubelirer SJ. Surveillance testing in patients with early stage breast cancer: a review. *W V Med J* 1998; 94: 14–17
- 172 Karasawa K, Katsui K, Seki K *et al.* Radiotherapy with concurrent docetaxel for advanced and recurrent breast cancer. *Breast Cancer* 2003; 10: 268–274
- 173 Kato T, Kameoka S, Kimura T *et al.* The combination of angiogenesis and blood vessel invasion as a prognostic indicator in primary breast cancer. *Br J Cancer* 2003; 88: 1900–1908
- 174 Kaufmann M, Hortobagyi GN, Goldhirsch A *et al.* Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. *J Clin Oncol* 2006; 24: 1940–1949
- 175 Kaufmann M, Morrow M, von Minckwitz G *et al.* Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. *Cancer* 2010; 116: 1184–1191
- 176 Kaufmann M, von Minckwitz G, Smith R *et al.* International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: review and recommendations. *J Clin Oncol* 2003; 21: 2600–2608
- 177 Kelly CM, Wilkins RM, Eckardt JJ *et al.* Treatment of metastatic disease of the tibia. *Clin Orthop Relat Res* 2003; 1 (415 Suppl.): S219–S229
- 178 Khatcheressian JL, Wolff AC, Smith TJ *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: 5091–5097
- 179 Kirova YM, Caussa L, Granger B *et al.* [Monocentric evaluation of the skin and cardiac toxicities of the concomitant administration of trastuzumab and radiotherapy]. *Cancer Radiother* 2009; 13: 276–280
- 180 Klemperer D, Lang B, Koch K *et al.* Gute Praxis Gesundheitsinformati-on. *Z Evid Fortbild Qual Gesundh wesen (ZEFQ)* 2010; 104: 66–68
- 181 Klijn JG, Blamey RW, Boccardo F *et al.* Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001; 19: 343–353
- 182 Koizumi M, Yoshimoto M, Kasumi F *et al.* Comparison between solitary and multiple skeletal metastatic lesions of breast cancer patients. *Ann Oncol* 2003; 14: 1234–1240
- 183 Kollias J, Evans AJ, Wilson AR *et al.* Value of contralateral surveillance mammography for primary breast cancer follow-up. *World J Surg* 2000; 24: 983–987
- 184 Kondziolka D, Patel A, Lunsford LD *et al.* Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. [DKG-N]. *Int J Radiat Oncol Biol Phys* 1999; 45: 427–434
- 185 Krag DN, Anderson SJ, Julian TB *et al.* 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; 11: 927–933
- 186 Kuehn T, Bembenek A, Decker T *et al.* A concept for the clinical implementation of sentinel lymph node biopsy in patients with breast carcinoma with special regard to quality assurance. *Cancer* 2005; 103: 451–461
- 187 Kunkler I. Adjuvant chest wall radiotherapy for breast cancer: black, white and shades of grey. *Eur J Surg Oncol* 2010; 36: 331–334
- 188 Kurtz JM, Amalric R, Brandone H *et al.* Local recurrence after breast-conserving surgery and radiotherapy. Frequency, time course, and prognosis. *Cancer* 1989; 63: 1912–1917
- 189 Kurtz JM, Jacquemier J, Amalric R *et al.* Is breast conservation after local recurrence feasible? *Eur J Cancer* 1991; 27: 240–244
- 190 Kyndi M, Sorensen FB, Knudsen H *et al.* Impact of BCL2 and p53 on postmastectomy radiotherapy response in high-risk breast cancer. A subgroup analysis of DBCG82 b&c. *Acta Oncol* 2008a; 47: 608–617
- 191 Kyndi M, Sorensen FB, Knudsen H *et al.* Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: the Danish Breast Cancer Cooperative Group. *J Clin Oncol* 2008b; 26: 1419–1426
- 192 Lakhani SR, Jacquemier J, Sloane JP *et al.* Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations. *J Natl Cancer Inst* 1998; 90: 1138–1145
- 193 Lakhani SR, Reis-Filho JS, Fulford L *et al.* Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. *Clin Cancer Res* 2005; 11: 5175–5180

- 194 *Lanitis S, Tekkis PP, Sgourakis G et al.* Comparison of skin-sparing mastectomy versus non-skin-sparing mastectomy for breast cancer: a meta-analysis of observational studies. *Ann Surg* 2010; 251: 632–639
- 195 *Lemieux J, Goodwin PJ, Bordeleau LJ et al.* Quality-of-life measurement in randomized clinical trials in breast cancer: an updated systematic review (2001–2009). *J Natl Cancer Inst* 2011; 103: 178–231
- 196 *Livi L, Borghesi S, Saieva C et al.* Benefit of radiation boost after whole-breast radiotherapy. *Int J Radiat Oncol Biol Phys* 2009; 75: 1029–1034
- 197 *Look MP, van Putten WL, Duffy MJ 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: 116–128
- 198 *Loprinzi CL.* Follow-up care after breast cancer treatment. *Mayo Clin Womens Healthsource* 2004; 8: Suppl. 1–2
- 199 *Lupe K, Truong PT, Alexander C et al.* Ten-year locoregional recurrence risks in women with nodal micrometastatic breast cancer staged with axillary dissection. *Int J Radiat Oncol Biol Phys* 2011; 81: e681–e688
- 200 *Lyman GH, Giuliano AE, Somerfield MR et al.* American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol* 2005; 23: 7703–7720
- 201 *Madjar H.* Role of breast ultrasound for the detection and differentiation of breast lesions. *Breast Care (Basel)* 2010; 5: 109–114
- 202 *Madjar H, Munding A, Degenhardt F et al.* Qualitätskontrolle in der Mamma-Sonographie. *Ultraschall in Med* 2003; 24: 190–194
- 203 *Madjar H, Ohlinger R, Munding A et al.* BI-RADS-analogue DEGUM criteria for findings in breast ultrasound – consensus of the DEGUM Committee on Breast Ultrasound. *Ultraschall Med* 2006; 27: 374–379
- 204 *Mamounas EP, Bryant J, Lembersky B 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: 3686–3696
- 205 *Mansel RE, Fallowfield L, Kissin M et al.* Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst* 2006; 98: 599–609
- 206 *Marchionni L, Wilson RF, Wolff AC et al.* Systematic review: gene expression profiling assays in early-stage breast cancer. *Ann Intern Med* 2008; 148: 358–369
- 207 *McCammon R, Finlayson C, Schwer A et al.* Impact of postmastectomy radiotherapy in T3N0 invasive carcinoma of the breast: a Surveillance, Epidemiology, and End Results database analysis. *Cancer* 2008; 113: 683–689
- 208 *McGuire SE, Gonzalez-Angulo AM, Huang EH et al.* 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: 1004–1009
- 209 *Moebus V, Jackisch C, Lueck HJ et al.* 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 Clin Oncol* 2010; 28: 2874–2880
- 210 *Moseley AL, Carati CJ, Piller NB.* A systematic review of common conservative therapies for arm lymphoedema secondary to breast cancer treatment. *Ann Oncol* 2007; 18: 639–646
- 211 *Mouridsen H, Sun Y, Gershanovich M et al.* First-line therapy with letrozole (Femara) for advanced breast cancer prolongs time to worsening of Karnofsky Performance Status compared with tamoxifen. *Breast Canc Res Treat* 2001a; 69: abstract
- 212 *Mouridsen H, Gershanovich M, Sun Y 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* 2001b; 19: 2596–2606
- 213 *NBOCC; National Breast and Ovarian Cancer Center.* Recommendations for use of Chemotherapy for the treatment of advanced breast cancer. *Surry Hills: NBOCC; 2010a*
- 214 *NBOCC; National Breast and Ovarian Cancer Centre.* Recommendations for follow-up of women with early breast cancer. *Surry Hills: NBOCC; 2010b*
- 215 *NCCN.* Practice guidelines in oncology – Version 2. Fort Washington, PA (USA): NCCN; 2006
- 216 *NCCN.* Clinical practice guidelines in oncology: breast cancer – Version V.1. Fort Washington, PA (USA): NCCN; 2007
- 217 *NCCN; National Comprehensive Cancer Network.* Breast cancer. V. 2.2011. Fort Washington, PA (USA): NCCN; 2011
- 218 *NCRI.* UK clinical guidelines for the use of adjuvant trastuzumab (Herceptin®) with or following chemotherapy in HER2-positive early breast cancer. London (UK): NCRI; 2005
- 219 *NHMRC.* Clinical practice guidelines for the management of early breast cancer. Canberra (Australien): NHMRC; 2001
- 220 *National Institute for Clinical Excellence (NICE).* Advanced breast cancer: diagnosis and treatment. London (UK): NICE; 2009a
- 221 *National Institute for Clinical Excellence (NICE).* Early and locally advanced breast cancer: diagnosis and treatment. London (UK): NICE; 2009b
- 222 *Nielsen HM, Overgaard M, Grau C et al.* Loco-regional recurrence after mastectomy in high-risk breast cancer – risk and prognosis. An analysis of patients from the DBCG 82 b&c randomization trials. *Radiother Oncol* 2006a; 79: 147–155
- 223 *Nielsen HM, Overgaard M, Grau C et al.* 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* 2006b; 24: 2268–2275
- 224 *NIH; National Institutes of Health Consensus Development Panel.* National Institutes of Health Consensus Development Conference statement: adjuvant therapy for breast cancer November 1–3, 2000. [CAN-ADA]. Bethesda 2001. Bethesda (MD): NIH. http://odp.od.nih.gov/consensus/cons/114/114_statement.htm; last access: 2001
- 225 *Nothacker M, Duda V, Hahn M et al.* Early detection of breast cancer: benefits and risks of supplemental breast ultrasound in asymptomatic women with mammographically dense breast tissue. A systematic review. *BMC Cancer* 2009; 9: 335
- 226 *Nothacker M, Lelgemann M, Giersiepen K et al.* Evidenzbericht 2007 zur S3-Leitlinie Brustkrebsfrüherkennung in Deutschland. Berlin: Ärztliches Zentrum für Qualität in der Medizin; 2007
- 227 *NZGG; New Zealand Guidelines Group.* Management of early breast cancer. Wellington: NZGG; 2009
- 228 *O'Higgins N, Linos DA, Blichert-Toft M et al.* European guidelines for quality assurance in the surgical management of mammographically detected lesions. *Eur J Surg Oncol* 1998; 24: 96–98
- 229 *O'Rourke N, McCloskey E, Houghton F et al.* Double-blind, placebo-controlled, dose-response trial of oral clodronate in patients with bone metastases. *J Clin Oncol* 1995; 13: 929–934
- 230 *Omlin A, Amichetti M, Azria D et al.* Boost radiotherapy in young women with ductal carcinoma in situ: a multicentre, retrospective study of the Rare Cancer Network. *Lancet Oncol* 2006; 7: 652–656
- 231 *Osborne CK.* Steroid hormone receptors in breast cancer management. *Breast Cancer Res Treat* 1998; 51: 227–238
- 232 *Overgaard M, Nielsen HM, Overgaard J.* Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. *Radiother Oncol* 2007; 82: 247–253
- 233 *Page DL, Jensen RA, Simpson JF.* Routinely available indicators of prognosis in breast cancer. *Breast Cancer Res Treat* 1998; 51: 195–208
- 234 *Page DL, Rogers LW.* Combined histologic and cytologic criteria for the diagnosis of mammary atypical ductal hyperplasia. *Hum Pathol* 1992; 23: 1095–1097
- 235 *Paik S, Shak S, Tang G et al.* A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004; 351: 2817–2826
- 236 *Paik S, Tang G, Shak S et al.* Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol* 2006; 24: 3726–3734
- 237 *Palli D, Russo A, Saieva C et al.* Intensive vs. clinical follow-up after treatment of primary breast cancer: 10-year update of a randomized trial. National Research Council Project on Breast Cancer Follow-up. *JAMA* 1999; 281: 1586
- 238 *Park CC, Mitsumori M, Nixon A 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: 1668–1675
- 239 *Pestalozzi BC, Luporsi-Gely E, Jost LM et al.* ESMO Minimum Clinical Recommendations for diagnosis, adjuvant treatment and follow-up of primary breast cancer. *Ann Oncol* 2005; 16 (Suppl. 1): i7–i9

- 240 Peto R. Highlights from the 2005/6 EBCTCG worldwide overview of every women in all the trials in early breast cancer. 29th Annual San Antonio Breast Cancer Symposium 2006; Abstract book # 40
- 241 Petrelli F, Barni S. Meta-analysis of concomitant compared to sequential adjuvant trastuzumab in breast cancer: the sooner the better. *Med Oncol* 2012; 29: 503–510
- 242 Pierce LJ, Hutchins LF, Green SR et al. Sequencing of tamoxifen and radiotherapy after breast-conserving surgery in early-stage breast cancer. *J Clin Oncol* 2005; 23: 24–29
- 243 Politi MC, Han PK, Col NF. Communicating the uncertainty of harms and benefits of medical interventions. *Med Decis Making* 2007; 27: 681–695
- 244 Poortmans P. Evidence based radiation oncology: breast cancer. *Radiother Oncol* 2007; 84: 84–101
- 245 Poortmans PM, Collette L, Bartelink H et al. The addition of a boost dose on the primary tumour bed after lumpectomy in breast conserving treatment for breast cancer. A summary of the results of EORTC22881–10882 “boost versus no boost” trial. *Cancer Radiother* 2008; 12: 565–570
- 246 Poortmans PM, Collette L, Horiot JC et al. Impact of the boost dose of 10 Gy versus 26 Gy in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10-year results of the randomised EORTC boost trial. *Radiother Oncol* 2009; 90: 80–85
- 247 Potter S, Brigid A, Whiting PF et al. Reporting clinical outcomes of breast reconstruction: a systematic review. *J Natl Cancer Inst* 2011; 103: 31–46
- 248 Recht A. Integration of systemic therapy and radiation therapy for patients with early-stage breast cancer treated with conservative surgery. *Clin Breast Cancer* 2003; 4: 104–113
- 249 Recht A. Radiotherapy, antihormonal therapy, and personalised medicine. *Lancet Oncol* 2010; 11: 215–216
- 250 Renton SC, Gazet JC, Ford HT et al. The importance of the resection margin in conservative surgery for breast cancer. *Eur J Surg Oncol* 1996; 22: 17–22
- 251 Robert NJ, Dieras V, Glaspy J et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J Clin Oncol* 2011; 29: 1252–1260
- 252 Robertson JF, Osborne CK, Howell A et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials. *Cancer* 2003; 98: 229–238
- 253 Roche H, Fumoleau P, Spielmann M et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS01 Trial. *J Clin Oncol* 2006; 24: 5664–5671
- 254 Romestaing P, Belot A, Hennequin C. Ten-year results of a randomized trial of internal mammary chain irradiation after mastectomy. *Int J Radiat Oncol Biol Phys* 2009; 75 (Suppl. 3): p S1 [Abstract 1]
- 255 Romestaing P, Lehingue Y, Carrie C et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 1997; 15: 963–968
- 256 Romond EH, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; 353: 1673–1684
- 257 Roos DE, O'Brien PC, Smith JG et al. A role for radiotherapy in neuro-pathic bone pain: preliminary response rates from a prospective trial (Trans-tasman radiation oncology group, TROG 96.05). *Int J Radiat Oncol Biol Phys* 2000; 46: 975–981
- 258 Rosen LS, Gordon D, Kaminski M et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J* 2001; 7: 377–387
- 259 Rosen PP, Groshen S, Kinne DW. Prognosis in T2N0M0 stage I breast carcinoma: a 20-year follow-up study. *J Clin Oncol* 1991; 9: 1650–1661
- 260 Rosen PP, Groshen S, Kinne DW et al. Factors influencing prognosis in node-negative breast carcinoma: analysis of 767 T1N0M0/T2N0M0 patients with long-term follow-up. *J Clin Oncol* 1993; 11: 2090–2100
- 261 Rosselli Del T, Palli D, Cariddi A et al. 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: 1593–1597
- 262 Rouesse J, de la Lande B, Bertheault-Cvitkovic F et al. A phase III randomized trial comparing adjuvant concomitant chemoradiotherapy versus standard adjuvant chemotherapy followed by radiotherapy in operable node-positive breast cancer: final results. *Int J Radiat Oncol Biol Phys* 2006; 64: 1072–1080
- 263 Rowell NP. Radiotherapy to the chest wall following mastectomy for node-negative breast cancer: a systematic review. *Radiother Oncol* 2009; 91: 23–32
- 264 Rowell NP. Are mastectomy resection margins of clinical relevance? A systematic review. *Breast* 2010; 19: 14–22
- 265 Russell NS, Kunkler IH, van Tienhoven G et al. Postmastectomy radiotherapy: will the selective use of postmastectomy radiotherapy study end the debate? *J Clin Oncol* 2009; 27: 996–997
- 266 S3 Leitlinie Magenkarzinom. Diagnostik und Therapie der Adenokarzinome des Magens und ösophago-gastralen Übergangs. AWMF; 2011
- 267 Sanjuan A, Vidal-Sicart S, Zanon G et al. Clinical axillary recurrence after sentinel node biopsy in breast cancer: a follow-up study of 220 patients. *Eur J Nucl Med Mol Imaging* 2005; 32: 932–936
- 268 Sautter-Bihl ML, Budach W, Dunst J et al. DEGRO practical guidelines for radiotherapy of breast cancer I: breast-conserving therapy. *Strahlenther Onkol* 2007; 183: 661–666
- 269 Schmoor C, Sauerbrei W, Bastert G et al. Role of isolated locoregional recurrence of breast cancer: results of four prospective studies. *J Clin Oncol* 2000; 18: 1696–1708
- 270 Seidman AD, Fornier MN, Esteva FJ et al. Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol* 2001; 19: 2587–2595
- 271 Selby P, Gillis C, Haward R. Benefits from specialised cancer care. *Lancet* 1996; 348: 313–318
- 272 Semrau S, Gerber B, Reimer T et al. Concurrent radiotherapy and taxane chemotherapy in patients with locoregional recurrence of breast cancer. A retrospective analysis. *Strahlenther Onkol* 2006; 182: 596–603
- 273 Shaffer R, Tyldesley S, Rolles M et al. Acute cardiotoxicity with concurrent trastuzumab and radiotherapy including internal mammary chain nodes: a retrospective single-institution study. *Radiother Oncol* 2009; 90: 122–126
- 274 Shafiq J, Delaney G, Barton MB. An evidence-based estimation of local control and survival benefit of radiotherapy for breast cancer. *Radiother Oncol* 2007; 84: 11–17
- 275 Sheard T, Maguire P. The effect of psychological interventions on anxiety and depression in cancer patients: results of two meta-analyses. *Br J Cancer* 1999; 80: 1770–1780
- 276 Shelley W, McCready D, Holloway C et al.; and the Breast Cancer Disease Site Group. Management of ductal carcinoma in situ of the breast: a clinical practice guideline. Evidence-based Series #1–10 Version 2.2006: Section 1. Hamilton, ON: Cancer Care Ontario; 2006
- 277 Shenkier T, Weir L, Levine M et al. Clinical practice guidelines for the care and treatment of breast cancer: 15. Treatment for women with stage III or locally advanced breast cancer. *CMAJ* 2004; 170: 983–994
- 278 Sherar M, Liu FF, Pintilie M et al. Relationship between thermal dose and outcome in thermoradiotherapy treatments for superficial recurrences of breast cancer: data from a phase III trial. *Int J Radiat Oncol Biol Phys* 1997; 39: 371–380
- 279 SIGN. SIGN 84: Management of breast cancer in women. Edinburgh (Scotland): SIGN; 2005
- 280 Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. [CANADA]. *N Engl J Med* 2001; 344: 783–792
- 281 Sledge Jr. GW, Hu P, Falkson G et al. Comparison of chemotherapy with chemohormonal therapy as first-line therapy for metastatic, hormone-sensitive breast cancer: An Eastern Cooperative Oncology Group study. *J Clin Oncol* 2000; 18: 262–266
- 282 Smith BD, Bentzen SM, Correa CR et al. Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011; 81: 59–68
- 283 Smith BD, Haffty BG, Buchholz TA et al. Effectiveness of radiation therapy in older women with ductal carcinoma in situ. *J Natl Cancer Inst* 2006; 98: 1302–1310
- 284 Stadtmauer EA, O'Neill A, Goldstein LJ et al. Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. Philadelphia Bone Marrow Transplant Group. *N Engl J Med* 2000; 342: 1069–1076

- 285 Steenland E, Leer JW, van Houwelingen H et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol* 1999; 52: 101–109
- 286 Stockler M, Wilcken N, Ghersi D et al. The management of advanced breast cancer: systemic reviews of randomised controlled trials regarding the use of cytotoxic chemotherapy and endocrine therapy. *Woolloomooloo* 1997; Canberra (Australien): NHMRC
- 287 Stockler M, Wilcken NR, Ghersi D et al. Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer. *Cancer Treat Rev* 2000; 26: 151–168
- 288 Stopeck AT, Lipton A, Body JJ et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010; 28: 5132–5139
- 289 Taylor CW, Green S, Dalton WS et al. Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. *J Clin Oncol* 1998; 16: 994–999
- 290 *The Association of Breast Surgery at BASO RCoSoE*. Guidelines for the management of symptomatic breast disease. *Eur J Surg Oncol* 2005; 31 (Suppl. 1): 1–21
- 291 Theriault RL, Lipton A, Hortobagyi GN et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. *Protocol 18 Aredia Breast Cancer Study Group*. *J Clin Oncol* 1999; 17: 846–854
- 292 Thuerlimann B, Price KN, Castiglione M et al. Randomized controlled trial of ovarian function suppression plus tamoxifen versus the same endocrine therapy plus chemotherapy: Is chemotherapy necessary for premenopausal women with node-positive, endocrine-responsive breast cancer? First results of International Breast Cancer Study Group Trial 11–93. [DKG-R]. *Breast* 2001; 10 (Suppl. 3): 130–138
- 293 Tjan-Heijnen VC, de Boer M. Minimal lymph node involvement and outcome of breast cancer. The results of the Dutch MIRROR study. *Discov Med* 2009; 8: 137–139
- 294 Torrens H, Fabry H, van der Jr. S 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
- 295 Truong PT, Olivetto IA, Kader HA et al. Selecting breast cancer patients with T1–T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys* 2005; 61: 1337–1347
- 296 Truong PT, Olivetto IA, Whelan TJ et al. Clinical practice guidelines for the care and treatment of breast cancer: 16. Locoregional post-mastectomy radiotherapy. *CMAJ* 2004; 170: 1263–1273
- 297 Truong PT, Vinh-Hung V, Cserni G et al. The number of positive nodes and the ratio of positive to excised nodes are significant predictors of survival in women with micrometastatic node-positive breast cancer. *Eur J Cancer* 2008; 44: 1670–1677
- 298 Tsoutsou PG, Belkacemi Y, Gligorov J et al. Optimal sequence of implied modalities in the adjuvant setting of breast cancer treatment: an update on issues to consider. *Oncologist* 2010; 15: 1169–1178
- 299 Turnbull L, Brown S, Harvey I et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. *Lancet* 2010; 375: 563–571
- 300 UICC. TNM classification of malignant tumours. In: Sobin L, Gospodarowicz M, Wittekind C, eds. 7th ed. New York: Wiley-Liss; 2010
- 301 Velikova G, Booth L, Smith AB et al. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. *J Clin Oncol* 2004; 22: 714–724
- 302 Velikova G, Wright EP, Smith AB et al. Automated collection of quality-of-life data: a comparison of paper and computer touch-screen questionnaires. *J Clin Oncol* 1999; 17: 998–1007
- 303 Veronesi U, Cascinelli N, Mariani L et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002; 347: 1227–1232
- 304 Veronesi U, Paganelli G, Viale G et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003; 349: 546–553
- 305 Vogel C, O'Rourke M, Winer E et al. Vinorelbine as first-line chemotherapy for advanced breast cancer in women 60 years of age or older. *Ann Oncol* 1999; 10: 397–402
- 306 Vogl TJ, Muller PK, Mack MG et al. Liver metastases: interventional therapeutic techniques and results, state of the art. *Eur Radiol* 1999; 9: 675–684
- 307 von Minckwitz G, Kaufmann M, Möhrle D et al. Hormonelle Folgetherapien nach Goserelin (Zoladex®) beim metastasierten Mammakarzinom prämenopausaler Patientinnen. [AGO]. *Arch Gynecol Obst* 1991; 250: 258–260
- 308 von Minckwitz G, Untch M, Nuesch E et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. *Breast Cancer Res Treat* 2011; 125: 145–156
- 309 Voogd AC, Nielsen M, Peterse JL 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: 1688–1697
- 310 Voordeckers M, Vinh-Hung V, Lamote J et al. Survival benefit with radiation therapy in node-positive breast carcinoma patients. *Strahlenther Onkol* 2009; 185: 656–662
- 311 Voskuil DW, van Nes JG, Junggeburst JM et al. Maintenance of physical activity and body weight in relation to subsequent quality of life in postmenopausal breast cancer patients. *Ann Oncol* 2010; 21: 2094–2101
- 312 Wald NJ, Murphy P, Major P et al. UKCCCR multicentre randomised controlled trial of one and two view mammography in breast cancer screening. *BMJ* 1995; 311: 1189–1193
- 313 Walker MP, Yaszemski MJ, Kim CW et al. Metastatic disease of the spine: evaluation and treatment. *Clin Orthop Relat Res* 2003; 415: S165–S175
- 314 Weaver DL, Krag DN, Ashikaga T et al. Pathologic analysis of sentinel and nonsentinel lymph nodes in breast carcinoma: a multicenter study. *Cancer* 2000; 88: 1099–1107
- 315 Whelan T, Clark R, Roberts R 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: 11–16
- 316 Whelan T, Darby S, Taylor C et al. Overviews of randomized trials of radiotherapy in early breast cancer. *ASCO's Annual Meeting Educational Book*. Chicago (USA): ASCO; 2007: 3–6
- 317 Whelan T, Levine M. Radiation therapy and tamoxifen: concurrent or sequential? That is the question. *J Clin Oncol* 2005; 23: 1–4
- 318 Whelan TJ, Pignol JP, Levine MN et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; 362: 513–520
- 319 WHO. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Breast and female Genital Organs. In: Tavassoli FA, Devilee P, eds. Lyon: IARC Press; 2003: 9–112
- 320 Wolff AC, Hammond ME, Schwartz JN et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol* 2007; 25: 118–145
- 321 Wunder JS, Ferguson PC, Griffin AM et al. Acetabular metastases: planning for reconstruction and review of results. *Clin Orthop Relat Res* 2003; 415: S187–S197

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