

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

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1.2 Funding of this guideline

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1.3 Lead professional associations

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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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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 |
|--------|---|
| | <p>Multidisciplinary counseling and genetic testing should be carried out at special centers if one line of the family includes:</p> <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 |
|--------------------------------|---|
| | <p>a. BRCA1-associated carcinomas of the breast frequently exhibit a characteristic histopathological and immunohistochemical phenotype:</p> <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) |
| | <p>b. In cases where these characteristics are present, the pathologist should draw attention to the possibility of an inherited susceptibility.</p> |
| GCP | (Honrado E et al. 2006; Lakhani SR et al. 1998; Lakhani SR et al. 2005) |

| Risk-3 | Intensified early detection |
|--------|--|
| | <p>Early detection measures in patients with a high* familial risk include:</p> <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 | <p>a. Necessary baseline examinations include:</p> <ul style="list-style-type: none"> ▶ clinical breast examination: Breast inspection and palpation of breast and lymphatic drainage areas ▶ Mammography ▶ Ultrasound <p>If the clinical breast examination produces abnormal findings, diagnostic imaging and histological examination should be performed to complete the diagnostic workup.</p> |
| Level of evidence 1a | (NICE 2009b; NZGG 2009) |
| Grade of recommendation A | <p>b. For the investigation of symptomatic findings in women under age 40, sonography is the imaging method of first choice.</p> |
| Level of evidence 3b | (Nothacker M et al. 2007) |
| Grade of recommendation B | <p>c. The effects of endogenous and exogenous hormones should be taken into account during the performance and interpretation of diagnostic procedures.</p> |
| 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 | <p>a. For the investigation of abnormal clinical findings in women under age 40, mammography is the imaging method of first choice.</p> |
| Level of evidence 1a | (NICE 2009b; NZGG 2009) |
| Grade of recommendation A | <p>b. In high mammographic density (ARC3 and 4), the sensitivity of mammography is limited and should be enhanced by an additional ultrasound scan.</p> |
| 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)§: ▶ 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: ▶ 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 (pNmic) 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 | (Burststein 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; Fournay 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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