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German Guideline Program in Oncology (GGPO)

Evidence-based Guideline for the Early Detection, Diagnosis, Treatment and Follow-up of Breast Cancer

Version 4.4 - May 2021
AWMF-Registernummer: 032/045OL

Guideline (Long Version)

DKG KREBSGESELLSCHAFT
Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.
AWMF

Important Updates

Concerning editorial changes in versions 4.1, 4.2, and 4.3, see chapter 1.6.

Version 4.4 (May 2021) was updated as an amendment.

The following chapters were updated:

Chapter 6.4.1

Chapter 6.4.2.

The update in the scope of the amendment was triggered by the authroisation of numerous CDK4/6 inhibitors.

In versions 4.1 to 4.3, no content-related changes were made (see see chapter 1.6).

Version 4.0 (2017)

The recommendations contained in the chapter on patient infeormation and Eductaion have been expanded and adpated to the information needs of the patients (see chapter 3.2)

Early Detection (previously a separate S3 Practice Guideline) has been incorporated herein: Specific recommendations therein describe the approach to be used in patients with a high breast density and how to handle specific examination procedures (e.g. tomosynthesis) (see Chapter 3.2).

In the past years, a growing amount of data has become available on women with an elevated familial or genetic predisposition and on the cancer occurrence in such special settings. In other words, the recommendations give explicit instructions and options on how to proceed (e.g. platinum-containing systemic therapy, counseling services and dealing with the increased lifetime risk of further malignancies) (see Chapter 3.3).

The Diagnostics chapter contains new recommendations on staging alongside the conventional breast-related gynecological examinations. For example, a CT scan of the chest and abdomen is now explicitly recommended in patients with a high risk of recurrence or metastases (see Chapter 4.1).

In the current version, Chapter 4.4 Surgical treatment of invasive carcinoma takes into account more modern surgical procedures and the method applied to axillary staging, while particularly focusing on the growing use of neoadjuvant therapies. Overall, the new recommendations are intended to reduce radical surgeries (narrowing the safety margin in the resection of invasive carcinoma, omitting axillary dissection under pre-defined conditions).

The recommendations on pathomorphological examinations also include more recent markers. This Guideline also counts Ki67 among the conventional prognostic factors and allows the use of multigene assays in defined settings (see Chapter 4.5).

As in the surgical setting, the recommendations on radiotherapy increasingly follow de-escalation strategies: Procedures like hypofractionation and partial breast radiation alone can be discussed with the patients, especially those with advanced age (see Chapter 4.6).

The updated S3 Practice Guideline outlines in detail the options for adjuvant endocrine therapy, including that of prolonged administration (5-10 years) and the administration of chemotherapies (see Chapter 4.7).

New recommendations regarding influenceable lifestyle factors are designed to increase patients' physical activity and weight loss in order to lower their risk of recurrence and heighten their subjective well-being (see Chapter 4.7.7).

The updated Guideline also gives clear recommendations relating to settings with metastasis and local recurrences: In patients with local recurrences, for example, options for repeated radiotherapy and reinduction of cytostatics should be evaluated besides complete resection (see Chapters 5.3 and 5.4).

In addition to the previous and now updated chapters from the 2012 Guideline, new chapters have been developed by the authors to do justice to the high therapeutic relevance of their subject matter and more extensive evidence. The following chapters have been added:

Chapter 4.7.6 Bone-targeted therapy

Chapter 4.7.7 Influenceable lifestyle factors

Chapter 7 Breast cancer during pregnancy and lactation, pregnancy after breast cancer, fertility preservation

Chapter 8 Breast cancer in elderly patients

Chapter 9. Breast cancer in men

1. Information about this Guideline

1.1. Editors

German Guideline Program in Oncology of the Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V., AWMF), the German Cancer Society (Deutsche Krebsgesellschaft e. V., DKG), and German Cancer Aid (Deutsche Krebshilfe, DKH).

1.2. Leading Scientific Societies

Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. (DGGG)

Deutsche Krebsgesellschaft vertreten durch Ihre Arbeitsgemeinschaften (DKG)

1.3. Funding of the Guideline

This Guideline was funded by the German Cancer Aid (Deutsche Krebshilfe, DKH) as part of the German Guideline Program in Oncology.

1.4. Contact

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1.5. How to cite

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1.6. Previous Changes

April 2018 Version 4.1: General editorial revision. The background text in Chapter 3.2.2. was edited, as were Figure 4 and Figure 5. In the recommendation boxes 3.8, 3.13, 4.40, 4.53, 4.69, 4.72, “Recommendation” was changed to “Statement”. The parentheses around “(SLNE ≥ 3 Lnn.)“ were omitted in Table 9. Correction made to QI 6 (mi added).

1.7. Special Comment

Medicine is constantly evolving. This makes all information—particularly about diagnostic and therapeutic procedures—only as good as the state of knowledge at the time the Guideline went to print. The greatest possible care has been taken with the recommendations given herein for treatment as well as for the choice and dosage of medications. Nevertheless, guideline users are advised to refer to the manufacturer's instruction leaflet and the prescribing information and, in case of doubt, consult a specialist. In everybody's general interest, please report any inconsistencies or discrepancies you may find to the editorial board of the German Guideline Program in Oncology.

The user remains personally liable for all diagnostic and therapeutic applications, medications and dosages.

Registered trademarks and brand names are not specifically identified in these care guidelines. It therefore cannot be inferred that a trademark is free merely by the lack of any such reference.

1.8. Objectives of the Guideline Program for Oncology

With the German Guideline Program in Oncology, the Association of the Scientific Medical Societies in Germany (AWMF), the German Cancer Society (DKG), and the German Cancer Aid (DKH) have set themselves the task of jointly promoting and supporting the development, updating and use of scientifically founded and practicable guidelines in oncology. The program is based on medical-scientific knowledge of the professional societies and the DKG, the consensus of medical experts, users and patients, as well as regulations of the guideline preparation of the AWMF and the expert support and funding by the German Cancer Aid. To map current medical knowledge and account for progress in the field of medicine, guidelines have to be reviewed and updated regularly. The AWMF Guidance Manual forms the basis for the development of high-quality oncologic guidelines. As guidelines constitute an important quality assurance and quality management tool in oncology, they should be incorporated specifically and consistently into routine care. Active implementation measures and evaluation programs are therefore an important component in promoting the Guideline Program in Oncology. The objective of the program is to create professional and medium-term financially secure preconditions for the development and production of high-quality guidelines in Germany. These high-quality guidelines serve not only the structured transfer of knowledge, but may also find their place in health care system structures. Worth mentioning here are evidence-based guidelines as the basis for preparing and updating disease management programs or for implementing guideline-derived quality indicators (QIs) for the certification of organ cancer centers.

1.9. Additional Documents relating to this Guideline

This document is the comprehensive version of the Interdisciplinary S3 Practice Guideline for the Early Detection, Diagnosis, Treatment and Follow-up of Breast Cancer and can be accessed via the links listed below: In addition to this comprehensive version, the following supplementary documents are available:

- Short version of the guideline
- Lay version (patient guideline)
- Guideline Report on its development process
- Evidence tables This Guideline and all additional documents are available via the following websites.
- Guideline Program in Oncology (http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/)
- AWMF (www.leitlinien.net)
- Guidelines International Network (www.g-i-n.net)

In addition, a print version of the Patient Guidelines can be ordered from the DKH (https://www.krebshilfe.de/informieren/ueber-krebs/infothek/)

1.10. Composition of the Guideline Group

1.10.1. Guideline Coordination

Guideline coordination

Prof. Achim Wöckel, M.D., Clinic for Women (Department of Obstetrics and Gynecology), University Hospital of Würzburg, Josef-Schneider-Str. 4, 97080 Würzburg, Germany

Co-coordinators:

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Guideline Secretariat

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1.10.2. Participating professional associations and organizations

Table 1: Participating professional associations and organizations

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Participating professional associations and organizations	Elected Representative(s)
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Arbeitsgemeinschaft Internistische Onkologie in der DKG (AIO)	Dr. Anja Welt Dr. Matthias Zaiss
Arbeitsgemeinschaft Prävention und integrative Medizin in der Onkologie der Deutschen Krebsgesellschaft (PRiO)	Prof. Dr. med. Volker Hanf Prof. Dr. Karsten Münstedt
Arbeitsgemeinschaft Psychoonkologie der Deutschen Krebsgesellschaft (PSO)	Prof.Dr. Joachim Weis
Arbeitsgemeinschaft Radiologische Onkologie (ARO)	Prof. Dr. Wilfried Budach Prof.Dr. Frederik Wenz
Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin (ASORS)	Prof. Dr. Hartmut Link Prof. Dr. Oliver Rick
Arbeitskreis Frauengesundheit (AKF)	Prof. Dr. Anke Steckelberg Gudrun Kemper
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Berufsverband für Frauenärzte e. V.	Dr. Klaus König
BRCA-Netzwerk e. V.	Andrea Hahne Traudl Baumgartner
Bundesverband Deutscher Pathologen e.V. (BDP)	Prof. Dr. Annette Lebeau Prof. Dr. Hans-Peter Sinn

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Deutsche Gesellschaft der Plastischen, Rekonstruktiven und Ästhetischen Chirurgen (DGPRÄC)	Prof. Dr. Christoph Heitmann
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Deutsche Gesellschaft für Palliativmedizin e.V. (DGP)	Dr. Christina Gerlach M.Sc. Dr. Susanne Hirsmüller
Deutsche Gesellschaft für Pathologie e.V. (DGP)	Prof. Dr. Hans H. Kreipe Prof. Dr. Carsten Denkert
Deutsche Gesellschaft für Psychosomatische Frauenheilkunde und Geburtshilfe (DGPFG)	Dr. Friederike Siedentopf
Deutsche Gesellschaft für Radioonkologie e.V. (DEGRO)	Prof. Dr. Cordula Petersen Prof. Dr. Jürgen Dunst
Deutsche Gesellschaft für Rehabilitationswissenschaften (DGRW)	Prof. Dr. Hans Helge Bartsch
Deutsche Gesellschaft für Senologie e.V. (DGS)	Prof. Dr. Rüdiger Schulz-Wendtland

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Deutsche Röntgengesellschaft e.V.	Prof. Dr. Markus Müller-Schimpfle (1)
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Gesellschaft der epidemiologischen Krebsregister in Deutschland (GEKID)	Prof. Dr. Alexander Katalinic
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Ultraschalldiagnostik in Gynäkologie und Geburtshilfe (ARGUS)	Prof. Dr. med. Dr. h. c. Friedrich Degenhardt

1: bis 31.12.16: Prof. Dr. Ulrich Bick, Berlin, ab 01.01.17: PD Dr. E. Fallenberg, Berlin

Table 2: Composition of Guideline Workgroups

Workgroup	Composition of Workgroup
3.1 Patientinneninformation und - aufklärung	**Leitung: Prof. Dr. Ingrid Schreer** Dr. Susanne Hirsmüller Roswita Hung Gudrun Kemper Dr. Klaus König Kerstin Paradies Dr. Renza Roncarati Prof. Dr. Anke Steckelberg

Workgroup	Composition of Workgroup
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4.2 Diagnostik bei der Abklärung auffälliger Befunde sowie prätherapeutische Ausbreitungsdiagnostik bei gesichertem Mammakarzinom	**Leitung: Prof. Dr. Sylvia Heywang-Köbrunner** Prof. Dr. med. Dr. h. c. Friedrich Degenhardt PD Dr. Eva Fallenberg Prof. Dr. Markus Hahn Prof. Dr. Markus Müller-Schimpfle
4.3 DCIS und Risikoläsionen	**Leitung: Prof. Dr. Bernd Gerber** Prof. Dr. Sara Brucker Prof. Dr. Wilfried Budach Prof. Dr. Carsten Denkert Prof. Dr. Tanja Fehm Prof. Dr. Christoph Heitmann Prof. Dr. Hans H. Kreipe Prof. Dr. Wolfgang Kühn Prof. Dr. Annette Lebeau Prof. Dr. Ingrid Schreer Prof. Dr. Hans-Peter Sinn
4.4 Operative Therapie des invasiven Karzinoms	**Leitung: Prof. Dr. Wilfried Budach** Prof. Dr. Vesna Bjelic-Radisic

Workgroup	Composition of Workgroup
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4.5 Pathomorphologische Untersuchung	**Leitung: Prof. Dr. Bernd Gerber** Prof. Dr. Sara Brucker Prof. Dr. Carsten Denkert Prof. Dr. Hans H. Kreipe Prof. Dr. Annette Lebeau Prof. Dr. Marcus Schmidt Prof. Dr. Rüdiger Schulz-Wendtland Prof. Dr. Hans-Peter Sinn
4.6 Adjuvante Strahlentherapie des Mammakarzinoms	**Leitung: Prof. Dr. Wilfried Budach** Prof. Dr. Volker Budach Prof. Dr. Jürgen Dunst Prof. Dr. Jutta Engel Prof. Dr. Tanja Fehm Prof. Dr. Petra Feyer Prof. Dr. Dieter Hölzel Prof. Dr. Alexander Katalinic Prof. Dr. Cordula Petersen Prof. Dr. Anton Scharl Prof. Dr. Rüdiger Schulz-Wendtland Prof. Dr. Christoph Thomssen
4.7.2 Endokrine Therapie	**Leitung: Prof. Dr. Marcus Schmidt** Prof. Dr. Hans Helge Bartsch Prof. Dr. Vesna Bjelic-Radisic Prof. Dr. Jens Blohmer Prof. Dr. Tanja Fehm Prof. Dr. Dieter Hölzel Prof. Dr. Christian Jackisch Prof. Dr. Hartmut Link Prof.Dr. Diana Lüftner Prof. Dr. Anton Scharl Prof. Dr. Hans Tesch
4.7.3 Adjuvante Chemotherapie	**Leitung: Prof.Dr. Diana Lüftner**

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4.7.5 Antikörpertherapie	**Leitung: Prof.Dr. Diana Lüftner, Prof. Dr. Marcus Schmidt, Prof. Dr. Andreas Schneeweiss** Prof. Dr. Jens Blohmer Prof. Dr. Elmar Stickeler Prof. Dr. Michael Untch
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6.3 Supportivtherapie	**Leitung: Prof. Dr. Hans Helge Bartsch** Prof. Dr. Petra Feyer Dr. Christina Gerlach M.Sc. Ulla Henscher Roswita Hung Prof. Dr. Hartmut Link Prof. Dr. Michael Lux Dr. Renza Roncarati
6.4 Nachsorge	**Leitung: Prof. Dr. Ute-Susann Albert** Prof. Dr. Matthias W. Beckmann Prof. Dr. Vesna Bjelic-Radisic Dr. Klaus König
6.5 Rehabilitation	Prof. Dr. Hans Helge Bartsch Prof. Dr. Wilfried Budach Ulla Henscher Prof. Dr. Dieter Hölzel Roswita Hung Prof. Dr. Wolfgang Janni Prof. Dr. Oliver Rick Dr. Renza Roncarati Prof. Dr. Rüdiger Schulz-Wendtland Prof.Dr. Joachim Weis
6.6 Komplementäre Medizin	**Leitung: Prof. Dr. Matthias W. Beckmann** Dr. Jasmin Festl

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7. Mammakarzinom in Schwangerschaft und Stillzeit, Schwangerschaft nach Mammakarzinom, Fertilitätserhalt	**Leitung: Prof. Dr. Nadia Harbeck** Prof. Dr. med. Dr. h. c. Friedrich Degenhardt Prof. Dr. Peyman Hadji Prof. Dr. Sibylle Loibl
8. Mammakarzinom der älteren Patientin	**Leitung: Prof. Dr. Hans-Jürgen Lück** Prof. Dr. Ute-Susann Albert Prof. Dr. Michael Denkinger Dr. Christina Gerlach M.Sc. Prof. Dr. med. Jens Huober Prof. Dr. Anton Scharl
9. Mammakarzinom des Mannes	**Leitung: Prof. Dr. Volkmar Müller** Prof. Dr. Ute-Susann Albert Prof. Dr. Christoph Thomssen

1.10.3. Additional Parties without voting Power

experts in an advisory capacity

Name	City
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Prof. Dr. Matthias Beckmann	Erlangen
Prof. Dr. Jens Blohmer	Berlin

Name	City
Prof. Dr. Peter Fasching	Erlangen
Prof. Dr. Nadia Harbeck	Munich
Prof. Dr. Peyman Hadji	Frankfurt
Prof. Dr. Hans Hauner	Munich
Prof. Dr. Sylvia Heywang-Köbrunner	Munich
Prof. Dr. Jens Huober	Ulm
Dr. Jutta Hübner	Berlin
Prof. Dr. Christian Jackisch	Offenbach
Prof. Dr. Sibylle Loibl	Neu-Isenburg
Prof. Dr. Hans - Jürgen Lück	Hanover
Prof. Dr. Michael Lux	Erlangen
Prof. Dr. Gunter von Minckwitz	Neu-Isenburg
Prof. Dr. Volker Möbus	Frankfurt
Prof. Dr. Volkmar Müller	Hamburg
Prof. Dr. Ute Nöthlings	Bonn
Prof. Dr. Marcus Schmidt	Mainz
Prof. Dr. Rita Schmutzler	Cologne
Prof. Dr. Andreas Schneeweiss	Heidelberg
Prof. Dr. Florian Schütz	Heidelberg
Prof. Dr. Elmar Stickeler	Aachen
Prof. Dr. Christoph Thomssen	Halle (Saale)
Prof. Dr. Michael Untch	Berlin
Dr. Simone Wesselmann	Berlin

Name	City
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Dr. Jasmin Festl (guideline evaluation, literature selection)	Würzburg
Steffi Hillmann, MPH (guideline research and evaluation)	Würzburg
PD Dr. Mathias Krockenberger (literature selection)	Würzburg
Stephanie Stangl, MPH	Würzburg
Dr. Tanja Stüber (literature selection)	Würzburg

1.10.4. Patient Involvement

This Guideline was prepared with the direct involvement of 4 patient advocates.

Ms. Roncarati and Ms. Hung of the German Self-Help Group for Women after Cancer (Frauenselbsthilfe nach Krebs) were involved from the very beginning in the preparation of the guideline and participated in the consensus conferences with their own voting rights. Prof. Steckelberg and Ms. Kemper "Working Group on Women's Health" (AKF) were also involved and took part in the consensus conferences with their own right to vote.

1.10.5. Methodological Support

Methodological support was provided by the Guideline Program in Oncology:

- Monika Nothacker, M.D. MPH (AWMF)
- Professor Ina Kopp, M.D. (AWMF)
- Dr. Markus Follmann MPH, MSc. (DKG)
- Thomas Langer, Social Scientist (DKG)

Through external sub-contractors:

- Simone Wesselmann, M.D., MBA (update of quality indicators)

1.11. Abbreviations Used

Table 3: Abbreviations Used

Abbreviation	Explanation
ADH	(intra-)ductal atypical hyperplasia
AI	aromatase inhibitor
AML	acute myeloid leukaemia
APBI	accelerated partial breast radiation
ASCO	American Society of Clinical Oncology
ATL	activities of daily living
AUC	area under the curve
BÄK	German Medical Association
bds	on both sides
BET	breast-conserving therapy
CISH	Chromogenic in situ hybridization
CNB	Core Needle Biopsy
CT	Computed tomography
DBT	digital breast tomosynthesis
DCIS	Ductal carcinoma in situ
DFS	disease-free survival (DFS)
DGS	German Society for Senology
DKG	German Cancer Society
ECE	extracapsular tumor growth at the lymph nodes
EIC	extensive intraductal component

Abbreviation	Explanation
EK	Expert consensus
ER	Estrogen receptor
ESA	erythropoiesis-stimulating agents
ESAS	Edmonton Symptom Assessment System
ET	Estrogen therapy
FEA	flat epithelial atypia
FISH	Fluorescence in situ hybridization
FN	febrile neutropenia
FNA	Fine needle aspiration
FNB	Fine needle biopsy
G-CSF	granulocyte colony-stimulating factor
GnRHa	gonadotropin-releasing hormone agonist
HADS	Hospital Anxiety and Depression Scale
HER2	Human Epidermal Growth Factor Receptor Type 2
HT	Hormone therapy
IARC	International Agency for Reserch on Cancer, international institute for cancer research
IBC	inflammatory breast carcinoma
iFE	intensified screening
IHC	Immunohistochemistry
IMRT	Intensity modulated radiotherapy

Abbreviation	Explanation
IORT	intraoperative radiotherapy
IQWiG	Institute for Quality and Efficiency in Health Care
ISH	In situ hybridization
ITC	intrathecal chemotherapy
KD	cognitive dysfunction
KM-MRI	Contrast magnetic resonance imaging
KPE	complex initial physical therapy
LABC	locally advanced breast cancer
LCIS	lobular carcinoma in situ
LK	Lymph nodes
LL	Guideline
LN	lobular neoplasia
LoE	level of evidence
LVEF	left ventricular ejection fraction
LVI	(lymphatic) vessel invasion
LWS	Lumbar spine
MAK	Nipple-Areola Complex
MDS	myelodysplatic syndrome
MG	Mammography
MRI	Magnetic resonance imaging
MSP	Mammography Screening Program

Abbreviation	Explanation
NACT	neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NNT	Number Needed to Treat
NZGG	New Zealand Guidelines Group
OP	Operation
OS	Overall Survival
PBI	partial breast radiation
pCR	pathological complete remission (Engl.: pathological complete remission)
PET	Positron Emission Tomography
PFS	progression-free survival (PFS)
PI	Proliferation Index
PMRT	postoperative radiotherapy
PNP	Polyneuropathy
POS	Palliative Care Outcome Scale
PST	primary systemic therapy
QoL	Quality of Life
RCT	randomized controlled trial
RFA	Radio Frequency Ablation
ROR	risk of recurrence
RR	Relative risk

Abbreviation	Explanation
RS	recurrence score
SABCS	San Antonio Breast Cancer Symposium
SBRT	stereotactic radiation
SGB	Social Security Code
SIB	simultaneous integrated boost
SIGN	Scottish Intercollegiate Guidelines Network
SISH	Silver enhanced in situ hybridization

2. Introduction

2.1. Scope and Purpose

2.1.1. Objective and Key Questions

The main rationale for updating the guideline is the consistently high epidemiological importance of breast cancer and the associated burden of disease. In this context, the effects of new care concepts in their implementation must be examined. The need to update the guideline also arises from the existence of new scientific findings and the further development of the guideline methodology. In addition, an editorial and content review and revision of the core statements and recommendations of the guideline is required at regular intervals. The objectives of the S3 guideline for the early detection, diagnosis, therapy and aftercare of breast cancer were retained from the original version and the first two updates and supplemented or specified for the third new edition:

- Consideration of current findings of evidence-based medicine and recognised treatment concepts
- consideration of the findings from disseminated guidelines and the comprehensive coverage of guideline-based quality indicators in the updating and implementation of the guideline
- Supporting the involvement of patients in therapy decisions and positioning their individual needs
- Comprehensive implementation of multidisciplinary, quality-assured and cross-sectoral care for breast cancer
- concrete efforts to improve the provision of needs-based and quality-assured psychosocial care and rehabilitation
- Support of the documentation of epidemiology and progression of breast cancer diseases by clinical cancer registers

- systematic consideration of the recommendations of initial, continuing and further training and in quality management systems
- systematic consideration of the recommendations and quality indicators derived from them in disease management programmes (DMPs), certification procedures of breast centres, cancer registries and external comparative quality assurance and standardisation of documentation requirements.

Improving the knowledge of the disease among non-affected persons and patients is an important goal for which there is a clear potential for improvement. It is a prerequisite for empowering women to participate in therapy decisions. At present, information is increasingly being made available on the Internet, but in many cases with very varying, sometimes unacceptable quality. Particularly in the area of breast cancer, a flood of information and educational material is available, the quality of which is predominantly assessed as poor. Within the framework of the OL-program, different versions of the patient guideline have been created, which are regularly adapted after the corresponding updates. The respective valid versions of the Women's and Patient Guidelines are available free of charge (see Chapter 1.9).

Addressees:

The recommendations of the interdisciplinary guideline (LL) are addressed to all physicians and members of professional groups involved in the care of citizens in the context of early detection and patients with breast cancer (gynaecologists, general practitioners, radiologists, pathologists, radio-oncologists, haemato-oncologists, psycho-oncologists, physiotherapists, nursing staff, etc.) and all women with breast cancer and their relatives.

Other indirect addressees are:

- medical and scientific societies and professional associations
- Representation of the interests of women (women's health organisations, patient and self-help organisations)
- Quality assurance institutions and projects at federal and state level
- health policy institutions and decision-makers at federal and state level
- those responsible for DMP programmes and integrated care contracts
- Cost unit
- as well as the public for information on good medical practice.

2.1.2. Validity and Update Process

The S3 guideline is valid until the next update, the validity period is estimated at 5 years. Shorter-term updates are planned in case of urgent need for changes. Comments and notes on updating the guideline are expressly requested and can be sent to the following address: mammakarzinom@leitlinienprogramm-onkologie.de

2.2. Methodology

The methodological procedure for the preparation of the guideline is described in the guideline report. It is freely available on the Internet, e.g. on the pages of the Oncology Guidelines Program (http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/) and the AWMF pages (http://www.awmf.org/).

2.2.1. Levels of Evidence (LoE)

To classify the risk of bias in the identified studies, this guideline uses the system of the Oxford Centre for Evidence-based Medicine in the 2009 version, as shown in Table 5. This system provides for the classification of studies for different clinical questions (benefit of therapy, prognostic significance, diagnostic value).

Scheme of evidence grading according to Oxford (version March 2009)

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity) of RCTs	SR (with homogeneity) inception cohort studies; CDR validated in different populations	SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centers	SR (with homogeneity) of prospective cohort studies	SR (with homogeneity) of Level 1economic studies
1b	Individual RCT (with narrow Confidence Interval)	Individual inception cohort study with > 80% follow-up; CDR validated in a single population	Validating cohort study with good reference standards; or CDR tested within one clinical centre	Prospective cohort study with good follow-up	Analysis based on clinically sensitive costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity) of Level >2 diagnostic studies	SR (with homogeneity) of Level 2b and better studies	SR (with homogeneity) of Level >2 economic studies
2b	Individual cohort study (including	Retrospective cohort study or follow-up	Exploratory cohort study with good	Retrospective cohort study,	Analysis based on clinically

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
	low quality RCT; e.g, <80% follow-up)	of untreated control patients in an RCT; Derivation of CDR or validated on split-sample only	reference standards; CDR after derivation, or validated only on split-sample or databases	or poor follow-up	sensitive costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity) of case-control studies		SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies
3b	Individual Case Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study; or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensitive variations
4	Case-series (and poor quality cohort and	Case series (and poor quality prognostic	Case control study, poor or non-independent	Case-series or superseded	Analysis with no sensitivity analysis

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
	case-control studies)	cohort studies)	reference standard	reference standards	
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles

2.2.2. Grades of Recommendation (GoR)

The methodology of the Oncology Guidelines Programme provides for the allocation of recommendation grades by the guideline authors in a formal consensus procedure. Accordingly, AWMF-certified guideline consultants moderated structured consensus conferences. Within the framework of these processes, the recommendations were formally agreed upon by the voting mandate holders (see Chapter 1.10.3). The results of the respective votes (consensus strength) are assigned to the recommendations according to the categories in Table 7.

For all evidence-based statements and recommendations, the guideline shows the evidence level of the underlying studies and, in the case of recommendations, the strength of the recommendation (recommendation level). With regard to the strength of the recommendation, this guideline distinguishes between three levels of recommendation (see table below), which are also reflected in the formulation of the recommendations.

Scheme of recommendation grading

Level of recommendation	Description	Language
A	Strong recommendation	shall/shall not
B	Recommendation	should/should not
C	Recommendation open	can/can be waived

Consensus strength

Consensus strength	Percentage approval
Strong consensus	> 95% of those entitled to vote
Consensus	> 75 - 95% of those entitled to vote
Majority approval	> 50 - 75% of those entitled to vote
Dissent	< 50% der Stimmberechtigten

The decision criteria for determining the degrees of recommendation are explained in the guideline report on this guideline.

2.2.3. Statements

Statements are descriptions or explanations of specific facts or questions without immediate call for action. In line with the procedure for recommendations, they are adopted in a formal consensus procedure and can be based either on study results or on expert opinions.

2.2.4. Expert Consensus (EK)

Statements/recommendations for which it has been decided to work on the basis of expert consensus of the Guidelines Group are identified as "Expert Consensus". No symbols or letters were used for the graduation of the recommendations based on expert consensus; the strength here results from the wording used (should/should/can) according to the graduation in Table 6.

2.2.5. Independence and Disclosure of Possible Conflicts of Interest

The German Cancer Aid provided the financial means through the Oncology Guidelines Programme (OL). These funds were used for personnel costs, office material, literature procurement and the consensus conferences (room rent, technology, catering, moderator fees and travel expenses of the participants). The guideline was developed with editorial independence from the financing organization. During the guideline

process, all members submitted a written declaration of any existing conflicts of interest.

Obtaining declarations of conflict of interest

From March 2016 onwards, declarations of conflict of interest were obtained from all persons involved using the updated AWMF form (see Guidelines Report), with step-by-step indication of the level of remuneration and explicit request for intellectual (academic) conflicts of interest (schools, publication activity, etc.). The completeness of the declarations was achieved in October 2016. Including methodologists, individual experts and deputies of mandate holders of the professional societies, the guideline group comprises about 90 persons.

Assessment of conflicts of interest

In the form used, those who had to fill in the form were asked to indicate whether there was a thematic link with the present guideline topic. However, a final self-assessment of whether a conflict of interest exists was no longer carried out. The conflict of interest declarations were evaluated by a working group nominated by the steering group. The working group consisted of Prof. Dr. R. Kreienberg (Senior Coordinator, Gynaecologist, former Director of the University Women's Hospital Ulm, DGGG), Prof. Dr. U.S. Albert (Senologist, DGS), Prof. Dr. W. Budach (Director of the Clinic for Radiotherapy of the University Hospital in Düsseldorf, DEGRO) and Dr. M. Nothacker, MPH (Methodologist, AMWF). All results were presented to an external consultant (Prof. Dr. Ludwig of the AKDÄ) and confirmed.

Evaluation criteria

The initial assessment of the declarations of conflict of interest was carried out by all evaluators for all persons, completely independently of the other evaluators, according to the classification: 0 = none, 1 = low, 2 = moderate, 3 = serious in terms of the assessed level of conflict of interest. Reasons for this were recorded. The assessments of the working group members were combined and the range of the assessments was determined. In a joint telephone conference, the assessments were discussed which had at least a 2 (moderate conflict of interest n=31) and/or a 3 (serious conflict of interest, n=15). After discussion, the final ranking was determined. The following criteria were examined with regard to the existing thematic reference and the absolute level of remuneration and the strength of the relationship:

1. Lectures financed by the industry
2. Review/Advisory Board: Paid review/advisory work for industrial companies (Scientific Advisory Board: work for industry)
3. Third-party funds directly financed by industry

With only a few presentations, the evaluation was "1 - low". In the case of the existence of relevant expert opinions/consultancy or activities in a scientific field, the assessment was "1 - low". In the case of relevant activities as an assessor/consultant or in a scientific advisory board and/or receipt of third-party funding from industry, the assessment was either "2 - moderate" or "3 - serious". The ratings were assigned by consensus in the overall view of the information and are subject to a subjective assessment, as the information provided in the conflict of interest forms did not consistently allow for a reliable quantitative assessment and there was no rationale for a fixed cut-off.

Finally, the evaluations were assigned as follows:

44 times = assessment 2 - 14 elected officials and 30 experts were affected 0 times = assessment 3

Dealing with conflicts of interest

The following approach was implemented:

- 0 -1 (no or minor conflict of interest): no special measures.
- 2 (moderate conflict of interest): double vote on the topics concerned (additional calculation of the result of the vote if persons with a moderate conflict of interest are excluded).
- 3 (serious conflict of interest): no vote on the topics concerned, review of the chapter by third parties is obligatory, optional exclusion from the discussion (review should be carried out by methodologists or members of the guideline group who are not biased with regard to content).

The issues potentially affected by conflicts of interest were identified on the basis of the substances listed.

Guidance coordinators and members of the steering group were excluded from the vote as a matter of principle. In order to create an empirical basis for the actual risk of bias in relation to the overall group assessment, the persons with moderate conflicts of interest were identified by means of a preceding question before the electronic voting process. Subsequently, this blinded grouping made it possible to conduct sensitivity analyses with regard to the group of persons with a moderate conflict of interest (result if all persons with a conflict of interest were involved vs.)

This procedure was discussed at the end of November with an independent expert and expert on conflicts of interest, Prof. Dr. Ludwig of the AKDÄ, who confirmed that the procedure was appropriate.

At this point we would like to thank all employees for their exclusively voluntary work on the project.

3. General

3.1. Patient information and education

Thanks to the utilization of new information technologies such as the Internet and the increasing need on the part of patients for information and involvement in decision-making about the treatment of their disease, the provision of appropriate information to patients plays a more important role than ever before. Numerous studies have confirmed the importance of this issue for the doctor-patient relationship, the course of the disease and for achieving the therapeutic aim [9], [10], [11].Non-prescriptive patient information combined with shared decision-making constitutes the basis for action by doctors. Two ethical principles are at work in this interaction: the patient's self-determination (autonomy) and the physician's duty of care [12]. The patient's autonomy takes priority in this context. A decision made by a patient is always voluntary and binding for action taken by doctors. Patients can make decisions for or against diagnostic and therapeutic measures or can decide in favor of "not wanting to know". Any existing information deficits are to be remedied by the physician so that the patient can make informed decisions (informed consent). The personal discussion between the patient and the doctor takes on special importance as the basis for an understanding based on mutual trust and respect. In this context, increased emphasis is placed on shared decision-making, i.e. enabling the patient to participate in decisions. Shared decision-making is characterized by a consultation process that follows certain rules and an intensive exchange of information between doctor and

patient, and culminates in the woman making a decision both she and her doctor support as regards the performance of medical procedures [12], [13], [14].

The precondition for this is the patient-centered consultation. The patient education provided by the doctor should be comprehensive, truthful and complete as regards the type of the measure, its purpose, benefits and risks and should most importantly be plainly worded and understandable (mentioning frequencies instead of relative percentages) [15], [16] (Patientenrechtegesetz, „Gute Praxis Gesundheitsinformation“ http://www.leitlinie-gesundheitsinformation.de/ und die Leitlinie evidenzbasierte Gesundheitsinformation http://www.ebm-netzwerk.de/pdf/publikationen/gpgi2.pdf; Raodmap des Nationalen Krebsplans). (German Law on Patients' Rights, "Good Health Information Practice" http://www.leitlinie-gesundheitsinformation.de/ http://www.leitlinie-gesundheitsinformation.de/ and the Guideline Evidence-Based Health Information http://www.ebm-netzwerk.de/pdf/publikationen/gpgi2.pdf; Roadmap of the German National Cancer Program (Roadmap des Nationalen Krebsplans]). The consultation should be conducted in a manner that takes account of the individual patient's somatic, psychological and social situation, gender, age and any comorbidities. The doctor should directly address the patient's anxieties and worries, any specific problems, and particularly her need for information and her expectations and preferences regarding the treatment [1], [2], [3], [4], [5]. If the patient wishes, she should be allowed to have a person of her choice (e.g. partner, family member, patient advocate) with her at this or future consultations. The information provided by the doctor should include information about the disease, results of examinations and tests, the treatment course to date, diagnostic and therapeutic options including expected side effects, as well as estimations of the respective prognoses and the influence on the patient's life planning [6], [7], [8].

3.1	**Consensus-based Recommendation**
EC	If the patient wishes, she should be allowed to have a person of her choice (e. g. partner, family member, patient advocate) with her at this or future consultations.
	Strong Consensus

Patient information is an interdisciplinary task of all professional groups involved in oncological care. Although the doctor is primarily responsible for the information of the patient, she should be supported by other professional groups such as caregivers or psycho-oncologists for specific topics.

3.2	**Consensus-based Recommendation**
EC	The doctor is primarily responsible for informing the patient about the medical aspects, but she should be supported by other professional groups such as caregivers or psycho-oncologists for specific topics.
	Strong Consensus

Hintergrund 3.2

The Dartmouth-Hitchcock Medical Center in New Hampshire, USA is an example of how patient education can be effective as an interdisciplinary task. Since 1999, female and male patients are offered a decision coaching at the Center for Shared Decision Making

to identify individual preferences and to prepare for the consultation with their doctor. During this process, decision-making aids are provided to the patients. The aim of this process is to facilitate shared decision-making and informed decisions. The role of the decision coaches is taken on mainly by caregivers (Dartmouth-Hitchcock Medical Center, 2016, [17]).

In Germany, relevant training curricula for qualified decision coaches have already been developed in the field of breast cancer [18] and multiple sclerosis [19]. These curricula should enable the caregivers to perform decision coaching including evidence-based decision-making aids.

Provision of printed material and access to such material are useful additional supportive measures to help the patient come to a decision [20], [21]. Such decision aids include qualified, competent, comprehensibly produced and quality-assured informational materials [20], [22].

3.3	**Consensus-based Recommendation**
EC	Evidence-based health information materials (Evidenzbasierte Gesundheitsinformationen, EBGI) are intended to improve informed decision-making. Evidence-based health information materials should therefore be based on defined quality criteria. If available, they should be made available to the patient.
	Consensus

3.1.1. Informing the patient about diagnosis

As soon as the histopathological diagnosis of breast cancer has been confirmed, the attending physician should inform the patient of her diagnosis by treating in line with the previously described criteria. It is up to the patient to decide whether her partner, a family member or a representative of a self-help group should be involved in the consultation(s). The consultation should take place in an appropriate setting and the information presented in a manner that is comprehensible to the patient and appropriate to her level of understanding[15], [16]. The doctor must inform the patient truthfully and without underplaying the gravity of the situation, but also without depriving her of the hope of recovery or relief. When presenting information, the doctor should make sure that his or her explanation follows the course of therapy.

3.4	**Evidence-based Recommendation**
GoR **A**	When conveying information to the patient, doctors shall observe the following basic principles of patient-centered communication, allowing the patient to share in the decision-making process: • 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 all salient points, using graphics etc.) • Encourage the patient to ask questions. • Allow and encourage the expression of feelings. • Offer further assistance (see psycho-oncology)
LoE **1b**	[23]; [24]; [25]; [26]; [27]; [28]; [29]
	Strong Consensus

3.1.2. Educating the patient about treatment

The physician informing the patient should present the rationale behind the recommendations for a special form of treatment, especially if a case-related consensus-based recommendation for treatment has been made at a multidisciplinary conference, and explain the principles of the treatment and the associated benefits and risks.

There is evidence that a repeated documentation of the patient's wishes (decision preferences) during the treatment process is necessary to appropriately involve the patient in the decision-making process [30].

Alternative forms of treatment which can be offered to the patient within the framework of clinical trials should also be explained. The impact of the proposed treatment on the patient's lifestyle and quality of life should be discussed.

With regard to the pharmacological therapies and regimens mentioned in the Guideline that are used outside the scope of their approved label, the patient must be informed about the "off-label-use".

Especially in premenopausal women, the influence of treatment on fertility and aspects of contraception should be addressed. Questions relating to the treatment of therapy-related ovarian insufficiency, its symptoms and the therapeutic options should also be discussed. The women should also be informed about the possibility of fertility-conserving measures and, if needed, be referred to the appropriate experts for advice [31].

Given the importance of tumor-associated fatigue caused by adjuvant therapy and based on the evidence for preventive strategies such as physical activity and educational measures, the patients should be informed as early as possible about prevention options [32].

The patient should also be informed about measures for preventing lymphedema, about the necessity of oncological follow-up-care, about rehabilitation (see below), and about social, financial and psycho-oncological support [29] informiert werden. Für If necessary, the patient should be advised to obtain further professional advice on the topics mentioned above (rehabilitation, social counseling and psycho-oncology), and the necessary arrangements made.

Any treatment requires the patient's cooperation. Aspects which are the patient's own responsibility should be discussed.

3.5	**Consensus-based Recommendation**
EC	During the consultation to inform the patient about treatment, the following issues should be addressed and information on the benefits and harms communicated: • Surgical therapy: Breast-conserving therapy options 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 (neo-)adjuvant or palliative therapy, therapy duration and mode of administration, 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 trials, 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: Options for prevention and treatment of therapy-related side effects and sequelae (e.g. fatigue, nausea, osteoporosis, lymphedema, etc.), necessity for follow-up, 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).
	Strong Consensus

Hintergrund 3.5

The physician must take the patient's somatic, psychological and social situation, age and any comorbidities she may have into account during the consultation. The patient's anxieties, worries, resilience, need for information, expectations regarding treatment and preferences should be documented by the doctor at diagnosis, at the beginning of and during therapy, after completion of therapy, in the event of recurrence as well as in the event of disease progression [1], [2], [3], [5], [28]. This also includes informing patients about "normal and unremarkable" test results and the course of treatment in order to provide reassurance, while giving prognostic information to facilitate them in planning their future lives [6], [7], [8].

Breast cancer is not an emergency. The patient must always be allowed sufficient time for decision-making. She can reject a particular procedure or treatment or withdraw previously granted consent to participate in a therapeutic trial or clinical study. She has

the right to review the clinical documentation at any time and to receive copies of her medical records, e.g. doctor's letters. In principle, patients have the right to choose their doctor and hospital freely, to change doctors and/or hospitals and to obtain a second opinion

[33].

Patients should be supported in their desire for further information and for involvement and should be given direct and practical assistance [20], [21], [34]. Such assistance includes tips on where to obtain written information (in particular patient guidelines and decision-making aids), addresses of self-help groups, help lines and websites. Each patient should be urged to keep a file of her own medical records.

The desire to obtain information and to share in medical decision-making varies greatly from patient to patient and can change over the course of time [35], [36], [37]. Therefore the patient's desire for and the extent of information must be documented during the entire diagnostic, therapeutic and chain of care to involve the patient in the medical decisions to be made according to her needs.

3.6	**Evidence-based Recommendation**
GoR **B**	Informational and educational needs of long-term survivors should be explored and appropriate support services as well as health-promoting measures communicated when sequelae such as neurocognitive impairment, fatigue, anxiety, depression, polyneuropathy, overweight etc. are present.
LoE **1b**	[31]
	Strong Consensus

3.7	**Consensus-based Recommendation**
EC	Women and men with breast cancer are to be reassured with respect to their right to self-determination and supported by means of practical assistance. It is at the patient's discretion whether representatives of self-help groups should participate in medical consultations and informational sessions. The patient should be informed about ways to contact self-help organizations. Informational material should be made available by the service providers.
	Strong Consensus

Hintergrund 3.6 und 3.7

In Germany, self-help is considered the "fourth pillar" of the health care system. In 2000, self-help funding was declared binding under Section 20 (4) Book V of the German Social Code (Sozialgesetzbuch V, SGB V) [38].

Self-help groups have been very active for many decades especially in the field of breast cancer for those affected and their family members. Cancer self-help provides established supplementary and independent services, as partners in the spectrum of care. Cancer self-help organizations provide information and counseling on diagnostic, therapeutic and rehabilitative options from the perspective of those affected. The common ground was and still is the original desire to exchange personal experiences

and knowledge and to encourage and mutually reassure each other. By offering empathic and pragmatic exchanges of experience, cancer self-help services can be very meaningful, especially, but not exclusively in those sectors where the disease has a significant impact on everyday life. This is why the involvement of self-help services in the healthcare system in general and their role as providers of information and assistance is of such inestimable value and so irreplaceable, especially to anyone seeking advice or affected by the disease.

Krebsselbsthilfeorganisationen bieten u. a. Informationen und Beratung über diagnostische, therapeutische und rehabilitative Möglichkeiten aus der Perspektive von Betroffenen an. Gemeinsam war und ist der ursprüngliche Wunsch, die persönlichen Erfahrungen und das erlebte Wissen miteinander auszutauschen, sich gegenseitig zu ermutigen und zu bestärken. Nicht nur, aber gerade in Bereichen, in denen die Krankheit erheblichen Einfluss auf das Alltagsleben nimmt, ist die Krebsselbsthilfe durch den empathischen und auch pragmatischen Erfahrungsaustausch von großer Bedeutung. Dies macht ihr Mitwirken im Gesundheitssystem generell und als Informations- und Hilfsangebot speziell für Ratsuchende und Betroffene so wertvoll und unersetzbar.

The services offered by cancer self-help groups are cross-sectoral and can be used free-of-charge whenever breast cancer is suspected, at diagnosis, during therapy and follow-up care as well. Members (and their relatives) are also offered psychosocial support and help "to help themselves" (empowerment strategies) as well as a forum sharing experiences and information aimed at sustainably improving quality of life [39]. Affected sufferers' work for cancer self-help services is of a voluntary nature.

There is a wide range of assistance and support services offered by cancer self-help organizations. Besides local discussion groups, information is available via the various media. These include written and illustrated brochures, websites and forums that enable modern interaction by means of chats, blogs and interaction online and in real-time. State and federal cancer self-help organizations are increasingly assuming patient advocacy roles on social and healthcare policy committees.

It is recommended in the S3 Practice Guideline "Psycho-oncology" [29] to inform patients about cancer self-help services and to offer informational materials. An agreement on the cooperation between self-help and service providers should ideally be made in writing in the form of a contract of cooperation. There is a great cross-sectoral need for research of the structure and efficacy of self-help services.

Up-to-date contact details of self-help groups and other self-help providers are accessible on the website of the National Contact Point for Self-Help (Nationale Kontaktstelle für Selbsthilfe) (www.nakos.de) If and how they use the services of the offered by cancer self-help organizations is left to the discretion of each affected individual and their family members.

3.2. Early detection, mammographic screening

3.8	**Consensus-based Statement**
ST	The most important population-related risk factor for the development of breast cancer in women and men is advanced age.
	Consensus

3.9	**Consensus-based Statement**
ST	Breast cancer of the man is a rare disease. Asymptomatic men should not be recommended special imaging breast cancer screening measures. Diagnosis is carried out with mammography and ultrasound in case of clinical symptoms. Diagnostic clarification should be carried out according to the recommendations for women.
	Strong Consensus

Hintergrund 3.8 und 3.9

Breast cancer occurs in both sexes. The morbidity and mortality risks, however, vary considerably. In Germany, men have a lifetime risk of 0.1% (absolute 1 out of 790) calculated across all age groups. The lifetime risk in women is 12.8% (absolute risk is 1 out of 8) [43]. No specific early detection measures are recommended for men. Please refer to Chapter 9 for detailed information about breast cancer in men. Next to the further improvement of treatment, the early detection of breast cancer in women (secondary prevention) is the most promising possibility for optimizing the diagnosis and treatment of breast cancer, for consequently reducing breast cancer mortality, and for improving the quality of life of women. The objective is to reduce the number of carcinomas detected at later stages (from UICC stage II) and hence effectively reduce breast cancer mortality. This is associated with the increased detection of carcinomas confined to the mammary gland (UICC stage I) [44], [45], [46], [47], [48], [49].

The improved prospects of a cure opened up by secondary prevention can be realized at early stages of the disease, when it is possible to employ less radical methods that place less stress on the patient, e.g. biopsy of sentinel lymph nodes (SLN) [50].

The examinations performed to achieve early breast cancer detection do not confer only benefits; they also pose risks. This fact deserves all the more attention since women who undergo examinations aimed at early detection are primarily healthy and constitute only 0.3% annually of new cases of the disease in the population (according to the prevalence round). Due to this relatively low number of newly diagnosed cases per year that add to a disease rate >12% in relation to life, the extent and burden of diagnostic investigations must be appropriate. False-positive findings must be taken into consideration as stressful components, while false-negative findings show the limits of the methods used [51], [52].

All effective early detection interventions lead to so-called overdiagnoses. These are actual breast cancers, diagnosed months to years in advance. If breast cancer would not have been detected in a woman without screening (because of slow growth or premature death of other causes) and would not have been fatal, this is referred to as overdiagnosis. This excessive detection rate also leads to additional treatments, called overtreatments, which (retrospectively) did not confer benefit on the woman. This has also to be taken into account, especially in the treatment of very early stages, e.g. DCIS (see Chapter 4.3. The precise impact of DCIS detection on the reduction of mortality is still being discussed [53], [54], [55], [56].

3.10	**Consensus-based Recommendation**
EC	The early detection of breast cancer is an interdisciplinary task. There shall be a quality-assured interdisciplinary combination of clinical examination, instrumental diagnostics, histological clarification and pathomorphological assessment.
	Strong Consensus

3.11	**Consensus-based Statement**
ST	The supply chain requires complex and quality-assured medical documentation in order to bring together the entire quality management.
	Strong Consensus

3.12	**Consensus-based Recommendation**
EC	A screening programme shall be continuously evaluated with regard to relevant outcomes (e.g. incidence, mortality, morbidity and patient-related outcomes) and risks (e.g. false positive and false negative findings, overdiagnosis). For this purpose, the process data of the screening programme, the breast centres and the data of the population-based cancer registers of the Länder are to be used together after the comparison. Cancer registries shall continuously provide the differentiated data for the respective federal state and the screening units, if possible before and from the start of the national screening programme in 2005. Patient lists of e.g. interval carcinomas, contralateral findings or local recurrences are part of the continuous evaluation. The independence of the evaluation should be ensured.
	Strong Consensus

3.13	**Consensus-based Recommendation**
EC	In order to ensure the best possible treatment, further therapy of breast cancer detected in screening shall be carried out in certified breast centres. Continuous quality assurance is to be ensured by communication and data acquisition between the screening centre and the certified breast centre.
	Strong Consensus

Background 3.10 to 3.13

In order to reduce mortality and benefits of early detection and therapy and to minimize the burden on healthy women, accurate monitoring, comprehensive evaluability and the highest possible quality assurance in early detection measures must be ensured [40], [57], [58].

As part of the quality assurance of mammography, independent double reporting is recommended. In screening mammograms, double reporting increases the sensitivity

of carcinoma detection by 2.9 -13.7 % (median 7.8 %). The specificity can be reduced (up to 2.1 %) or increased (up to 2.8 %) [40], depending on the decision procedure after double findings. The use of computer-assisted detection systems cannot replace double findings [40], [59], [60], [61] due to the current study situation.

An individually supplementary recommendation of further early detection examinations can be useful, taking into account the individual risk-benefit ratio. In women with increased risk (usually increased familial risk, presence of histologically confirmed risk lesions, condition following malignancy of the breast or ovaries), supplementary methods or an additional examination at intervals may be considered.

Individually adapted screening tests can also be considered for women before the age of 50 and after the age of 70, depending on the individual risk. At an older age, in addition to the individual risk of breast cancer, the overall survival prognosis must be taken into account, since the risk of overdiagnosis increases significantly in the presence of competing risks, especially in older women.

Overall, it can be assumed that side effects such as overdiagnosis occur in other early detection examinations to at least a comparable extent as in quality assured screening, false positive findings to a far greater extent.

Therefore, these groups should be involved in a quality assurance programme for the implementation and evaluation of structural, process and outcome quality as well as in the diagnostic and care chain (anamnesis, risk counselling, information on health behaviour, clinical examination, instrumental diagnostics, interventional tissue removal techniques, surgical clarification and histopathological findings). In terms of age, risk and findings, management in the context of early detection of breast cancer should be based on the algorithm of the diagnostic chain (see Chapter 12.1) [40] [41], [62], [63], [64], [65].

3.2.1. Shared decision-making

3.14	**Consensus-based Recommendation**
EC	Early detection examinations can lead to physical and psychological stress. This circumstance shall be taken into account through careful education and an effective communication strategy.
	Strong Consensus

3.15	**Consensus-based Recommendation**
EC	In the context of breast cancer screening, information and education shall not be limited to pre-formulated texts, but require a medical information interview that takes into account the preferences, needs, concerns and fears of the woman and allows for participatory decision-making. In mammography screening, information and clarification shall be provided to the woman primarily in writing, with a supplementary reference to the possibility of a medical consultation in the invitation letter.
	Consensus

Background 3.14 and 3.15

Informed self-determination and participation in medical decision-making processes is a particularly high priority for women interested in participating in screening. During the medical consultation, anamnesis, the individual risk constellation, fears and worries must be addressed and women must be supported in their decision-making processes in a participatory manner. In risk communication, absolute and relative figures and their reference periods should be included. Benefits and harms should be assessed and communicated in relation to the relevant periods. In particular, life-saving and overdiagnosis should be determined, estimated and communicated in relation to the life of the woman according to their definition [40], [66] see also Chapter 4.1: Patient information and education. In addition to the hoped-for effect, the side effects must be adequately explained according to their occurrence in any screening tests, even outside the screening programme.

For information purposes and as a decision-making aid for women, the patient information on the Oncology Guidelines Programme is available (http://www.leitlinien-programm.de) as well as the website http://www.mammo-programm.de, in accordance with the quality requirements "Good Practice Health Information" [67]. The decision support of the Joint Federal Committee of Physicians and Health Insurance Funds (GBA fact sheet updated 2017) is based on IQWIG's Rapid Review and can be accessed at http://www.mammo-programm.de The figures given there are very conservative estimates. Nevertheless, it is confirmed that mammography screening is the only imaging method with a proven reduction in breast cancer mortality and, if there is a desire for early detection, participation in the quality-assured screening programme is recommended.

3.2.2. Mammographic screening

3.16	Evidence-based Statement
ST	Mammography is the only method with guaranteed reduction of breast cancer mortality.
LoE **1a**	[40]; [41]; [42]; [44]; [53]; [54]; [58]; [65]; [68]
	Strong Consensus

3.17	**Evidence-based Recommendation**
GoR **A**	For women between the ages of 50 and 69, participation in the National Mammography Screening Program shall be recommended.
LoE **1a**	[40]; [41]; [45]; [52]; [58]; [65]; [68]; [69]; [70]
	Consensus

3.18	**Evidence-based Recommendation**
GoR **B**	Women from the age of 70 should be offered participation in screening measures, taking into account their individual risk profile and health status and a life expectancy of more than 10 years.
LoE **1a**	[40]; [41]; [45]; [52]; [58]; [65]; [68]; [69]; [70]
	Consensus

3.19	**Evidence-based Recommendation**
GoR **B**	The reduction in breast cancer mortality has also been demonstrated for women aged between 40 and 49 years and outweighs the risks resulting from radiation exposure. However, it is lower than in the age group of women between 50 and 69 years and results in relatively more false positive and false negative findings. Therefore, the decision should be based on an individual risk analysis, a risk-benefit analysis and taking into account the preferences and objections of the woman.
LoE **1b**	[40]; [41]; [65]; [71]
	Strong Consensus

3.20	**Consensus-based Recommendation**
EC	The structural, process and result quality shall be applied to the same extent to so-called curative mammography,
	Strong Consensus

3.21	**Consensus-based Recommendation**
EC	After a mammographic finding of categories 0, III, IV and V, further clarification should take place within one week in order to keep the psychological stress on the woman as low as possible.
	Strong Consensus

Background 3.16 to 3.21

In Germany, mammography screening for women from the age of 50 until the end of the 70th year of life is part of the guideline of the Joint Federal Committee on the early detection of cancer (source: Guideline of the Joint Federal Committee on the early detection of cancer (Cancer Screening Guideline / KFE-RL) in the version of 18. June 2009 published in the Federal Gazette 2009, No. 148a entered into force on 3 October 2009 last amended on 21 April 2016, published in the Federal Gazette AT 08.07.2016 B2, entered into force on 1 January 2017 https://www.g-ba.de/informationen/richtlinien/17/).

For mammography screening, the reduction in mortality with regard to breast cancer can be regarded as assured for the group of invited versus uninvited women. The evaluations of randomized studies show a mortality reduction of 20% for all age groups from [45], [52], [68], [69], [70]. In preparing the present update of the S3 guideline recommendations, the recommendations of the American Cancer Society ACS (ACS) [41], the US Preventive Services Task Force [51], [65], [70] and the evaluation of cancer prevention and control measures by the International Agency for Research on Cancer (IARC) of WHO [42], [45], [68] have been taken into account.

The IARC assessment of the WHO will be considered in more detail below, as it is of great importance in the international context of drawing up national health measures. 29 experts from 16 countries were involved in the preparation of the comprehensive data analysis of the effects and side effects of IARC mammography screening. IARC confirms the results of the meta-analyses on the old RCTs. However, considering the considerable progress in diagnostics (mammographic technique, quality assurance of the screening chain) and therapy, the relevance of these studies, which are more than 20 years old, is questioned. Instead, IARC assesses well-controlled observational studies of modern screening programmes as better suited to assess the effectiveness of current mammography screening. Special emphasis has been placed on studies with sufficient follow-up to reduce the so-called length time bias, taking into account temporal and regional trends. Based on the available literature, approximately 20 incidence-based cohort studies and another approximately 20 case-control studies fulfilled these requirements.

The following statements were made:

For regular participants, a reduction in mortality compared to non-participants can be expected through mammography screening. It is currently assumed that in Europe up to 8 lives can be saved by screening women between 50 and 69 years of age (about 10 rounds) for every 1000 participants who are healthy today. Further data are needed to map the specific effect strength of the screening measure in the screening population.

A further reduction in mortality through continued screening up to and including the age of 74 is considered proven.

The data available for the age group between 40 and 49 years was still considered to be limited.

For none of the other imaging tests (tomosynthesis, sonography, MRI or other procedures) is there sufficient evidence for a reduction in breast cancer mortality. This applies to both complementary and substitutive use for mammography screening.

With regard to screening of BRCA1- or -2-positive women, IARC recognizes the significant increase in sensitivity in the context of intensified monitoring, but with significantly reduced specificity. For the proof of a mortality reduction the data situation was still insufficient.

Among the potential side effects, the IARC counts overdiagnosis and false positive findings in addition to the very low risk of radiation exposure.

The overdiagnosis rate was calculated only on the basis of studies that had sufficient follow-up and that sufficiently considered *length time bias* and other disturbing influences. (To understand: If follow-up is insufficient, early diagnoses are erroneously counted as overdiagnoses, which leads to an overestimation of the overdiagnosis rate and an underestimation of the mortality reduction). The rate of overdiagnosis after 25 years of follow-up is given as 6.5% (1%-10%) of breast cancer diagnoses. This means that out of 1000 women regularly screened over 20 years, 71 instead of 67 women learn of their actually existing breast cancer or DCIS. These 4 additionally diagnosed diseases would not have become known to women during their lifetime without screening.

In screening, false positive diagnoses are defined as findings on the basis of which a woman is again invited for additional examinations because of an ultimately benign finding. The additional examinations usually consist of imaging procedures, if necessary also histological clarifications (mostly punch or vacuum biopsies). Re-appointments for additional imaging in case of ultimately benign findings affect about 2% of the screened women per subsequent round in Europe. Histological clarifications (usually image-guided minimally invasive biopsies) with a benign result occur in up to 0.6% of screened women. Cumulated over 20 years of screening, this corresponds to a one-time order of about 20% of the participants in 20 years or biopsies in about 6% of the participants because of a finally benign finding.

Technological developments: 2D mammography and 3D mammography (digital breast tomosynthesis (DBT))

For 3D mammography (digital breast tomosynthesis (DBT)), there are very large numerical evaluations from the USA, although only retrospectively collected, as well as at least 3 prospective controlled studies from European screening programmes. The latter are based on systematic double examinations using digital full-field 2D mammography and 3D mammography. There are now 3 systematic reviews of the studies, [68], [72], [73].

The comparisons of all studies almost exclusively concern the comparison between 2D mammography and 2D + 3D mammography. However, an additional study on one type of device indicates that an "2D synthetic mammography" additionally calculated from 3D mammography should be comparable to primary 2D mammography and thus no double image (with double the radiation dose) should be necessary in the future [74]. For another type of device, wide-angle tomosynthesis, only 3D was compared with 2D (at least with regard to the first and second findings). For this device type, additional 2D mammography also did not appear necessary [75].

Data to date indicate a significant increase in detection rate for the combination of 2D + 3D mammography, which was present at all density levels, but appeared to be most pronounced at density levels ACR 2-3. This increase in the detection rate almost exclusively related to an increased detection of invasive carcinomas while maintaining the same detection at DCIS. With regard to the individual findings, 2D + 3D mammography showed an increase in specificity in most studies, but according to consensus a slight deterioration. In addition, a slight increase in the biopsy rate was observed with 3D-DBT, although the PPV remained the same. Summarizing these results, 2D + 3D mammography shows a significantly improved detection proven in prospective screening with comparable specificity and slightly increased radiation exposure.

First results show a slight reduction of the interval carcinoma rate. At present, no statements on overdiagnosis are possible. These would have to be taken into account in screening and especially in any application for early detection outside the screening program. There are still open questions regarding the comparability of the results of the device types, the quality assurance of findings and technology and logistical issues (compatibility; effects of a learning effect; fatigue in systematic reading) and require further studies. Nevertheless, due to the significant gain in sensitivity and the very good specificity, this method currently appears to be the most promising method for screening applications.

3.2.3. Measures for the early detection of breast cancer

3.22	**Consensus-based Recommendation**
EC	As part of the statutory early cancer diagnosis, women shall be offered an anamnesis and an explanation of possible risk factors.
	Consensus

3.23	**Evidence-based Statement**
ST	Breast self-examination, even with regular use and training, is not the only method capable of reducing breast cancer mortality.
LoE **1a**	[40]; [41]
	Strong Consensus

3.24	**Consensus-based Recommendation**
EC	Through qualified information, women should be encouraged to become familiar with the normal changes in their own bodies. This includes the appearance and feel of the breasts in order to detect any deviations themselves.
	Strong Consensus

3.25	**Consensus-based Recommendation**
EC	Clinical breast examination, i.e. inspection, palpation of the breast and assessment of lymphatic drainage, should be offered to women aged 30 years and older as part of the statutory early detection examinations. Clinical examination of the breast and axilla should not be recommended as the sole method for early detection of breast cancer.
	Strong Consensus

3.2.3.1. Sonography

3.26	**Consensus-based Recommendation**
EC	The systematic use of sonography cannot be recommended as the sole method for early detection of breast cancer.
	Strong Consensus

Background 3.26

No studies are available on the sole use of sonography instead of mammography for the early detection of breast cancer. Sonography has not yet been recommended by the international committee for systematic screening [76], [77], [78].

In the context of complementary complementary diagnostics, the use of sonography can lead to an increase in sensitivity, especially in women with an increased risk of breast cancer,

Technological enhancements through the use of automated 3D-sonography (ABUS/AVUS) in comparison to medical 2D-sonography (HHUS) have not yet been able to identify any advantages in terms of sensitivity and specificity. Initial study data indicate that the use of automated ultrasound may be able to reduce examiner dependency. A lack of systematic quality assurance for diagnostics and screening, different device applications and availability as well as a heterogeneous study situation currently allow only limited recommendation of the method within the framework of studies [79], [80],[81], [82], [83], [84], [85], [86], [87], [88].

3.2.3.2. Complementary diagnostic imaging in high mammographic density for early detection

3.27	Evidence-based Statement
ST	Increased mammographic density is an independent, moderate risk factor for the occurrence of breast cancer. Mammographic density and sensitivity correlate negatively.
LoE **3a**	[40]; [89]; [90]; [91]
	Strong Consensus

3.28	Evidence-based Recommendation
GoR **B**	The evidence on the use of complementary imaging methods is limited. Outside of the high-risk situation, sonography currently appears to be the most suitable method to complement mammography. Sonography can increase the density dependent sensitivity, a reduction in mortality is not proven. In early detection it is associated with a higher rate of biopsies than the National Mammography Screening Programme.
LoE **3a**	[40]; [65]; [68]; [72]; [73]; [92]; [93]
	Strong Consensus

3.29	Evidence-based Recommendation
GoR **B**	Tomosynthesis can increase sensitivity. Its testing in a quality assured program should be considered.
LoE **1b**	[74]; [75]; [94]
	Strong Consensus

Background 3.27 to 3.29

Increasing mammographic density is associated with a decrease in sensitivity and specificity and an increase in the risk of interval carcinoma. High mammographic density also represents an independent risk factor [89], [90], [95], which, however, is only low in relation to the risk of the normal population with a factor of approx. 1.3 [91], [96].

The data basis on which the density-related risk calculations are based has so far been based exclusively on visual density estimates using the previous density definition of classes ACR1-4 (corresponding to ACR-Lexicon, 4th ed. [97]) or (semi-) quantitative

density measurements. According to this previous definition, 4 density classes were defined according to the percentage of dense tissue in the mammogram (ACR1= density up to 25%, ACR2 = density of 25-50%; ACR3 = density of 50-75%; ACR4= density > 75%).

Overall, the reproducibility of the density categories is unsatisfactory (re-classification of 12.6-18.7% of mammograms) [73]. According to the updated version of the 2013 classification [98], the density is no longer given according to the percentage of density areas as ACR 1-4, but according to BIRADS density ad according to descriptive characteristics. However, objective criteria for a standardized density measurement are still missing. This limits the reliability of recommendations for the use of additional imaging for mammography screening as well as for mammography in early detection a [45], [73].

In principle, the use of additional imaging (sonography, KM-MRI, tomosynthesis) at high parenchyma density leads to the detection of additional (mostly invasive) carcinomas, but is associated with an increased false positive rate as well as increased control examination and biopsy rates. There is also a lack of long-term data on the effect on survival and overdiagnosis. When using complementary methods, data on the correlation between age and other influencing breast cancer risk factors [99] are missing.

On the basis of previous studies, medical sonography (HHUS, handheld US) performed and evaluated as a complement to mammography appears to show the best balance between benefit and risk, which is indicated by first evaluations from an Italian screening program [93].

Women should therefore be included in the decision on complementary imaging in cases of high mammographic density and negative 2D mammography and informed about the benefits and risks of such complementary imaging, taking into account the overall risk of disease.

3.2.4. Needs for research for the early detection of breast cancer

After discussion of the current data situation in the working groups as well as in the plenum of the S3 Guidelines Commission, the testing of the following topics is considered necessary:

- Optimisation of the screening programme with regard to age limits
- and the benefit/risk ratio regarding screening between 45-49 years and > 70 years
- Optimization of the screening interval, especially for younger women (
- Optimization of the investigation methodology for identified problem areas
    - stratified addition of sonography (2D/3D)
    - selective substitution/addition by 3D mammography (digital breast tomosynthesis (DBT))
- Optimised adaptation of therapy for prognostically favourable early breast carcinomas and pre-stages with the aim of reducing possible overtherapies without significant loss of efficancy

3.3. Women at increased risk of developing breast cancer

3.3.1. Familial breast cancer

About 30% of all women with a breast cancer in Germany have a family history of breast cancer and meet the inclusion criteria for genetic testing established and validated by the German Consortium for Familial Breast and Ovarian Cancer (see statement 3.14) [101]. These are based on a mutation detection rate of at least 10% [100].

3.30	Evidence-based Recommendation
GoR **B**	Genetic testing should be offered if there is a familial or individual exposure that is associated with at least a 10 % probability of mutation detection. This is the case when, in one line of the family • at least 3 women have breast cancer • at least 2 women suffer from breast cancer, 1 of which before the age of 51 • at least 1 woman has breast cancer and 1 woman has ovarian cancer • at least 2 women have ovarian cancer • at least 1 woman has breast and ovarian cancer • at least 1 woman with 35 years or younger is suffering from breast cancer • at least 1 woman aged 50 years or younger has bilateral breast cancer • at least 1 man has breast cancer and 1 woman has breast or ovarian cancer A reasonable period of reflection should be allowed before making the diagnosis.
LoE **2a** **For mutation likelihood** **5**	[102]
	Consensus

Background 3.30

In about 25% of these women a germline mutation can be detected in one of the known predisposing high-risk genes BRCA1 or BRCA2 [101]. Women with a BRCA1 or BRCA2 mutation fall ill about 20 years earlier than women without family risk and have a lifelong risk of developing breast cancer of on average 60%, of an average of 40% of a contralateral breast cancer and 16 - 55% of an ovarian cancer [103].

In unselected patients with a triple-negative breast carcinoma (TNBC) a mutation prevalence of BRCA1 mutations in 8.5% and of BRCA2 mutations in 2.7% could be detected [104]. However, the exact prevalence rates for gene mutations in the presence of TNBC without further familial predisposition have not yet been conclusively clarified.

In the meantime, other risk genes have also been identified, e.g. CHEK2, PALB2 and RAD51C. While CHEK2 is associated with a moderate breast cancer risk [105], PALB2 seems to be associated with a similarly high risk as BRCA1/2 [106], RAD51C is primarily associated with an increased ovarian cancer risk [107].

Even if gene panel analyses are already offered, genotype-phenotype studies should be awaited in order to recommend concrete preventive measures based on the clinical appearance [104].

3.31	Evidence-based Recommendation
GoR **A**	The consultation shall enable participatory decision-making. This requires comprehensive information for women and the clarification and inclusion of women's preferences in the decision-making process. Evidence-based decision-making aids can improve women's decisions.
LoE **1a**	[108]; [109]; [110]; [111]; [112]; [113]
	Consensus

3.32	**Evidence-based Recommendation**
GoR **B**	In risk counselling prior to genetic testing, the following contents should be considered in particular: • Probability for the presence of a mutation • Disease risks in the case of positive findings • the benefits and harms of preventive and therapeutic options, including the option of doing nothing • Probability of false negative findings • The importance of genetic testing for family members After receipt of the genetic findings, the following contents in particular should be deepened in the risk consultation before offering preventive measures: • Disease risk depending on genetic findings, age and concomitant diseases (natural course) • Probability of false positive and false negative test results of intensified screening • Use of preventive options (intensified early detection, prophylactic surgeries, drug therapies) with regard to mortality reduction, morbidity reduction and quality of life • Risks of the preventive options including long-term consequences • Competing risks, prognosis and treatability in case of disease occurrence without preventive measures taking into account the specific appearance of the genetically defined tumor subtype • Possible risks for associated tumours, • Psycho-oncological counselling services
LoE **5** **1a**	[114]; [115]; [116]; [117]; [118]; [119]
	Consensus

Background 3.31 and 3.32

The desire of women and men for detailed information and a joint decision on prevention and treatment options has been documented several times. These findings apply, at least in Germany, largely independent of educational level, age or state of health [112]. Such so-called evidence-based health information is a prerequisite for participation and informed decisions. It has also been shown that evidence-based health information can improve decision-making [120].

Although various working groups worldwide have been working for about 20 years on the question of how information on health and disease topics can be presented in such a way that it can serve as a basis for informed decisions [116], implementation in practice and in concrete health information is currently hardly successful [117].

3.33	**Evidence-based Statement**
ST	BRCA1-associated breast carcinomas often exhibit a characteristic histopathological and immunohistochemical phenotype: • invasive carcinoma with medullary properties • G3 morphology • Estrogen receptor, progesterone receptor and HER2 negativity (triple negative)
LoE **2a** **for histopathologic characteristic**	[118]; [121]
	Strong Consensus

3.34	**Consensus-based Recommendation**
EC	If these characteristics are present, the pathologist should point out the possibility of a hereditary background.
	Strong Consensus

Background 3.33 and 3.34

Breast carcinomas, which develop on the basis of a genetic disposition, can have a distinct driver gene profile, which can manifest itself in phenotypic peculiarities. This has been demonstrated for BRCA1-associated breast carcinomas. While BRCA2-associated breast carcinomas are sporadic carcinomas, BRCA1-associated carcinomas frequently exhibit a particular phenotype which shows characteristics of a medullary carcinoma without, however, forming the full picture of the classic medullary type of breast carcinoma [103], [122], [123], [124], [125]. These special features include macroscopically relatively smooth outer boundaries with displacing rather than infiltrating growth and a prominent, less coarse aspect. Also characteristic are a G3 morphology with high grade nuclear pleomorphism, high mitotic activity and lack of tubule formation with often syncytial growth as well as a lack of expression of steroid hormone receptors and HER2 (triple-negative). The Ki-67 proliferation index is usually above 30% and the tumor cells often show expression of basal cytokeratins (CK5/6, CK14). The tumour stroma shows a pronounced lymphoplasmacellular infiltration and in the neighbouring tumour-free breast tissue a so-called lymphocytic lobulitis is more frequently observed, which is a weaker indication criterion, however. The presence of these characteristics should be a reason to consider a genetic disposition and to stimulate a family anamnestic survey.

3.35	Evidence-based Recommendation
GoR **B/0**	In patients with a pathogenic BRCA1/2 mutation (IARC class 4/5) (recommendation level B) and in patients with a remaining lifetime risk of >/= 30% (recommendation level 0), an intensified early detection with the addition of MRI should only be carried out within the framework of a transparent quality assurance and corresponding evaluation. The additional mammography from the age of 40 should be performed within the framework of a transparent quality assurance and corresponding evaluation (recommendation grade B).
LoE **2a**	[100]; [126]; [127]; [128]; [129]; [130]; [131]
	Strong Consensus

Background 3.35

On average, women with a genetic risk for breast cancer develop the disease earlier than women from the general population. Therefore, the usual early detection measures do not appear to be sufficient. The German Mammography Screening Program (MSP) according to § 25 para. 2 and 3 SGB V for the early detection of breast cancer in the general female population is aimed at asymptomatic women between the ages of 50 and 69. Special features of women from familial/hereditary high-risk collectives (including higher lifetime risks for breast cancer, mostly younger at the time of first diagnosis) are not separately considered in the MSP. Internationally, different recommendations are given on measures for intensified early detection (iFE) (including age limits, inclusion criteria and/or the scope of measures), whereby the breast MRI is included (e.g. [100], [129], [130], [132]). However, the significance of iFE with regard to patient-relevant outcomes has not been conclusively clarified.

Evaluations of the diagnostic quality of the procedures as iFE measures (e.g. for mammography or MRI, including age and/or mutation status) have been published [128].

In the systematic search for clinical studies on the significance of iFE measures in relation to outcome parameters (mortality, incidence rates, tumour stages, quality of life), which were carried out within the framework of the S3 guideline update, one prospective and two retrospective cohort studies (LoE 2a-3c) with limited significance of their results on high-risk collectives and BRCA mutation carriers were identified [123], [133], [134], which allow impressions to be made, e.g. on detection or incidence rates. For the evaluation of the benefit of the intensified early detection measures in high-risk collectives or in BRCA mutation carriers, there is no direct evidence of a reduction in mortality through intensified early detection. However, iFE can detect breast carcinomas in early stages [134]. However, intensified monitoring is also associated with an increase in the number of investigations due to false positive findings.

In addition, only a part of the family-related risk has so far been clarified. Based on new and inexpensive high-throughput methods of gene analysis, new risk genes have recently been identified, and more are to be expected. For these new genes, the clinical appearance, e.g. the age-related disease risks and the possible occurrence of special

genetically defined histological tumour types with possible effects on the natural course of the disease and the effectiveness of imaging procedures, is still largely unknown. Against this background, special demands must be placed on the assurance of structural, process and result quality.

For this reason, structured measures of intensified early detection (iFE) (including MRI) were implemented within the framework of contracts pursuant to § 140a SGB V at the nationwide centers of the German Consortium for Familial Breast and Ovarian Cancer. These address women with proven pathogenic germline mutation in the genes BRCA1 and BRCA2, as well as women from negatively tested families with a lifetime disease risk of > 30% or heterozygote risk of > 20%. An essential component of this care is the recording of the quality of the iFE results on the basis of accompanying pseudonymised documentation. A mortality-based evaluation is only possible and absolutely desirable by linking to cancer registers.

Extensive measures have been established to ensure structural and process quality in breast diagnostics, e.g. within the framework of the mammography screening programme or diagnostic breast examinations. Recommendations and qualification measures of professional associations support the process of strengthening quality in the application of breast diagnostics. The German Radiological Society takes this process into account by establishing a structured continuing education program in senological radiology. A closer networking and cooperation of already established care structures with externally audited breast and screening centres should be promoted and consolidated.

3.36	**Evidence-based Statement**
ST	The surgical therapy of BRCA-associated breast cancer is based on the guidelines for sporadic breast cancer. Mastectomy has no survival advantage over breast-conserving therapy. Drug therapy for BRCA-associated breast cancer is based on the guidelines for sporadic breast cancer.
LoE **2b**	[135]; [136]; [137]; [138]; [139]; [140]
	Strong Consensus

3.37	**Evidence-based Statement**
ST	There are indications that chemotherapy containing platinum can lead to a better response than standard chemotherapy.
LoE **2b**	[135]; [136]; [137]; [138]; [139]; [140]
	Consensus

Background 3.36 and 3.37

If a woman with a mutation in the BRCA1 or BRCA2 genes develops breast cancer, treatment is currently based on the recommendations for sporadic breast cancer.

However, several preclinical and retrospective studies indicate a reduced sensitivity of BRCA-incompetent cells to spindle toxins such as vinca alkaloids and taxanes [141], [142] and an increased sensitivity to DNA-intercalating substances such as platinum derivatives [137]. These observations are currently being reviewed in prospective randomized studies. However, a retrospective mutation analysis of study patients of the TNBC arm of the Geparsixto study did not show a benefit for the BRCA1/2 mutation carriers through the addition of platinum [143]. The direct comparison between platinum and taxane will be examined in the ongoing TNT study in the metastatic situation. Preliminary results here indicate a benefit of platinum [144].

Research on BRCA-deficient cell lines has led to the substance class of PARP inhibitors being used in clinical trials [145], [146]. While efficacy has already been proven in metastatic BRCA1/2-associated ovarian cancer and has already led to the approval of PARP inhibitors, final proof of efficacy for breast cancer is still pending and is currently being tested in prospective clinical trials.

3.38	**Evidence-based Statement**
ST	**Risk reducing surgery in healthy BRCA1/2 mutation carriers (IARC class 4/5): prophylactic mastectomy:** Healthy women with a BRCA1 or BRCA2 mutation have an increased lifetime risk of developing breast cancer. In healthy women with a pathogenic BRCA1 or BRCA2 gene mutation, bilateral prophylactic mastectomy leads to a reduction in the incidence of breast cancer. A reduction of breast cancer-specific mortality or total mortality by bilateral prophylactic mastectomy is not sufficiently ensured. Therefore, a decision for or against a bilateral prophylactic mastectomy always requires case-related comprehensive information and detailed multidisciplinary consultation on the potential advantages and disadvantages of such an intervention, taking into account the possible alternatives.
LoE **2a**	[100]; [147]; [148]; [149]; [150]; [151]; [152]; [153]; [154]; [155]
	Strong Consensus

Background 3.38

As risk-reducing surgical procedures in healthy women affected by corresponding gene mutations, bilateral prophylactic mastectomy (BPM) and bilateral prophylactic salpingo-oophorectomy (BPSO) are available. BPM reduces the risk of breast cancer by over 95%. An effect of BPM on the reduction of breast cancer-specific mortality is not conclusively proven. Whether BPM has an influence on overall survival has not yet been sufficiently proven by 90% [147], [148], [149], [152], [153], [154], [155].

Prophylactic bilateral salpingo-oophorectomy reduces the risk of ovarian cancer by 97%. Whether this prophylactic intervention also reduces the risk of breast cancer is

not clearly established at present. First retrospective examinations described a risk reduction for the first carcinoma by 50%, 30-50% for the contralateral second carcinoma [156], [157], [158]. In addition, a 75% reduction of total mortality could be shown for the prophylactic bilateral salpingo-oophorectomy [149], [158]. More recent prospective studies indicate a significantly lower effect or could not prove it at all [159], [160]. However, both studies are also subject to possible bias, so that the question is not finally clarified at present. The prophylactic bilateral salpingo-oophorectomy is recommended in women affected by BRCA mutations by laparoscopiam around the age of 40 years and after completed family planning. Hormone replacement therapy is indicated until the age of about 50 years.

The rate of metachronous ipsilateral secondary carcinomas (newly developed carcinoma of the same side) does not seem to be significantly increased in patients with proven BRCA1/2 mutation according to the current state of knowledge, so that a breast-conserving therapy is adequate [161]. However, these patients have an increased risk for a contralateral breast carcinoma of about 25-45% in 15 years [161], [162], [163], [164]. The risk depends mainly on the affected gene and the age at the time of the first disease. Bilateral or contralateral mastectomy reduces the incidence of secondary breast cancer. Studies also indicate an improvement in overall survival by contralateral mastectomy, although its significance has not yet been conclusively assessed. The prognosis of the first carcinoma must also be considered [149], [153], [165], [166].

For healthy women or women already suffering from a breast carcinoma from BRCA1/2 negatively tested risk families the benefit of prophylactic surgery is not proven [153] The indications should therefore be very strict. This also applies to women with evidence of a mutation in a non-BRCA1/2 risk gene.

Before every prophylactic surgery a comprehensive clarification with risk calculation is necessary which takes into account the affected gene and, if applicable, the age at first disease and the prognosis after first disease [162], [164]. During the preoperative consultation the possibilities for immediate reconstruction (expanders, implants, pedicled and free flap plasty) should also be discussed in detail.

A possible risk reduction through the prophylactic administration of tamoxifen has not been clearly proven. While in one study a significant reduction of the contralateral second carcinoma by 70% was described [167], another study in multivariate analysis showed no significance [157].

3.39	Evidence-based Statement
ST	**Risk reducing surgery in healthy BRCA1/2 mutation carriers (IARC class 4/5): prophylactic adnexectomy** Women with a pathogenic BRCA1 or BRCA2 mutation have an increased lifetime risk of ovarian cancer, tuberculosis and/or primary peritoneal carcinoma. In healthy women with a pathogenic BRCA1 or BRCA2 gene mutation, prophylactic adnexectomy leads to a reduction in ovarian cancer incidence and total mortality. Therefore, prophylactic bilateral salpingo-oophorectomy should be discussed and recommended on a case-by-case basis in the context of a comprehensive, multidisciplinary consultation on the potential advantages and disadvantages of such an intervention, taking into account the lack of effective early detection options.
LoE **2a**	[123]; [147]; [149]; [151]; [156]; [159]; [168]
	Strong Consensus

3.40	Evidence-based Statement
ST	**Risk reducing surgery for BRCA1/2 mutation carriers (IARC class 4/5) already unilaterally infected with breast cancer: contralateral mastectomy and prophylactic adnexectomy** Women with a pathogenic BRCA1 or BRCA2 gene mutation who already have breast cancer have an increased risk of developing contralateral breast cancer. This risk depends, among other things, on the affected gene and the age of the first disease and must be taken into account during the consultation. In women with a pathogenic BRCA1 or BRCA2 gene mutation, contralateral secondary prophylactic mastectomy leads to a reduction of the contralateral carcinoma risk. The prognosis of the initial carcinoma should be taken into account when determining the indication for contralateral secondary prophylactic mastectomy. In patients with a pathogenic BRCA1 or BRCA2 gene mutation, prophylactic adnexectomy leads to a reduction in breast cancer-specific mortality and an increase in overall survival.
LoE **2a**	[102]; [157]; [162]; [164]; [166]; [169]; [170]; [171]; [172]

3.41	**Evidence-based Statement**
ST	**Risk reducing surgery in risk individuals without proven pathogenic (IARC class 4/5) BRCA1/2 mutation** In women without a proven BRCA1 or BRCA2 gene mutation, the benefit of prophylactic or secondary prophylactic contralateral mastectomy has not been proven.
LoE **2a**	[164]; [173]; [174]
	Strong Consensus

Background 3.39 to 3.41

Bilateral prophylactic mastectomy (BPM) and bilateral prophylactic salpingo-oophorectomy (BPSO) are available as risk-reducing surgical procedures for healthy mutation carriers. The prophylactic bilateral mastectomy reduces the risk of breast cancer by more than 95%. An effect of BPM on the reduction of breast cancer-specific mortality is not conclusively proven. Whether BPM has an influence on overall survival has not yet been sufficiently proven [147], [148], [149], [152], [153], [154], [155].

3.42	**Consensus-based Recommendation**
EC	Contact with cancer self-help should be offered to healthy and high-risk women and men, in order to meet their need for further information and to support their right to self-determination. They should be supported: • in the event of suspected family problems • in the context of genetic testing • before prophylactic measures Appropriate written information material should be kept available.
	Strong Consensus

Background 3.42

A confirmed or suspected genetic disposition leads to further burdens (genetic testing, early detection of cancer, prophylactic surgeries, desire to have children, socio-legal consequences) in addition to the actual cancer. They do not only concern concern about one's own health and/or the individual course of the disease, but also about children and grandchildren. Feelings of guilt for having inherited a predisposition are not rare. Children of mutation carriers worry about losing their mother or have already accompanied the death of close relatives and have to deal with their own potential predisposition in parallel. Partners of mutation carriers are afraid of losing their partner and having to experience a recurrence of cancer in the near future in their children. Within a relationship, women also have the fear of losing their physical integrity and attractiveness. The genetic disposition is often experienced as a flaw, as a "disability", which is perceived as a constant threat.

In addition to an interdisciplinary care structure, which also includes psycho-oncological services, the experience of those affected also offers support. Women and

men who have a family disposition have an experienced, experience-based knowledge that can supplement the decision-making process with specialist medical information. The time spent at the doctor's office is often not sufficient to make decisions regarding this complex topic. Fears and worries additionally prevent the cognitive reception of all the information provided. Therefore, the processing of the information during the conversation and the exchange of experiences with people who are also affected can be helpful. In particular, descendants of confirmed mutation carriers require comprehensive information in order to be able to decide for or against the performance of a predictive genetic test and preventive measures. Persons from families with an increased risk of breast and ovarian cancer should therefore be offered contact with cancer self-help organisations. Whether and in what form this is used is at the discretion of each and every individual. Further information on cancer self-help for families with a family history of cancer can be found at https://www.brca-netzwerk.de/.

4. Locoregional primary disease

4.1. General diagnostic and therapeutic concepts

The incidence of breast cancer increased in Germany until the end of the 1980s and has only decreased significantly in recent years. Since 1990, the mortality rate has also been declining. In the USA and England a decrease in mortality of more than 20% is also observed, which is associated with consistent early detection and adjuvant systemic therapy. It is to be hoped that the mammography screening now implemented throughout Germany on the basis of the Cancer Early Detection Guidelines (KFÜ) and the federal mammography contracts created for this purpose, in which asymptomatic women between the ages of 50 and 69 are personally invited to mammography screening, will lead to the earlier detection of breast carcinomas and a further reduction in mortality in the medium term.

Decisive progress has been made in imaging diagnostics both for palpable as well as clinically unclear or suspicious findings and the establishment of interventional methods in preoperative diagnostic clarification.

For patients with breast carcinoma, unclear or suspicious findings and precancerous lesions, in addition to careful clinical examination

- Mammography including additional mammographic images (e.g. enlargement mammography),
- Mammary sonography with radiofrequency probes (7.5-12 MHz analogous to the DEGUM recommendation),
- the interventional methods such as punch biopsy and vacuum biopsy,
- magnetic resonance imaging (MRT) with the administration of contrast medium,
- the galactography,
- the rarely used pneumocystography (largely replaced by high-frequency sonography technology) and
- fine needle puncture only in special individual cases (e.g. lymph node puncture axilla).

at your disposal. The arsenal of these non-invasive and invasive diagnostic methods, in combination with the histological processing of the preoperatively removed punches including the immunohistochemical findings obtained there (estrogen and progesterone receptor, HER2 status), allows targeted surgical planning within the framework of a pretherapeutic consultation. Here, the extent of the surgery, taking into account the oncological safety margins, any oncoplastic surgeries that may be necessary to reconstruct the surgical defect and the patient's wishes can be brought together to form an overall surgical concept.

In addition to this early, comprehensive surgical planning, the introduction of sentinel node biopsy in particular has led to progress in the surgical treatment of primary breast cancer. The restriction of conventional axillary lymphonodectomy to cases with clinically or sonographically affected axilla allows for a limitation of surgical radicality in the axilla with a significant reduction of short and long-term morbidity for almost 70-80% of our patients. Here the surgical standard has changed substantially.

The same applies to the oncoplastic surgical techniques. The increased use of intramammary reconstructions using the glandular rotational flap technique to avoid larger tissue defects and defect coverage using local flap techniques, in particular thoracoepigastric displacement flaps, today make it possible to preserve breasts with

acceptable cosmetic results and restored body integrity with maximum oncological safety even in the case of larger tissue resections.

The diagnostic and surgical advances in the therapy of primary breast cancer are complemented by the success of primary systemic therapy. Here, chemotherapy - for receptor-negative tumors - has led to remarkable histopathological complete remission rates. With the help of this primary systemic therapy, breast carcinomas that were previously considered inoperable can be operated on and the rate of breast-conserving surgeries can be increased.

Postoperative radiotherapy leads to an improvement in local tumor control. Meta-analyses have shown that mortality is also significantly reduced. The effects are largely independent of the patient's age. This applies to percutaneous radiotherapy after breast-conserving surgery as well as after mastectomy. The effects of radiotherapy on regional lymph drainage have not been conclusively clarified.

The adjuvant systemic therapy has gained a new significance, especially due to the consensus meetings in St. Gallen as a result of the renaissance of adjuvant endocrine therapy in post-menopausal women with hormone receptor positive tumors. Especially in post-menopausal patients with endocrine sensitive tumours, the use of aromatase inhibitors as upfront therapy, as sequence therapy ("switch"), i.e. the use of aromatase inhibitors following a shortened tamoxifen therapy of 2-3 years and a total therapy duration of 5 years, as well as in the form of an extended adjuvant therapy with aromatase inhibitors after regular 5-year tamoxifen therapy have proven to be promising.

The data available to date from large, multi-centre prospective randomised studies must be supported by the long-term results, especially in order to better sound out previously unrecognised late effects of long-term treatment with aromatase inhibitors.

In adjuvant systemic chemotherapy, too, further therapeutic successes can be expected in the short and medium term if the taxanes or the dose-dense and dose-intensified chemotherapy are used optimally. The results of adjuvant therapy with trastuzumab (Herceptin®) have received particular attention. US studies show a significant prolongation of the absence of relapse and a reduction in the rate of metastasis as well as an improvement in overall survival through the use of this antibody.

Overall, the treating physicians have a large arsenal of diagnostic and therapeutic options at their disposal for their patients. It is certainly crucial for the improvement of the overall results that our patients are treated according to the recommendations of these guidelines. Under- or over-therapy, i.e. therapy that does not comply with the guidelines, reduces the quality of results (disease-free survival, overall survival).

4.2. Diagnostics on abnormal findings and pretherapeutic diagnosis of spread in confirmed breast cancer

4.2.1. Basic diagnostic workup

Basic diagnostics as described in Recommendation 4.1 are recommended for the clarification of abnormal findings and as part of the pretherapeutic diagnosis of confirmed breast cancer. An algorithm for the diagnostic procedure for women with abnormal findings of the breast can be found in Chapter 12.1 (Algorithm: Diagnostics of women with abnormal or suspicious findings of the breast from early detection) and

also applies to women whose suspicious findings were collected outside of screening programmes.

4.1	**Consensus-based Recommendation**
EC	The following are considered basic tests: • Medical history and clinical breast examination: inspection, palpation of breast and lymph drainage areas • Mammography • Ultrasound If the clinical breast examination reveals abnormal findings, the diagnosis shall be completed by appropriate imaging procedures and, if necessary, a histological examination.
	Strong Consensus

4.2	**Evidence-based Recommendation**
GoR **B**	The effects of endogenous and exogenous hormones should be taken into account when performing and reporting diagnostic measures.
LoE **2b**	[175]; [176]; [177]; [178]
	Strong Consensus

Background 4.1 and 4.2

If the assessability of the diagnostic procedures is only possible to a limited extent due to the effect of hormone treatment, an individual decision must be made on how to proceed. The following measures must be taken into account [175], [176], [177], [178], [179], [180]:

Modification, discontinuation or interruption of hormone intake (taking into account the histological result)

Adapted choice of imaging methods

Education about hormone-related limitations of diagnostic safety (increased false positive and false negative rates) of all methods. In particular, the use of MRI is to be examined under consideration of increased false-positive rates [181], [182].

4.2.2. Imaging methods

Mammography

4.3	**Consensus-based Recommendation**
EC	Women over 40 years of age shall be given a mammography if the findings are abnormal.
	Strong Consensus

4.4	**Consensus-based Recommendation**
EC	In women under 40 years of age, mammography shall be used where a suspected malignancy cannot be ruled out with sufficient certainty on the basis of clinical examination, sonography and - if indicated - percutaneous biopsy.
	Strong Consensus

4.5	**Consensus-based Recommendation**
EC	Suitable additional images shall be considered for mammographic clarification.
	Strong Consensus

4.6	**Consensus-based Recommendation**
EC	In the case of currently detected malignant tumours, a mammography shall be performed pre-therapeutically.
	Strong Consensus

4.7	**Evidence-based Recommendation**
GoR **A**	In cases of high mammographic density or limited mammographic assessability, a sonography shall be performed as a supplement.
LoE **3a**	[73]; [92]; [183]
	Strong Consensus

Background 4.3 to 4.7

Mammography in symptomatic and pre-therapeutic patients serves to assess the original findings as correctly as possible (with regard to dignity and extent) and thus to ensure optimal therapy planning and to exclude further changes requiring clarification.

Good sensitivity and high accuracy for mammography are comprehensively documented for women over 40 years of age [45], [64], [92]. The pre-test probability increases by a factor of 2 or more even in asymptomatic women if there is a familial risk or a breast carcinoma already detected on the opposite side. In the case of clinical suspicion this increase is usually even significantly higher depending on the type of clinical findings.

Thus, in symptomatic women > 40 years of age, the risk of overlooking or misjudging a carcinoma far exceeds the risk of carcinoma initiation through exposure to X-rays in quality-assured mammography [51], [184]. Therefore, mammography should be used in symptomatic patients from the age of 40 onwards. Pretherapeutically, the mutual breast should also be completely examined mammographically if a mammary carcinoma has already been found on one side [28], [185].

In order to exploit the full potential of mammography, suitable additional images (individually or anatomically adapted projections, so-called rolled images, spot and magnification images or, if available, tomosynthesis) should be used in addition to standard images if necessary to clarify unclear findings.

For the targeted use of tomosynthesis in the diagnostic situation, there is now sufficient evidence for at least equivalent results for the differentiation of soft tissue changes compared to additional mammographic images before [186], [187], [188], [189], [190], [191].

There is insufficient data for the primary use of tomosynthesis in the symptomatic situation. However, results from studies on the use of tomosynthesis in the screening situation suggest an increase in sensitivity even in combination with synthetic mammography. The extent to which these can be transferred from the screening situation to the curative situation has not been conclusively clarified [74], [192].

If a reliable exclusion of malignant tumours is not possible with the above mentioned procedures including sonography, interventional clarification (punch biopsy) is primarily indicated.

In cases in which no reliable diagnosis can be made with the above techniques or in which a biopsy is problematic (multiple findings, pronounced scarring, extreme localization), the use of contrast medium MRI can be considered.

If MRI is not feasible (e.g. pacemaker, cochlear implant, claustrophobia), studies are available for contrast agent mammography that demonstrate an improvement in detection, especially in dense glandular tissue. These studies show a comparable diagnostic accuracy for contrast medium mammography as for contrast medium MRI with regard to detection and expansion assessment [193], [194], [195], [196], [197], [198], [199].

The preparation and reporting of mammography images should be restricted to equipment and persons who are subject to appropriate quality assurance (as part of the screening programme or existing quality assurance agreements).

Like any imaging method, mammography does not achieve 100% sensitivity. In women ≥ 40, it is usually between 85-90% [92]. Therefore, depending on the findings and glandular tissue in symptomatic women ≥ 40, mammography must be supplemented with suitable additional imaging or interventional methods (usually sonography and percutaneous biopsy) until a definite clarification is achieved with the highest possible certainty.

In women below the age of 40, benign changes and tumours are far more common than malignancies. In total, less than 5% of all breast cancer cases occur before the age

of 40 (Tumor Register Munich 2016). In addition, in the glandular tissue which is often denser in adolescents the accuracy of mammography decreases [200] and the risk of X-ray radiation increases with younger age. Nevertheless, about 50% of breast carcinomas can be reliably detected with mammography.

These changed conditions have to be taken into account in the indexing of mammography examinations. Screening mammograms are not recommended before the age of 40 for women without risk. In symptomatic patients, clinical and sonographic examination should be performed first. If sonography (and possibly percutaneous biopsy) cannot exclude breast cancer with sufficient certainty, the use of mammography should be considered depending on the clinical suspicion or remaining uncertainty, individual risk and age of the patient. (For the use of early detection mammography before the age of 40 at high risk, see Chapter 4.3).

Sonography

4.8	**Evidence-based Recommendation**
GoR **A**	Sonography shall be used for the clarification of clinically unclear and mammographic as well as MR-tomographic findings of evaluation categories 0, III, IV and V.
LoE **1b**	[185]; [201]; [202]; [203]; [204]; [28]; [73]; [92]; [183]
	Strong Consensus

4.9	**Consensus-based Recommendation**
EC	The aim of standardized mammary sonography is the systematic and reproducible examination of the mammary gland and axilla. The findings shall be reproducibly documented.
	Strong Consensus

4.10	**Consensus-based Recommendation**
EC	Structural, process and result quality should also be demonstrated as a basic requirement for the application of mammary sonography.
	Strong Consensus

Background 4.8 to 4.10

Sonography should be used for clarification of clinically unclear and mammographic as well as MR-tomographic findings of evaluation categories 0, III, IV and V. The examination should be performed systematically and reproducibly. Additional criteria to the B-image such as Doppler sonography, 3D sonography and elastography can be helpful in differentiating between malignant and benign findings [205], [206], [207]. Automated 3D chest ultrasound can be performed using a system positioned by assistant personnel. The images are automatically generated and forwarded to a workstation. Image interpretation and reporting by the physician takes place at the

workstation. The diagnostic indices are essentially identical to the hand-held ultrasound [213], [214], [208].

The intraoperative use of ultrasound in the context of carcinoma surgery (direct visualization of the incision boundaries) can reduce the postoperative resection rate [209], [210], [211]. It may be helpful to use ultrasound for postoperative quality control of residual glandular tissue after prophylactic mastectomy in high-risk patients.

Regular participation in certified advanced training courses on breast diagnostics (e.g. via DEGUM) is generally recommended [212].

Contrast medium MRI

4.11	Evidence-based Recommendation
GoR **B**	In the diagnostic situation, KM-MRI should be limited to those cases that cannot be resolved with sufficient certainty using conventional diagnostics (MG, US) and percutaneous biopsy.
LoE **2a**	[215]
	Strong Consensus

4.12	Evidence-based Recommendation
GoR **B**	The performance of a pre-therapeutic KM-MRI for a diagnosed breast carcinoma only makes sense in justified cases. The indication for this should be made in a multidisciplinary conference.
LoE **1a**	[216]; [217]; [218]
	Strong Consensus

4.13	Consensus-based Recommendation
EC	A KM-MRI of the breast shall only be performed where the possibility of an MRI-supported intervention exists or is bindingly regulated and the histological results of the MRI intervention are presented in a multidisciplinary conference in the sense of documenting the quality of results.
	Strong Consensus

Background 4.11 to 4.13

In the majority of cases in the diagnostic situation, the confirmation or exclusion of a breast carcinoma can be achieved with sufficient certainty by a combination of clinical examination, mammography, sonography and percutaneous biopsy. In the following situations, however, the complementary performance of a KM-MRI can help to solve the problem:

- Currently percutaneous biopsy with benign result but insufficient radiological-pathological correlation
- Suspicious palpation findings without sufficient correlation in mammography and sonography
- Suspicious findings in mammography or sonography in which a percutaneous biopsy is not feasible (e.g. focus can only be defined in one plane, focus not accessible due to the location of a percutaneous biopsy, multiple suspicious foci of the same type)

In these cases, KM-MRI enables a relevant increase of the positive and especially the negative predictive value [215].

The available data on the use of KM-MRT ***for preoperative tumor staging*** do not justify the routine use of this procedure in all patients with a newly diagnosed breast carcinoma [216], [217], [218]

In selected cases, however, the use of complementary KM-MRI can optimize locoregional propagation diagnostics and improve therapeutic decision making [219], [220], [221], [222]. These cases include

- unclear locoregional spread after conventional diagnostics
- lobular carcinoma
- high genetic or familial risk of disease
- young, premenopausal patients
- planned partial breast radiation

Whenever possible, additional findings in preoperative CMM MRI that lead to a change in the therapeutic procedure should be histologically confirmed preoperatively. This requires a sufficient time interval between preoperative MRI and the planned surgery appointment as well as the existence of the professional and technical prerequisites for performing an MRI-guided biopsy at the treating breast centre. The determination of the indication for preoperative KM-MRI in a multidisciplinary conference enables the optimal consideration of all relevant diagnostic and therapeutic aspects.

4.2.3. Diagnostic confirmation

Imaging guided minimally invasive biopsy

4.14	Evidence-based Recommendation
GoR **A**	The histological clarification of findings shall be carried out by punch biopsy, vacuum biopsy and, in exceptional cases which must be justified, by open excision biopsy.
LoE **3a**	[223]; [28]
	Strong Consensus

4.15	**Consensus-based Recommendation**
EC	The biopsy shall be controlled by means of imaging that clearly shows the findings. When selecting the collection method, diagnostic certainty and the risk of side effects shall be taken into account. The examiner shall take suitable measures to ensure that the localisation of the finding can be found again (e.g. by clip insertion).
	Strong Consensus

4.16	**Consensus-based Recommendation**
EC	Even if the findings are primarily detected by mammography or MRI, the sonographically controlled punch biopsy shall be performed if the sonographic correlate is reliable.
	Strong Consensus

4.17	**Evidence-based Recommendation**
GoR **A**	If microcalcification is present without accompanying focal findings, stereotactically controlled vacuum biopsy shall be used.
LoE **2b**	[223]
	Strong Consensus

4.18	**Consensus-based Recommendation**
EC	Vacuum biopsy should be used for mammographic or MRI-guided tissue collection.
	Strong Consensus

4.19	**Consensus-based Recommendation**
EC	For all biopsies, the correlation between the histological result and the suspected clinical diagnosis shall be checked and documented.
	Strong Consensus

4.20	**Consensus-based Recommendation**
EC	In case of histopathologically benign findings of imaging category 4 or 5, which have been biopsied representatively, an imaging control with the appropriate examination method should be performed once after 6 months.
	Consensus

4.21	**Evidence-based Recommendation**
GoR **A**	The punch biopsy shall be used primarily for the fine-tissue clarification of suspect lymph nodes.
LoE **2a**	[224]; [225]; [226]; [227]
	Consensus

4.22	**Evidence-based Recommendation**
GoR **B**	For interventional, preferably sonographically guided punch biopsy, ≥ 3 samples should be taken at ≤ 14 G with verifiable target detection of the punch needle.
LoE **3b**	[228]; [229]; [230]
	Strong Consensus

4.23	**Consensus-based Recommendation**
EC	For vacuum biopsies, ≥ 12 samples should be obtained using a 10 G needle. For other calibres (between 8-G and 11-G), the number of samples taken should provide an equivalent sample volume.
	Strong Consensus

Open excision biopsy

4.24	Evidence-based Recommendation
GoR **A**	The primary, open diagnostic excision biopsy shall only be performed in exceptional cases.
LoE **3a**	[223]; [231]

4.25	Consensus-based Recommendation
EC	Pre-operative or intraoperative marking shall be carried out using the method that allows the findings to be clearly visualized, especially in the case of non-palpable changes. Proof of adequate resection shall be provided intraoperatively by means of specimen radiography or specimen sonography. If MR-guided marking has been performed, an MR control should be performed within 6 months in case of histologically unspecific benign findings.
	Strong Consensus

4.26	Consensus-based Recommendation
EC	In the case of preoperative wire marking of non-palpable findings, the wire shall lie in the focus and protrude less than 1 cm beyond it. If the wire does not penetrate the focus, the distance between the wire and the edge of the focus shall be ≤1 cm. In the case of extensive findings, marking the surgically relevant target volume with several markings can be useful. The surgical material shall be clearly marked topographically and sent to the pathologist without incision on the tissue material obtained.
	Strong Consensus

Background 4.14 to 4.26

Histological clarification should be performed minimally invasive by punch or vacuum biopsy. Punch and vacuum biopsies are used to determine tumor biological factors that are necessary for pretherapeutic treatment planning (tumor type, grading, hormone receptor status, HER2neu, Ki-67, etc.). In exceptional cases where minimally invasive intervention is not possible, open excision biopsy can be used. Independent of the preoperative needle marking, direct intraoperative sonographic targeting can optimize the resection volume [209], [210], [211]. After open excision biopsy a primary systemic therapy is no longer possible. A biopsy should always be performed with the imaging technique that allows the findings to be clearly displayed. If the findings can be displayed with several methods, the gentlest method should be selected. When a biopsy is performed, the correlation between the histological result and the suspected imaging diagnosis should always be checked. If a biopsy has not been performed

representatively, another biopsy must be performed to obtain a representative result. A tumor cell dissection in the punch channel takes place. The puncture channel does not have to be removed during breast-conserving therapy with radiotherapy [232], [233].

Punch biopsy should be primarily used for the fine tissue clarification of suspect lymph nodes, since current comparative studies show a higher sensitivity for CNB than for FNB with the same specificity [224], [225], [226], [227]. FNA should be reserved for centers with extensive experience in cytological punctures as well as in the evaluation of cytology.

Staging

4.27	Evidence-based Recommendation
GoR **B**	In the case of newly diagnosed breast carcinoma from UICC stage II with increased risk and III and IV without symptoms of metastasis, staging (lung, liver, skeleton) should be performed.
LoE **2a**	[234]
	Consensus

4.28	Evidence-based Recommendation
GoR **A**	In case of newly diagnosed breast cancer and the clinical suspicion of metastases, imaging staging shall be performed.
LoE **2a**	[235]
	Consensus

4.29	Consensus-based Recommendation
EC	Whole body staging should only be performed in women with a higher risk of metastasis (N+, > T2) and/or aggressive tumor biology (e.g.: HER2+, triple-negative), clinical signs, symptoms and if a planned decision on systemic chemo/antibody therapy is planned. Whole body staging should be performed using CT thorax/abdomen and skeletal scintigraphy.
	Consensus

Background 4.27 to 4.29

Current international guidelines [28], [234] do not recommend general whole-body staging at the time of diagnosis of early breast cancer. The prevalence of distant metastases is given as 0.2% for stage I and 1.2% for stage II. The lack of

recommendation for staging in the early stage serves to avoid unnecessary further examinations and stress due to false positive incidence findings in imaging staging. The prevalence of distant metastases is increased in N+ [236]. In addition, this guideline contains a consensus recommendation for staging in aggressive tumor biology if this has a decisive influence on the therapeutic procedure.

The available evidence on the selection of staging methods is limited. Studies have shown sensitivities and specificities of the individual methods. However, there are no studies on the influence of the selected methods on the actual outcome (survival as a function of any resulting changes in therapy or quality of life).

Due to better sensitivity and specificity, CT thorax/abdomen and skeletal scinitgram have replaced the earlier staging with thoracic x-ray and abdominal ultrasound as basic staging examinations (ESMO 2015/17).

A general recommendation for PET or PET-CT is not given based on the NCCN 2014, ESMO and NCGBCI Ireland 2015 guidelines, since even here false negative findings (for slower growing metastases and metastases

The question of when further imaging examinations are useful, there is a layman's understanding "Make smart decisions together" -Recommendation based on this guideline.

4.3. DCIS and high-risk lesions

4.3.1. Preliminary remarks

DCIS and risk lesions are usually clinically occult changes that are detected during early clinical diagnosis or mammography screening. This chapter deals with ductal carcinoma in situ (DCIS), atypical ductal epithelial hyperplasia (ADH), lobular neoplasia (LN), flat epithelial epidermis (FEA) and intraductal papilloma. These changes have the character of a neoplasia in common, but with quite different risk of progression. The aim of diagnostic and therapeutic measures, especially excision, is on the one hand to avoid progression into invasive carcinoma and the associated morbidity and mortality. Since it is not only a question of precursor but also indicator changes, the aim is also to reduce the risk of ipsi- or contralateral carcinoma not directly associated with the lesion.

4.3.2. DCIS

4.3.2.1. Clinical presentation, risk and course in DCIS

4.30	Consensus-based Recommendation
EC	**DCIS - General** In the treatment of a patient with ductal carcinoma in situ (DCIS) without invasive components, the advantages and disadvantages of available forms of therapy or their combination shall be explained. The relative and absolute effects of adjuvant therapy measures in relation to the local recurrence probability and overall survival shall be presented.
	Strong Consensus

Background 4.30

The incidence of DCIS has increased significantly in the last decades and amounts to approximately 5,500 per year [43] in Germany. Clinically, about 80% of DCIS behave asymptomatically and only 20% of DCIS manifest themselves as symptom-related disease [237].

Recently, studies have shown a low breast-cancer-specific long-term mortality of pure DCIS in the US population [238] of 3.3% after 20 years (and 1.7% if cases with contralateral second carcinoma are excluded [eTable 5 in the supplement]), thus triggering a discussion about the importance of early detection of DCIS and its treatment [239]. The mortality rate after diagnosis of DCIS is partly due to cases with undiscovered occult invasion or microinvasion [240], and partly to invasive tumor recurrence or ipsilateral second cancers which may occur many years after diagnosis of DCIS [241]. The overall low mortality rate can be regarded as an expression of an adequate therapy for patients with DCIS according to current standards. The epidemiological data do not allow the conclusion that DCIS generally takes an indolent natural course of the disease. Rather, case series with overlooked DCIS indicate a long-term mortality of breast cancer which can be attributed to tumor progression [242], whereas the mean time interval between overlooked DCIS and the occurrence of invasive breast cancer in the Nurses Health Study was about 9.0 years [243]. As these were low risk cases, the time interval for the untreated DCIS until the occurrence of an invasive carcinoma should be altogether shorter, however, concrete data are not available in the literature. For the DCIS discovered in the screening a connection with the avoidance of an invasive interval carcinoma could be proven [55].

With regard to the risk factors for an unfavorable course, i.e. for the occurrence of an intramammary tumor recurrence, clinical factors play a role, in particular the age of the patient and the findings of a clinically manifest disease compared to a disease detected in screening, as well as radiological factors such as the density of glandular tissue, and last but not least histological and tumor biological factors. The age of the patient was a significant risk factor for tumor recurrence in several prospective-randomized and retrospective clinical studies [244], [245], and in patients

Much of the uncertainty regarding the clinical management of DCIS is due to the fact that DCIS histologically and biologically represents a heterogeneous disease with varying malignancy potential, and that an invasive disease can only be excluded when the lesion has been pathomorphologically fully examined [247]. Pathomorphological factors which reflect the malignancy potential of the DCIS are the grading and subtype of the DCIS [248], the size of the lesion and (to a certain extent) the immunohistological phenotype. Recently, gene expression analysis has also been discussed to better estimate the aggressiveness of the DCIS [249]. Among these parameters, grading is the most important risk factor [244], followed by lesion size and detection of comedotype necrosis [246]. It could be shown that the group of patients with high-grade DCIS and extensive comedotype necroses in > 50 % of ductuli has a significantly increased risk of both ipsilateral invasive and non-invasive tumor recurrence [250]. The role of gene expression analysis in this context has not yet been conclusively clarified. In a low-risk collective defined by means of a DCIS-specific multiassay the 10-year local recurrence rate after breast-conserving surgery without radiotherapy was still 10.8% [251], which is similar or worse compared to collectives with breast-conserving surgery without radiotherapy defined by conventional risk factors [252], [253].

The determination of the size of the DCIS is not necessary for the assessment of the T/pT category according to TNM, but nevertheless important for the pathological-radiological correlation and for the management of the patient [254]. The larger the

DCIS, the more probable the presence of multifocality and marginal infestation as well as tumor residuals, and thus the probability of a local recurrence with the possibility of a metachronous tumor invasion [255], [256], [257], [258], [259], [260]. In addition, the risk of an occult invasion increases with an increase in tumor size [261]. A threshold value for a critical size of the DCIS, up to which breast-conserving therapy is possible, cannot be given. The DCIS size is often underestimated due to mammographic evaluation or preparation radiography, but can also be overestimated in cases with well differentiated DCIS at the base of a mastopathy with benign calcifications. A relatively accurate estimation of the total extent of the DCIS is possible by serial, lamellar processing with an accuracy of 3 - 5 mm. Small DCIS of 1 cm or less can be measured directly histologically in the sectional preparation [262]. It should be noted that, especially with low-grade DCIS, the propagation of the DCIS can be discontinuous. It is therefore recommended to indicate the total size including these gaps and not the size of the individual foci in the case of a supposed multifocality [262]. When resecting a DCIS in several parts, the pathologist should try to reconstruct the size of the DCIS taking into account the topography of the individual sub-preparations [263].

4.3.2.2. Surgical therapy of DCIS

4.31	Evidence-based Recommendation
GoR **A**	Complete excision is the therapeutic basis for the treatment of DCIS. The resection limits shall be at least 2 mm for pure DCIS when adjuvant radiotherapy is connected.
LoE **2b**	[264]; [265]; [266]; [267]; [268]
	Strong Consensus

Background 4.31

Just as in invasive breast cancer, breast-conserving therapy can be considered standard today in DCIS, especially when there is a favourable relation between the extent of the lesion and the breast size. However, in contrast to invasive carcinoma, there is no randomized controlled trial for DCIS that has compared the outcome after breast conservation therapy with that after mastectomy. Histopathological studies on the spread pattern of DCIS show that DCIS is a usually (90%) unicentric, but potentially multifocal lesion, which can theoretically be rehabilitated by surgery alone, provided that a targeted (segmentally oriented) surgery with sufficient resection limits is performed [269], [270].

The question of which resection limits have to be adhered to in the breast-conserving therapy of DCIS is directly related to the implementation or the renunciation of postoperative radiotherapy. With a resection margin of 10 mm or more, the benefit of radiotherapy is only slight [271], [272]. A 2 mm wide safety margin is associated with a lower risk of recurrence than a 1 mm wide margin, but does not differ statistically from a 5 mm wide resection margin if breast-conserving surgery is performed with subsequent whole breast radiation [273]. In case of mastectomy and affected resection margin or narrow resection of

Taking into account careful pathological work-up and radiological-pathological correlation with respect to the topography and the size of the DCIS, a minimum

resection margin of at least 2 mm therefore appears to be sufficient if adjuvant radiotherapy is performed [264], [265], [266], [268], [274]. If radiotherapy is not performed, wider safety margins should be aimed for, although no optimum margin can be given here. Here, further risk factors should be taken into account, especially whether the DCIS extends over a wide area or only with an extension close to the edge [271] as well as size and grading of the DCIS [259]. If a complete excision cannot be achieved by resection(s), a secondary mastectomy should be considered. In the case of a marginal margin of less than 2 mm, the necessity of a follow-up resection should be discussed as an individual case decision in the interdisciplinary team, taking into account the clinical situation (topography of the marginal situation, size and grading of the DCIS, age of the patient, etc.).

Radiotherapy of DCIS

4.32	Evidence-based Recommendation
GoR **A**	An axillary dissection shall not be performed in DCIS. A sentinel node biopsy shall only be performed if a secondary sentinel node biopsy is not possible for technical reasons, e.g. in the case of a mammary ablatio.
LoE **1b**	[185]; [275]
	Strong Consensus

Background 4.32

Since DCIS is by definition a non-metastatic lesion, no staging examination is required, and usually no sentinel lymph node (SN) biopsy is needed. However, an SN biopsy can be performed in the case of primary mastectomy or very peripheral tumour site, as the morbidity of the SN intervention is low and the SN biopsy cannot be performed in this constellation for technical reasons if an invasive carcinoma has been subsequently identified [185], [275], [276], [277]. When a DCIS is diagnosed by means of punch or vacuum biopsy, an invasive carcinoma is found in about 20% of the surgical specimens subsequently obtained [278], [279], [280]. There is an increased risk in palpable lesions and DCIS with a radiological size of > 4 cm [279], [281], [282]. However, even in this situation, the probability of a clinically relevant, positive sentinel lymph node being present in the case of occult tumor invasion is low and can be clinically neglected [279], [283], [284]. An SN biopsy should therefore be performed secondarily in BET because of DCIS, if necessary.

4.3.2.3. Radiotherapy of the DCIS

4.33	Evidence-based Recommendation
GoR **B**	Adjuvant radiotherapy reduces the risk of local recurrence after breast-conserving therapy by up to 50%, but at low risk the benefit for the patient is small. The possibility of radiotherapy should be offered to the patient depending on the individual risk profile.
LoE **1a**	[238]; [285]; [286]; [287]; [288]
	Strong Consensus

Background 4.33

The radiotherapy of DCIS aims to reduce the intramammary recurrence risk and the associated morbidity [285], [289]. However, it is not an obligatory component of the breast-conserving therapy of DCIS, but an individual therapy decision which depends on clinical, radiological and pathological criteria. In the EBCTCG meta-analysis the 10-year in-breast recurrence rate with negative resection margin was 26.0% without radiotherapy compared to 12.0% with postoperative whole breast radiation (p 3 mm 6.7% and 0.9% (p = 0.0003) for the sole excision compared to excision plus whole breast radiation (p = 0.0003) in the RTOG-9804 study [252]. The risk of an intramammary recurrence after 10 years is currently given as 11% for patients with postoperative follow-up radiation and 19% without follow-up radiation. Thus, the risk of recurrence has been significantly reduced compared to older data [290]. This can be attributed to improvements in diagnosis and therapy of DCIS. These include the radiological diagnosis and early detection of the DCIS, the pathomorphological processing and evaluation of the tissue samples [291] and last but not least the surgical treatment of the DCIS. In a low risk collective (G1/G2 to 2.5 cm) the intramammary recurrence rate after 12 years without radiotherapy was 12.5% and thus approx. 1% per year [252], and in a further prospective-retrospective analysis of 209 low risk patients without radiotherapy (size 2 cm or less, age 50 years or more, grade 1 or 2) the 12-year intramammary recurrence rate was only 7.8% and thus 0.65% per year [253]. These recurrence rates are lower than the 15% after 10 years considered acceptable by EUSOMA for invasive carcinomas [292].

Although half of the tumor recurrences after DCIS are invasive tumor recurrences, no survival benefit from postoperative radiotherapy of DCIS has been shown in several prospective randomized studies and a follow-up of up to 20 years [285], [286]. In a retrospective analysis, however, the hazard ratio for the mortality probability after breast cancer for the invasive intramammary recurrence was 18.1 (95% AI: 14.0 - 23.6) [238]. There are indications for the association of breast cancer mortality in DCIS with pathological risk factors (grading, size, comedotype necroses of DCIS) [287]. In low-grade DCIS no significant mortality could be detected in this cohort, independent of the performance of surgical intervention [293]. The possible reduction of the intramammary recurrence risk by radiotherapy must therefore be seen together with the unclear effect on mortality and requires an individual therapy decision taking into account the risk factors for an intramammary recurrence.

According to the available data, the number needed to treat (NNT) to prevent a local recurrence by follow-up radiation is 7 [288] for all DCIS and 17 for a low-risk collective

(50 years). The patient should be informed about the personal (absolute) benefit as well as the possible risks of radiation on the basis of an individual risk assessment. There is evidence that hypofractionation, similar to invasive carcinoma, can reduce radiotherapy-associated morbidity in DCIS and is similarly effective in preventing intramammary recurrence [294], [295].

4.3.2.4. Antihormone therapy in DCIS

Similar to radiotherapy the risk of intramammary recurrence after BET due to DCIS can be reduced by adjuvant antihormonal therapy [289]. This also applies to the contralateral risk of an invasive second carcinoma [296]. However, the effect on the intramammary risk of recurrence is less than for adjuvant radiotherapy, and likewise without a detectable influence on survival [296], [297], [298], [299]. The number of patients to be treated (NNT), for the detection of a locally protective effect by the administration of tamoxifen over 5 years is 15 patients [297]. The NNT rate for subgroups is: ipsilateral DCIS 47; contralateral DCIS 93; ipsilateral invasive carcinoma 63 and contralateral invasive carcinoma 54 patients [297]. Aromatase inhibitors have a similar protective effect in DCIS as tamoxifen [300]. Due to the relatively low benefit for the individual patient with DCIS, [301] is recommended as a cautious indication for adjuvant antihormonal therapy in DCIS. This shows a higher benefit in postmenopause than in premenopause [302]. If an indication for antihormonal therapy is given, the determination of the estrogen receptor in DCIS is necessary [296].

4.3.3. Risk lesions

4.3.3.1. Preliminary remarks

4.34	Consensus-based Recommendation
EC	The therapeutic concept for high-risk lesions shall be developed on an interdisciplinary basis (radiodiagnostics, surgeon, pathology) after the histological findings from a punch/vacuum biopsy are available.
	Strong Consensus

Background 4.34

Clinical screening and mammography screening programs are increasingly detecting clinically occult risk lesions of the mamma, which may be associated with microcalcifications or architectural defects. The risk of progression of these lesions [57], grouped together as "benign lesions with uncertain malignant potential (B3)", is quite heterogeneous and generally lower than in DCIS. The recommendations for excision of risk lesions refer to the natural course, subtype and extent of the lesions. In recent years the literature base for recommendations for the management of occult risk lesions has broadened significantly and this has led to a more conservative approach [303]. However, the literature on risk lesions is mainly based on non-randomized, retrospective case series of individual institutions, where information on the radiological-pathological correlation is often missing as well as information on the indication for surgery, if the lesions caused excision in only a part of the patients. This could at least partly explain the range of variation in the published upgrade risk with open biopsy. In principle, the procedure for risk lesions should be decided individually in an interdisciplinary conference, taking into account pathological-radiological correlation diagnostics.

4.3.3.2. Atypical ductal hyperplasia (ADH) in punch or vacuum biopsy

4.35	Consensus-based Recommendation
EC	If ADH is diagnosed, an open PE shall be performed to exclude a higher grade lesion.
	Strong Consensus

Background 4.35

Atypical ductal epithelial hyperplasia (ADH) is a proliferation of isomorphic ductal epithelia of terminal ductuli or duktulo-lobular units (TDLUs) with cytological and structural features of a well differentiated DCIS. ADH is morphologically similar to a small, well differentiated DCIS and is only differentiated by quantitative criteria. A well-differentiated DCIS can only be diagnosed if the change in a TDLU exceeds a size of 2 mm or at least two separate duct structures are homogeneously affected [248], [304]. Even in the WHO expert group there is no agreement on which of the two quantitative criteria is to be preferred [248], [304]. In the punch biopsy, the diagnosis of a well differentiated DCIS should be made with caution due to the problematic differential diagnosis. In most cases it is sufficient to describe an alteration as atypical ductal epithelial proliferation to induce an excision [303]. However, it can be assumed that an ADH is usually small and extends over less than 2 - 3 mm [305] (http://www.euref.org/european-guidelines). If no further changes are found in the resectate, the therapy should be based on the diagnosis of ADH [248], [304]. The risk of breast carcinoma in the long-term course of ADH is 3 - 5 times higher [306], [307], [308] and the cumulative risk of invasive or insitu carcinoma is indicated with 21% (95% CI 14-28%) [309] or with 20% for a median follow-up of 17 years [310].

In clinical studies in which ADH was diagnosed by punch biopsy, the upgrade rate to DCIS or invasive carcinoma in open biopsy is 28% to 56% [311], [312], [313], [314], [315], but is lower if there is concordance between radiological and pathological findings [316]. In a meta-analysis, the upgrade rate for Z. n. vacuum biopsy and diagnosis of ADH was significantly lower and was 20.9% [317]. There are different approaches to achieve a better estimation of the risk in ADH. These include, for example, a postinterventional mammogram and close monitoring [313], the number of affected TDLUs [318], [319], [320] or cytological atypes or necroses [320], [321]. Suggestions to avoid an open biopsy try to define subgroups by combining these criteria or by complete removal of microcalcifications [322], [323]. This may help in individual cases to plan the therapy. However, the predictive criteria cannot be regarded as sufficiently validated due to the small number of cases in the available studies. Therefore, open PE is currently recommended for diagnosis of ADH in punch or vacuum biopsy [303], [324].

4.3.3.3. Lobular neoplasia (LN) in punch or vacuum biopsy

4.36	Consensus-based Recommendation
EC	In case of isolated or incidential findings of an LN (classic variant) in punch or vacuum biopsy and concordance with imaging, further bioptical clarification is not necessary. In the case of LN with increased risk (pleomorphic LN, florid or tumorous LN, LN with comedotype necroses) an excision of the change should be performed, as well as in the case of discordance with the radiological findings.
	Strong Consensus

Background 4.36

Lobular neoplasia (LN) is characterized by an atypical proliferation of loosely cohesive or discohesive and generally small, uniform epithelia within a terminal ducto-lobular unit with or without pagetoid spread into the ducts. It includes both atypical lobular hyperplasia (ALH) with distension and distortion of less than 50% of the azini in the affected terminal dukto-lobular unit (TDLU) [325], and lobular carcinoma in situ (LCIS). The LN is considered a non-obligate precursor lesion for breast carcinoma [326] and at the same time a risk lesion with increased tumor risk ipsi- and contralateral. The risk for invasive carcinoma is given as about 1 - 2% per year and the lifetime risk is calculated at 30 - 40% [327], [328]. The risk for pleomorphic LCIS is possibly higher [329].

The management of diagnosing an LN in punch biopsy depends on whether the LN is the only pathological change, on the subtype of the LN and on any associated pathological changes. In case of an incidence of a classic LN in punch biopsy (ultrasound or vacuum biopsy) there is no definite indication for an open biopsy for further clarification and the further procedure should be determined in the interdisciplinary findings conference. A wait-and-see approach with follow-up is acceptable in this situation, since the risk of carcinoma at the biopsy site within 3 - 5 years (i.e. the probability of an overlooked carcinoma) is indicated with ≤ 2% [303]. In contrast, in the case of radiological-pathological discordance of the findings, i.e. if the pathological findings do not explain the radiological index lesion (e.g. focal findings or malignoma-typical microcalcifications), there is a higher risk. In this situation further clarification should be carried out by means of a representative open biopsy [248], [330], [331].

Among the variants of the LN and at the same time lobular intraepithelial neoplasias with increased risk of later invasive carcinoma are the LCIS with comedotype necroses, the pleomorphic LCIS and the florid LCIS. These special forms of LCIS can be clinically associated with a focal finding or radiologically extensive microcalcifications, as in DCIS, and are frequently associated with a (micro-)invasion [332], [333]. In pleomorphic LCIS, higher grade cellular atypia are found, sometimes accompanied by massively distended lobules and infestation of the ducts as well as formation of comedotype necroses and microcalcifications. The pleomorphic LCIS differs from a ductal carcinoma in situ by the cellular morphology and the loss of the E-cadherin expression [334]. If these variants of an LN with increased risk are present (pleomorphic LN, florid or tumor-like LN, LN with comedotype necroses) an excision of the alteration should be performed [303], [330], [335], [336]. The B classification of the classic LN is B3, unless the criteria for a pleomorphic LN or an LN with comedotype necroses are present which justify classification as in the B5a category [337].

4.3.3.4. Flat epithelial atype (FEA) in punch or vacuum biopsy

4.37	Consensus-based Recommendation
EC	In the case of diagnosis of FEA, an open PE can be forgone with if the suspicious calcifications have already been completely or almost completely removed by means of vacuum biopsy imaging. In the case of radiologically extensive calcifications or in case of discordance with the radiological findings, a representative open PE shall be performed.
	Strong Consensus

Background 4.37

The term flat epithelia (FEA) is the term preferred by the WHO for columnar cell hyperplasia with nuclear atypes [248], [338]. In a typical case, intraluminal microcalcifications, which represent secretion calcium, are associated with FEA and lead to the clarification and diagnosis of FEA. Morphologically and on the molecular level there are multiple relationships and similarities of FEA with atypical ductal epithelial hyperplasia (ADH) and lobular neoplasia [339]. Not infrequently, these changes occur together on [340] and are considered early, non-obligatory precursor lesions in the low-grade pathway for multistep carcinogenesis of breast cancer [341], [342], [343].

The risk of a higher grade lesion (DCIS or invasive carcinoma) in a subsequent open biopsy is less than 10% [344], [345], [346], [347] in more recent studies and taking into account the pathological-histological correlation. In case of complete or largely complete removal of microcalcifications, further clarification by means of open biopsy is therefore not necessary [303], [348], [349]. This concerns the removal of microcalcifications by means of 9G or 11G vacuum biopsy [350].

4.3.3.5. ADH, LN, FEA in open biopsy

4.38	Consensus-based Recommendation
EC	Bei Vorliegen einer klassischen LN oder einer FEA (alleine oder in Kombination mit einem invasiven Karzinom) am Resektionsrand ist keine Nachresektion erforderlich. Bei Vorliegen einer isolierten ADH am Resektionsrand sollte eine Nachresektion erfolgen. Ebenso sollte bei Vorliegen einer LN mit erhöhtem Risiko am Resektionsrand (alleine oder in Kombination mit einem invasiven Karzinom) eine Nachresektion erfolgen.
	Strong Consensus

Background 4.38

For the procedure in the diagnosis of a risk lesion (ADH, LN, FEA) in open biopsy, a distinction must be made as to whether it is an accompanying finding associated with an invasive carcinoma or ductal carcinoma in situ or an isolated change. In the low-risk lesions (classic LN or FEA) at the resection margin, no resection is necessary [330], [351]. On the other hand, in the case of an LN with increased risk at the resection margin (alone or in combination with an invasive carcinoma), resection is recommended because this change spreads intraductally and is biologically similar to a low-grade DCIS [330], [335], [351], [352]. In the case of isolated atypical ductal

hyperplasia (ADH) at the resection margin in the open biopsy, similar to ADH in the punch biopsy, it must be taken into account that the findings may not be representative. Since ADH is only differentiated from a well differentiated DCIS on the basis of quantitative criteria, a resection should be performed here if necessary to exclude higher grade changes.

4.3.3.6. Papilloma in the punch or vacuum biopsy

4.39	Consensus-based Recommendation
EC	In the case of histological diagnosis of a lactiferous papilloma detected by imaging or a papilloma with ADH, an excision shall be performed; this can also be performed as a vacuum biopsy, provided that no atypia are present.
	Strong Consensus

Background 4.39

The diagnosis of a lactiferous papilloma in the punch biopsy (ultrasound-guided or vacuum biopsy) means, similar to the other B3 lesions, a risk of a higher grade lesion in a subsequent open biopsy. This applies less to the histological differential diagnosis compared with a papillary DCIS or a papillary or solid-papillary carcinoma, which can be made without further ado at the punch biopsy. Rather, there is the problem of the heterogeneity of the lactiferous papilloma and the possibility of association of the lesion with a DCIS or an invasive carcinoma. The background is the question of the representativeness of the punch biopsy. Therefore, it must first be considered whether the finding is an incident lesion, i.e. a small papilloma or micropapilloma that is only histologically detectable (with negligible risk), or an imaging finding that is only partially recorded in the punch biopsy. Furthermore, the upgrade risk depends on whether atypical papilloma is present, i.e. whether it is a papilloma with ADH or an atypical papilloma.

In a recent meta-analysis of 34 studies, the upgrade rate for papilloma was 7.0% compared to 36.9% for atypical papilloma. Furthermore, a lower tendency to upgrade was found in the newer studies after 2005 [353]. Despite the relatively low risk of upgrade in benign papilloma, the literature predominantly recommends post-excision in punch biopsy diagnosis of papilloma [354], [355], [356], [357]. An exclusively radiological evaluation of the course of the disease is justifiable in the case of small or incident papillomas, also if the papilloma has already been completely excised by the punch biopsies or vacuum biopsies and the mamma can be easily monitored by imaging [303], [358]. As an alternative to open biopsy, completion can also be carried out by vacuum biopsy [359].

4.3.3.7. Papilloma in open PE

4.40	**Consensus-based Recommendation**
EC	If a papilloma or papilloma with ADH is detected in an open biopsy, no further intervention is necessary. If atypia are present at the edge of the resection, a follow-up resection should be performed.
	Strong Consensus

Background 4.40

The further procedure in case of a benign lactiferous papilloma or a papilloma with ADH in an open biopsy depends on the question of possibly accompanying atypical changes, for example a DCIS in the surrounding parenchyma. In the absence of such changes, no further intervention is required. The recommendation to complete the excision of an atypical papilloma in the resection margin is based on the possible association with a well differentiated DCIS, which otherwise would not be completely excised [360], [361].

4.4. Surgical therapy of invasive carcinoma

4.4.1. General recommendation

4.41	**Evidence-based Recommendation**
GoR **A**	The basis of therapy for all non-advanced breast carcinomas is tumour resection in sano (R0 status).
LoE **1a**	[362]; [363]
	Strong Consensus

4.42	**Evidence-based Statement**
ST	The resection margin status has a prognostic effect in invasive breast cancer. There is a significant correlation between the resection margin status (positive vs. negative) and the local recurrence rate.
LoE **1a**	[362]; [364]
	Strong Consensus

Background 4.41 and 4.42

The complete removal of the tumor with free resection limits is a prerequisite for a low local recurrence risk. The local recurrence risk is decisively determined by the tumor

biology. The extension of the resection limits in biologically aggressive tumours (e.g. triple-negative, HER2-positive) does not lead to a reduction in local recurrence. Therefore, for all intrinsic subtypes, including concomitant DCIS, resection is considered sufficient if no tumour tissue is detectable at the edge of the incision ("no ink on tumour"). A metrically defined minimum distance between tumour tissue and the edge of the incision is not required [365]. However, these statements are only valid under the condition that the indicated adjuvant therapy measures (systemic therapy, radiotherapy including boost) are performed [364].

Retrospective resection is not indicated for R0 resection, even in the case of narrow free cut margins. In the case of extensive intraductal components, a larger safety margin may be appropriate (see Chapter 5.3.2 DCIS).

Adjuvant radiation and systemic therapy also have an influence on the local recurrence rate. However, R0 resection is a prerequisite for its optimal local effectiveness. Thus, the effects of boost radiation after breast-conserving surgery can only be recognized with regard to the local recurrence rate if R0 resection has been performed [366]. The influence of adjuvant therapy and biological factors such as age of the patient and degree of differentiation of the tumor on the local recurrence rate is unclear, especially in the case of R1-resection. So far available data come from mainly retrospective studies with small collectives.

Basically, the macroscopic and microscopic assessment of the resection margins as well as the specification of the minimum safety distance, taking into account the topography and tumor type (DCIS or invasive), are an indispensable prerequisite for quality assurance of breast-conserving therapy. For this purpose, the resection margins must be clearly marked (e.g. suture marking) in order to enable targeted resection if necessary. The tumour bed should be marked intraoperatively with (titanium) clips to enable a targeted boost radiation (avoidance of "geographic miss").

4.4.2. Breast conserving therapy

Randomized clinical studies have shown that, taking into account certain clinical and histological parameters, breast-conserving therapy achieves identical survival rates as mastectomy.

4.43	**Evidence-based Statement**
ST	The aim of surgical therapy is the removal of tumours in healthy people. Thereby, a breast-conserving therapy (BET) with subsequent radiotherapy of the entire breast is equivalent to a mastectomy alone in terms of survival.
LoE **1a**	[362]; [363]; [367]; [368]; [369]; [370]; [371]; [372]; [373]
	Strong Consensus

4.44	**Consensus-based Recommendation**
EC	All corresponding patients with or without previous primary systemic therapy shall be informed about the possibility of breast conservation therapy (BET) and mastectomy with the option of primary or secondary reconstruction.
	Consensus

Background 4.43 and 4.44

Indications for the breast-conserving therapy of the breast carcinoma are:

- locally limited non-invasive carcinomas of the breast (DCIS, see Chapter 5.3)
- invasive carcinomas with a favourable relation of tumour size to breast volume
- invasive carcinomas with intraductal accompanying component as long as the resection margins run in healthy tissue

The resection margins should be tumor free (R0) during histopathological examination, no tumor at the ink margin [362]. A resection is not indicated for R0 resection even if the free incision margins are narrow. In the case of extensive intraductal components, a larger safety margin may be useful (see Chapter 5.3.2 DCIS).

Breast-conserving therapy should be avoided for (see Chapter 5.4.3 Mastectomy) [185], [374], [375], [376]:

- Incomplete removal of the tumor (incl. intraductal component), even after resection
- Inflammatory breast carcinoma (as a rule also in pathological complete remission)
- in case of contraindications for post-radiation after breast-conserving therapy in case of absolute indication for radiation
- wish of the informed patient

It should be noted that patients under 40 years of age with a slightly differentiated breast carcinoma and insufficient adjuvant systemic and radiation therapy have an increased risk of local recurrence after BET [377].

In the presence of a multicenter carcinoma, a breast-conserving therapy can be considered in individual cases if the edges of the incision are tumor-free (see Chapter 5.4.3 Mastectomy) [378], [379], [380], [381], [382], [383], [384], [385].

If the lesion is not palpable preoperatively, it must be localized by an imaging guided marking, such as a wire marker, and extirpated according to this marking [386], [387], [388] The harvested tissue must be checked for completeness by the same imaging procedure that was used for marking. An additional postoperative mammographic or sonographic check can confirm the completeness of the extirpated findings.

The removed breast tissue must be marked so that the pathologist can orientate it.

The tumor bed should be fitted with clips for the subsequent boost radiation in order to enable correct application of the boost radiation even after intramammary displacement plasty [366], [389].

For defect coverage with local tissue after breast-conserving surgery, various surgical methods can be used within the scope of oncoplastic therapy concepts (e.g. local glandular flap plasty, tumor position-adapted reduction or rotational flaps) [390].

4.4.3. Mastectomy

4.45	**Evidence-based Recommendation**
GoR **A**	Mastectomy shall be performed for the following indications: • Incomplete removal of the tumour (incl. intraductal component), even after resection • inflammatory breast carcinoma (usually also in pathological complete remission) • in case of contraindications for post-radiation after breast-conserving therapy in case of absolute indication for radiation • wish of the informed patient
LoE **2b**	[185]; [374]; [375]; [376]
	Consensus

4.46	**Evidence-based Recommendation**
GoR **0**	Taking into account tumour-free resection margins, the mastectomy can also be performed as a skin-saving procedure with or without preservation of the MAK.
LoE **2a**	[391]; [392]; [393]; [394]
	Strong Consensus

4.47	**Evidence-based Recommendation**
GoR **0**	Taking into account tumor location and tumor size, mastectomy can be forgone in individual cases with multicentric location.
LoE **2a**	[378]; [379]; [380]; [381]; [382]; [383]; [384]; [385]
	Strong Consensus

4.48	Evidence-based Recommendation
GoR **B**	A contralateral prophylactic mastectomy should not be performed in non-mutation carriers or in patients without evidence of a familial high-risk situation to reduce the risk of contralateral breast cancer.
LoE **2b**	[164]; [174]; [363]; [395]
	Strong Consensus

Background 4.45 to 4.48

Modified radical mastectomy is always performed when a breast-conserving procedure is not possible or the tumour size expansion and thus the risk of recurrence is increased. This also applies to inflammatory breast carcinoma, even after neoadjuvant chemotherapy, for incomplete removal of the tumour even after resection, and in principle always due to the patient's wishes. Which cosmetic result is achievable and expected in view of the oncologically possible procedure even after reconstructive measures must be realistically assessed in dialogue with the patient. The incision should take into account later reconstruction possibilities. The entire mammary gland tissue, the skin and the nipple-areola complex and the pectoralis fascia are removed. The pectoralis muscles are preserved.

Skin-saving mastectomy forms have not yet been compared with modified radical mastectomy in prospective randomized studies, but show comparable recurrence rates in long-term studies and meta-analyses. A prerequisite is the histopathologically proven tumor resection in sano, i.e. the removal of the entire glandular body (as far as possible).

In recent years, modified radical mastectomy has increasingly been abandoned in favour of skin-sparing mastectomy (SSM) with or without preservation of the nipple-areola complex (MAK). Numerous cohort studies and meta-analyses confirm that these techniques do not lead to an increased local redictivity rate compared to modified radical mastectomy [393], [394]. Prerequisite for this is an adequate adjuvant therapy according to the guidelines and, if the MAK is maintained, an areolaferous tumor and histologically tumor-free retroareolar tissue [391]. Patients with advanced tumor size also do not show an increased local recurrence rate due to SSM, but suffer more often a recurrence due to metastasis.

Several retrospective cohort studies indicate that breast-conserving therapy is not associated with an increased local recurrence rate compared to mastectomy even in the presence of multifocality or multicentricity under the condition of adjuvant therapy according to guidelines and under the assurance of histologically free resection margins. The limited data available does not justify a general recommendation for a BET. However, a breast-conserving surgery can be considered individually with the patient while informing her about the advantages and disadvantages, provided that a cosmetically satisfactory result can be achieved.

At this time there is no evidence that prophylactic mastectomy of the opposite side in patients with breast cancer and without a familial high-risk situation or without BRCA1/2 mutation improves the prognosis with regard to survival [164], [174], [395]. For patients with a familial high-risk situation or with a proven mutation, the decision

for prophylactic contralateral mastectomy should be made after detailed discussion with the patient in an interdisciplinary team.

4.4.4. Plastic reconstructive surgeries

4.49	Evidence-based Recommendation
GoR **A**	Every patient undergoing a mastectomy shall be informed about the possibility of immediate or later breast reconstruction or the possibility of refraining from reconstructive measures; contact shall be offered to those affected or to self-help groups or self-help organisations.
LoE **2b**	[28]; [363]; [393]; [396]
	Strong Consensus

Background 4.49

Breast reconstruction seems to have no influence on the oncological course of the disease or the detection of local recurrence [393], [396], [397]. However, due to the lack of randomized studies, the data available is not sufficient. The decision whether breast reconstruction is performed immediately or at a later time depends on the individual situation of the patient and her wishes [398]. An immediate reconstruction can be associated with less psychological stress for the patient. However, some women wish to have a time lag after the diagnosis and primary therapy of breast cancer in order to be able to take time to consider the possibilities of plastic surgery in peace. The possibilities of breast reconstruction include implants, autologous tissue or a combination of both. Which procedure is suitable for the individual patient depends not only on the patient's personal ideas but also on the physical conditions (size of the breast, own tissue available) and whether radiotherapy is planned or has been carried out earlier. After previous radiation therapy, breast reconstruction with autologous tissue is preferable to the use of expanders or implants, since irradiated tissue can only be stretched and shaped to a limited extent [399]. If radiotherapy is planned, an expander or an implant in the sense of a spacer should be inserted first and the tissue reaction after radiation should be waited for to decide on the optimal reconstruction technique (autologous/alloplastic) [400], [401], [402]. An approximating surgery of the mutual breast may be necessary to achieve a symmetrical image. The reconstruction of the nipple is performed by reconstruction of the nipple-areola complex and/or by tattooing [390]. The possibilities and indications for plastic reconstruction are shown in Appendix 11.2. : Figure 6, the classification of procedures in Figure 7 [390].

4.4.5. Surgical therapy of the axilla

4.50	Consensus-based Recommendation
EC	The axillary staging shall be a component of the surgical therapy of invasive breast cancer.
	Consensus

4.51	Evidence-based Recommendation
GoR **A**	Axillary staging shall be carried out with the help of sentinel lymph node removal (SLNB) for lymph node status that is inconspicuous on palpation and sonography.
LoE **1a**	[275]; [28]; [363]; [403]
	Strong Consensus

4.52	Evidence-based Recommendation
GoR **B**	Clinically conspicuous but bioptically negative lymph nodes should be removed as part of the SLNB.
LoE **2b**	[28]; [404]
	Strong Consensus

4.53	Evidence-based Recommendation
GoR **B**	In patients with pT1-pT2/cN0 tumors who undergo breast-conserving surgery followed by percutaneous radiation via tangential counterfields (tangential radiation) and who have one or two positive sentinel lymph nodes, axilla dissection should be avoided.
LoE **1b**	[275]
	Consensus

4.54	Evidence-based Recommendation
GoR **B**	Patients who are having a mastectomy or who do not meet the criteria mentioned under d. should receive axillary dissection or radiotherapy of the axilla.
LoE **1b**	[275]; [405]
	Strong Consensus

4.55	**Evidence-based Recommendation**
GoR **A**	In the case of exclusive micrometastasis, a targeted therapy of the lymph drainage areas (surgery, radiotherapy) shall be avoided.
LoE **1b**	[406]; [407]
	Strong Consensus

4.56	**Evidence-based Recommendation**
GoR **B**	In patients receiving primary systemic therapy (PST) and who have a pretherapeutically and sonographically negative lymph node status, the SLN should be performed after PST.
LoE **2b**	[363]; [408]; [409]
	Consensus

4.57	**Evidence-based Recommendation**
GoR **B**	In patients who receive primary systemic therapy (PST) and have a punch biopsy positive (cN1) and a clinically negative nodal status after PST (ycN0), an axilla dissection should be performed.
LoE **2b**	[410]; [411]
	Consensus

4.58	**Consensus-based Recommendation**
EC	In patients who receive primary systemic therapy (PST) and have a positive nodal status before and after PST, an axilla dissection shall be performed.
	Strong Consensus

4.59	**Consensus-based Recommendation**
EC	In the case of evidence of distant metastasis, axial staging shall be avoided.
	Strong Consensus

Background 4.50 to 4.59

The sentinel node biopsy (SLNB) is a targeted surgical procedure for determining the nodal status of breast cancer. The procedure is used to identify patients with increased systemic and local risk and to plan adjuvant therapy.

Provided that the procedure is standardized and quality-assured, the SLNB has a high staging accuracy and a significantly reduced shoulder-arm morbidity. The SLNB goes with a safe local control (axillary recurrence

The SLNB is indicated in all patients with a clinically negative lymph node status and for whom axillary staging is necessary [275].

The SLNB is not indicated in cases of clinical suspicion of advanced lymph node involvement and tumour-transmitted lymph nodes [275]. To clarify preoperatively whether lymph node metastasis is actually present in clinically and/or sonographically suspicious lymph nodes, an ultrasound-guided FNA or a biopsy of the suspicious lymph nodes may be helpful. Histological evidence of lymph node metastasis precludes the use of sentinel node biopsy.

In patients with histologically proven tumor involvement of the axilla, surgical removal of the axillary lymph nodes may be indicated. In patients with positive nodal status, the number of affected lymph nodes or the ratio of affected to examined lymph nodes may provide information for the selection of subsequent antineoplastic systemic therapy and adjuvant radiotherapy.

A randomized study of the American College of Surgeons Oncology Group (ASOG Z0011-study) examined the significance of axilla dissection in patients with T1 and T2 tumors and 1-2 positive SLN, in whom a breast-conserving therapy with subsequent percutaneous radiotherapy of the entire affected breast via tangential radiation fields (WBI) had been performed, with regard to the locoregional recurrence rate and overall survival. No advantage for axilla dissection could be identified [406], [412]. Due to methodological limitations of the study, an evidence search was performed in which the probability of error of the study was classified as "unclear" [413].

In further randomized studies, the clinical value of a dissection of axillary or other regional lymph nodes was examined in different patient groups with a low risk profile [370], [414], [415], [416], [417]. In these studies, axillary dissection was not associated with a survival benefit either.

Apart from the NSABP-B-04 study, the above mentioned studies generally included tangential field radiation of the breast and thus partial radiation of the axilla (at least in Level I). The NSABP-B-04 study is thus the only available study in which no further therapy (i.e. no surgery, no systemic therapy, and no radiotherapy) was performed on positive axillas. In this study 38% of the patients in the axillary operated collective had histological lymph node metastases. In the non-treated group, 19% had follow-up surgery for axillary recurrence. This allows the conclusion that with untreated axilla tumour-affected lymph nodes become clinically apparent in only about 50% of cases. It is therefore not clear what influence radiotherapy has on the risk of axillary recurrence in affected sentinel lymph nodes and the absence of axillary dissection, and which therapeutic procedure is most suitable for reducing the regional risk of recurrence with the least side effects or late effects.

Based on the available data, there is a well-founded option to refrain from axilla dissection in the above-mentioned group of patients in the Z0011 study with a positive SLN. This is particularly relevant for patients in whom no further affected lymph nodes are expected and/or in whom the identification of additional lymph node metastases

would not result in changes in adjuvant therapy. Patients with a T1 or T2 tumour and 1-2 positive SLN can thus be offered the option of foregoing axillary dissection with breast-conserving therapy, provided that they are made aware of the current data situation. A replacement of the axilla dissection by radiotherapy of the axilla can be considered as an alternative.

Patients with micrometastases in the SLN should not be recommended for axillary dissection because there is no evidence for an increased regional risk of local recurrence [407].

Patients who undergo a mastectomy or who do not undergo postoperative radiotherapy of the affected breast are usually not suitable patients for waiving axilla dissection.

In exceptional situations (e.g. old age, multimorbidity, etc.), a waiver of any axillary intervention may be considered [370], [414], [415], [417]. In Germany, the Insema Study (LKP: Prof. Dr. Th. Reimer, sponsored by the DKH) is currently being conducted to prospectively identify patients who can do without axillary staging. Axillary staging is not indicated in patients in the stage of distant metastasis (M1).

In patients treated with primary systemic therapy (PST), the optimal procedure in the area of lymphatic outflow pathways has not been conclusively clarified. A distinction must be made between women who primarily have clinically (palpatory and sonographic) inconspicuous lymph nodes and those whose nodal status is primarily classified as suspicious.

Women with a clinically unremarkable lymph node status benefit from axillary staging after PST. They avoid surgery (before PST) and possible follow-up therapies for clinically occult, positive lymph nodes that are successfully treated by systemic therapy [418]. In addition, histopathological complete remission (response of systemic therapy to the tumor in the breast and lymph nodes), an important endpoint in clinical trials, can only be determined if the lymph node status is recorded after systemic therapy. The feasibility (detection rate) as well as the accuracy (false negative rate) seem to be comparable in this collective with primarily operated patients [408].

In patients without clinical and/or imaging suspicion of axillary metastasis and in whom PST is planned, SLNB can therefore be performed either before or after PST. The decision depends on the weighing of the clinical relevance and the consequences for possible therapy decisions [418].

In patients with primarily suspect lymph node status, a minimally invasive clarification of the suspicious lymph node should be performed by punch biopsy or fine needle aspiration. In the case of a confirmed primary lymph node involvement, the success rates of SLNB (detection rate, false negative rate) after PST are clearly limited [410], [411]. Therefore, an axilla dissection after PST is recommended for these patients.

Newer procedures that could possibly lead to an improved detection and accuracy of SLNB (in primarily nodal-positive patients) after PST, such as the clip or seed marking [419], are currently still insufficiently evaluated and cannot be recommended for clinical routine.

Sufficient data regarding the locoregional risk of recurrence of an SLNB after PST are not yet available. In particular, it is not clear whether the unfavourable false negative rate of SLNB after PST in women with primary positive nodal status translates into an increased rate of locoregional recurrence or unfavourable overall survival.

In view of the insufficient information available, the conduct of clinical studies on this issue and the encouragement of suitable patients to participate in these studies are expressly supported.

4.5. Pathomorphological examination

4.5.1. Preliminary remarks

This chapter deals with the pathomorphological examination of the tissue samples. This is used to establish the diagnosis and to determine prognostic and predictive factors that are helpful in assessing the course of the disease and the response to therapy.

Recommendations from internationally recognized guidelines and published protocols [420], [421], [422], [423], [424], [425], [426], [427], [428] were used as a basis.

Preceded by "General Principles", which give general information on the qualitatively good performance of the pathomorphological examination and its prerequisites. Special aspects of examinations of "Percutaneous biopsies in the context of interventional diagnostics", "Excision biopsies", "Mastectomy preparations" and "Lymph nodes" are presented separately and are divided into the following topics:

- Macroscopic processing ("cutting") with removal of tissue for histological examination
- Microscopic processing (sectional planes, staining, special methods) and review (including criteria of classification)

These instructions are supplemented in the appendix (see Chapter 12.3) by the recommended classifications and grading systems as well as proposed forms for the "Begleitschein zur Einsendung" and the "Dokumentation der Gutachterlichen diagnostischen Beurteilung".

4.5.2. General principles

4.5.2.1. General patient data, preliminary findings, anamnestic information

The patient data, preliminary findings and further information to the pathologist are best communicated using a form (see Chapter 12.3: Figure 9), which records the following information:

- Patient data (name, date of birth, gender, identification number, if available)
- Physician in charge
- day of collection
- Clinical diagnosis or indication for tissue sampling
- further clinical information:
    - location of tissue sample collection (e.g. right breast, upper outer quadrant)
    - Type of collection (e.g. high-speed punch biopsy, modified radical mastectomy)
    - Clinical findings and imaging (e.g. findings palpable/non-palpable; microcalcification present/not present; if necessary with transmission of the preparation radiography)
    - Possibly previous neoadjuvant therapy
    - Preliminary findings and essential details of the medical history

General principles for surgical material

4.60	**Consensus-based Recommendation**
EC	The surgical material shall be marked clearly topographically with details of the problem and the clinical-radiological findings and sent in full to the pathologist.
	Strong Consensus

Background 4.60

A well-organized cooperation between the disciplines involved is a prerequisite for pathomorphological diagnostics.

For the most accurate pathomorphological diagnosis possible, the biopsy or surgical material must meet certain conditions, which are listed below:

- All biopsy and surgical material should be sent to the pathologist.
- The excisate/mastectomy preparations must be clearly topographically marked by the surgeon (e.g. with different coloured sutures); the location of the markings must be noted on the clinical accompanying form (see Chapter 12.3: : : Figure 9).
- If material is to be taken from the tumour (or other tissue) (e.g. for scientific investigations, tumour bank), this must be done under the control of the pathologist. For this purpose, the surgical specimens are to be sent to the pathologist immediately after removal, unfixed.
- In such a material removal it must be taken into account that necessary classifications of a tumor (especially R-classification, pTNM-classification, tumor heterogeneity) must not be affected.
- Tissue fixation is carried out in 10 % neutral buffered formalin in sufficient quantity. A fixation period between 6 h and 72 h [426] is recommended.

4.5.2.2. Documentation of the macroscopic processing

For documentation of the macroscopic processing, see the sections on the respective type of tissue sample.

4.5.2.3. Documentation of the microscopic processing and assessment

The following information is documented, possibly using a form (see Figure 10 and Figure 11):

- Type of tissue sample
- Page reference
- Major pathological changes (e.g. invasive carcinoma, intraductal carcinoma, atypical ductal hyperplasia, fibrocystic mastopathy, mastitis)
- Carcinoma:
    - Histological type
    - Grading (for invasive carcinomas and DCIS)
    - Presence of an associated intraductal carcinoma/DCIS (for invasive carcinomas)
    - tumour size*\footnote {not collected in percutaneous biopsies} (DCIS and invasive carcinomas; for invasive carcinomas with extensive intraductal component [Def. see extent of intra-ductal tumour component]: indication of the size of the invasive component and additionally indication of the size of the associated DCIS)

  - If necessary, indication of additional, additional tumour foci, if present (multifocality/multicentricity)*
  - resection margin*\footnote {not collected in percutaneous biopsies} (for invasive carcinomas and DCIS)
    - Tumour directly at the edge of the resection ("border forming")
    - tumour not directly at the edge of the resection; then minimum safety distance of the tumour from the edge of the resection in mm with indication of localisation (if necessary, separate for intraductal components)
  - Peritumoral vascular invasion (if present under light microscopy)
  - pTNM Classification*\footnote {not collected in percutaneous biopsies} [429] (if necessary including further tissue samples)
  - Additional immunohistological tests:
    - Estrogen receptor (ER) or progesterone receptor (PgR) status (for invasive carcinomas; for DCIS if therapeutically relevant)
    - Human Epidermal Growth Factor Receptor (HER)2 and Ki-67 status (for invasive carcinomas)
- Microcalcifications, if available: Location or indication of association with benign or malignant lesion
- Comments:
  - Reference to the intraoperatively communicated frozen section findings
  - Reference to clinical/radiological findings (especially microcalcifications: e.g. "finding is compatible with" or "correlation not certain")
- Reference to findings on other tissue samples/preliminary examinations (in the case of findings on surgical specimens after percutaneous mammary biopsy: statement required whether or not biopsy cavity is included in the surgical specimen).

4.5.2.4. Clarification of mammographically detected microcalcification

In the clarification of mammographically suspect microcalcifications, the correlation of the histopathological findings with the findings of the imaging procedures is necessary (preparation radiography or disc radiography required).

It should be noted that mammography not only detects calcium phosphate (type II microcalcifications), which can be stained with hematoxylin-eosin, but also calcium oxalate (type I microcalcifications) in rare cases. The latter can be detected in polarized light or dark field.

If there is no evidence of radiologically relevant microcalcification (> 100 µm) in the initial sections, further sections should be made, possibly supplemented by special staining (Kossa), and any remaining material should be embedded.

Occasionally, radiography of the paraffin blocks or of the remaining tissue not yet embedded is also helpful for finding the radiologically relevant microcalcification in larger tissue samples.

When detecting radiologically relevant microcalcifications, their localization in relation to the histopathological change should be indicated.

4.5.2.5. frozen section examination

4.61	**Consensus-based Recommendation**
EC	The intraoperative frozen section examination shall only be performed if there is an immediate surgical consequence. Fields of application are: • Dignity assessment of palpable focal findings >10 mm, if a preoperative diagnosis by means of minimally invasive biopsy was not possible • Determination of the resection margin status • Assessment of the sentinel lymph nodes • A frozen section examination shall not be performed for non-palpable lesions and minimally invasive biopsies (punch biopsies, vacuum-assisted biopsies).
	Strong Consensus

Background 4.61

The aim of the intraoperative frozen section examination on surgical preparations of the breast is to evaluate those criteria which directly influence the further surgical procedure:

- Dignity of the lesion: benign or malignant (DCIS or invasive carcinomas), if a preoperative diagnosis by means of minimally invasive biopsy was not possible,
- Size and extent of a tumour (if necessary, detection of multiple tumour foci),
- Tumor detection at the edge of the incision [430], [431].

The intraoperative examination of the sentinel lymph nodes (SLN) allows in positive cases a one-stage surgery of the axilla. However, if the result is negative, it must be taken into account that subsequent processing of the formalin-fixed and paraffin-embedded residual material will still find metastases in the sentinel lymph nodes in up to 21% of cases [432], [433]. An intraoperative work-up of the lymph nodes in sections is not justified in view of the limited assessability of frozen sections and the effort involved.

As an alternative to frozen section examination, a preoperative punch biopsy or fine needle aspiration can be performed to examine the lymph node status under certain conditions. With appropriate expertise, aspiration cytology can also be performed.

The material examined in the frozen section is to be processed using the paraffin technique.

4.5.2.6. Histological classification and grading

4.62	**Consensus-based Recommendation**
EC	All invasive carcinomas shall be histologically classified (according to the current WHO classification [118]).
	Strong Consensus

4.5.2.6.1. Histological classification

The WHO classification of breast tumours is the international basis for the classification and nomenclature of breast carcinomas [118]; see Chapter 12.3: Table 17.

The histological classification is carried out both on the punch and vacuum biopsies and on the surgical specimens. In particular with the special types of breast carcinoma (e.g. tubular, mucinous) a final classification is only possible on the surgical specimen. Due to intratumoral heterogeneity, there may be differences between the punch/vacuum biopsy and the surgical specimen. The published agreement rates are between 65% and 100% [434].

4.5.2.6.2. Expansion of intraductal tumor component

If the invasive carcinoma is accompanied by an intraductal component that extends beyond the border of the invasive carcinoma, not only the distance of the invasive carcinoma but also the distance of the intraductal component to the nearest resection edges should be given in mm.

The evidence for the fact that with a negative resection margin ("no ink on tumor"/no color on the tumor), an extensive intraductal component (EIC) is associated with an increased risk of local recurrence is contradictory and depends on the definition of the EIC [435], [436], [437]. The presence of an EIC is associated with a significantly increased risk of local recurrence if the size of the intraductal tumor component in one dimension is at least twice the size of the invasive carcinoma [437]. It is therefore appropriate to apply this definition and to indicate the presence of such an EIC.

In addition, significant DCIS residuals are found more frequently in patients with EIC with positive or dense resection margins in post-resectates than in patients without EIC [438]. Therefore, the guidelines of the Society of Surgical Oncology (USA) and the American Society for Radiation Oncology also recommend that postoperative mammography should be considered in micro calcified EIC-positive carcinomas, as residual calcifications would justify a post-excision [435]. It is also pointed out that the characteristics of young age and several narrow resection margins in patients with EIC-positive carcinoma are associated with an increased local recurrence risk. Patients with these characteristics could benefit from a post-excision [365], [436].

Grading of invasive carcinomas

4.63	Consensus-based Recommendation
EC	For all invasive breast carcinomas a grading according to Elston and Ellis [439] (modification of Bloom and Richardson grading) shall be performed.
	Strong Consensus

4.5.2.6.3. Histological grading

Histological grading is also carried out on the punch and vacuum biopsies as well as on the surgical specimens of the breast (see Chapter 12.3: Table 18). It should generally also be indicated numerically (G1, G2 or G3).

The agreement between the histological grading of punch biopsies and surgical specimens is moderate (kappa value: 0.35-0.65) [440], [441], [442], [443], [444], [445], [446], [447], [448], [449], [450]. The punch biopsies tend to show a lower grading,

especially due to an underestimated mitosis number [440], [441], [442], [444], [445], [447], [448], [451]. Possibly the Ki-67 (Mib-1) proliferation index in the punch biopsies correlates better than the mitosis number with the low and high mitosis rates in the excidates [451].

For the decision for or against neoadjuvant therapy, the differentiation between grade 2 and grade 3 is of particular relevance preoperatively. In particular for carcinomas with minimal tubular differentiation (3 score points) and high nuclear pleomorphism (3 score points), there are various suggestions for modified mitosis scoring on punch biopsies for better assignment of the grade on the non-invasive biopsies. On the one hand, the halving of the limit values for the mitosis scores is recommended [452], [453], on the other hand, the use of the Ki-67 index instead of the mitosis score is advocated [454], so that breast carcinomas with a Ki-67 index > 25% would receive a score of 3 for proliferative activity.

Neither of these two proposals has yet been sufficiently validated and generally accepted internationally. However, they can be helpful in borderline cases to achieve a better match of the grading of the punch biopsy and the surgical specimen.

4.5.2.6.4. DCIS-Grading

The grading is based on the grading scheme according to WH0 [118] (see Chapter 12.3, Table 16).

For all DCIS, the following parameters should be listed in addition to the grading:

- Core degree according to "Consensus Conference on the Classification of DCIS in Philadelphia, 1997" [455] (see Chapter 12.3 Table 15)
- Comedo-like necroses existing/not present

4.5.2.7. Multifocality/multicentricity

Currently there is no internationally uniform definition of the terms "multifocality" and "multicentricity" before [456], [457]. The following classification is recommended:

- Multifocality: Occurrence of macroscopically recognizable, separate carcinoma foci in one quadrant or according to Faverly [458] with a distance between the foci of less than 4 cm.
- Multicentricity: Occurrence of separate carcinoma foci in more than one quadrant or according to Faverly [458] at a distance of at least 4 cm between foci.

4.5.2.8. Peritumoral lymph vessel invasion

The presence of peritumoral (lymphatic) vascular invasion (LVI) should be reported, as LVI is an important independent prognostic factor [459], [460]. This is especially true for nodal-negative T1 tumors, where the detection of LVI means that the risk of recurrence and the development of distant metastases is significantly increased [461], [462].

In the diagnosis of peritumoral LVI, strict criteria must be applied to delimit tumor cell complexes located in artificially created tissue gaps (e.g. as a result of shrinkage artifacts) [118], [463], [464]:

- Detection in peritumoral tissue.

- The tumor cells are located in capillary vascular spaces that are lined by an endothelial border.
- The arrangement of the tumor cells often doesn't match the shape of the vascular space.
- Occurs at the site of normal lymphatic vessels:
  - Associated with other vascular structures
  - Periductal
  - In the interlobular stroma

Occasionally, immunohistochemistry (e.g. D2-40 detection) can be helpful.

4.5.3. Determination of hormone receptor and HER2 status and the Ki-67 proliferation index of invasive carcinomas

4.64	**Evidence-based Recommendation**
GoR **A**	In invasive breast carcinoma, the primary diagnosis of invasive breast cancer shall determine the estrogen and progesterone receptor status as well as the HER2 status, preferably already at the punch biopsy.
LoE **2a**	[421]; [426]; [465]; [466]
	Strong Consensus

4.65	**Consensus-based Recommendation**
EC	Additionally, the proliferation rate can be determined by immunohistochemical detection of Ki-67.
	Strong Consensus

4.66	**Consensus-based Recommendation**
EC	The determination of estrogen and progesterone receptor status shall be performed immunohistochemically. The percentage of positive tumour cell nuclei and the average intensity of staining shall be reported. In addition, scores can be obtained by stating the method (Allred (Quick) Score, Immunore according to Remmele and Stegner). The evaluation as ER- or PgR-positive requires at least 1 % positive tumour cell nuclei.
	Strong Consensus

4.67	**Evidence-based Recommendation**
GoR **A**	As a prerequisite for trastuzumab therapy, HER2 positivity is defined as immunohistochemically proven protein overexpression with a score of 3+ or gene amplification, preferably detected by in situ hybridization (ISH).
LoE **1b**	[426]; [467]; [468]
	Strong Consensus

4.68	**Consensus-based Recommendation**
EC	When determining the hormone receptor and HER2 status and the Ki-67 proliferation index, the reliability of the detection methods used shall be ensured. This includes internal test validation, the use of standardized protocols, on slide and internal controls as well as regular successful participation in external quality assurance measures.
	Strong Consensus

Background 4.64 to 4.68

The quality of the detection methods used, including pre-analytics (including fixation) and evaluation, should be ensured by the use of SOPs and regular internal and external quality controls. For external quality control, the regular, annual successful participation in interlaboratory comparisons is recommended, which is offered, for example, by the "Pathology Quality Assurance Initiative" (QuIP), a joint venture of the German Society of Pathology (DGP) and the Federal Association of German Pathologists (BDP).

In the guidelines of the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) it is recommended that the ER/PgR determination is preferably performed on punch biopsies [421] because of the faster fixation of the tissue. The HER2 determination can be carried out primarily on punch biopsies as well as on surgical specimens [426]. The decisive factor is the time until fixation (cold ischemia time, /= 0.81 or concordance >/= 95%). It must also be ensured that artificially altered tissue (edge, retraction or squeezing artifacts) is excluded from the assessment.

The validity and reproducibility of the HER2 determination can be more easily ensured with standardized test kits, which is why the use of such test kits is recommended. For the detection of HER2 gene amplification, the various methods of in situ hybridization (fluorescence, chromogenic, silver-amplified) can be used, taking into account quality requirements. If test kits are used, the application follows exactly the manufacturer's instructions.

The expected HER2-positivity rate for invasive breast cancer is currently averaging 15%. Deviations from this average value can result from the composition of the examination collective. Potential influencing variables are the histological degree of differentiation, the hormone receptor status, the histological tumor type as well as the nodal status of the examined carcinomas and the age of the patients (all P<0.0001) [469]. Es wird

empfohlen, die HER2-Positivitätsrate zur Qualitätssicherung kontinuierlich zu überwachen.

4.5.3.1. Interpretation Hormonrezeptorstatus

Interpretation of immunohistochemical reaction results should follow the recommendations of the ASCO/CAP guidelines [421]:

Evaluation as ER- or PgR-positive requires at least 1% positive tumor cell nuclei [421], [470], [471]. Tumors are evaluated as ER- or PgR-negative when less than 1% of tumor cell nuclei are immunoreactive with positive internal control. The recommendation of the 1% threshold is based on the results of a systematic review [472]. However, this review is based exclusively on retrospective studies in which a cutoff value for endocrine therapy was established. Different threshold levels were not tested against each other in the studies.

There is now evidence that tumors with low ER positivity (1-9% positive cells) should be considered separately [470]. Several studies have shown that they are tumor biologically and prognostically closer to ER-/PgR-negative or triple-negative breast carcinomas (ER-, PgR-, and HER2-negative) than ER-positive (>10% positive tumor cells) [473], [474], [475], [476], [477].

Therefore, the following subdivision is recommended [472], [478]:

- ER-/PgR-positive: >10% positive tumor cells.
- ER-/PgR-gering positive: 1%-9% positive tumor cells
- ER-/PgR-negative: <1% positive tumor cells

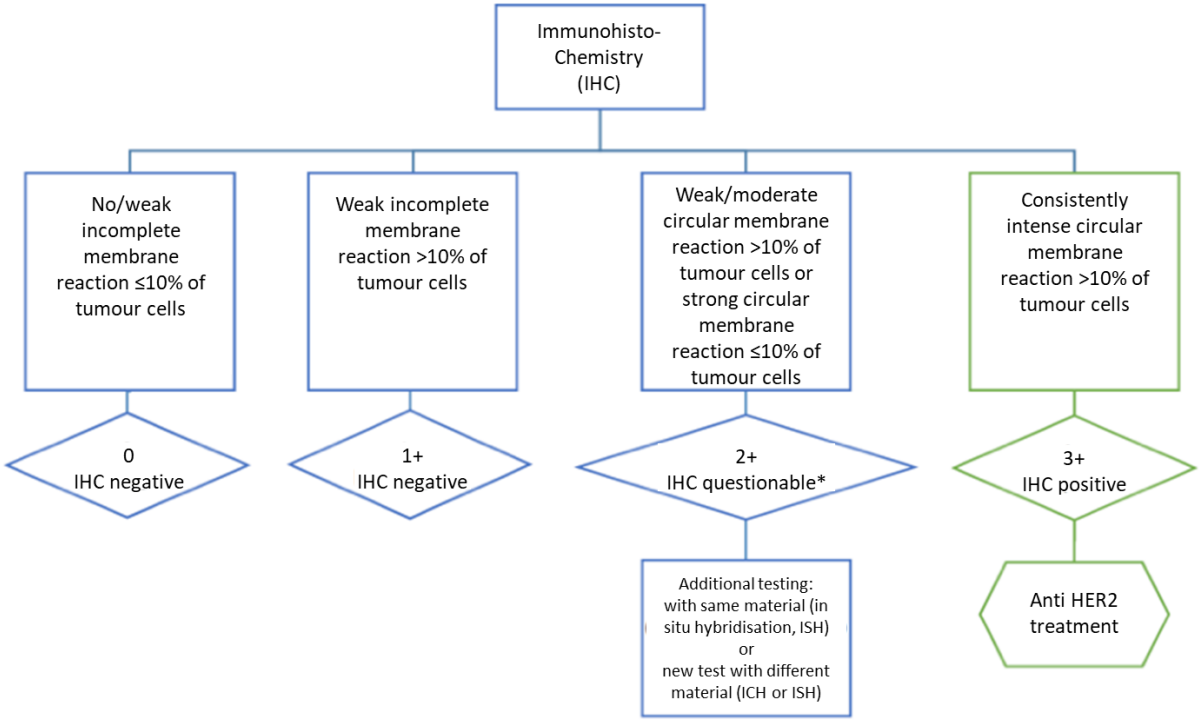
In addition to the percentage of positive tumor cell nuclei, the average staining intensity must also be reported according to the ASCO/CAP guidelines [421]. As a supplement, the internationally accepted Allred score [479 or the immunoreactive score (IRS) according to Remmele and Stegner [480] can be reported (see Chapter 12.3 Table 21).

Immunohistochemistry is not usable and should possibly be repeated on another specimen if

- external or on-slide controls do not give the expected result,
- artifacts occupy the majority of the material,
- normal epithelial cells within the specimen do not show nuclear staining,
- the tissue has been decalcified in strong acids,
- an ER-negative/PgR-positive phenotype is present (to exclude false negative ER or false positive PgR testing),

fixation of the tissue was not optimal (cold ischemia time > 1h, fixati-on < 6h or > 72h) and the test result is negative in the absence of internal control.

Even in the presence of a histological type that is usually ER-/PgR-positive (tubular, mucinous), testing should be repeated as a precaution (possibly also on another tissue sample) if the result is ER-/PgR-negative.



* Rarely, gland forming or micr papillary breast cancer can show an incomplete but strong membrane reaction (basolateral or U-shaped) that may be associated with HER2 gene amplification. These cases should be given a IHC score of 2+ as well and be tested via ISH.

Figure 1: Currently suggested HER2 testing algorithms for immunohistochemistry

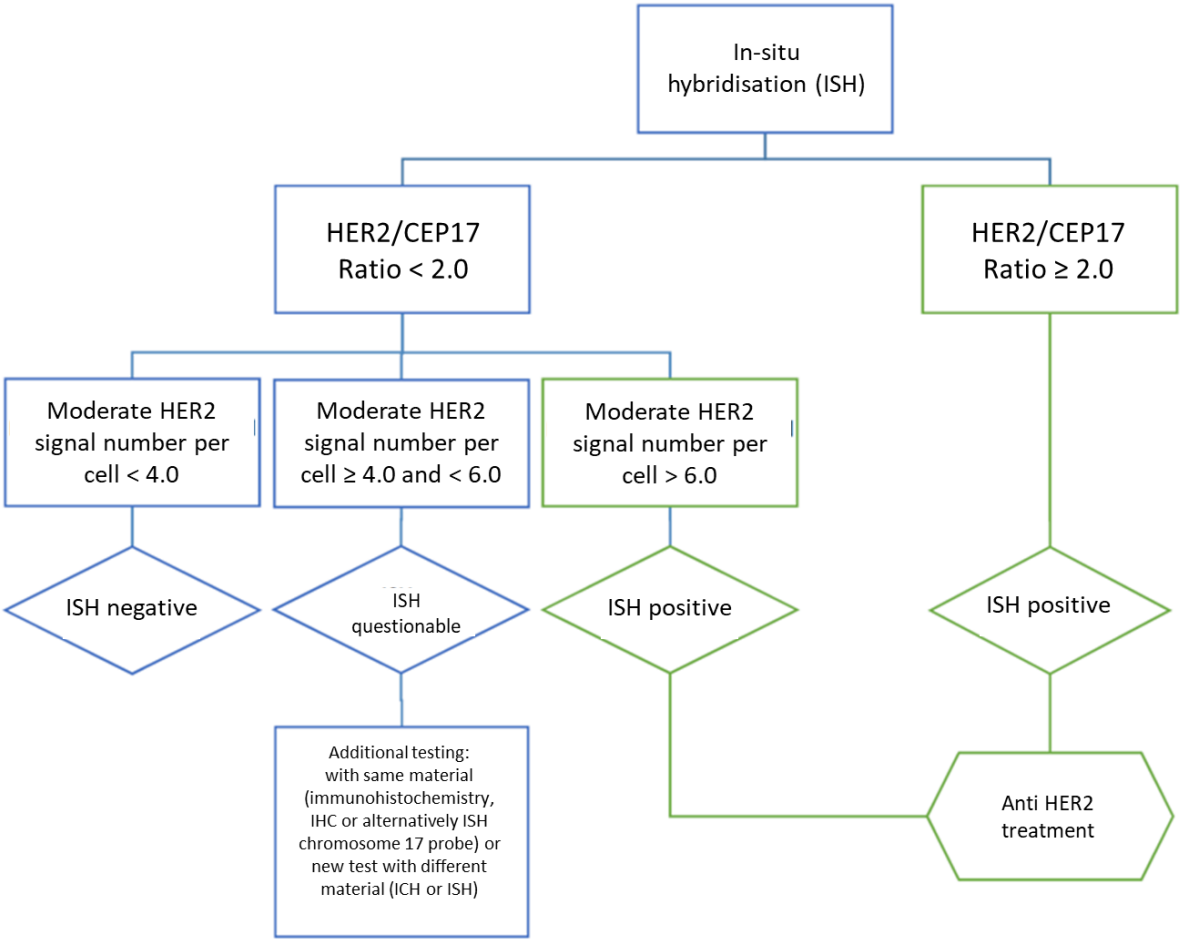


Figure 2: Currently suggested HER2 testing algorithms for in-situ hybridization, adapted from [426][468]

The increase of the immunohistochemical cut-off for the score 3+ from 10% to 30% [481] recommended in the 2007 ASCO/CAP guidelines has been withdrawn. Thus, the prerequisites for an immunohistochemically HER2-positive test result again meet the criteria applied in the pivotal studies for anti-HER2 therapy (Figure 1). The update committee also cited as reasons for the reduction of the cut-off to the original level the fact that the increase affected only a few patients [0.15%; [482]] and that the analytical quality of HER2 testing had generally improved since 2007, [426].

A weak point of the ASCO/CAP guideline published in 2013 is the contradictory definition of the 2+score with unclear differentiation from the 1+-score [426]. This ambiguity was corrected in 2015 by revising the definition to reapply the original criteria from 2007 [468].

The threshold value for an ISH-positive test result was also readjusted to the criteria used in the approval studies for anti-HER2 therapy. Accordingly, a HER2/CEN17 ratio > 2.0 is considered HER2-positiveFigure 2).

However, the addition of the pericentromere region of chromosome 17 can lead to false negative results if only the ratio is taken into account as a criterion for distinguishing HER2-positive and negative cases. Therefore, according to the current update, a ratio of 4.0 (Figure 2). A test result in the borderline category should trigger re-testing as before (other validated method on the same material or re-testing on other material, for example on excidate if borderline result on needle biopsy). The ultimate goal is to

achieve a clear HER2 test result (negative or positive) as a basis for clinical decision making. The "borderline" category is a subgroup that has not yet been adequately investigated and where it is uncertain how many of the affected patients will benefit from anti-HER2 therapy.

In the 2013 update, criteria for the evaluation of HER2-heterogeneous tumours were defined for the first time, i.e. for tumours containing cell populations with and without HER2 gene amplification. The experts assume that a HER2-amplified cell population is only clinically relevant if the HER2-amplified cells can be separated as aggregated complexes from HER2-negative cell assemblies. To identify areas with HER2-amplified cells, the preparation should be completely screened before at least 20 cell nuclei are evaluated. Alternatively, areas with potential HER2 amplification can be narrowed down using IHC. If a second contiguous cell population with elevated HER2 signaling levels exists, representing more than 10% of the cells on the section, it will be evaluated separately. In both populations the signals should be counted in at least 20 adjacent cells in at least 2 areas each and evaluated separately. Tumours that contain amplified and non-amplified areas under these conditions are considered HER2-positive. In the report of findings, the percentage of the tumour with HER2 gene amplification should be stated.

In summary, the 2013 update recommends that primary testing be performed on the punch biopsy. If the test result is clearly negative or positive according to the criteria in Fig. 1, no re-testing is usually required.

Exceptions are, among other things, test results that are discrepant to the histopathological findings or if the tumor in the excidate shows a different tumor type or histological grading than in the punch biopsy.

A new HER2 test on the excidate of the tumor should be requested if

- HER2 status at punch biopsy unclear (IHC and ISH in borderline area)
- heterogeneous HER2 status at the punch biopsy
- HER2 test positive for invasive carcinomas, G1, of the following histological types:
    - ductal or lobular, ER- and PgR-positive
    - tubular, mucinous, cribriform
    - adenoid-cystic carcinoma (usually triple-negative)
- HER2 test negative and
    - less invasive tumor contained in punch biopsy
    - resectate G3 carcinoma, which is morphologically different from the carcinoma in the punch biopsy
    - there are doubts about the sample handling of the punch biopsy (too long ischemia time, too short fixation, etc.)

A general retesting of G3 carcinomas on the resected tissue, whose testing on the needle biopsy showed a HER2 negative result, is not necessary [468], [483]

HER immunohistochemistry is not usable and should be repeated or replaced by ISH if

- controls do not deliver the expected result,
- artifacts take up most of the material,
- normal gangetic epithelia show a strong membrane coloration (internal control).

The HER-ISH is not usable and should be repeated if

- controls do not deliver the expected result,
- at least two tumour areas cannot be evaluated,

- > 25 % of the signals are too weak to be evaluated,
- > 10% of the signals appear in the cytoplasm,
- Core resolution is bad,
- autofluorescence is strong (FISH).

4.5.3.2. Evaluation Ki-67 proliferation index

For the determination of the Ki-67 proliferation index (PI), no generally accepted, comprehensive recommendation for standardisation is available to date. The background to this is that the methodological approach in the studies that have demonstrated a prognostic or predictive relevance of Ki-67 is very heterogeneous [484]. As a consequence of the lack of standardization, increased interobserver variability in the determination of Ki-67-PI was repeatedly observed in reproducibility studies, especially in the middle range or in G2 mammary carcinomas [484], [485], [486], [487]. Due to the heterogeneous approach in the studies, the consensus recommendation of an international working group on Ki-67 in breast cancer also focuses only on certain key points regarding the methodological procedure including evaluation and interpretation of the results [488]. The experts emphasized that it is not possible to give generally valid Ki-67 limits for prognosis, prediction and monitoring. Limit values defined in studies could only be applied locally if the local results were validated against the study results.

In the meantime, however, the above mentioned international working group and other study groups have shown that the reproducibility of the Ki-67 determination can be significantly improved by systematic training and application of uniform criteria [489], [490], [491]. However, an acceptable reliability of the determination can be achieved with different procedures (e.g. counting and semi-quantitative estimation). This means that it is currently not possible to favor a particular procedure, especially since different evaluation strategies were used in the recently published studies that prove the prognostic or predictive relevance of Ki-67-PI [492], [493], [494], [495], [496].

Nevertheless, it is possible to define certain framework conditions on which there is general consensus in order to improve reproducibility:

Application of a standardized staining protocol with internal and external quality control

- Evaluation preferably at the invasion front of at least 3 visual fields at high magnification, 400x (exception: needle biopsy, if the invasion front cannot be delimited or the extent of the infiltration
- Exclusive evaluation of the nuclear staining, which stands out from the nuclear counterstain (nucleoli alone are not counted, staining intensity is irrelevant)
- Indication of the percentage of Ki-67-positive tumour cells in relation to the total number of tumour cells
- Determination of percentage by single cell counting, semi-quantitative estimation in 5% steps or by image analysis possible [489], [492], [497], [498], [499]

The use of image analysis procedures requires that the result of each individual measurement is critically reviewed by the pathologist and the size of the measurement field is adjusted if necessary [500].

There is no uniform view on the question of which cell number should be analysed. The recommendations range from 100 to 2000 cells [488], [489], [497]. In the studies on the reproducibility of the Ki-67 determination, it was unanimously shown that - regardless of the number of cells analysed - the agreement<10%) und hoch

proliferierenden Tumoren (> is good at low (<10%) und hoch proliferierenden Tumoren (> 25%). The deviations are most pronounced in the middle range (10-25%) [486], [487]. Recently published studies of various working groups unanimously show that the concordance, also in this middle range, can be improved by evaluating 4 or 5 different, randomly selected visual fields [489], [491]. It is therefore obvious, especially in the middle proliferation range, to evaluate several visual fields (> 3) in order to record the proliferation activity of the tumor in a representative manner.

4.5.4. Prognostic and predictive factors

4.69	Evidence-based Recommendation
GoR **A**	To assess the course of the disease (prognosis), the pTNM status (locoregional tumor spread, locoregional lymph node involvement, distant metastasis) shall be assessed according to the current TNM classification (currently 8th edition [501].
LoE **1a**	[501]; [466]; [502]; [503]; [504]; [505]; [506]; [507]; [508]
	Strong Consensus

4.70	Evidence-based Recommendation
GoR **A**	To assess the course of the disease (prognosis), the resection margin status (R-classification, according to current TNM-classification, currently 8th edition [501]) as well as safety margins shall be assessed.
LoE **1b**	[364]; [501]; [465]; [466]
	Strong Consensus

4.71	Evidence-based Recommendation
GoR **A**	To assess the course of the disease (prognosis), the histological type (according to current WHO classification) shall be determined.
LoE **2b**	[118]; [466]; [509]
	Strong Consensus

4.72	**Evidence-based Recommendation**
GoR **A**	To assess the course of the disease (prognosis) the histological grading according to Elston and Ellis [510] shall be determined.
LoE **2a**	[510]; [466]; [492]; [506]; [511]; [512]
	Strong Consensus

4.73	**Evidence-based Recommendation**
GoR **A**	To assess the course of the disease (prognosis) the peritumoral lymph vessel invasion (according to the current TNM classification, currently 8th edition [501]) shall be assessed.
LoE **2b**	[459]; [460]; [466]; [506]; [513]
	Strong Consensus

4.74	**Consensus-based Recommendation**
EC	In order to assess the course of the disease (prognosis), age shall be determined.
	Strong Consensus

Ki-67

4.75	**Evidence-based Statement**
ST	The addition of Ki-67 to the conventional prognostic factors (age, pT, pN, grade, ER, PR, HER2) improves the prognostic assessment in women with histologically confirmed ER/PR-positive and HER2-negative invasive breast cancer for the decision whether adjuvant chemotherapy should be given.
LoE **1b**	[484]; [492]; [493]; [496]
	Consensus

4.76	**Consensus-based Statement**
ST	Ki-67 is a continuous marker of proliferation activity. With a Ki-67-positivity >/= 25% an increased risk can be assumed.
	Strong Consensus

4.77	**Consensus-based Statement**
ST	The reproducibility of the Ki-67 determination can be significantly improved by applying uniform criteria. The determination should therefore be standardised.
	Strong Consensus

Multigenic tests for nodal-negative carcinomas

4.78	**Evidence-based Recommendation**
GoR **0**	Only if the conventional prognostic parameters including Ki-67 do not allow a clear decision for or against adjuvant chemotherapy in women with ER/PR-positive, HER2-negative, nodal-negative invasive breast cancer, a methodologically standardized and clinically validated multigene test can be used for the decision. However, there is a need for further research with regard to the benefit of multi-dimensional tests, as the study situation and follow-up times in the available studies are not yet sufficient.
LoE **2b**	[485]; [514]; [515]; [516]
	Strong Consensus

4.79	**Consensus-based Recommendation**
EC	When a multi-test is performed, no more than one test shall be used for decision making.
	Consensus

Background 4.69 to 4.79

The recommendation to collect the listed conventional pathomorphological and clinical parameters follows international guidelines [465], [466]. A recent meta-analysis also confirmed the importance of the resection margin status [364]. Retrospective analysis of SEER registry data including more than 100,000 patients supports the effect of grading on disease progression as well as the results of the PlanB study, where multivariate analysis confirmed that grading (locally and centrally determined) is an independent prognostic factor [492], [512]. In the current edition of the AJCC Cancer Staging Manual (8th ed.) for the new prognostic stage grouping to be implemented on January 1, 2018, in addition to the TNM classification also histological grade, ER, PgR

and HER2 status and the Oncotype DX® Recurrence Score are considered [517]. The anatomical stage grouping remains unaffected.

4.5.4.1. uPA/PAI-1

Although the invasion factors uPA/PAI-1 according to the current ASCO guidelines can be used to decide for or against adjuvant systemic therapy in ER/PgR-positive and HER2-negative nodal-negative breast cancer [485], the majority of the guideline group has spoken out against a renewed recommendation in the current revision of the S3 guideline. The main reason for this is that the results of the prospective randomized chemo-N0 study in nodal-negative breast cancer are not transferable to current treatment standards. This is also the conclusion reached by the experts of the ASCO guideline in the explanatory text to the statement [485] - despite their open recommendation. The patients in the group with low uPA/PAI-1 did not receive any systemic treatment in the chemo-N0 study, i.e. also no endocrine therapy as is standard today for ER/PgR-positive tumors [518]. It is therefore not possible to say what the additional benefit of chemotherapy for high uPA/PAI-1 in ER/PgR-positive tumours would be under current conditions if the patients in the comparative arm received endocrine therapy. In addition, the HER2 status of the tumours analysed in the chemo-N0 trial is unknown. There are indications that there is a correlation between uPA/PAI-1 and intrinsic subtypes. HER2-positive or triple-negative carcinomas are significantly less likely to be uPA/PAI-1-negative than luminal A-type carcinomas [519]. The question therefore arises whether uPA/PAI-1 is actually an independent prognostic parameter. Furthermore, the prognostic value seems to be different for the individual subtypes and is not detectable in hormone receptor-positive breast carcinomas if the HER2-positive tumors are excluded [520]. The assessment of the S3 guideline group is therefore in line with that of the Institute for Quality and Efficiency in Health Care (IQWiG) in its final report on the evaluation of uPA/PAI-1 in primary breast cancer with intermediate risk of recurrence after R0 resection. It concludes that the patient-relevant benefit or harm of an uPA/PAI-1-supported therapy decision is unclear due to a lack of suitable studies [521].

4.5.4.2. Ki-67

The correlation between the immunohistochemically determined Ki-67 proliferation index and the prognosis of breast cancer has been shown in numerous clinical studies. Nevertheless, Ki-67 is not recommended in the current ASCO biomarker guidelines as a decision aid for or against adjuvant chemotherapy [485]. In the S3 guideline update, the question was raised whether more recent evidence is available to show that the addition of Ki-67 to conventional factors improves the prognosis estimate for invasive breast cancer. For this purpose, a systematic literature review was conducted for the period 2015-10/2016. A meta-analysis was identified that included more than 64,196 patients from 41 studies. The meta-analysis concludes that Ki-67 is an independent prognostic parameter for the overall survival of patients with breast cancer. The prognosis of tumours with high Ki-67-positivity is significantly worse than that of Ki-67-low-expressing tumours (hazard ratio, HR=1.57; 95% CI 1.33-1.87; p<0,00001). Dies gilt ebenso für die Subgruppe der ER-positiven Tumoren (HR=1,51; 95% CI 1,25-1,81; p<0,0001) [484]. In kürzlich publizierten prospektiven Studien wurde außerdem der stärkere Nutzen einer Chemotherapie bei Frauen mit hoch proliferierenden ER-/PgR-positiven, HER2-negativen invasiven Mammakarzinomen gezeigt [492], [493], [496]. Aus Sicht der Leitliniengruppe liegt daher ausreichende Evidenz vor, den Ki-67-Proliferationsindex bei Frauen mit histologisch gesichertem ER-/PgR-positivem, HER2-negativem invasiven Mammakarzinom bei der Entscheidung für oder gegen eine adjuvante Chemotherapie einzubeziehen.

Nevertheless, there are objections to the use of Ki-67 as a prognostic factor (Harris 2016). One of the points of criticism is that the studies use very different threshold values (1-30%) [484] and that there is no uniform threshold value to differentiate the risk groups. For daily practice it would be desirable to be able to clearly differentiate between different prognosis groups on the basis of defined limit values. However, it should be remembered that Ki-67 is to be understood as a continuous marker of the proliferation rate of a tumor. Ki-67 must probably also be understood in the context of subgroups of breast carcinoma (e.g. hormone receptor-positive versus negative tumours), which have different proliferation activity.

<=10% als niedrig. Gemäß der Metaanalyse von Petrelli et al. [484] ist der Grenzwert mit der höchsten prognostischen Signifikanz bislang noch nicht bekannt. Allerdings konnte anhand der Auswertung von 25 Studien, die hinsichtlich des Zusammenhangs zwischen Grenzwert und Überleben informativ waren, gezeigt werden, dass das Gesamtüberleben bei einer Ki-67-Positivität>The general consensus is that carcinomas can be divided into those with low, intermediate and high proliferation activity. In the case of hormone receptor-positive, HER2-negative breast carcinoma, Ki-67-positivity is generally valid /= 25% was significantly lower than Ki-67-positivity < 25% (HR=2,05; 95% CI 1,66-2,53, p<0,00001). Diese Schlussfolgerung der Meta-Analyse bildet die Grundlage für die offene Empfehlung der S3-Leitliniengruppe, dass bei einer Ki-67-Positivität >/= 25% an increased risk can be assumed. This is also supported by the multicenter data from one of the German clinical cancer registries [494]. In the intermediate range of more than 10% to 25% Ki-67 is not safe to use for therapy decisions in daily practice.

Another criticism of Ki-67 as a prognosis marker is the lack of reproducibility between laboratories and examiners [485].

The international working group on Ki-67 in breast cancer as well as other working groups have therefore carried out a number of studies and interlaboratory comparisons to improve the analytical validity of Ki-67, from which conclusions can be drawn for a standardised evaluation (see Section 4.5.3 Evaluation Ki-67). It can also be assumed that the variability of the determination has improved over the years due to increasing automation of immunohistochemistry, training and participation in interlaboratory comparisons. The data for the already mentioned study of a clinical cancer registry were collected multicenter in different pathologies [494] and prove the prognostic relevance of Ki-67.

Ki-67 can also provide useful information on the proliferation rate of hormone receptor negative tumors.

4.5.4.3. Intrinsic subtypes

By analyzing gene expression profiles, molecular subtypes of breast cancer were identified that differ significantly in their clinical course and treatment response: Luminal A and Luminal B, HER2-positive, basal-like [522], [523]. Since the array analyses required for this are not feasible in daily diagnostics, the commercially available PAM50 gene expression test was developed, which can reliably detect these intrinsic subtypes in clinical diagnostics and has prognostic significance [524]. Alternatively, a simplified classification was proposed in which the tumors are differentiated by an immunohistochemical algorithm [525], [526], [527]:

- Luminal A: ER and/or PgR positive and HER2 negative and Ki-67 low
- Luminal B:
    - HER2 negative: ER and/or PgR positive and HER2 negative and Ki-67 high

    - HER2-positive: ER- and/or PgR-positive and HER2-positive and Ki-67 high or low
- HER2 positive: ER and PgR negative and HER2 positive
- triple negative: ER, PgR and HER2 negative.

This stratification of breast carcinomas offers itself as a biological model for therapeutic strategies. Accordingly, the last St. Gallen Consensus recommendations were based on this biological model [470], [471], [528], [529]: For a tumor of the type Luminal A, a sole endocrine therapy is considered necessary, while for the other subtypes, chemotherapy is recommended in the majority of cases, in HER2-positive disease supplemented by anti-HER2 therapy. However, when transferring the molecularly defined subtypes into immunohistochemical categories, it should be borne in mind that these are not congruent. Thus, with 79% most but not all triple-negative tumors are basal-like and on the other hand 31% of basal-like tumors are not triple-negative [530]. The indication for chemotherapy in ER/PgR-positive tumors respectively the differentiation of Luminal A and Luminal B HER2-negative depends in the proposed immunohistological classification exclusively on the Ki-67 proliferation index. The question of the optimal threshold value for Ki-67 to differentiate Luminal A and B is not answered (see also section Ki-67). When stratifying luminal tumors for treatment planning, it must also be taken into account that their leading feature is ER expression. The PgR status can provide helpful additional information, especially if high positivity is present. If ER is highly expressed and Ki-67-PI is low, strong PgR expression confirms the presence of a luminal A type tumor. A low PgR expression (1-9% positive tumor cell nuclei) is not sufficient to classify ER-negative tumors into the group of luminal tumors. Like tumors with low ER-positivity, they are biologically more likely to be classified as ER/PgR-negative or triple-negative breast carcinomas (see also Chapter 5.5.3.1: Interpretation of hormone receptor status). In the meantime, other factors are also being considered to stratify the luminal tumors for treatment planning. In addition to the extent of ER/PgR positivity, these include grading and risk stratification based on gene expression profiles (multigene tests) [470], [471], [528]. However, a prospective validation of selectivity is also lacking for most of these parameters. The risk groups of the gene expression tests described in the following section can be helpful for clinical decisions in the borderline area.

4.5.4.4. Multi-gene tests

It is undisputed that patients with breast cancer benefit overall from adjuvant drug therapy [531]. In addition to the acute toxicities (e.g. nausea, vomiting, alopecia), chemotherapy can also have a not inconsiderable rate of undesirable side effects, which can have a potentially long-term negative impact on quality of life (e.g. amenorrhoea, fatigue, sensory polyneuropathy, "chemobrain") or even life-threatening (e.g. heart failure, secondary leukemias) are [532], [533], [534], [535], [536]. Therefore, an accurate risk assessment plays a decisive role. In addition to the classic clinical-pathological prognostic factors, multi-test methods are playing an increasingly important role. Risk assessment is of great importance, since patients with a low absolute risk have only a low absolute benefit from adjuvant chemotherapy [531]. For this reason it is crucial that predictive biomarkers in general and multi-test in breast cancer in particular are assessed according to clear and stringent criteria of evidence [537].

Different commercially available multigene tests for breast cancer

This compilation includes some of the most frequently used gene expression tests in Germany (EndoPredict®, MammaPrint®, Oncotype DX®, Pro-signa®), it does not claim to be complete.

Three of these multigene tests were extensively investigated prospectively and retrospectively in early hormone receptor-positive breast cancer. Both EndoPredict® (EP) [538], [539], [540], [541] as well as Oncotype DX® [542], [543], [544], [545], [546] and Prosigna® were evaluated. (PAM50) [547], [548], [549], [550] could consistently show in these studies that they were able to identify patients in a low-risk group with a 10-year risk of distant metastases below 10% with pure endocrine therapy and without adjuvant chemotherapy. The multivariate analysis showed the prognostic significance independent of classical clinical-pathological factors such as age, tumor size, nodal status [105].

For both Oncotype DX® and MammaPrint® prospective evidence is available in the meantime. In the prospective-randomized PlanB study, Gluz and collaborators were able to show that patients with a low recurrence score (RS) ≤11 with pure endocrine therapy had an excellent 3-year disease-free survival of 98% even without adjuvant chemotherapy [492]. The very good survival of patients with hormone receptor-positive, HER2-negative and nodal-negative tumors with a low RS (<11) unter rein endokriner Therapie wurde ebenfalls im Rahmen der prospektiv randomisierten TAILORx-Studie gezeigt [516]. Patientinnen, die als low-risk mit einem RS 32% hatten diskordante Ergebnisse zwischen genomischer (G) und klinisch-pathologischer (C) Risikoeinteilung. C high-risk / G low-risk-Patientinnen hatten ein erkrankungsfreies Überleben von 90,3%, wenn sie zur genomischen Risikoeinteilung randomisiert wurden und dementsprechend keine Chemotherapie erhielten. In der Chemotherapiegruppe wurde für die Patientinnen eine Risikominderung von absolut etwa 3 Prozentpunkten beobachtet, die in der Per-Protokoll-Auswertung statistisch signifikant war (p=0,03; Hazard Ratio 0,64). Daraus ergibt sich, dass ein relevanter Effekt der Chemotherapie nicht ausgeschlossen werden kann.

Concordance of different gene expression tests

In the OPTIMA (Optimal Personalised Treatment of early breast cancer usIng Multiparameter Analysis) Prelim Feasibility Study, 313 patients with early ER-positive, HER2-negative breast cancer were randomised prospectively between chemotherapy followed by endocrine therapy and therapy after risk assessment using Oncotype DX® [551], [552]. In this study, the results of the risk assessments between Oncotype DX®, Prosigna®, MammaPrint®, MammaTyper®, NexCourse Breast® (IHC4-AQUA) and the classification into subtypes using Blueprint®, MammaTyper® and Prosigna® were then compared. The agreement between different tests was only moderate in terms of risk classification (kappa 0.33-0.60) and subtype determination (kappa 0.39-0.55). These results show that for the individual patient, different tests can result in different risk assessments and thus divergent recommendations for or against chemotherapy.

Comparison of prognostic significance between different multi-tests

A comparison of the prognostic significance between the two gene expression assays Oncotype DX® and PAM50 in the TransATAC study showed that the risk of recurrence (ROR) determined by PAM50 provided more prognostic information in ER-positive, endocrine treated patients than the recurrence score (RS) [553] calculated by Oncotype DX®. A further comparison of different gene expression tests (Endopredict® and PAM50) was performed retrospectively in 536 nodal-positive, ER-positive, HER2-negative patients treated in the randomized GEICAM/9906 Phase III study [554]. Between PAM50-ROR and EP a 20-21% recurrence score was found. Both gene expression tests identified a low risk group without significant differences between the tests (10-year MFS: ROR-S 87%, ROR-P 89%, EP 93%). The addition of pathological parameters achieved a superior prognostic significance (10-year MFS ROR-T 88%, ROR-PT 92%, EPclin 100%). A further direct comparison of two gene expression signatures

was performed in the TransATAC study in 928 ER-positive/HER2-negative patients treated with either tamoxifen or anastrozole [514]. EP and EPclin showed a greater prognostic significance than RS (EP: LR-χ2=49.3; EPclin: LR-χ2=139.3; RS: LR-χ2=29.1). This effect was particularly strong in nodal-positive tumours and late metastases. However, the comparison of the RS with the EPclin score in this study cannot be readily interpreted clinically, as the established limits of the RS were not considered.

Systematic review of biomarkers by the American Society of Clinical Oncology (ASCO)

In the meantime, extensive studies have been carried out for numerous biomarkers in breast cancer. The American Society of Clinical Oncology Clinical (ASCO) published in 2016 a guideline for the use of biomarkers for adjuvant systemic therapy decisions in patients with early breast cancer and known ER/PgR and HER2 status [485]. Systematic reviews, meta-analyses and randomized studies were used in the literature search. For the preparation of this guideline 50 studies from the years 2006-2014 were used. One randomized prospective and 18 prospective-retrospective studies had evaluated the clinical benefit of additional biomarkers for the decision on adjuvant systemic therapy. Following the publication of the MINDACT study, a focused update of the ASCO biomarker guideline for the use of the MammaPrint® was also published in July 2017 [555]. In summary, no study could be identified for the selection of a specific therapy. In addition to ER, PgR, and HER2, sufficient evidence for a clinical benefit of the above mentioned multi-target tests Oncotype DX®, EndoPredict®, and Prosigna® and MammaPrint were confirmed in nodal-negative patients with ER/PR positive, HER2 negative carcinomas. The quality of evidence for Oncotype DX®, Prosigna® and MammaPrint® was rated "high" and for EndoPredict® "medium". The focused update also identified a potential benefit of MammaPrint® in nodal-positive patients with ER/PR-positive, HER2-negative breast carcinomas and 1 to 3 affected lymph nodes as well as high clinical risk (according to MINDACT categorization) (quality of evidence: high).

Final report "Biomarker-based tests for the decision for or against adjuvant systemic chemotherapy in primary breast cancer" (D14-01) by the Institute for Quality and Efficiency in Health Care (IQWiG)

The final report of IQWiG [556] is contradictory. For this report, 3 randomized [515], [541], [543] and 5 prognosis studies [514], [540], [546], [549], [557] were initially identified. However, none of the five forecast studies and only two of the three randomized studies [515], [541] were considered for IQWiG's evidence assessment. In the final report, the work result was classified as follows: "In the present report, only results of 2 of the 8 included studies could be used for the present report. The results of the remaining 6 studies were not used for the evaluation due to the high proportion of data not included. The data available on the basis of the 8 included studies were not sufficient to answer the question".

Justification of the level of recommendation of the S3 Guidelines presented here

The statement in the present guideline is based on the current ASCO Biomarker Guideline and a systematic literature review, which was conducted in the context of the S3 guideline update and covers the period 2015 to 10/2016. The statement was carefully formulated after extensive discussion at the meeting of the S3 Guidelines Commission in December 2016 and achieved consensus in the current wording. IQWIG's report on gene expression tests for breast cancer, which was published at the same time, was also discussed and taken into account in the S3 Guidelines Commission's decision.

It is noticeable that the ASCO biomarker guideline takes into account the evidence from a total of 19 publications, whereas only 2 studies were used for IQWiG's decision. In IQWiG's final report, a major counter-argument against the prognosis studies referred to above and largely used in the current systematic review for ASCO biomarkers was that less than randomly adjusted 70% of the tumour samples recruited in the studies could be examined with the above-mentioned multi-test. It should be critically noted here that the 70% required by IQWiG cannot be derived from the literature. Since there is no plausible evidence for an exact percentage of the archive material to be examined, in prognosis studies it is important that the patients examined are representative of the study population and have sufficient statistical power to be able to demonstrate differences in survival. Both are given in the above-mentioned studies, which were not considered by IQWiG. A further point of criticism by IQWiG of the prospective-retrospective prognosis studies was that the 95 % confidence interval includes the limit of 5% of the occurrence of metastases after 10 years, as defined by IQWiG. The problem here is that 10% is not accepted as the limit between low and high risk, as is common international practice.

According to IQWIG's defined methodology, test combinations that combine both molecular and clinical factors to a common score were explicitly not considered (final report p. 23) [556]. These include EPclin, but also the ROR-T and ROR-PT scores. This appears problematic, since recent studies with a direct comparison of the different test systems show that the test combinations are superior to the purely molecular tests, especially in nodal-positive patients and late metastases [514], [558]. However, this can also be interpreted to the effect that the test combinations have sufficient prognostic significance only by the addition of clinical parameters, whereby the clinical factors in EPclin are of great importance [540]. In the clinical context the consideration of both molecular and clinical factors is of central importance for a valid risk assessment.

Another critical point raised by IQWiG is the rate of recurrences or deaths that seem "acceptable" for patients to avoid chemotherapy. If metastases / recurrences / deaths due to breast cancer are to be avoided with the highest probability, each patient would have to be treated with adjuvant chemotherapy in addition to endocrine therapy, as this would be the only way to do the maximum possible. However, since chemotherapy, as mentioned above, can have a considerable rate of undesirable side effects, every patient has the right to the best possible medical advice in order to make the best possible decision for herself (for or against chemotherapy). Even if the arguments against multi-dimensional tests, which IQWiG has carefully compiled on 212 pages in the present final report [556], are to be respected, from a medical perspective it must be asked whether we currently have better instruments for our counselling than multi-dimensional tests. As sufficiently published in the prognosis studies mentioned above, the different gene expression signatures consistently have an independent and superior prognostic significance in comparison to the classical prognostic factors such as tumor size, nodal status, histological differentiation grade, lymphangioinvasion or Ki-67. These classical prognostic factors are what we have available to advise patients when multi-tests are not used. After a detailed and critical discussion of the limitations of multi-tests and the above mentioned pros and cons, the guideline group therefore assigned recommendation level 0 after weighing the benefits and harms. Therefore, if in women with ER-/PgR-positive, HER2-negative, nodal-negative invasive breast cancer the conventional prognostic parameters including Ki-67 do not allow for a clear decision for or against adjuvant chemotherapy, a methodologically standardised and clinically validated multigene test can be used for the decision.

For the use of gene expression tests in the nodal-positive situation, the following statement was discussed at the guideline meeting: "In women with ER/PgR-positive,

HER2-negative, nodal-positive (1-3 affected lymph nodes) primary invasive breast cancer, a methodologically standardized and clinically validated multigene test can be used in the decision against (neo)adjuvant chemotherapy if it predicts a low risk of relapse". However, there was no majority in favour of this statement, so that it is only presented here in the background text and therefore no consensual recommendation can be formulated for the nodal-positive situation.

It is important that all experts see an urgent need for further investigation and clinical validation of gene expression tests. Randomised therapy studies in which the gene expression test leads to the chemotherapy being given or omitted appear justifiable from an ethical point of view where there is still uncertainty about the best course of action. Otherwise, the recruitment of ongoing randomised trials (e.g. RxPONDER) would have to be stopped immediately. Unfortunately the results from the randomized part of the TAILORx study are not yet available, although they have been announced for some time. In any case, the current results of the MINDACT study do not indicate that refraining from chemotherapy in patients with a low risk of multi-test is clearly the best recommendation. Registry studies are already available for the Oncotype DX® and prove the prognostic significance of the multi-test, also in the context of adjuvant chemotherapy, in the nodal-negative and in the nodal-positive situation [554], [555], [556].

Prediction of adjuvant systemic therapies

4.80	Evidence-based Recommendation
GoR **A**	To assess the probable effect of adjuvant systemic therapies (prediction), the estrogen/progesterone receptor status for endocrine systemic therapy shall be assessed.
LoE **1a**	[421]; [559]; [560]
	Strong Consensus

4.81	Evidence-based Recommendation
GoR **A**	To assess the probable effect of adjuvant systemic therapies (prediction), the HER2 status for a targeted anti-HER2 therapy shall be determined.
LoE **1b**	[426]; [465]; [466]; [467]
	Strong Consensus

4.82	**Evidence-based Recommendation**
GoR **A**	To assess the likely effect of adjuvant systemic therapies (prediction), menopausal status shall be assessed for the use of antiestrogenic therapy.
LoE **1c**	[561]
	Strong Consensus

Background 4.80 to 4.82

The recommendations of the predictive factors for endocrine and anti-HER2 therapy are based on international evidence-based guidelines [421], [426], [465], [466] and the results of systematic literature searches and meta-analyses [467], [560], [561].

Menopause status is predictive for all endocrine therapies (see Chapter 5.7.2)

Predictive factors in the context of a neoadjuvant systemic therapy

4.83	**Evidence-based Recommendation**
GoR **A**	Various predictive factors have a significant predictive value for the occurrence of pathological complete remission (pCR). In the run-up to a neoadjuvant systemic therapy, the following data shall be collected • Age • cT* • cN* • histological type • histological grading • ER and PgR status • HER2 status *Clinical parameters
LoE **1a**	[562]; [563]
	Strong Consensus

Background 4.83

The response of the tumor to neoadjuvant systemic therapy provides information on the prognosis of the disease. The pCR, defined as the absence of invasive tumor residuals in mamma and lymph node [564], correlates with the survival of patients [565]. However, the close correlation between pCR and course obviously does not apply equally to all subtypes [564], [565], [566]. Only in triple-negative and HER2-positive breast carcinomas is pCR currently recognized as a surrogate marker for the benefit of chemotherapy or anti-HER2 therapy [564].

According to the pooled data from 7 German neoadjuvant studies including 3332 patients [563] and the results of a meta-analysis including 11,695 patients from 30 studies [562], pCR rate and subtype are significantly associated. The highest pCR rates are achieved in triple-negative and HER2+/HR- subtypes. In patients with a positive HER2 status, an additional neoadjuvant anti-HER2 treatment further increases the pCR rate.

In addition, there is a significant correlation between age, pre-therapeutic tumor size and nodal status as well as histological tumor type and degree of differentiation with the pCR [563].

Other factors are currently under discussion to predict a higher response to neoadjuvant systemic therapy. These include in particular:

- Ki-67 proliferation index
- Tumor infiltrating lymphocytes (TILs)

Based on the determination of the Ki-67 proliferation index in 1166 punch biopsies of the GeparTrio study it was shown that Ki-67 is a significant predictive marker for the response to neoadjuvant chemotherapy [567]. However, the discussion about the results of the study also made clear that the definition of a uniform threshold value for the prediction of the therapy effect is difficult [568], [569] Ki-67 showed a significant predictive and prognostic value over a wide range of cut-offs, so that an optimization of the threshold value based on study data might be problematic. Rather, it can be assumed that the level of the optimal cut-off value is context-dependent, i.e. influenced by the composition of the study collective, the molecular tumor types and the therapeutic agents. The decision for a neoadjuvant therapy is mainly controlled by the hormone receptor and HER2 status. Triple-negative and HER2-positive carcinomas are usually treated neoadjuvantly. In this situation the Ki-67 level is no longer necessarily relevant. Therefore, the majority of the S3 guideline group decided against a recommendation of Ki-67 as a predictive factor for the response to neoadjuvant systemic therapy.

Tumor infiltrating lymphocytes (TILS) can be understood as an immunological biomarker. In recent years, an increasing number of studies have been published showing that the quantification of TILs has a prognostic and predictive value, especially in HER2-positive and triple-negative breast carcinomas [570], [571], [572]. A meta-analysis including 13,100 patients from 23 studies concluded that an increased number of TILs predicts the achievement of pCR and is associated with an improved survival rate [572]. However, different methods for the detection of TILs are used in the studies (HE staining; immunohistochemistry: CD45, CD3, CD8) [572], [573]. Also the procedure of evaluation and the amount of cut-off are different [572], [573], so that from the point of view of the S3-guideline group no recommendation for this parameter can be derived from the study data available so far.

4.5.5. Percutaneous biopsies in the context of interventional diagnostics

Currently available methods for interventional diagnostics:

- High-speed punch biopsy (e.g. 14 gauge)
- vacuum biopsy (e.g. 11 gauge or 8 gauge)

4.5.5.1. Percutaneous biopsy (high-speed punch biopsy, vacuum biopsy)

Indications: Diagnostic confirmation for therapy planning, clarification of unclear and suspected malignant findings.

4.5.5.1.1. Macroscopic processing

Description:

- High-speed punch biopsy: number and (total) length of punch cylinders/parts;
- vacuum biopsy: number of punching cylinders/parts; if necessary, further description (colour, consistency)

Tissue embedding:

- complete embedding of the tissue samples sent

4.5.5.1.2. Microscopic processing and assessment

Processing:

- Sectional stages (see Statement 4.34.; H&E; additional examinations if required)
- special additional examinations in case of detection of invasive carcinoma (hormone receptors; HER2, Ki-67)

Cutting steps for percutaneous biopsies

4.84	**Consensus-based Recommendation**
EC	At least 3 HE incisions should be made and examined from tissue cylinders removed for the clarification of calcifications. For tissue cylinders that were removed for the clarification of focal findings, one HE incision may be sufficient. Further incision steps may be necessary if there is no correlation to the clinical-radiological findings or to clarify the diagnosis.
	Strong Consensus

Background 4.84

The diagnostic reliability at the punch and vacuum biospies is improved, especially in the presence of microcalcifications, by the preparation of cutting steps [574]. This is also related to the diameter of the cylinders, which is usually larger in biopsies from microcalcifications associated lesions, since vacuum biopsies are increasingly used here. The addition of 2 incision steps on a collective of 40 punch and 63 vacuum biopsies changed the diagnostic category in 13% of biopsies from lesions with microcalcifications. On the other hand, the addition of 266 punch biopsies and 6 vacuum biopsies resulted in a change in the diagnostic category in only 1.5% of the biopsies from other lesions.

Assessment:

- The information is documented as in Chapter 5.5.2.3, possibly using a form (see Chapter 12.3: Figure 10).

In punch biopsies, the displacement of benign or malignant epithelial cell clusters into the stroma and/or vessels is possible; in individual cases, the differentiation of true stroma and/or vessel invasion may be difficult.

If necessary, point out the necessity of further bioptic clarification in case of

- lack of a morphological correlate for the imaging findings,
- questionable dignity of the identified lesion (e.g. detection of atypical ductal hyperplasia (ADH) or fibroepithelial neoplasia, where a reliable distinction between fibroadenoma and phylloides tumour is not possible).

In addition, the pathomorphological findings on the punch and vacuum biopsies are classified into the 5 categories of the B-classification (B1-B5) [420], [425] in the mammography screening. Classification of the categories is also recommended on punch and vacuum biopsies of symptomatic findings outside mammography screening [425].

Table 4: B-classification for punch and vacuum biopsies [420], [424]

B1	**Normal tissue or non-recyclable material** • *Insufficient/not usable material, e.g. only Koagel* • *Normal findings with or without glandular tissue* ○ Only fatty tissue (exception: lipoma - B2) or only stroma ○ Without any further conspicuous features (exception: Hamartom - B2) ○ Regressive changes / involution ○ Minimal mastopathy / fibrosis / apocrine metaplasia, even with non-significant microcalcification ○ Lactation changes (exception: lactating adenoma - B2)
B2	**Benign lesions** • *Lesion report:* ○ Fibroadenoma, tubular adenoma ○ Fibrocystic changes, adenosis, ductectasia ○ Mammary hamartoma ○ Completely recorded small milk duct papilloma/micropapilloma ○ Pseudoangiomatous Stromahyperplasia (PASH) ○ mastitis, abscess ○ Fatty tissue necrosis ○ Myofibroblastoma • *Radiologically relevant microcalcification:* ○ Fibrocystic mastopathy/(papillary) apocrine metaplasia ○ Adenosis with/without columnar cell metaplasia/-hyperplasia ○ Calcified fat tissue necrosis
B3	**Benign lesions with uncertain biological potential** • *Lesions with increased risk of associated DCIS or invasive carcinoma:* ○ Atypical ductal hyperplasia (ADH) or atypical epithelial proliferation of the ductal type (depending on the extent, possibly B4) ○ Flat epithelial atypia (FEA) ○ Classical lobular neoplasia (LN; ALH and LCIS)

	○ Atypical apocrine adenosis • *Potentially heterogeneous lesions with risk of incomplete sampling:* ○ Cell-rich fibroepithelial lesion or phylloidal tumor without suspected malignancy ○ Intraductal papilloma without/with atypia, not completely removed with certainty (in the case of atypia depending on the extent, possibly B4) ○ Radial scar or complex sclerosing lesion (exception: if radial scar is not the cause of the radiological change: B2) ○ Hemangioma ○ atypical vascular lesion • *Rare changes:* ○ Adenomyoepithelioma ○ Microglandular adenosis ○ Mucocelous lesion ○ Nodular Fasciitis ○ Fibromatosis of the desmoid type ○ Unclear spindle cell lesion
B4	**Suspected malignancy** • *Atypical intraductal epithelial proliferation depending on the extent and degree of atypia* • *Not to decide whether lobular neoplasia (LN) or low-grade DCIS* • *Too few suspicious cells for definitive carcinoma diagnosis* • *suspected carcinoma, but high-grade fixation artefacts or crush artefacts*
B5	**Malignancy** • *B5a: In-situ carcinoma* ○ Ductal carcinoma in situ (DCIS) ○ Classical LN/LCIS with comedotype necroses and pleomorphic LN/LCIS ○ M. Paget of the nipple without invasion ○ Malignant, non-invasive papillary lesion (encapsulated papillary carcinoma, solid papillary carcinoma) • *B5b: Invasive carcinoma* ○ Microinvasive carcinoma ○ Invasive carcinoma (no specific type, NST, or special types) • *B5c: Not to decide whether invasive or in situ* • *B5d: Malignoma of other histogenesis or metastasis* ○ Malignant phylloid tumor ○ malignant lymphoma ○ Sarcoma (e.g. angiosarcoma)

	○ Intramammary metastasis of a primary tumor located elsewhere

4.5.5.2. Fine needle puncture/aspiration cytology (FNAC)

Is not recommended in Germany to confirm the diagnosis of suspected breast cancer, among other reasons because it is not possible to differentiate reliably between non-invasive and invasive changes. The only areas of application are the clarification of cysts or suspect lymph nodes.

4.5.6. Excision biopsies

In principle, all forms of excision biopsies are handled in the same way as a breast-conserving surgical procedure (possible exception: diagnostic excision).

Forms of excisional biopsy:

- Open biopsies/diagnostic excisions
- Tumour resections/lumpectomies/segmental resections

(in case of non-palpable findings after preoperative localization using a marking wire)

4.5.6.1. Macroscopic processing

Description:

- Total tissue sample received:
- Size (3 dimensions) and weight
- Cut/not cut
- Size and texture of pendulous skin parts
- Marking for topographic orientation of the tissue sample (if performed by the surgeon)
- if necessary, localization of a marking wire
- Palpable tumor:
- Size (3 dimensions)
- Cut surface: boundary (sharp/blurred), consistency, colour
- Correlation to marker wire/preparation radiography, if applicable
- Minimum distance from the resection margin (in mm) taking into account the topography
- Other noticeable findings

Preparation:

- Marking of the surface of the preparation with ink, latex or other suitable material to assess the cut edges
- Lamination of the specimen by parallel cuts perpendicular to the longitudinal axis of the specimen (lamella thickness approx. 5 mm) from one end of the specimen to the other; if necessary, oriented towards the nipple if the topographical markings are appropriate

Tissue samples are used for statements on:

- non-palpable findings or palpable tumour (see below)
- Resection margins
- other changes/surrounding tissue
- special questions (additional examinations)

Note:

The number of tissue blocks depends on the size and type of the material sent in, the number and size of the mammographically and/or palpatorily conspicuous lesions and the underlying process (e.g. macroscopically clearly recognizable carcinoma versus non-demarcable DCIS).

Non palpable findings:

It is necessary to embed the entire mammographically conspicuous focus for the exact identification of the localized and marked change as well as the resection margins and of compacted tissue outside the radiologically conspicuous area (especially low-grade DCIS can be much more extensive than the radiologically conspicuous microcalcifications suggest). Tissue sampling is systematic and oriented to reconstruct, if necessary, the size and topography of the lesion with relation to resection margins; possibilities for this:

- Systematic placing of preparation discs after lamination on a foil and preparation of a preparation radiography or photocopy. In the case of radiologically conspicuous microcalcifications, the preparation radiography of the tissue lamellae enables targeted removal and microscopic examination for exact histological-radiological correlation. Entry of the tissue samples with the corresponding block designations on the radiography or photocopy.
- Use of prefabricated sketches for noting the withdrawals with block designation (see Figure 4).

Palpable tumour:

- Size of the tumor is essential for the extent of the embedding:
- Small tumours up to about 1 cm in diameter: Embedding in toto
- Larger tumours: At least 3 tumour blocks or a complete tumour cross-section desirable
- For representative detection of very large tumours, the removal of at least one tissue block per cm maximum diameter is recommended. If possible, acquisition of the tumour margin with the nearest excision margin in at least one block.
- Always also examination of surrounding fibrous tissue that appears tumour-free

Processing in the presence of a DCIS:

- Goals: Determination of the size, assessment of the resection margins, exclusion of invasive growth
- Tissue sampling: Procedure depending on lesion (non-palpable or palpable; see above)

Mammographic sizing alone is unreliable. In about 30 % of the cases that are operated on with breast-conserving surgery, the size is underestimated in mammography, so that follow-up resections are necessary [575]. Therefore, a complete, sequential histopathological embedding of the surgical specimen is recommended for breast-conserving therapy under consideration of the topographic orientation. Even large DCIS should be completely embedded, since they may contain foci of microinvasion [576].

Surgical preparations after neoadjuvant therapy:

- The processing of the surgical specimens is essentially analogous to the procedure for primary surgical therapy.

- However, the therapy-induced thinning of the tumor can make the macroscopic identification of residual tumor foci difficult and often requires the embedding of more tissue samples.

4.5.6.2. Microscopic processing and assessment

Bearbeitung:

- Bei Nachweis eines invasiven Karzinoms: spezielle Zusatzuntersuchungen (Hormonrezeptoren, HER2, Ki-67), falls nicht bereits an prätherapeutischer Stanzbiopsie erfolgt

Begutachtung:

- Dokumentiert werden die Angaben wie unter Chapter 5.5.2.3, evtl. unter Verwendung eines Formblattes (s. Chapter 12.3: Figure 11).

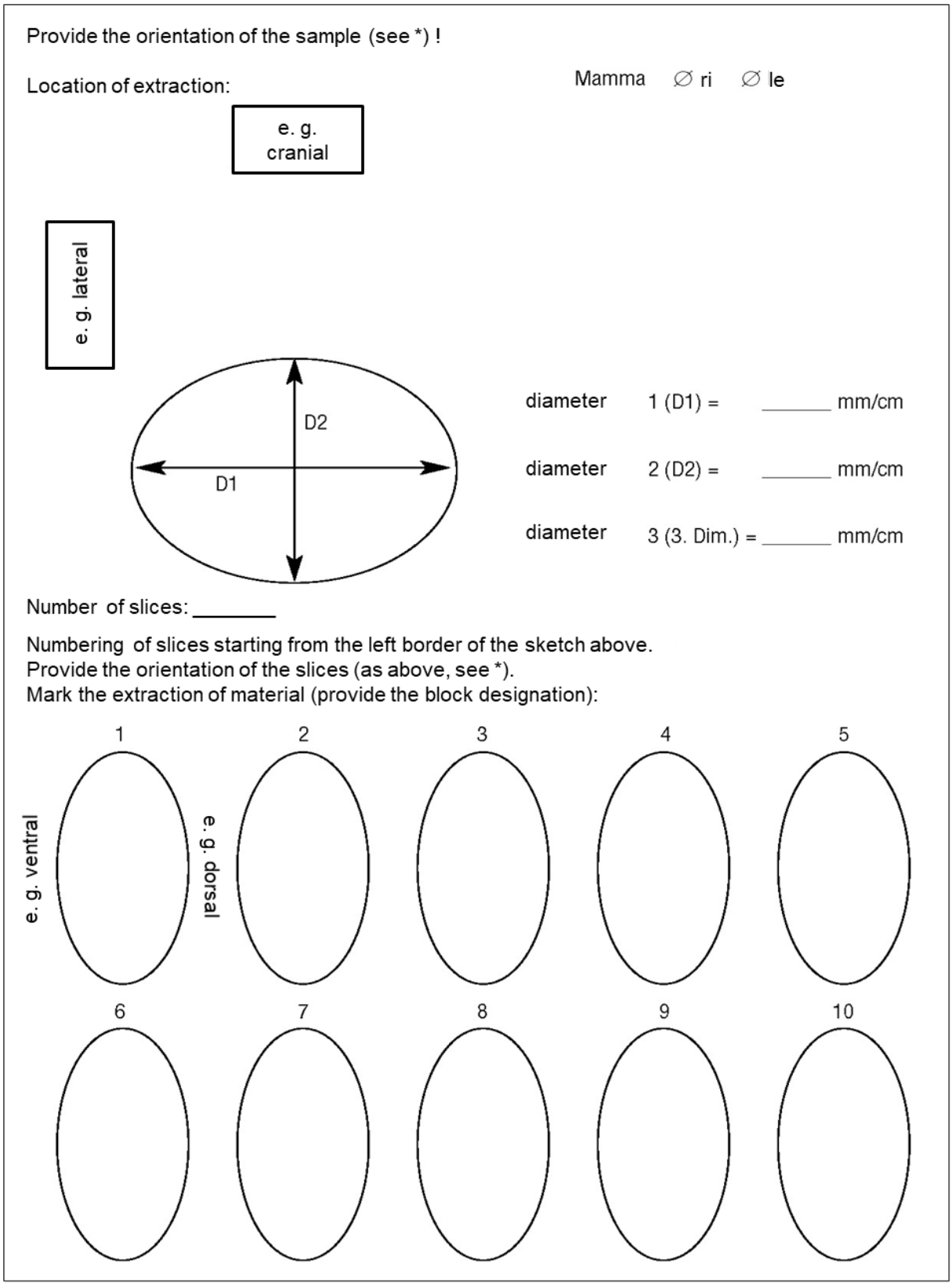


Figure 3: Sketch of tissue samples

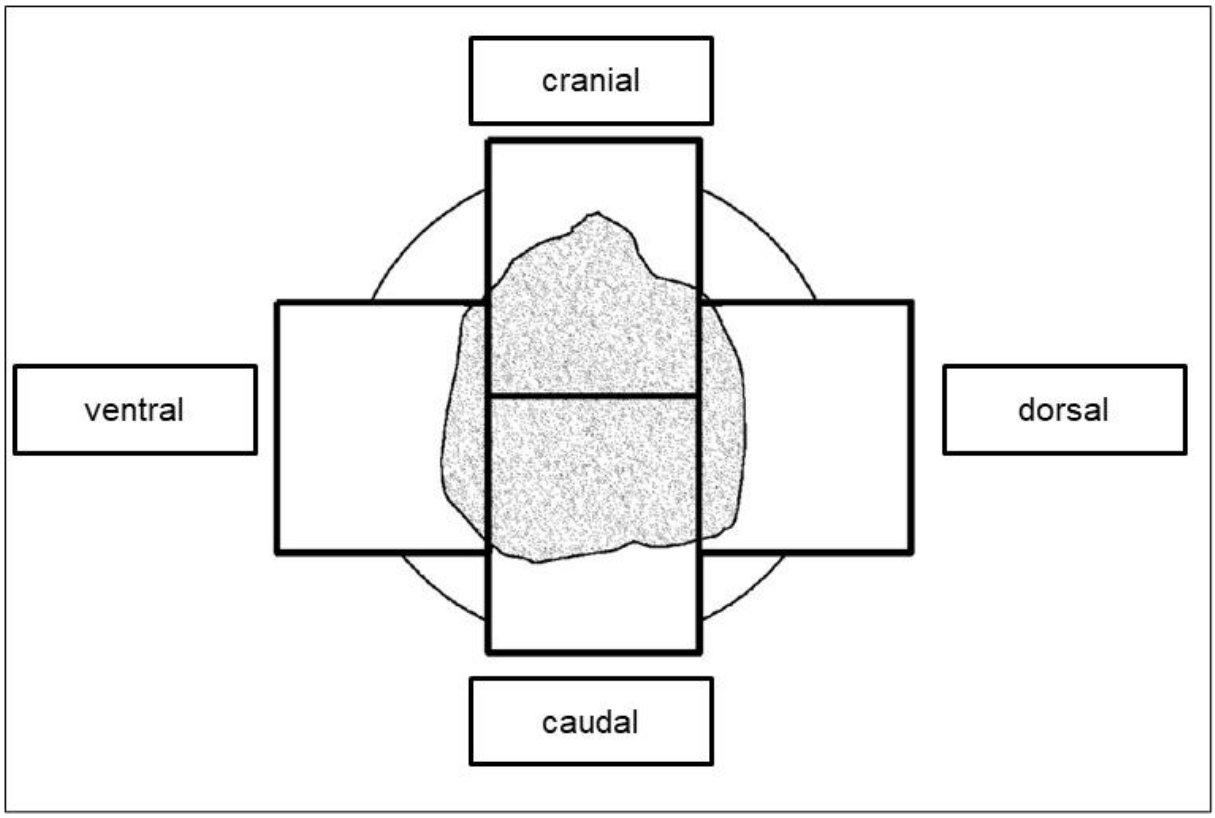


Figure 4: Tissue samples in patients with a palpable focal lesion

4.5.7. Mastectomy specimens

A mastectomy is usually performed after securing a carcinoma by interventional diagnostics or excisional biopsy. It leads to the final tumor classification and determination of the degree of differentiation with determination of the tumor extent; if necessary, identification of further changes.

In order to achieve a rapid fixation of the tissue, it is recommended to send the preparation to the pathologist immediately after the surgery in order to accelerate the tissue preservation by laminating the preparations.

Forms of mastectomy are the simple mastectomy, "skin-sparing" mastectomy, modified radical mastectomy according to Patey, radical mastectomy according to Rotter-Halstedt or extended mastectomy.

4.5.7.1. Macroscopic examination

Description:

- Mastectomy prep:
- Size (3 dimensions) and weight
- attached tissue (e.g. intact pectoralis fascia, pectoralis muscles, axillary fat tissue)
- Size and condition of the attached skin spindle, location of the nipple (e.g. central, eccentric)
- Orientation of the tissue sample (if performed by the surgeon)
- Location of a pre-biopsy/excision or tumor (quadrant, relation to the resection margins)

- Tumor:
- Size (3 dimensions)
- cut surface: boundary (sharp/unsharp), consistency, colour
- Reference to the resection margin
- other conspicuous findings (e.g. prosthesis capsule, fibrocystic changes)

Preparation:

- if necessary, staining of the preparation margin with ink or pigments to identify the resection margin
- Lamination of the preparation from lateral to medial in parallel slices of 5-10 mm thickness, with lamellae remaining in contact with the skin

Tissue samples are used for statements on:

- Nipple/submammary tissue
- Tumor (number of paraffin blocks depending on size)
- Pre-biopsy/excision cave margin (3-4 tissue samples in total)
- Resection margins
- other changes
- additional breast gland tissue from the 4 quadrants (at least 1 block each)
- special questions/additional examinations

If the mastectomy was performed because of a DCIS or if there were radiologically extensive microcalcifications, a preparation radiography of the tissue lamellae can be helpful in order to localize the changes precisely and to be able to carry out a targeted removal to determine the extent and reference to the resection edges.

4.5.7.2. Microscopic examination and assessment

The information is documented as in Chapter 5.5.2.3, possibly using a form (see Chapter 12.3: Figure 11).

4.5.8. Lymph nodes

4.85	**Consensus-based Recommendation**
EC	**Lymph node status** The lymph node status is determined by histological examination of all removed lymph nodes. The following assessments shall be obligatory: Number of removed and affected lymph nodes, extent of the largest tumour settlement, capsule rupture, pN category (according to TNM classification, 8th edition UICC 2017). The aim of the work-up is to detect all macrometastases (> 2.0 mm).
	Strong Consensus

Background 4.85

Sentinel lymph node biopsy (SLNB):

- Removal of the so-called sentinel lymph node (dye and/or radionuclide labeling).
- Nowadays common primary procedure for the determination of the nodal status. Prerequisite is compliance with the recommended quality criteria [577].

- The minimal aim of the histological examination is the detection of all macrometastases (> 2 mm) [427], [532]. Desirable, but not obligatory, is also the identification of micrometastases (> 0.2 mm and/or more than 200 tumor cells, but not larger than 2 mm). In the presence of micrometastases, it is to be expected that other lymph nodes will be affected in approx. 20 % of cases [578], and with a size of > 1 mm even in approx. 30 % of cases [579]. The histological examination of the SLN does not aim to detect isolated tumor cells (ITC). If ITCs are detected, their correct classification (see below) must be ensured.

Axillary lymphadenectomy:

- Nowadays only in exceptional cases primary surgical procedure to determine the lymph node status. Mostly for completion in case of affected SLN.
- The aim of the histological examination is to detect all macrometastases (> 2 mm).

4.5.8.1. Macroscopic examination

Description:

- Size (3 dimensions) and weight of the entire tissue sample (for axillary lymph node dissection)
- Orientation (if marked)
- Number of lymph nodes
- Dimension of the largest lymph node

Preparation:

- Careful examination of the fatty tissue for lymph nodes
- Histological examination of all contained lymph nodes
- In macroscopically affected and interconnected lymph nodes: Examination of a representative cross-section
- In case of macroscopically not clearly affected lymph nodes: complete embedding for histological examination
- If the size of the lymph nodes permits, they should be halved along the longitudinal axis or laminated in slices 2-3 mm thick

4.5.8.2. Microscopic examination and assessment

Processing:

- Sentinel lymph node [427], [577]:
- For macroscopically affected lymph nodes: one H&E incision per block
- In macroscopically not clearly affected lymph nodes: Cutting steps (distance /= 500 µm) H&E stained; number for reliable detection of all macrometastases depending on tissue thickness
- Immunohistochemical reactions with antibodies against cytokeratins are not recommended as standard procedures, but may be diagnostically helpful in individual cases (e.g. invasive lobular carcinoma)
- Axillary lymph node dissections:
- For macroscopically affected lymph nodes: one H&E cut per block
- In macroscopically not clearly affected lymph nodes: According to international guidelines one H&E incision is sufficient [427], [428]. However, depending on the thickness of the total blocked lymph node tissue, it is recommended to

make at least 2-3 incisions (distance 100-500 µm) to ensure the detection of all macrometastases (> 2 mm).

- Assessment:
- The following information is documented, possibly using a form (see Chapter 12.3: Figure 11):
- Type of tissue sample
- Page reference
- Number of lymph nodes examined (with localization, if marked)
- Number of lymph nodes affected
- Extent of the greatest metastatic infiltration
- Extranodal infiltration, if any
- pTNM stage (including additional tissue samples if necessary) (see Chapter 5.5.6 and Chapter 5.5.7)

Remarks:

- If the pathological classification is based on a sentinel lymph node examination, this is indicated by the suffix (sn), for example pN0(sn) [429].

The detection of isolated tumor cells (ITC) in regional lymph nodes is classified as pN0(i+). ITC are defined as single tumor cells or small clusters of cells not larger than 0.2 mm in the largest dimension. As an additional criterion it has been proposed to include a cluster of less than 200 cells (in a histological section) in this category [429].

4.6. Adjuvant radiothepary of breastc ancer

4.86	**Evidence-based Recommendation**
GoR **A**	After breast-conserving surgery due to invasive carcinoma, radiation of the affected breast shall be performed. For patients with clearly limited life expectancy (<10 years) and a small (pT1), node-negative (pN0), hormone receptor-positive HER2-negative tumor receiving endocrine adjuvant therapy, conditional upon free excision margins and taking an increased risk of local recurrence into account, radiation can be dispensed with after individual counselling. *Note for all recommendations: All individual items are "or" combinations. "And" links are represented by an "and".*
LoE **1a**	[580]; [581]; [582]; [583]; [584]; [585]; [586]; [587]
	Strong Consensus

Background 4.86

Postoperative radiation is the most important and effective measure to reduce the risk of intramammary recurrence; the effectiveness is proven with the highest evidence by numerous randomized studies and meta-analyses [580], [581] To date, no subgroup has been identified in randomized studies where there is no significant effect in terms of improving local tumor control. According to the current state of knowledge, the effectiveness of radiotherapy is also independent of tumor-specific or patient-related prognostic factors. In recent studies, in which the effectiveness of radiotherapy was examined in tumor subgroups defined by molecular biology or gene expression analyses, significant effects of radiotherapy were found in all subgroups [557]. Therefore, although it is possible to identify patient groups with a low risk of relapse, these patients also benefit from radiotherapy with regard to an optimization of local tumor control. Therefore, in contrast to the individualized indication of systemic therapies, predictive markers cannot be used to make a decision on radiotherapy after breast-conserving surgery.

In meta-analyses [580], [581] the radiation reduced the locoregional relapse rate as well as the rate of all relapses (locoregional and distal relapses). Although primary or adjuvant drug systemic therapies also increase locoregional tumor control, their effect is not sufficient to dispense with radiotherapy after breast-conserving surgery. If the relative risk reduction (i.e. the hazard ratio, similar to the evaluation of drug therapy procedures) is used as a measure of the effectiveness of radiotherapy, the effectiveness of radiotherapy on local tumour control has actually improved considerably in recent years. The hazard ratio in the meta-analyses, which mainly contain studies from the 1970s and 1980s, is about 0.35; of 10 possible recurrences without radiation, 6 to 7 were prevented by radiotherapy [581]. In more recent studies, hazard ratios of about 0.2 or even less are consistently reported, i.e. of 10 possible recurrences without radiation, 8 are prevented by radiotherapy [583], [584], [586]. This improvement in relative effectiveness can be explained radiobiologically well and is based essentially on standardized surgical techniques and improved pathohistological diagnostics (fewer

undetected R1 resections, thus less "tumor burden" with a higher success rate with standardized radiation dose).

The improved local tumor control leads to a reduction of breast cancer-specific mortality; this effect was confirmed in consecutive meta-analyses. In the last meta-analysis of the EBCTCG data [581] percutaneous radiotherapy leads to a reduction of disease-specific mortality in pN0 patients by 3.3% in absolute terms and by 8.5% in absolute terms in pN+ patients after 15 years. These effects have been proven for all age groups, but the benefit decreases in older patients [588].

The effect of radiotherapy of the breast on survival - since it is generated secondarily by optimizing local tumor control - is detectable only after a longer follow-up period and increases over time [581]. The greatest benefit of radiotherapy is achieved by patients in whom the risk of relapse is reduced by > 10% by adjuvant radiotherapy. Thus, statistically speaking, 4 local recurrences prevented within the first 10 years can prevent cancer-related deaths within 15 years [580], [581]. The positive effect on survival is lower in more recent studies with overall more favorable tumor stages or is not given in very favorable collectives in the first 10 years after therapy. Nevertheless, radiotherapy remains the most important measure to optimize local control. In more recent studies the risk for intramammary recurrence is lower than the risk for contralateral new carcinomas, so that a protective effect on new carcinomas is discussed [589].

Patients with low-risk tumors also benefit from adjuvant radiotherapy of the breast. The positive effect with regard to local tumor control is clearly documented in all randomized studies [583], [584], [586], [590], [591]. The most important risk factor for a local recurrence in the breast is also in these patients with very favorable tumors the renunciation of radiotherapy [584]. The risk for side effects was not different with and without radiotherapy; most of the side effects result from the adjuvant endocrine therapy [586]. Data from population-based analyses also show that the renunciation of radiotherapy in patients at an advanced age is associated with an increased mortality rate from breast cancer [592]. Radiotherapy of the breast should therefore also be the rule for these patients.

If adjuvant radiotherapy is used, the free resection margin plays a minor role; a R0 resection ("no ink on tumor") is sufficient from [362], [593]. Radiotherapy can therefore help to avoid unnecessary follow-up resections and limit the resection volume (a factor relevant for the final cosmetic outcome).

The risks of radiation therapy are low nowadays; radiation of the breast has the lowest risks of all therapy methods used in the adjuvant therapy of breast cancer. The risk of symptomatic pneumonitis is less than 1%. In older studies, increased cardiac mortality was found in patients with left-sided breast cancer and adjuvant radiotherapy; cardiac excess mortality correlated with the cardiac radiation dose [594]. In studies conducted after about 1990 (i.e. after the introduction of 3D conformational radiation), significant cardiac excess mortality was no longer detectable. In more recent studies, neither co-radiation of the regional lymph nodes nor combination with trastuzumab was observed to increase the risk of cardiac events [595], [596], [597], [598]. In addition, with Intensity Modulated Radio Therapy **(IMRT**) and Volu-Metric-Arc-Therapy **(VMAT**) modern therapy methods with sufficient Level Ib/IIa evidence are available today, which report lower acute skin reactions, late fibrosis and telangiectasia of the breast and thus better cosmetic results than after 3D-radiation. At the same time, effective protection of the lungs and heart is guaranteed. However, IMRT/VMAT should not be used generally, but should be limited to patients with larger breasts and/or abnormal chest curvature (e.g. funnel chest) [599], [600], [601], [602]. A further method by which the

radiation dose to the heart can be minimized to non-critical values even with left-sided radiation is radiation in controlled deep inspiration [603]. The risk for radiation-induced secondary malignancies is basically given with radiation application and amounted in the early studies (therapy before 1990) to about 1% after 20 years. However, more recent data from cancer registries (e.g. from the SEER database) show that only a small proportion (<10%) der nach Strahlentherapie auftretenden Zweitmalignome durch die Strahlentherapie bedingt ist [604], [605].

Fractionation

4.87	Evidence-based Recommendation
GoR **B/0**	Radiotherapy of the breast should be performed in hypofractionation (total dose approx. 40 Gy in approx. 15-16 fractions in approx. 3 to 5 weeks) or can be performed in conventional fractionation (total dose approx. 50 Gy in approx. 25-28 fractions in approx. 5-6 weeks).
LoE **1a**	[606]; [607]; [608]; [609]; [610]; [611]; [612]
	Consensus

Background 4.87

Until a few years ago, treatment with small single doses (daily 1.80 Gy to 2.00 Gy, so-called conventional fractionation) was considered the only sensible fractionation for curative therapy intentions. This applied to all tumours and was well justified from a radiobiological point of view. In the meantime, data are available from four large randomized studies with a total of more than 7000 patients, which have shown equally good results both in terms of tumor control and late toxicity with moderate hypofractionation (about half as many fractions as with conventional fractionation) in breast cancer [607], [608], [611], [612]. This surprising result is explained by an unexpectedly low α/β value of breast carcinomas, which according to more recent calculations is in the order of 3 to 3.5 Gy.

Hypofractionation means that the number of fractions is reduced; the individual dose increases, and the total dose is reduced according to radiobiological calculations. However, a distinction must be made between pure hypofractionation (the total treatment time remains the same, e.g. only every second day of radiation, e.g. START-A study) and accelerated hypofraction (the treatment time is shortened by daily radiation). From the data available so far, it can be concluded that moderate hypofractionation (15 to 16 fractions for breast radiation instead of 25 to 28 fractions for conventional fractionation) is well possible and can be combined with moderate acceleration (reduction of the total treatment time from 5-6 weeks to three weeks). These variants are well justified not only by studies but also by radiobiological model calculations.

It is unclear whether a further reduction in the number of fractions (extreme hypofractionation) or the treatment time (extreme acceleration) is possible. Two British studies (FAST and FAST-FORWARD) test these concepts [613]. So far, only data on acute toxicity are available, which (as expected) is not amplified [614]. The crucial questions of tumor control and late toxicity are expected to be answered from about 2020.

In summary, based on the data available, a moderate hypofractionation with moderate acceleration (i.e. about 15 to 16 fractions with radiation on workdays, total treatment time about 3 weeks) can be recommended for the follow-up radiation of the whole breast in breast cancer; a possibly indicated boost should be administered sequentially (after the hypofractionated radiation of the breast). The advantage of hypofractionation in comparison to conventional fractionation with the same local tumor control is a clear reduction in acute skin reactions and also a tendency to slightly lower late sequelae [607], [615]. A further advantage for the patients is the shortened treatment period of only 3 to 5 weeks in connection with hypofractionation. So far, there is no evidence that clinical or molecular biological factors can be used to identify subgroups which benefit from the use of a specific fractionation regime [616]. The recommendation for hypofractionation is therefore currently valid across the board for all adjuvant radiotherapy of the mammary gland without lymph drainage channels.

Exceptions concern patients with radiation of the lymphatic outflow pathways. These were underrepresented in the hypofractionation studies. Although the data available to date (in accordance with radiobiological models) do not show any increased late toxicity for this collective with significantly larger radiation volumes, the data situation is considered weak. Furthermore, an increased risk of late sequelae at the nerve plexus and with regard to the occurrence of lymphedema is possible [617] The late toxicity of hypofractionated regimens when irradiating also the regional lymph nodes is currently being investigated in large studies. In practice (outside of studies), conventional fractionation is therefore recommended as the fractionation of first choice when the lymph nodes are also irradiated.

4.88	**Evidence-based Recommendation**
GoR **A/B**	**Boost radiation** Local dose saturation (boost radiation) of the tumor bed lowers the local recurrence rate in the breast without providing a significant survival benefit. The boost radiation • shall therefore be used for all /= 50 year old patients and • should only be performed in > 51-year-old patients with an increased local risk of relapse (G3, HER2-positive, triple-negative, > T1).
LoE **1a**	[618]; [619]; [620]; [621]
	Strong Consensus

Background 4.88

A local dose saturation of the tumor bed (so-called boost) can further reduce the relapse rate after breast-conserving surgery. Data are available from two large randomized studies. Both studies compared radiation of the whole breast (dose 50 Gy) versus radiation of the breast with subsequent boost. In the French study the boost dose was 10 Gy [621]; in the larger EORTC study the boost dose was 16 Gy [619]. In both studies the risk of relapse was significantly reduced. Follow-up data from the larger EORTC study are available for 20 years, which were updated and published every 5 years; furthermore, several analyses of prognostic factors have been published from this study [366], [618], [619], [620], [622], [623], [624]. The benefit of the boost on local tumor control has remained stable over 20 years or even increased. Local control was also significantly improved for prognostically favorable subgroups; there is no

subgroup that does not benefit from a boost with respect to local tumor control. The relative risk reduction is similar in all subgroups; the absolute advantage is greater in younger patients with higher risk than in older patients with low-risk tumours. The rate of late complications (fibrosis grade 3 in boost volume) was low in the EORTC study and higher in older patients than in younger ones; therefore, the individual benefit-risk ratio (local control versus fibrosis) is very favourable in younger patients and decreases with age.

As a consequence of these data, a boost is strongly recommended and clearly indicated in all premenopausal patients as well as in postmenopausal patients with an increased risk of relapse or histological risk factors (G3, HER2-positive, tripelnegative, > T1) - Elderly patients with evidence of concomitant DCIS, affected lymph nodes, missing hormone receptors, lymph vessel invasion and after close R0 or R1 resection may also benefit from a boost. A boost is generally unnecessary in older patients without risk factors.

In the past, the boost was predominantly (e.g. in the EORTC study) applied with electrons with five to eight fractions following the radiation of the breast (so-called sequential boost). After the introduction of 3D radiation planning, techniques with photons have become standard. Alternative procedures are interstitial brachytherapy or a single intraoperative radiation (with KV-radiation or electron radiation). All procedures have advantages for certain clinical situations and limitations. However, there is no evidence to date that any of these procedures is clearly superior to others. For boost radiation, therefore, the procedures that are available locally and with which experience exists should be selected.

A new procedure is the simultaneous integrated boost (SIB) during external radiation. Here, the sequential boost dose of 10-16 Gy/5-8 fractions, which was previously administered after breast radiation, is divided into the number of fractions (25-28) required for breast radiation and integrated at the tumor bed as a simultaneous boost. The SIB has physical-technical and biological advantages (overdoses outside the boost volume are reduced) and leads to a reduction of the total treatment time by about 1 to 1.5 weeks depending on the amount of the boost dose [625], [626], [627]. A major disadvantage of the boost (namely the extension of the treatment time of the external radiation) is eliminated by the SIB. When using a SIB, the indication for boost radiation can therefore be set rather generously. The combination of conventional fractionation when irradiating the breast with SIB has been evaluated in large prospective non-randomized studies and is considered safe and effective [589], [628]. The combination of hypofractionation when irradiating the breast and SIB is still considered experimental. Several randomized studies worldwide are currently investigating this question (in Germany: HYPOSIB study).

Partial breast radiation and IORT

4.89	Evidence-based Recommendation
GoR **0**	Partial breast radiation alone (as an alternative to post-radiation of the entire breast) can be performed in patients with a low risk of recurrence.
LoE **1a**	[629]; [630]; [631]; [632]; [633]; [634]
	Strong Consensus

Background 4.89

An individual risk-based indication for adjuvant partial breast radiation (PBI (partial breast radiation) or APBI (accelerated partial breast radiation)) after complete tumor excision with breast preservation and limitation of the radiation volume to the tumor region can be performed in patients with a low (local) risk of recurrence.

The different concepts with different radiation qualities and technical procedures for partial breast radiation mostly correspond to those used in PBI as boost RT before or after radiation of the entire breast (WBI) [635], [636], [637], [638], [639], [640], [641], [642], [643], [644], [645], [646].

In multi-catheter brachytherapy, the applicator tubes can be placed during or even after the surgery. The same applies to balloon brachytherapy, in which the balloon is inserted into the wound cavity with a central brachytherapy catheter already during the surgery ("open cavity"), but also afterwards ("closed cavity"). Radiation is typically performed over a few days, sometimes several times a day (e.g. twice a day for 5 days).

Two prospective randomized studies with long follow-up times are available for multicatheter brachytherapy. The Budapest study [630] showed similar results with APBI and WBI up to 10 years after therapy, but this monoinstitutional study was closed early due to poor recruitment, so that it did not have enough power for the hypothesis of non-inferiority of APBI. Results from the randomized phase III study of the GEC-ESTRO group were recently published [633]. 1184 patients (> 40 years, tumor up to 3cm) were randomized between 2004 and 2009. The primary endpoint was ipsilateral local recurrence with a non-inferiority margin of 3% after 5 years. The 5-year recurrence rate was 0.9% for EBRT and 1.4% for APBI as the sole RT modality (p = 0.42). Overall survival was 95.6% for EBRT and 97.3% for APBI (p = 0.11).

The IORT as sole radiotherapy modality represents the extreme variant of the combination of hypofractionation and APBI and is performed immediately after surgical tumor extirpation as a single radiation treatment limited to the tumor resection cavity with application of a total dose considered curative to the expanded tumor bed. For an IORT, electrons of a linear accelerator (= IOERT), an orthovolt therapy with 50 kV X-rays of a miniature X-ray device or a balloon brachytherapy technique are used [636], [637], [640], [642], [647], [648]. Altogether, almost 5000 patients were randomized in two prospective randomized studies (TARGIT, ELIOT). Although the results of the studies available to date showed a slightly increased recurrence rate in the breast for the overall group of patients, local tumor control rates for certain subgroups of older patients with unifocal small breast cancer were comparable to those achievable with radiotherapy of the entire breast [631], [632], [649].

A monocentric study [650] randomized 520 patients over 40 years of age with tumors up to 2.5 cm for percutaneous APBI with 5 x 6 Gy as IMRT compared to conventional whole breast radiation. After a median follow-up of 5 years the local recurrence rate was 1.5% in both arms with a more favorable toxicity profile and better quality of life according to APBI [651].

A recently published meta-analysis [652] summarized all published prospective studies on APBI that had published survival data and could clearly show that there is by no means an inferiority of APBI in terms of overall survival after 5 years to whole breast radiation, whereby the studies essentially included older patients with small, clinically nodal-negative breast cancer. In terms of disease-free survival, APBI also does not appear inferior to whole breast radiation, although possibly increased local recurrence rates and reduced non-breast-cancer mortality seem to compensate.

Radiation treatment of parts of the breast (PBI) limited to the primary tumor area as the sole ("definitive") intra- or postoperative radiation treatment may also be an option for selected patients with a higher risk of local recurrence in whom homogeneous radiation of the entire breast is not feasible (e.g., patients with a high risk of localized tumor recurrence, patients with a high risk of localized tumor recurrence, patients with a high risk of localized tumor recurrence, patients with a high risk of localized tumor recurrence, patients with a high risk of localized tumor recurrence, patients with a high risk of localized tumor recurrence, patients with a high risk of localized tumor recurrence, patients with a high risk of localized tumor recurrence). e.g. pre-radiation, age, comorbidity) [28], [466], [629], [643], [653], [654].

Postmastectomy radiotherapy (PMRT)

4.90	Evidence-based Statement
ST	Postoperative radiotherapy of the chest wall after mastectomy reduces the risk of locoregional recurrence and improves overall survival in locally advanced and nodal-positive breast cancer.
LoE **1a**	[655]
	Strong Consensus

4.91	**Evidence-based Recommendation**
GoR **A**	Radiation therapy of the chest wall after mastectomy shall be indicated in the following situations • PT4, • pT3 pN0 R0 in the presence of risk factors (lymph vessel invasion (L1), grading G3, premenopausal, age < 50 years), • • R1-/R2-resection and lack of the possibility of a rehabilitative resection. a) In more than 3 affected axillary lymph nodes, postmastectomy radiation shall be performed regularly. b) In 1-3 axillary lymph nodes affected by tumours, post-mastectomy radiation shall be performed if there is an increased risk of recurrence (e.g. if HER2-positive, triple-negative, G3, L1, Ki-67 > 30%, > 25% of the removed lymph nodes are tumour-infected; age ≤ 45 years with additional risk factors such as medial tumor localization or tumor size > 2cm, or ER negative). c) PMRT shall be avoided in 1-3 tumour-infected axillary lymph nodes and tumours with a low risk of local recurrence (pT1, G1, ER-positive, HER2-negative, at least 3 characteristics must apply). d) For all other patients with 1-3 tumour-infected axillary lymph nodes, the individual indication shall be determined on an interdisciplinary basis.
LoE **1a**	[274]; [655]; [656]; [657]; [658]; [659]; [660]; [661]; [662]; [663]; [664]; [665]; [666]; [667]; [668]
	Consensus

Background 4.90 and 4.91

This update of the S3 guideline presents the current evidence on the indication for postmastectomy radiotherapy. Compared to the S3-Guideline version of 2012, the indication is more clearly differentiated according to risk constellations and, under certain circumstances, completely withdrawn. The authors emphasize that the indication for postoperative radiotherapy always includes information about possible treatment alternatives with all their consequences and is based on a clear "informed consent" of the patients. With a normal risk constellation, postoperative radiation of the chest wall and lymph drainage channels can be avoided after a mastectomy. There are, however, situations with a high risk of locoregional recurrence, in which adjuvant radiotherapy of the chest wall with possibly lymph drainage pathways is indispensable in view of the otherwise threatening high locoregional recurrence rates. Analogous to the situation after breast-conserving surgical therapy, postoperative radiotherapy also has a positive influence on local and regional tumour control after mastectomy and ultimately on tumour-specific and overall survival. The locoregional risk of relapse and the indication for postoperative radiotherapy correlate positively. The higher the risk of locoregional relapse, the higher the absolute improvement of locoregional tumor control and survival by postoperative radiotherapy. The high risk of relapse is defined as > 20% and the intermediate risk as 10-20% probability of a locoregional relapse.

A high risk of relapse exists for patients with T4 tumours, pT3 pN0 R0 with risk factors (lymph vessel invasion (L1), grading G3, premenopausal status, age

There is an intermediate risk of relapse for patients with T1 or T2 tumors with only 1-3 tumor-affected axillary lymph nodes with the simultaneous presence of other risk factors, such as grading G3, lymph vessel invasion (L1), intravascular tumor cell detection (V1), Ki-67 > 30%, > 25% of removed lymph nodes tumor-affected, age ≤ 45 years and medial tumor site.

There is a low risk of relapse for patients with 1-3 tumor-affected axillary lymph nodes if 3 of the 4 following factors are present simultaneously: pT1, G1, ER-positive, HER2-negative. For other patients with 1-3 tumour-infected lymph nodes, the individual indication must be determined on an interdisciplinary basis.

In general, the benefit of chest wall radiotherapy in patients with a high risk of locoregional relapse is assured and is recommended internationally in this situation. For patients with pN1 (1-3 LC) and intermediate risk, radiotherapy may have a survival benefit. For patients with pN0 and intermediate risk, the indication for radiotherapy after mastectomy is not secured due to pending data.

After primary (neoadjuvant) systemic therapy, the indication for radiotherapy of the chest wall, possibly including locoregional lymph drainage areas, continues to be based on the pre-therapeutic T-N category due to the lack of available RCTs, regardless of the extent of response to primary systemic therapy. In analogy to adjuvant radiotherapy after mastectomy, the indication for radiotherapy after neoadjuvant chemotherapy is also given in the case of histopathologically confirmed full remission (ypT0), although prospectively randomized phase III studies that could support this recommendation are currently lacking.

Postmastectomy radiotherapy after primary systemic therapy

4.92	Evidence-based Recommendation
GoR **A**	After primary (neoadjuvant) systemic therapy, the indication for postmastectomy radiotherapy shall be based on the pretherapeutic clinical stage; for pCR (ypT0 and ypN0), the indication shall be determined in the interdisciplinary tumour board depending on the risk profile.
LoE **1a**	[669]; [670]; [671]; [672]
	Strong Consensus

Background 4.92

The neoadjuvant systemic therapy aims to bring the tumour into remission. The degree of remission is on the one hand associated with the prognosis of the disease, on the other hand it could also have an influence on the local therapy [565]. The significance of adjuvant radiotherapy of the chest wall and the lymphatic outflow pathways within the neoadjuvant therapy concept is not clarified by evidence from randomized studies [673]. Data from retrospective observational studies mainly refer to the indication for postmastectomy radiation.

Under the hypothesis that the combination of all therapy modalities contributes to the survival benefit, the order in which the therapies are administered should be irrelevant. This would speak for the indication for radiotherapy after the initial stage [674], [675],

[676]. In view of the lack of randomized studies on this question, this will continue to be the standard, especially for *high-risk patients*. This is especially true for patients who have not achieved pathologically complete remission in the breast or axilla [677].

On the other hand the histopathologically proven complete remission after neoadjuvant therapy is a strong prognostic factor independent of the primary tumor biology. In cases of a pathologically complete remission in the tumor area as in the axilla, it seems obvious to reduce the extent of local adjuvant radiotherapy [678], [679]. However, data of randomized clinical studies are missing.

The indication for radiotherapy after neoadjuvant therapy is complicated by the fact that following national and international therapy recommendations the excision of the sentinel lymph node is preferred after neoadjuvant therapy [680], [681]. The pre-therapeutic information on axillary lymph node infiltratrion is lost in some cases. However, this concerns only a very small group of patients, because in the case of suspicious pretherapeutic findings the diagnosis should be histologically confirmed [680], [681]. A potential undertherapy would only exist in patients with mastectomy who had three or more clinically occult lymph node metastases, but which were no longer detectable in the posttherapeutic sentinel excision.

Breast-conserving therapy: Regardless of the response to neoadjuvant chemotherapy, radiotherapy of the breast within the framework of breast-conserving therapy is generally indicated [682].

Complete remission: In pathologically proven complete remission (ypT0/is ypN0), most patients undergo breast-conserving surgery. The indication for radiotherapy of the lymph drainage system is under discussion. Arguments for radiation of the lymphatic drainage system are preoperative nodal status (≥ 3 lymph nodes), estrogen receptor status (ER-negative), grading (G3), tumor size (T3), age (

A rule of thumb could be [663], [682], [683]:

1. in pathologically complete remission of primarily clinically positive lymph nodes (generally histologically confirmed by needle biopsy), radiotherapy of the lymphatic outflow pathways can be limited to the high-risk cases according to current guidelines (see footnote 4).
2. in patients with pathologically complete remission (ypT0/is ypN0) with primarily clinically negative lymph nodes, radiotherapy should be performed within the framework of BET as in the situation without neoadjuvant therapy (radiotherapy of the breast with standard tangent). This would correspond to the procedure of the ACOSOG Z0011 study [412].
3. no recommendation can be made for the rare situations in which a mastectomy has been performed and primarily no high-risk situation was present, but only the suspicion (cN1) or possibility (cN0) of axillary lymph node metastases.

No remission (non-pCR): It is generally agreed that there is an increased risk of relapse in the absence of remission of the primary tumor or axillary lymph nodes. The indication for postoperative radiotherapy (radiotherapy of the lymphatic outflow pathways and - in case of mastectomy - also of the chest wall) should be determined after the stage before the start of therapy and adapted to the current tumor development if necessary [663].

In inflammatory breast carcinoma (IBC) and primarily inoperable breast carcinoma the therapy concept basically consists of primary systemic therapy, mastectomy and radiation; a reduction of this concept is associated with a shorter mean survival time [684], [685]. Postoperative radiotherapy (PMRT) must therefore be considered

obligatory. Radiotherapy of the lymphatic outflow pathways in inflammatory breast carcinoma should be based on the original tumor stage.

In any case the indication and the radiation field should be discussed interdisciplinary and should be determined bindingly for all treatment partners.

Table 5: Indication algorithm for radiation therapy after neoadjuvant therapy

Pretherapeutic	Posttherapeutic	RT-BET[1]	PMRT[2]	RT-LAW[3]
Locally advanced	pCR / no pCR	yes	yes	yes
cT1/2 cN1+	ypT1+ or ypN1+ (no pCR)	yes	yes	yes
cT1/2 cN1+	ypT0/is ypN0	yes	At-risk cases[4]	
cT1/2 cN0 (Sonogr. obligato)	ypT0/is ypN0	yes	no	no

1 with classic tangent,

2 if a mastectomy was performed,

3 together with PMRT or RT because of BET

4 criteria for high risk of relapse:

- pN0 premenopausal, high risk: central or medial seat, and (G2-3 and ER/PgR negative)

- pN1a high risk: central or medial seat and (G2-3 or ER/PgR negative) or premenopausal, lateral seat and (G2-3 or ER/PgR negative)

Radiotherapy of the regional lymph nodes

4.93	Evidence-based Statement
ST	Adjuvant radiation of regional lymph drainage areas improves disease-free survival and overall survival in subgroups of patients.
LoE **1a**	[595]; [596]; [597]; [686]; [687]
	Consensus

Radiation of the supra-/infraclavicular lymph nodes

4.94	Evidence-based Recommendation
GoR **0**	Radiation of the supra-/infraclavicular lymph nodes can be performed in patients with pN0 or pN1mi in the following situation, provided that the following conditions are all met Premenopausal and central or medial seat and G2-3 and ER/PgR negative.
LoE **2a/ 2b**	[595]; [596]; [597]; [686]; [687]; [688]; [689]
	Consensus

4.95	Evidence-based Recommendation
GoR **B**	Radiation of supra-/infraclavicular lymph nodes should be performed in patients with 1-3 affected lymph nodes in the following situations: • central or medial seat and (G2-3 or ER/PgR negative) • premenopausal, lateral seat and (G2-3 or ER/PgR negative)
LoE **2a**	[595]; [596]; [597]; [686]; [687]; [688]; [689]
	Strong Consensus

4.96	Evidence-based Recommendation
GoR **A**	Radiation of supra-/infraclavicular lymph nodes shall generally be performed in patients with > 3 affected axillary lymph nodes.
LoE **2a**	[595]; [596]; [597]; [686]; [687]; [688]; [689]
	Strong Consensus

Radiation of the A. mammaria interna lymph nodes

4.97	Evidence-based Recommendation
GoR **0**	Radiation of the A. mammaria internal lymph nodes can be performed in axillary pN0 or axillary pN1mi patients in the following situation: Premenopausal and central or medial seat and G2-3 and ER/PgR negative
LoE **2b**	[595]; [596]; [597]; [686]; [687]

4.98	Evidence-based Recommendation
GoR **B**	Radiation of the A. mammaria interna lymph nodes should be performed in patients with 1-3 affected lymph nodes in the following situations: • central or medial seat and (G2-3 or ER/PgR negative) • premenopausal, lateral seat and (G2-3 or ER/PgR negative)
LoE **2b**	[595]; [596]; [597]; [686]; [687]
	Consensus

4.99	Evidence-based Recommendation
GoR **B**	Radiation of the A. mammaria interna lymph nodes should be performed in patients with > 3 affected axillary lymph nodes in the following situation: G2-3 or ER/PgR negative
LoE **2b**	[595]; [596]; [597]; [686]; [687]
	Consensus

4.100	Evidence-based Recommendation
GoR **B**	If there is evidence of infestation of the A. mammaria interna lymph nodes, these should be irradiated.
LoE **2b**	[595]; [596]; [597]; [686]; [687]; [688]; [689]
	Strong Consensus

4.101	Evidence-based Recommendation
GoR **A**	Radiation of the A. mammaria interna lymph nodes should be decided individually and interdisciplinarily in case of increased cardiac risk or therapy with trastuzumab.
LoE **4**	[690]; [691]
	Strong Consensus

Background 4.93 to 4.101

Adjuvant radiotherapy of supra- and infraclavicular and parasternal lymph nodes was investigated in 3 large randomized studies [595], [597], [686] and a population-based cohort study [596], [687] in more than 10,000 patients. In a meta-analysis of the 3 randomized studies, a consistent, statistically significant survival advantage for radiation [687] was demonstrated, which is also supported by the Danish cohort study [596]. The improvement in survival results from a reduced remote metastasis rate (HR = 0.84). The absolute survival advantage is 2-3% on average of all included patients after 10 years. In patients who received both chemotherapy and hormone therapy, the survival advantage was significantly higher in the EORTC study [595]. In the Canadian study [597], patients with hormone receptor negative tumors benefited the most from lymph drainage radiation. In both studies the supra- and infraclavicular as well as parasternal lymph nodes were irradiated either together or both regions were not irradiated. In contrast, radiation of the breast/breast wall was performed in all patients. In the French study [686] an advantage could only be shown for the subgroup of patients who also received adjuvant chemotherapy. In the Danish cohort study, the greatest benefit was found in the group of premenopausal patients and those with > 3 affected axillary lymph nodes. In the latter two studies, supra- and infraclavicular lymph drainage was irradiated in all patients and only the additional effect of irradiating parasternal lymph drainage was investigated. Although the patients included and the subgroups analysed were different in the studies, the results of all studies indicate that patients with an increased risk of distant metastasis have the greatest benefit from lymph drainage radiation. As HER2 status is not available in any of the trials, no conclusions can be drawn in this respect.

Fears that lymph drainage radiations more frequently lead to more late effects for the patients due to the significantly more extensive radiation volumes have not been confirmed. Although a significantly increased rate of low-grade radiogenic pneumonitis (grade I-II) was reported [595], [597], but not for higher-grade pneumonitis. In the Canadian study [597], lymphatic drainage radiation led to a 4% higher probability of grade II and III lymphedema of the arm (p 10 years). Studies [595], [686] have not observed an increased rate of cardiac late sequelae due to lymphatic drainage radiation. Whether the radiation of the parasternal lymph nodes after more than 10 years still induces a higher cardiac toxicity or whether more secondary tumors are induced by the higher load on the lungs cannot be conclusively assessed at present.

In the EORTC [595] and the French study [686], patients without axillary lymph node involvement could be treated with central or medial tumor site, and in the Canadian study [597] with an increased risk of relapse regardless of the location (>/= 5 cm tumor, >/= 2 cm tumor and

In the case of nodal-positive breast carcinomas, the advantage of additional lymph drainage radiation is not generally greater than in nodal-negative patients, but due to the higher number of cases, it is statistically more reliable. Especially in the Danish study [596], patients with > 3 affected axillary lymph nodes benefited significantly from lymph drainage radiation, whereas in 1-3 affected lymph nodes a clinically relevant advantage of lymph drainage radiation results only in premenopausal patients and higher grading (G2-3) [687]. The indications for radiation of the mammary internal lymph nodes differ from those of supra/infraclavicular lymph drainage only in so far that in case of proven lymph node infestation the mammary internal lymph nodes should be irradiated independently of other risk factors, predominantly based on the results of the Danish study [596]. The importance of radiation of only the mammaria internal lymph nodes without additional radiation of the supra/infraclavicular lymph nodes was not investigated in any study and therefore no recommendation could be made in this respect.

In summary, the benefit of lymph drainage radiation in patients with an increased risk of relapse clearly outweighs the risks. Since the currently available study results do not allow a good differentiation between the benefits of radiation of the supra- and infraclavicular lymph nodes and the benefits of radiation of the parasternal lymph nodes, the indication for lymph drainage radiation was largely seen as a package in the statements of the guideline. Isolated radiation of the supra- and infraclavicular lymph nodes is only recommended for a smaller proportion of patients, especially those with previous cardiac diseases and with additional adjuvant therapy with trastuzumab. If the radiation of the parasternal lymph nodes exceeds the typical dose loads on the heart and lungs [692], [693], which can be a problem especially with left-sided tumors, the benefits and risks of radiation therapy must be weighed individually and a waiver of parasternal radiation is a sensible option in these cases. In these cases a radiation with held breath in deep inspiration can often reduce the dose to heart and lungs in such a way that a low-risk radiation of the parasternal lymph nodes is possible after all [694].

Whether radiation of the supra- and infraclavicular lymph nodes alone without radiation of the parasternal lymph nodes in addition to radiation of the breast/breast wall leads to a survival advantage cannot be answered from randomized studies. However, in more than 3 affected axillary lymph nodes, the relapse rate in the supraclavicular lymph nodes is so high (approx. 17% [688]) that radiation of the supra- and infraclavicular lymph nodes is indicated for this reason alone. In patients with 1-3 affected axillary lymph nodes with additional risk factors, the supraclavicular relapse rate without radiotherapy is 9.6% (G2 with 2 positive lymph nodes or G3 with 1 positive lymph node) and 21% (G3 with 2-3 positive lymph nodes or G2 with 3 positive lymph nodes), respectively, and is also so high that radiation of the supra- and infraclavicular lymph nodes alone is also indicated [689].

Radiation of the axillary lymph nodes

4.102	Evidence-based Recommendation
GoR **A/0**	An extended axillary radiation can be performed in patients with 1-2 affected axillary sentinel lymph nodes, provided that no axillary dissection has been performed or no further local axillary therapy has been agreed upon (analogous to ACOSOG Z0011). The decision on the appropriate procedure shall be made on an interdisciplinary basis.
LoE **2b**	[406]; [695]; [696]; [697]
	Strong Consensus

Background 4,102

All radiation techniques used for homogeneous radiation of the entire breast lead to co-radiation of parts of the ipsilateral axillary lymph drainage area. The amount of this portion and the doses achieved there differ depending on the volume of the breast to be irradiated in Levels I and II and also depend on the individual positioning of the patient during the radiation treatment. The total doses resulting in these axilla portions are between 20 - 40 Gy for a standard 50 Gy CT of the entire breast and thus influence the rate of axillary recurrence [698].

If radiation of supra- and infraclavicular lymph nodes is performed, according to the current recommendations of ESTRO and RTOG the axillary lymph node level III is included in the clinical target volume [699], [700] and the radiation technique is chosen in such a way that there is no gap between the target volume for lymph drainage and the target volume for the breast/breast wall. Because of the positioning uncertainties in the shoulder region, a safety margin is added around the clinical target volumes to generate the planning target volumes. This ensures that the medial portion of Level II in particular is irradiated with the full dose. Consequently, in radiation therapy of the supra- and infraclavicular lymph nodes and the entire breast/breast wall, only the cranial portions of Level I and the lateral portions of Level II are not irradiated with the full dose. Radiation of the axilla is usually understood by the radiooncologist as an expansion of the target volume to include the lateral portions of level II and the cranial portion of level I according to the expansion in the ESTRO consensus [700].

Radiation of the entire axilla, also called "extended axillary radiation" in the statements, is only sensible if there is a high risk of infestation of these regions and no surgical removal has been performed. In the AMAROS study [695], patients were randomized to receive either axillary radiotherapy (50 Gy in 25 fractions in 5 weeks) or dissection of the axillary lymph nodes prior to axillary sentinel lymph node biopsy in the case of axillary lymph node involvement (n =1425). The majority of the included patients had 1-2 positive sentinel lymph nodes. The axillary relapse rate, DFS and overall survival after 5 and 10 years did not differ statistically and clinically significantly in both arms. The rate of arm edema of all degrees was significantly higher after axillary dissection (23% after 5 years) than after axillary radiotherapy (11% after 5 years).

In the Z0011 study [406], after breast-conserving surgery with 1-2 positive sentinel lymph nodes, either an axillary dissection was randomized to receive an axillary dissection or no targeted axillary therapy was performed. According to the protocol,

radiation of the breast was planned for all patients. Overall survival and DFS in the 856 evaluable patients were not significantly different after 5 years (p=0.24/p=0.14). According to this, a further axillary therapy can be dispensed with in 1-2 affected sentinel lymph nodes. However, the study shows a number of weaknesses: The study was closed prematurely before the planned number of patients was reached; 38% of the patients had only micrometastases; and the radiation techniques were only examined in a subgroup of 228 patients. Of these 228 patients, about 50% had a so-called high tangent to the radiation of the breast and another about 17% had radiation of the entire axilla, i.e. a considerable proportion of the patients had received partial or complete radiation of the axilla [697]. Consequently, there remains an uncertainty as to which patients with positive sentinel lymph nodes can be spared further axillary therapy by dissection or radiation therapy without risk. If more than 2 sentinel lymph nodes are affected and the axilla is not dissected, extended axillary radiation is clearly recommended. In 1-2 affected lymph nodes, the indication must be discussed in the interdisciplinary tumor board. If only micrometastases are present, further axillary therapy is not necessary. Since caked lymph nodes or lymph nodes with massive extracapsular tumor growth (ECE) were an exclusion criterion for treatment in the Z0011 study, the further procedure should also be coordinated interdisciplinarily in these cases. Although ECE is an independent negative prognostic factor for DFS and overall survival [701], the axillary relapse rate after axillary dissection without radiotherapy is low [696] and does not represent an indication for extended axillary radiotherapy. In the AMAROS study, ECE was not an exclusion criterion, although the results for patients with ECE were not reported separately. If there is no axillary dissection [702], extended axillary radiotherapy may be considered in these cases. Radiation therapy is to be considered if a residual tumor is detected in the axilla.

Dose and fractionation for radiation of the regional lymph drainage

4.103	**Consensus-based Recommendation**
EC	Radiotherapy of lymphatic drainage should be performed in conventional fractionation (1.8 Gy to 2.0 Gy 5 times a week, total dose approx. 50 Gy in approx. 5-6 weeks) or can be performed in hypofractionation (total dose approx. 40 Gy in approx. 15-16 fractions in approx. 3 to 5 weeks).
	Strong Consensus

Background 4,103

All studies on radiation of the lymphatic drainage system were carried out in conventional fractionation with 5x2 Gy per week up to a total dose of 50 Gy. In the studies on hypofractionated radiotherapy of the breast or breast wall, less than

Radiotherapy for locally advanced tumours and primary inoperability

4.104	Evidence-based Recommendation
GoR **A**	Patients with primarily inoperable or inflammatory carcinomas shall receive primary systemic therapy followed by surgery and postoperative radiotherapy, or if inoperability of sole or preoperative radiotherapy persists.
LoE **1b**	[703]; [704]
	Strong Consensus

Background 4,104

Locally advanced breast cancer (LABC) describes a group of tumors that combine two criteria: 1. primary resection is not possible or is not considered appropriate. 2. neoadjuvant therapy is primarily considered.

Hagensen and Stout first coined the term "locally advanced breast cancer" in 1943 and established diagnostic criteria which today roughly correspond to stages IIIA and B: Lymphedema of the skin, satellite lesions, inflammatory carcinoma, non-mobilizable lymph node metastases. In practice, the following criteria, of which at least one must be fulfilled, have become established for the definition of "locally advanced": tumours > 5 cm (T3), skin or chest wall infiltrations (T4a, T4b), inflammatory carcinomas (T4c), fixed axillary lymph node conglomerates (cN2) or infraclavicular lymph node metastases (cN3). The term "inflammatory carcinoma" also has a vague definition. It is a clinical-pathological entity in which there is a tumor-associated inflammation of at least part of the skin with the classic sign of inflammation.

The initiation of primary systemic therapy is considered the standard of care for patients with locally advanced breast cancer and inflammatory carcinoma as well as for patients with distant metastases. The response to neoadjuvant chemotherapy (NAC), in particular the achievement of pathological complete remission (pCR), has been shown to be a favourable prognostic marker associated with improved survival. Randomized clinical studies focused on the further development of effective systemic therapies, with radiotherapy usually being an integral part of these studies, as its importance for locoregional tumor control was undisputed. Here, the scientific field has changed to the extent that the significance of radiotherapy in the case of complete remission after mastectomy is being questioned.

The neoadjuvant therapy concept with systemic therapy for LABC used today was first described in the late 1970s by De Lena [705]. By neoadjuvant chemotherapy often a reduction of tumor size and inflammatory components could be achieved. Furthermore, a down-staging of the axillary lymph node involvement and thus a secondary surgical therapy could be enabled. Neoadjuvant therapy concepts with a multimodal approach have therefore long been accepted as standard treatment for primarily inoperable LABC. If no invasive and non-invasive tumour cells are detectable in breast tissue and axillary lymph nodes after neoadjuvant therapy, this is referred to as pathologically complete remission (pCR). In the NSABP-18 study as well as in other studies, a close correlation was found between the response of the primary tumour and the long-term prognosis. Patients who had a histopathological complete remission (pCR) had a significantly better disease-free survival than patients with only partial remission. This

led to the fact that pCR serves as an early surrogate marker for survival and therefore different neoadjuvant therapy regimes can be compared against each other.

Careful examination of the local tumor extent with lymph node determination as well as good staging examinations are essential for the determination of the therapeutic concept, since the pre-therapeutic disease extent influences the type of surgery and the radiotherapy.

In 1971, EORTC's phase III study for the treatment of locally advanced and inflammatory breast cancer was published. A total of 410 patients were randomized to receive either radiotherapy alone, radiotherapy plus chemotherapy (CMF), radiotherapy combined with tamoxifen, or radiotherapy combined with tamoxifen and CMF. The surgery was not a planned part of the treatment sequence, but was reserved as a "salvage measure" in case of local recurrence. With radiotherapy alone, a 10-year overall survival of 13% and a distant metastasis-free survival of 15% was achieved, which was considered an indication of curative potential. As expected, the addition of chemo- or hormone therapy led to a significant increase in the time to local recurrence, to distant metastasis or to an improvement in overall survival. With the combination treatment the greatest therapeutic effect could be achieved. The 10-year overall survival could be improved by 8-15% by the addition of the systemic therapy.

In the following years, the systemic therapy could be improved by the addition of anthracyclines and taxanes within the framework of corresponding studies, with a gradual improvement in 5-year overall survival for LABC of approx. 70% and 40% for inflammatory breast carcinomas, respectively. Radiation after mastectomy (in case of resectability) after neoadjuvant chemotherapy was performed in the majority of patients. Here, too, it was shown that patients with pCR during mastectomy had substantially better overall survival than patients with partial response or residual tumour. This supported the use of the pCR rate as a surrogate marker of overall survival for future treatment concepts. However, the subgroup analyses also showed that the pCR rate was determined to a greater extent by the biology of the tumours than by the chosen chemotherapy regimen.

Regardless of the response to the neoadjuvant therapy, the question arose to what extent additional local treatments would improve the results. Randomized studies on the necessity of surgery and radiotherapy in this situation are not available. Radiation therapy is usually recommended for persistent resectability after NAC. Resectability should then be re-examined approximately 6-12 weeks after completion of radiation.

In stage III patients with resectable tumors after neoadjuvant chemotherapy (NAC), the effect of surgery and radiotherapy was investigated in three small randomized trials. Patients undergoing neoadjuvant chemotherapy (in two studies with anthracyclines, in one study with CMF) were randomized to undergo either mastectomy or radiotherapy. Overall survival, disease-free survival and locoregional tumour control were comparable between both local therapies. However, the local relapse rate after 2-5 years was in the order of 40-60%, regardless of whether surgery or radiation was performed. Finally, an indirect indication that patients should be operated and irradiated in order to reduce the local recurrence rates. In none of these studies was the response rate after neoadjuvant therapy documented. In this respect, the question remains open as to the extent to which surgery **and** radiation therapy are required after complete remission after neoadjuvant chemotherapy.

The challenge for radiotherapy lies in the decision which patients after NAC followed by mastectomy will benefit from post-mastectomy radiotherapy (PMRT). Ultimately, this decision is subject to numerous (additional) influences. At present, the current data situation tends to favour an extension of the indication for PMRT to nodal positive

carcinomas with low lymph node involvement (1-3 positive lymph nodes). The addition of different systemic therapies has increased the rate of patients with complete remission after NAC. It could be shown that a ypN0 status after neoadjuvant chemotherapy was associated with a low risk of locoregional recurrence, even without the use of PMRT.

The role of PMRT was finally substantiated in the two large studies of the Danish Breast Cooperative Group (DBCG) and the so-called British Columbia Trial. In the DBCG study 82 b and c [667], [668] as well as in the so-called British Columbia Clinical Trail [706], more than 3500 women were randomized in the period 1979-1990, either in favor of PMRT or only follow-up after surgery and systemic therapy. Systemic therapy in these studies included either CMF or Tamoxifen. More than 90% of these patients in these studies had positive lymph node metastases (pN+). These studies showed a substantial decrease in the long-term locoregional recurrence rate, which was also reflected in improved breast cancer-specific and overall survival. Based on these results, PMRT is ultimately recommended without restriction for patients with ≥ 4 pathologically affected lymph nodes or patients in stage III.

Two smaller studies investigated the significance of surgery after radiotherapy (after neoadjuvant chemotherapy):

Merajver et al. [707] initially treated 90 patients in stage III with 9 cycles of an anthracycline-containing neoadjuvant chemotherapy. After the last cycle the initial tumor region was biopsied again. In case of complete remission patients received radiotherapy of the thoracic wall and regional lymph node stations without surgery. Patients with residual tumor as part of the biopsy received a mastectomy followed by radiotherapy at the same dosage. Renouncing surgery in patients with pCR was not associated with a higher local recurrence rate, which was about 20% after five years of follow-up.

Ring et al [708] (n=136) and Daveau et al [709] (n=165) extracted from their prospective data collections the treatment results of stage III patients with complete remission after neoadjuvant chemotherapy who had received radiotherapy but no surgery. These were compared to patients with pCR after chemotherapy, who had received a mastectomy including postoperative radiation. The treatment results regarding overall survival, disease-free survival and distant metastasis-free survival were almost identical. A trend towards improved locoregional tumor control was observed in patients who received both surgery and radiation. Even in the absence of evidence, surgery is ultimately recommended after neoadjuvant systemic therapy regardless of response, if complete resection seems possible.

The determination of the type of surgical procedure following neoadjuvant chemotherapy (NAC) is complex and not standardised. There are no defined criteria according to which breast-conserving therapy (BET) may/can be sought for patients after NAC and for which a mastectomy offers more safety. Due to the high local recurrence rate, mastectomy with axilla clearance is generally recommended for primarily inoperable LABC and inflammatory tumours, even if good remission is achieved after preoperative therapy. In the case of "large operable" tumours, the primary goal is to operate in a breast-conserving manner. The pattern of tumour reduction also influences the further surgical procedure. If there is concentric shrinkage to a single tumour node, it may also be possible to remove it completely by BET.

There are two retrospective studies on the extent to which radiotherapy is required after mastectomy, especially in cases of complete pathological remission:

Huang et al. [710] examined the clinical outcome of 670 breast cancer patients who had received six different neoadjuvant chemotherapy regimens in clinical trials after mastectomy and axilla dissection. Of these patients, 134 did not receive PMRT, while 542 patients received radiotherapy after mastectomy. The patients had been treated between 1974 and 2000, with a median follow-up of 69 months. As expected, a selection bias was found in the non-randomised comparison, with significantly higher T and N stages among the patients who were irradiated: In the PMRT cohort 83% of the women represented stage III (-IV) compared to only 50% in the cohort that did not receive radiation. The pCR rate after neoadjuvant chemotherapy was 14% in the PMRT arm versus 6% without radiation. Overall, the 10-year local recurrence rate was 11% for women receiving PMRT versus 22% without radiation (p=0.0001) and overall survival was also better with radiation therapy. In a subgroup of 46 patients in clinical stage III (-IV) (35 received PMRT, 11 were not irradiated), who each achieved complete remission after neoadjuvant chemotherapy, the 10-year local recurrence rate was 3% with radiotherapy (PMRT) compared to 33% without PMRT (p=0.0006).

In the multivariate analysis regarding the factors associated with local recurrence, the most significant factor was found to be the decision not to undergo postmastectomy radiotherapy (PMRT) (HR 4.7; 95% CI: 2.7-8.1). Other factors were ≥ 20% pathological lymph nodes involved according to NICE, clinical stage ≥ I IIB, no tamoxifen, and hormone receptor negative status. Overall cancer-specific survival after 10 years was comparable in both treatment groups: 58% versus 55%. However, the univariate analysis showed an improvement in disease-specific survival for the subgroup of patients with PMRT, including those with clinical stage ≥ IIIB, cN2-N3 status and stage ≥ IV pathological lymph nodes.

In another publication McGuire et al. [674] identified 106 patients in stage II-III who had been treated with neoadjuvant chemotherapy (92% anthracycline-based chemotherapy, 38% with taxanes) and mastectomy between 1982 and 2002 and who had pCR at the time of surgery. Of these, 34 patients received PMRT, compared to 72 patients who did not receive radiation. Overall, the 10-year local recurrence rate did not differ between the PMRT and non-PMRT group (5% versus 10%, p=0.4), probably most influenced by the 0% 10-year recurrence rate of the 32 patients in clinical stage I-II. In contrast, PMRT led to a significant decrease in the 10-year local recurrence rate for the 74 patients in stage III (7% versus 33%, p=0.04). Overall survival was also significantly improved for stage III patients who received PMRT (77.3% vs. 33.3%, p=0.002). Consequently, the authors concluded that PMRT should be performed in stage III patients who had achieved complete pathologic remission after neoadjuvant chemotherapy.

From this database, further specific subgroups were retrospectively analysed. Garg et al. [711] analysed the effect of radiotherapy on 107 younger patients (younger than 35 years) in stage IIA-IIIC treated with neoadjuvant chemotherapy and mastectomy with PMRT (n = 80) or without PMRT (n = 20) in the period 1975 to 2005. 84% of stage III patients received PMRT compared to 42% who did not receive any. The pCR rate was 19% in the PMRT group versus 1% in the non-irradiated group. As documented in the preliminary analysis (Huang et al.), PMRT significantly improved locoregional control (88% versus 63%) and overall survival (67% versus 48%) in this subgroup of young patients.

Nagar et al. [675] reported on 162 women in clinical stage T3 N0 treated from 1985-2004 after neoadjuvant chemotherapy followed by mastectomy and PMRT (n =119) or no PMRT (n = 43). The 5-year local recurrence rate was 9%, but was significantly higher in patients who had not received PMRT (24% versus 4%, p

In summary, these study results show that women in clinically advanced stage III (especially those with cN2-N3 involvement and with ypN+ lymph nodes that were still affected at the time of surgery) are at the highest local recurrence risk after neoadjuvant chemotherapy and mastectomy. The risk of local recurrence seems to be significantly lower for patients in clinical T3N0 stage, especially with a ypN0 status at the time of surgery.

Locoregional radiation in patients with synchronous metastasis

Locoregional radiation is currently being investigated in the oligometastasis concept together with other tumor entities in various ongoing studies, without any reliable results so far. Radiation therapy can certainly contribute to symptom relief, but the influence on survival is inconsistent in the retrospective data. Some retrospective analyses document improved survival for both surgery and radiotherapy, but in some cases there is no influence from local therapy.

By Badwe et al. [712] the data of the randomized study from India were finally published in 2015. Untreated patients with "de novo" metastasis were randomized to surgical local therapy followed by radiation (n =173) vs. no local therapy (n =177) or chemo-/hormone therapy alone [712]. Median overall survival was 19.2 months with local therapy vs. 20.5 months without local therapy (p = 0.79). Therefore, local therapy is not recommended as standard for initial metastasis. However, this negative result does not exclude a possible benefit for subgroups. A second randomized study on the same issue was initiated in Turkey. Results have so far only been published in abstract form at congresses. For the endpoint overall survival no benefit for local therapy was seen in this data collective: after 54 months 35% with local therapy vs. 31% without local therapy. However, subgroup analyses (HR+, patients

Therapy sequence of adjuvant systemic therapy and radiotherapy

4.105	Evidence-based Recommendation
GoR **A**	Postoperative chemotherapy and radiotherapy shall be sequential. Note: the superiority of a specific sequence (first chemotherapy or first radiotherapy) is not proven. In clinical practice, the sequence of chemotherapy followed by radiotherapy has become established.
LoE **1b**	[713]; [714]; [715]; [716]
	Strong Consensus

4.106	Evidence-based Recommendation
GoR **B**	In the case of single RT, this should be initiated postoperatively within an 8-week period.
LoE **2b**	[717]; [718]
	Strong Consensus

4.107	**Evidence-based Recommendation**
GoR **0**	Adjuvant endocrine therapy can be initiated independently of radiotherapy. (1a) A therapy with trastuzumab can be continued during radiotherapy. In the case of simultaneous A. mammaria lymph node radiation, the procedure should be determined on an interdisciplinary basis. (4)
LoE **1a** **4**	[598]; [690]; [691]; [719]
	Strong Consensus

Background 4.105 to 4.107

So far, there is no evidence that a specific sequence of radiotherapy and drug therapy is clearly superior in the adjuvant situation. In principle, both drug therapy and radiotherapy should be started as early as possible and not unnecessarily delayed [677], [720], [721].

Antihormonal therapy can be carried out independently of radiotherapy (even simultaneously); this has now been proven by randomized studies [719], [722], [723], [724], [725], [726]. If only endocrine therapy (without chemotherapy) and radiotherapy are indicated, radiotherapy should therefore normally be started within 4 to 6 weeks after surgery; anti-hormonal therapy can be started before, during or even shortly after radiotherapy. A delayed start of radiotherapy (time interval between surgery and the start of radiotherapy 8 - 12 weeks) may not be disadvantageous; in the case of justified delays (e.g. intercurrent diseases) a longer time interval can be accepted. However, unnecessary delays should be avoided.

A sequential approach is recommended for the combination of chemotherapy and radiotherapy (first chemotherapy, then radiotherapy or vice versa); randomized studies and meta-analyses showed no advantage for a specific temporal sequence [713], [714], [715], [716]. The sequence of the therapeutic procedures should take into account the dominant individual risk of recurrence (systemic or locoregional) and be determined on an interdisciplinary basis. In most cases chemotherapy is performed first and then (usually within 2 to 4 weeks after the last course of chemotherapy) radiation therapy is followed by [727]. This is particularly useful for patients with a high systemic risk of relapse. In the case of very long adjuvant therapy regimens, this can result in a time interval of about 6 months up to a maximum between surgery and the start of radiotherapy. Fears that this long delay in radiotherapy (which is considered to be clearly disadvantageous in the case of radiotherapy alone without chemotherapy) could be associated with a reduced effect of radiotherapy and an increased locoregional relapse rate have not been confirmed. However, if the planned chemotherapy cannot be started postoperatively within the usual time frame for individual reasons, radiotherapy should be brought forward if necessary. This should be discussed in particular when using hypofractioned radiotherapy regimens.

A therapy with targeted drugs for HER2-positive tumours can be continued during radiotherapy. All studies show no increased toxicity or increased rate of cardiac events, not even with left-sided radiotherapy [728]. However, there is very little data concerning the combination of trastuzumab and simultaneous radiotherapy of the left parasternal

lymph nodes; in these cases indication and therapy sequence should be determined interdisciplinary.

4.7. Systemic adjuvant therapy (endocrine, chemo-, antibody therapy)

4.7.1. Selection of adjuvant therapy and risk assessment

The recommendations for adjuvant therapy of breast cancer consider tumor size, lymph node status, grading, hormone receptor status, HER2 status, menopause status and age as the most important factors in deciding on the necessity and type of adjuvant therapy [367], [529].

The St. Gallen recommendations of 2009 point to endocrine sensitivity and the recommendations of 2011 to molecular subtypes as decisive criteria for the indication of adjuvant chemotherapy [529]. The immunohistochemically determined markers ER, PgR, HER2 and Ki-67 [529] are considered as surrogate parameters for the molecular subtypes. ER- and/or PgR-positive, HER2-negative tumours with a low proliferation rate are considered to be Luminal A, while Luminal B is these tumours with a high proliferation rate. It must be taken into account that there is no validated threshold value for Ki-67 (e.g. for the classification of Luminal A vs. B or for the decision for/against adjuvant chemotherapy).

Indications for adjuvant chemotherapy are

- In HER2-positive tumors, simultaneous anti-HER2 therapy with trastuzumab for 1 year in combination with (neo)adjuvant chemotherapy is standard
- for endocrine non-sensitive tumours (ER- and PgR-negative)
- for endocrine sensitive tumours
- in the case of nodal-positive tumours (studies are currently evaluating whether adjuvant chemotherapy can be dispensed with in patients with low nodal infestation (1-3 affected LK) and favourable tumour biology (Luminal A))
- G 3
- young age of disease (

Chemotherapy is always indicated when the individual expected benefit is higher than possible side effects and late damage. This requires a differentiated education of the patients, especially if the expected benefit is only small.

4.7.2. Endocrine therapy

Indications for endocrine therapy

4.108	Evidence-based Recommendation
GoR **A**	Patients with estrogen- and/or progesterone receptor-positive (˚) invasive tumors shall receive endocrine therapy. ˚ (>/=10% progesterone receptor-positive tumor cell nuclei)
LoE **1a**	[28]; [729]; [730]; [731]; [732]
	Strong Consensus

4.109	Evidence-based Recommendation
GoR **A**	Endocrine therapy shall not be started until after completion of chemotherapy, but can be done in parallel with radiotherapy.
LoE **1a**	[28]; [585]; [729]; [730]; [731]; [732]
	Strong Consensus

Background 4.108 and 4.109

Adjuvant endocrine therapies such as tamoxifen and aromatase inhibitors significantly reduce the probability of a relapse by about 40% and the probability of death by about 30% [234], [367], [730], [734].

This relative risk reduction is independent of the age of the patient, the tumor stage and the pre-therapy like adjuvant chemotherapy, but always refers to women with hormone receptor-positive breast cancer.

These favorable effects of endocrine therapy are only realized with sufficient adherence to therapy. But only about half of the women with breast cancer carry out this treatment over the recommended 5 years. This lack of compliance is associated with a significantly increased risk of death. It is important to convince patients of the necessity of therapy, to raise awareness of side effects and of symptoms that occur independent of therapy by means of careful anamnesis and to treat them adequately. In the case of serious side effects that jeopardise the adherence to therapy, a switch from aromatase inhibitors to tamoxifen and vice versa or between aromatase inhibitors (steroidal vs. non-steroidal) can be considered in postmenopausal patients. If these measures succeed in increasing adherence to therapy, this may save more lives than additional chemotherapy.

In some analyses ([733] N=251) the group of patients with a weakly ER-positive breast carcinoma (1-9% stained tumor cell nuclei) behaves prognostically more like receptor-negative patients and shows (examined on smaller numbers of patients, N=26) similar molecular characteristics to triple-negative breast carcinomas on [473], [474]. In a

study of 314 patients with a low ER staining (1-9%), they showed a similar frequency of BRCA-1 mutations as ER-negative patients [476].

Since this group of patients (1-9% positive ER) obviously behaves prognostically differently than those with an ER-positivity of > 10% [735], an additional adjuvant or neoadjuvant chemotherapy should be considered.

Carcinomas with a weak PR staining (<10%) und negativen ER-Färbung könnten molekular dem triple-negativen Mammakarzinom entsprechen [736], [737]. Diese Daten werden unterstützt durch die EBCTCG-Analyse von 2008 "Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer", in der nachgewiesen wurde, dass Tamoxifen nur einen geringen Effekt auf die Rezidivrate und das Überleben bei Patientinnen mit einer schwachen Östrogenrezeptor-Expression hatte und einen nur geringen zusätzlichen Effekt zur adjuvanten Chemotherapie.

Data from some studies (such as Tam-02, [738], [739]) indicate that a later start (up to 5 years after completion of local therapy and/or chemotherapy) with adjuvant endocrine therapy is better than dispensing with this endocrine therapy altogether. This later start of endocrine therapy also prolonged DFS and OS or DDFS. The MA.17 study [740], which also allowed a longer therapy-free interval between tamoxifen and letrozole, showed similar results. These are indications that in case of side effects a therapy break is preferable to a general discontinuation.

Endocrine therapy

4.110	Evidence-based Recommendation
GoR A/B	After 5 years of tamoxifen, the indication for extended endocrine therapy shall be evaluated for each patient with ER+ breast cancer. Indications should be based on the weighing of the risk of relapse and the therapy-associated side effects (toxicity, reduced adherence). The current menopausal status of the patient shall be taken into account when choosing endocrine therapy.
LoE 1a	[741]
	Strong Consensus

Background 4,110

Endocrine adjuvant treatment of early breast cancer is one of the most effective therapeutic options. Recent publications prove this for a time interval of up to 15 years. A distinction was made between initial adjuvant therapy (IAT, years 0-5) and extended adjuvant therapy (EAT: years 6-10).

The therapy-associated side effect rate of these continuous therapies reduces therapy adherence and leads to a loss of effectiveness. Therefore, studies should be conducted to determine whether intermittent adjuvant endocrine therapy could be as effective as EAT.

Currently, there is a lack of reliable diagnostic tools to reliably predict the risk of late metastasis (after year 5) for such an intervention. To this end, multi-gene assays, for example, could be prospectively evaluated in studies.

After 5 years of tamoxifen, a further 5 years of adjuvant tamoxifen reduces the recurrence rate (-2.8% in absolute terms in the ATLAS study) and prolongs overall survival (-2.48% in absolute terms in the ATLAS study, [742], [743], [744]) in patients with hormone receptor-positive breast carcinomas, regardless of menopausal status (however, only 9% of patients in the ATLAS study were premenopausal). The incidence of pulmonary embolism and endometrial carcinoma was significantly increased after 10 years of tamoxifen compared to 5 years of tamoxifen without effect on mortality. Ischemic heart disease and myocardial infarction were significantly less common after 10 years than after 5 years of tamoxifen.

If the patients became postmenopausal after 5 years of adjuvant tamoxifen, the subsequent administration of letrozole for 5 years adjuvant improved DFS and OS, especially in women who were premenopausal before letrozole or had lymph node metastases [740]. Approved for this EAT in Germany after 5 years of tamoxifen are tamoxifen and letrozole.

Therapy for premenopausal patients

4.111	**Evidence-based Recommendation**
GoR **A**	Premenopausal patients shall be treated with tamoxifen for at least 5 years. Antiestrogenic therapy with tamoxifen 20 mg per day shall be carried out over a period of 5 - 10 years or until relapse, depending on the risk of relapse. The indication for extended therapy depends on the risk of recurrence and the patient's wishes.
LoE **1a**	[729]; [730]; [742]; [743]; [745]
	Strong Consensus

Background 4,111

Extending the administration of tamoxifen from 5 to 10 years will reduce ipsi and contralateral recurrence rates and prolong overall survival in the ATLAS study. However, the rates of pulmonary embolism and endometrial carcinoma are increased without any influence on mortality [742], [743], [744]. The risk-adapted duration of tamoxifen administration (longer administration with increased risk of recurrence) is recommended by ASCO [741].

Endocrine therapy

4.112	**Consensus-based Recommendation**
EC	For patients with an ER+ breast cancer and increased risk, who are still premenopausal after completion of chemotherapy, an aromatase inhibitor can be used to eliminate ovarian function.
	Consensus

4.113	**Evidence-based Recommendation**
GoR **0**	Ovarian suppression alone can be considered either by administration of GnRHa or by bilateral ovariectomy for premenopausal women with ER+ breast cancer who cannot or do not wish to receive tamoxifen.
LoE **1b**	[734]
	Strong Consensus

4.114	**Evidence-based Recommendation**
GoR **A**	Ovarian suppression (GnRHa or bilateral ovariectomy) in addition to tamoxifen or an aromatase inhibitor shall only be considered in cases of high risk of recurrence and premenopausal situation after adjuvant chemotherapy. If an aromatase inhibitor is used, ovarian suppression shall be mandatory.
LoE **1b**	[734]
	Strong Consensus

Background 4.112 to 4.114

In various studies (e.g. SOFT, TEXT, [746]), the effect of suppressing ovarian function for up to 5 years together with the administration of Exemestan or together with tamoxifen vs. the administration of tamoxifen alone in the adjuvant therapy of women with hormone receptor-positive breast cancer who were premenopausal or became premenopausal again within 8 months after completion of adjuvant chemotherapy. After the individual analysis of each of these studies and after the combined analysis of two of these studies (SOFT, TEXT), an increased effectiveness of the additional elimination of ovarian function was found only in the group of patients under 35 years of age who had a high risk of recurrence (and therefore received chemotherapy). In a meta-analysis of all these studies [747] showed a higher efficacy in terms of DFS, but an increased rate of side effects up to more deaths for the combination of ovarian function suppression with an aromatase inhibitor than for the combination of ovarian function suppression together with tamoxifen. The higher rate of side effects implies a risk of reduced adherence to therapy.

According to the results of various studies (e.g. ZIPP study, [748]) and meta-analyses, the administration of a GnRH analogue is equivalent to the administration of tamoxifen alone, but is associated with an increased rate of side effects and thus a higher discontinuation rate compared to tamoxifen. Although reliable data are lacking, an increased late toxicity (e.g. coronary diseases, osteoporosis, dementia) can also be expected.

Therapy in postmenopausal patients

4.115	Evidence-based Recommendation
GoR **B**	Adjuvant endocrine therapy for postmenopausal patients with ER+ breast cancer should include an aromatase inhibitor.
LoE **1b**	[734]
	Strong Consensus

Background 4,115

In the meta-analyses [367], [729], [730], [749], a superiority of the adjuvant administration of aromatase (AI) alone or in sequence with tamoxifen compared to tamoxifen alone in postmenopausal patients with a hormone receptor-positive mammary carcinoma was shown with regard to OS and DFS. In the EBCTCG meta-analysis 2 cohorts were formed:

Cohort 1 as a comparison between 5 years of AI vs. 5 years of tamoxifen and cohort 2 with the administration of AI after 2-3 years of tamoxifen for a total of 5 years. The administration of 5 years of AI after 5 years of tamoxifen was not included in this meta-analysis. Since the analysis only included data up to 2006, the ABCSG 12 studies and the switch arms of the BIG 1-98 study were not included in this meta-analysis. In cohort 1, the significant superiority of AI administration over tamoxifen was demonstrated in terms of DFS but not in terms of mortality. In cohort 2, the significant benefit of additional AI administration was shown in terms of DFS and survival compared to tamoxifen alone.

The administration of the aromatase inhibitor alone over 5 years reduces the recurrence rate particularly effectively in high-risk breast carcinomas and/or lobular invasive breast carcinomas.

If after 5 years of tamoxifen the patient has become postmenopausal and has an increased risk of recurrence, the MA.17 study recommends the administration of letrozole for another 5 years [740]. This procedure is also recommended by ASCO [750] after its meta-analysis of all studies completed by 2013.

At the SABCS 2016 further studies on the prolonged (EAT) administration of an aromatase inhibitor after 5 years were presented, e.g. NSABP B-42 (10 vs. 5 years AI, [751]) or IDEAL trial (5 years AI after 5 years of adjuvant endocrine therapy with tamoxifen and/or AI) [752]. In none of these studies a significant prolongation of survival or a significant reduction of mortality could be shown by this prolonged AI administration, at best a reduction of the ipislateral and contralateral recurrence rate (summary by Gnant 2016). The MA.17R study, which has already been published [753], came to the same results. With younger postmenopausal patients who had already received endocrine therapy with AI in the first 5 years and tolerated it well, an extended endocrine therapy with AI can be discussed under certain circumstances (increased risk of recurrence e.g. with positive nodal status, no osteopenia/osteoporosis) [754].

4.7.3. Adjuvant chemotherapy

4.116	**Evidence-based Recommendation**
GoR **B**	An indication for adjuvant chemotherapy should be provided at: • HER2-positive tumours (from pT1b, N0; pT1a, N0 if further risk: G3, ER/PR neg., Ki-67 high) • Triple-negative tumors (ER- and PgR-negative, HER2-negative) • Luminal B tumors with high risk of recurrence (Ki-67 high, G 3, high risk multigene assay, young age, lymph node involvement)
LoE **1a**	[185]; [367]; [755]; [756]; [757]; [758]
	Strong Consensus

4.117	**Evidence-based Recommendation**
GoR **A**	Chemotherapy shall be administered in the recommended dosages. If the cycles are underdosed or reduced, there is a risk of loss of effectiveness.
LoE **1a**	[757]; [759]; [760]; [761]; [762]; [763]
	Strong Consensus

Administration of the cytostatic drugs

4.118	**Evidence-based Recommendation**
GoR **B**	Cytostatic drugs can be administered simultaneously or sequentially (according to evidence-based protocols). In cases of high tumour-related mortality risk and suitable patients, dose-controlled therapies should be used.
LoE **1b**	[764]; [765]; [766]; [767]; [768]; [769]
	Strong Consensus

Anthracycline/taxane containing adjuvant standard chemotherapy

4.119	Evidence-based Recommendation
GoR **B**	The adjuvant chemotherapy should contain a taxane and an anthracycline.
LoE **1b**	[770]; [771]; [772]; [773]; [774]; [775]
	Strong Consensus

4.120	Evidence-based Recommendation
GoR **0**	6 cycles of TC (docetaxel/cyclophosphamide) can be recommended for a medium clinical risk (
LoE **1b**	[770]; [771]; [772]; [773]; [774]; [775]
	Consensus

4.121	Evidence-based Recommendation
GoR **A**	Standard adjuvant chemotherapy shall last 18-24 weeks.
LoE **1a**	[755]; [765]; [776]; [777]; [778]; [779]; [780]; [781]; [782]; [783]; [784]
	Consensus

Background 4.116 to 4.121

The positive effects of adjuvant chemotherapy on the risk of recurrence and death, as proven by data of the Oxford Review (EBCTCG), are most pronounced in women under 50 years of age. There is also a benefit for postmenopausal women [757].

The data on adjuvant chemotherapy with taxanes is supported by current study results. Especially women with lymph node involvement or with nodal-negative carcinomas and additional risk criteria (e.g. G2/3, ER- and PgR-negative, pT > 2 cm, age

Several effective regimes are available. Against an adequate anthrazylin standard have been tested: FEC x 3 → Doc x 3 (PACS-01), 3 x FEC → 8 x Pac weekly as well as DocAC (TAC, BCIRG 006) [785]3, [785], [786], [787]. 6 x DocAC and 4 x AC → 4 x Doc are equi-effective but differ in their spectrum of side effects.

In the sequence after 4 x AC, 4 x docetaxel every 3 weeks (100 mg/m2) and 12 x paclitaxel weekly (80 mg/m2) are to be considered equivalent to [756], [788]. 4 cycles of AC - 4 x paclitaxel q21 (Henderson-like) are inferior to 6 x CEF (MA-21 [789]).

The dual combination 4 x DocC (TC) is superior to the old standard 4 x AC with regard to DFS and OS and avoids anthracycline-associated toxicities [756]0, [790].

In general, the administration of a longer adjuvant chemotherapy seems to be advantageous, as the comparison of 4 cycles vs. 8 cycles has shown [763], [779]. Several studies show that 6 cycles of TC are as effective as an anthracycline-taxane sequence therapy for certain patient groups. Whether these current efficacy data for 6 cycles of TC also apply to 4 cycles of TC cannot be decided at present on the basis of the available data. A corresponding reduction in the number of cycles should therefore only be made in the case of intolerable toxicities.

The Danish DBCG-07-READ study in TOPO2A-normal early breast cancer showed no difference in DFS and OS for 6x TC vs. 3x EC - 3x DOC [783]. The WSG-PlanB study also showed no difference between 6x TC and 4x EC - 4x docetaxel for HER2-negative early breast cancer [784]. The pooled analysis of 3 US studies (ABC Trials) could not formally confirm the non-inferiority between 6x TC and an anthracycline-taxane-containing sequence therapy (iDFS HR 1.202; 95% KI 0.97-1.49 with a predefined threshold value of 1.18). However, the absolute difference between the two arms was small (difference 4-year iDFS 2.5%) and subgroup analyses showed that the greatest benefit in favour of anthracycline-taxane-containing sequence therapy was found in [782] when the clinical risk was high (e.g. > 3 affected lymph nodes).

The significance of new substances in adjuvant therapy (e.g. gemcitabine, capecitabine) as the fourth substance in addition to anthracyclines, taxanes and cyclophosphamide cannot yet be conclusively assessed. While the addition of Gemcitabine is not associated with an advantage [791], some data for Capecitabine indicate a trend towards a further improvement of DFS or OS [792], [793]. However, this improvement was associated with increased toxicity [767]0, [793]. In the FinXX study, the improvement of DFS and OS was no longer significant after 5 years in the overall collective, only in risk patients (triple-negative, > 3 LK), Cave: Standard arm [794].

In recent studies, a higher efficacy of the dose-dense (q2w) [765], [769] or the dose-intensified dose-dense chemotherapy [768], [795] could be shown compared to conventional chemotherapy (q3w). Especially for patients at high risk (≥ 4 affected LK), dose-intensified dose-dense chemotherapy (ETC) is a standard regime. Patients with a low or moderate risk of recurrence, however, do not benefit from dose-intensified therapy compared to standard chemotherapy [796], [797].

Myeloablative high-dose chemotherapies currently have no place in unselected high-risk collectives: Compared to conventional chemotherapy they show a better event-free survival, but overall survival remains unaffected [798], [776]0. Therapy-associated mortality and side effects are significantly increased [799], [800].

4.7.4. Neoadjuvant therapy

Neoadjuvant systemic therapy

4.122	**Consensus-based Recommendation**
EC	A neoadjuvant (primary, preoperative) systemic therapy is regarded as the standard treatment for patients with locally advanced, primarily inoperable or inflammatory breast carcinomas as part of a multimodal therapy concept.
	Strong Consensus

4.123	**Consensus-based Recommendation**
EC	If the same postoperative adjuvant chemotherapy is indicated, neoadjuvant systemic therapy should be preferred.
	Strong Consensus

Neoadjuvant or adjuvant chemotherapy

4.124	**Evidence-based Statement**
ST	If chemotherapy is indicated, it can be carried out before the surgery (neoadjuvant) or afterwards (adjuvant). Both procedures are equivalent in terms of overall survival. The neoadjuvant therapy can lead to a higher rate of breast-conserving therapies.
LoE **1a**	[563]; [565]; [801]
	Strong Consensus

4.125	**Evidence-based Statement**
ST	The effect (pathohistological remission) is greatest in hormone receptor negative carcinomas.
LoE **1a**	[563]; [565]; [802]; [803]
	Strong Consensus

4.126	**Consensus-based Statement**
ST	A resection in the new tumor borders is possible if an R0 resection can be achieved.
	Strong Consensus

Primary hormone therapy in postmenopausal patients

4.127	**Consensus-based Recommendation**
EC	In postmenopausal patients with endocrine sensitive breast cancer, if surgery or chemotherapy is not possible or not desired, primary endocrine therapy can be performed.
	Strong Consensus

4.128	**Consensus-based Recommendation**
EC	The neoadjuvant endocrine therapy is not a standard therapy, in special situations (inoperable, multimorbid patient) a neoadjuvant endocrine therapy can be considered.
	Strong Consensus

Neoadjuvant chemotherapy combination

4.129	**Consensus-based Recommendation**
EC	If a neoadjuvant chemotherapy combination is used, it should contain an anthracycline and a taxane. The duration of preoperative therapy should be 18-24 weeks. For HER2-positive tumours and indication for neoadjuvant chemotherapy, therapy with trastuzumab should be used. In case of HER2-positivity and high-risk situation (clinical/sonographic or punch biopsy N+, tumor size > 2cm) therapy should be supplemented with pertuzumab.
	Strong Consensus

4.130	**Consensus-based Recommendation**
EC	Platinum salts increase the complete remission rate (pCR rate) in triple-negative breast cancer (TNBC) regardless of the BRCA status. The benefit on progression-free survival (PFS) and overall survival is not conclusively clarified. The toxicity is higher.
	Strong Consensus

Postneoadjuvant treatment

4.131	**Consensus-based Recommendation**
EC	With adequate anthracycline-taxan-containing neoadjuvant chemotherapy, no additional adjuvant chemotherapy is recommended for tumor residuals in the breast and/or lymph nodes. Postneoadjuvant chemotherapy treatment should only be carried out within the framework of studies.
	Strong Consensus

Background 4.122 to 4.131

Numerous studies have shown that there is no difference in long-term survival between neoadjuvant and adjuvant chemotherapy when the same therapeutic agents are used and the same dose and number of cycles are administered. In some studies, the local risk of recurrence seems to be increased with neoadjuvant therapy, whereby chemotherapy regimens and surgical strategies that are inferior or no longer up to standard were used [804], [805].

Reasons for the use of neoadjuvant chemotherapy (NACT) are, in addition to the improvement of operability or the increase in the rate of breast-conserving surgery, the gain in knowledge about the effectiveness of the therapy and the possibility of developing individual therapy approaches more quickly in post neoadjuvant studies [801]. In patients with HER2-positive/hormone receptor-negative or triple-negative disease a very favorable long-term prognosis can be assumed in the case of pathological complete remission (pCR) [563], [565].

The NACT should contain an anthracycline and a taxane and should be performed for at least 6 cycles, all prior to surgery. In patients with HER2-overexpressing tumor, the preoperative administration of trastuzumab as well as trastuzumab and pertuzumab simultaneously with chemotherapy can significantly increase the pCR rate [806], [807], [808], [809], [810], [811]. Trastuzumab therapy should be completed postoperatively for a period of one year.

Histopathological complete remission (pCR), defined as non-invasive detection of tumor cells in the breast and axilla after NACT, has shown a clear correlation with long-term survival in studies, i.e. patients who do not respond to NACT until surgery or already after the first chemotherapy cycles have a less favorable prognosis than those who respond to therapy [565], [802], [803]. Despite this observed correlation within the studies, there are no reliable data to date that show that differences in the pCR rate in study arms reliably predict differences in event-free survival or overall survival [565], [812], [813]. Thus, the pCR rate currently does not represent a valid surrogate endpoint for assessing the efficacy of neoadjuvant therapy with regard to patient-relevant endpoints.

The most important predictive marker for the response of a taxane-anthracycline containing regime is the hormone receptor status. In patients with negative hormone receptor status a pCR rate of up to 70-80% can be achieved. Predictors of response are: Younger age of onset of disease, patients with cT1 or cT2 carcinoma, nodal negativity, G3, negative hormone receptor status, triple-negative breast cancer

In postmenopausal patients with endocrine sensitive breast cancer, neoadjuvant endocrine therapy can be performed if surgery and chemotherapy are not possible. In this indication aromatase inhibitors of the third generation are recommended [814], [815], [816].

After completion of the NACT, the patient should receive surgical therapy as described above. The extent of excision should make use of the achieved effect of the neoadjuvant therapy and can be performed in the new tumor borders. Since the identification of the original tumor site can be difficult when a pCR is achieved, the localization of the tumor bed with the help of a clip is recommended already at the pre-therapeutic punch biopsy. In the case of radiologically complete remission under primary systemic therapy, an excision of the former tumor localization should be performed to determine whether vital tumor cells are still present in the tumor bed. The indications for postoperative radiotherapy correspond to those described for the adjuvant situation and are based on the pre-therapeutic initial findings [801]. The de-escalation of the locoregional radiotherapy is clarified in prospective studies (NSABP B 51).

For surgery or axillary intervention before and after adjuvant chemotherapy see Operative Chapter 5.4

4.7.5. Antibody Therapy

Indications for antibody therapy

4.132	**Evidence-based Recommendation**
GoR **A**	Patients with HER2-overexpressing tumours with a diameter of ≥ 1 cm (immunohistochemical score 3+ and/or ISH-positive) shall receive (neo-)adjuvant treatment with anthracycline followed by a taxane in combination with trastuzumab. Trastuzumab should be administered over a total period of one year.
LoE **1b**	[185]; [28]; [817]
	Strong Consensus

4.133	**Evidence-based Recommendation**
GoR **B**	Adjuvant treatment with trastuzumab should preferably be started simultaneously with the taxane phase of adjuvant chemotherapy.
LoE **2a**	[818]
	Strong Consensus

4.134	**Consensus-based Recommendation**
EC	If there is an indication for chemotherapy for HER2+ tumours /= 5 mm, trastuzumab should be given additionally. TCH (docetaxel, carboplatin, trastuzumab) can also be recommended adjuvant over 6 cycles every 3 weeks. Cardiotoxicity is lower than after anthracyclines.
	Consensus

Background 4.132 to 4.134

A prerequisite for trastuzumab therapy is the quality-assured determination of the HER2 status (algorithm see Chapter 5.5). The detection of the amplification of the HER2 gene by means of in situ hybridisation (ISH) can technically be carried out as fluorescence in situ hybridisation (FISH) or chromogenic in situ hybridisation (CISH) (approved kits see Chapter 5.5). For silver enhanced in situ hybridization (SISH) less data is available for [481], [819], [820], [821]. A currently published algorithm can help to critically question one's own results and to start a quality initiative [822].

The participating laboratories have to undergo quality assurance by means of ring tests [823], [824].

Five studies independently showed that adjuvant treatment with trastuzumab in sequence or in combination with standard chemotherapy consistently reduced the recurrence rate of HER2-overexpressing tumours by relatively 45% to 50% and mortality by approximately 30% [818], [825], [826], [827], [828], [829], [830], [831], [832], [833], [834], [835], [836], [837], [838] [839].

In a meta-analysis with a follow-up period of 2.9 to 5.5 years (median values of the examined studies) it could be shown that the simultaneous therapy (trastuzumab simultaneously to the taxane phase of the applied adjuvant chemotherapy regimen) is probably superior to the sequential therapy with trastuzumab after completion of the adjuvant chemotherapy: for DFS HRsim = 0.62 vs. HRseq = 0.74, for OS significant benefit only with simultaneous application with an HRsim = 0.68 [817], [818].

Several retrospective case series show that even in patients with small tumours (diameter

Even in patients with small tumours (diameter

Adjuvant treatment with trastuzumab is generally indicated in patients with nodal-positive tumors and nodal-negative tumors ≥ 1 cm diameter with HER2 overexpression. The duration of therapy is one year. The infusions can be administered in weekly or 3-weekly intervals. Additional studies were conducted on the duration of therapy. The two-year arm of the Hera study showed no significant difference compared to the one-year arm [840]. The Phare study compared half a year with one year of trastuzumab and it could not be shown that the shorter duration is not inferior. Thus, one year of trastuzumab therapy remains the standard [841], [842].

A further prerequisite for adjuvant trastuzumab treatment is adequate cardiac function. Monitoring of the left ventricular ejection fraction during therapy is also obligatory, since trastuzumab can cause clinically relevant heart failure (NYHA III/IV) up to 4.1% especially after anthracyclines [831], [843]. In retrospective analysis, this seems to affect mainly older patients (> 50 years) with previous cardiac diseases. The 3-year analysis of the American studies did not show an increased late cardiotoxicity, it was 2.5% after 3 years. The long-term results of the NSABP /NCCTG, the Hera study as well

as the BCIRG study showed that after 18 months no additional trastuzumab-related cardiotoxicity occurred [837], [838], [839], [842].

In the Cochrane analysis by Moja et al (2012), the absolute benefits and risks are summarised as follows: Mortality is relatively reduced by 30% with trastuzumab and the cardiac risk is five times higher compared to chemotherapy alone. If 1,000 patients are treated with chemotherapy without trastuzumab, 900 survive and 5 have cardiotoxicity.

If 1,000 patients were treated with chemotherapy and trastuzumab, 933 would survive (i.e. 33 more than without trastuzumab), 740 would survive without disease relapse (95 more than in the arm without trastuzumab) and 26 would have cardiotoxic side effects (i.e. 21 more than without trastuzumab). This Cochrane publication is based on the 2010 analysis, but long-term data are now available from these trials. No additional cardiotoxicities occurred.

4.7.6. Bone-directed therapy

In breast cancer, interactions between the bone and its metabolism on the one hand and the tumor cells on the other hand can be observed. These effects can be achieved directly by the breast carcinoma cells or indirectly via systemic therapeutics.

Bone targeted treatment plays an important role in breast cancer in several respects:

- Therapy and prevention of cancer treatment induced bone density and structure loss (cancer treatment induced bone loss)
- Adjuvant therapy of primary breast carcinoma to improve bone metastasis-free and overall survival
- Preventive therapy of skeletal related events (SRE) in osseous metastasized breast cancer

Bone modifying agents used in breast cancer are bisphosphonates and the antibody Denosumab, which is directed against the ligand of the Receptor Activator of Nuclear Factor-Kappa B (RANK ligand).

4.7.6.1. Therapy and prevention of cancer treatment induced bone loss

In malignant diseases the risk of loss of bone density, destruction of bone structure and thus therapy-associated osteoporosis with a consecutively increased risk of fracture is significantly increased [844]. In addition to the frequently observed immobilization and lifestyle changes (e.g. discontinuation of estrogen therapy), drug therapies are the most important factors for the osseous changes. Supportive therapies (e.g. cortisone preparations) can damage the bone as well as cytotoxic or endocrine medications. In particular, the high cure rates of numerous solid tumours and especially breast carcinoma are causing the problem to become increasingly prominent.

In premenopausal women with a hormone receptor-positive breast cancer a suppression of ovarian function (ovarian function suppression, e.g. by GnRH analogues) alone as well as in combination with tamoxifen or an aromatase inhibitor and therapy with tamoxifen alone lead to a loss of bone density and to an increased incidence of osteoporosis compared to a healthy control collective [845], [846], [847]. The combination of ovarian suppression combined with an aromatase inhibitor leads to the greatest decrease in bone density [845].

In postmenopausal women, therapy with aromatase inhibitors also leads to a loss of bone density and an increased incidence of fractures compared to women treated with tamoxifen [848], [849], [850], [851].

Chemotherapy can also lead to a relevant loss of bone density [852], [853].

An indication for preventive treatment should be based on gender, age and bone density, taking into account family history and lifestyle. Primary prevention of cancer-therapy induced bone loss should be considered in particular if there is a special risk constellation [854], [855]. This includes, among other things: advanced age, low body mass index, nicotine abuse, aromatase inhibitor therapy, family disposition, long-term cortisone therapy, immobility, endocrine diseases, medication intake (Dachverband der deutschsprachigen wissenschaftlichen Osteologischen Gesellschaft e.V., http://www.dv-osteologie.org; [856].

Bone-directed therapy

4.135	**Consensus-based Recommendation**
EC	Patients with an increased risk of bone loss due to medical history or cancer therapy should have a bone density measurement performed at the beginning of therapy. Depending on the result and other risk factors, the bone density measurement should be repeated at regular intervals.
	Strong Consensus

4.136	**Consensus-based Recommendation**
EC	To avoid cancer-therapy induced osteoporosis, preventive treatment should be considered depending on the individual risk constellation for the development of osteoporosis (http://www.dv-osteologie.org; ESMO bone health guidance).
	Consensus

4.137	**Evidence-based Recommendation**
GoR **B**	Bone protective therapy should be considered in premenopausal patients with GnRH and/or tamoxifen and in postmenopausal patients on aromatase inhibitor therapy.
LoE **1b**	[845]; [848]; [850]; [856]
	Strong Consensus

Background 4,135 to 4,137

Preventive treatment of cancer-associated bone loss differs little from the treatment of non-cancer-associated osteoporosis. The following general recommendations can be given to affected patients:

- Avoidance of underweight

- Avoidance of noxious substances (e.g. nicotine (ab)usus)
- Avoidance of cortisone preparations and drug therapies that negatively influence bone metabolism as far as possible
- Avoidance of vitamin D deficiency and reduced daily calcium intake
- Avoidance of immobilization or increase of physical activity as far as possible

4.138	**Evidence-based Recommendation**
GoR **B**	Hormone therapy with estrogens should not be used in breast cancer patients to prevent cancer-associated osteoporosis, as an increased recurrence rate cannot be ruled out, especially in hormone receptor-positive patients.
LoE **1a**	[857]
	Strong Consensus

4.139	**Consensus-based Recommendation**
EC	In addition to the general recommendations, bisphosphonates or denosumab can be used for the primary prevention of cancer therapy-induced bone loss.
	Strong Consensus

Background 4.138 and 4.139

In a primary prevention study in postmenopausal breast cancer patients treated with aromatase inhibitors, the RANK ligand antibody Denosumab led to a prevention of bone density loss and to a significant reduction of the fracture rate by 50% [860], independent of age and bone density.

A primary preventive use of bisphosphonates could significantly prevent a loss of bone density under endocrine therapy in both pre and postmenopause (postmenopausal: [861], [862], [863]; premenopausal: [858], [859]). However, in no study could a significant reduction of osteoporotic fractures be demonstrated by the bisphosphonates. The greatest evidence for the prevention of bone density loss exists for the bisphosphonate zoledronate [858], [862], [863], but other bisphosphonates have also been investigated in smaller RCTs for the prevention of therapy-induced bone density loss in breast cancer: clodronate, ibandronate, pamidronate, alendronate, risedronate.

4.140	**Evidence-based Statement**
ST	A risk reduction for fractures as part of endocrine therapy has only been clearly demonstrated for Denosumab, but not for bisphosphonates at present.
LoE **1**	[860]
	Strong Consensus

4.141	**Consensus-based Recommendation**
EC	The bone-directed therapy to prevent therapy-associated osteoporosis should be carried out as long as the endocrine therapy is performed.
	Strong Consensus

4.7.6.1.1. Therapy of cancer therapy induced osteoporosis

4.142	**Consensus-based Recommendation**
EC	If a fracture occurs without adequate trauma, a bone metastasis should be ruled out.
	Strong Consensus

Background 4.142

After exclusion of the bone metastasis an adequate therapy of the osteoporosis should be carried out. This should consider all possible aspects and, if necessary, be interdisciplinary (e.g. pain therapy, surgical stabilization and reconstruction, minimally invasive procedures (e.g. vertebroplasty, kyphoplasty, radiotherapy, drug therapy)).

4.7.6.2. Adjuvant therapy to improve bone metastasis-free and overall survival

According to the "seed and soil" theory, luminal breast cancer cells in particular metastasize preferentially in the bone and can be detected there as disseminated tumor cells [864], [865], [866]. Bisphosphonates and probably also denosumab seem to have a therapeutic effect on the persistence of these cells and thus on the incidence of secondary bone metastases [867].

Two meta-analyses investigated studies on the adjuvant use of different bisphosphonates. Ben-Aharon and colleagues found a positive effect on survival in postmenopausal breast cancer patients (HR 0.81 (0.69-0.95) [868]. An Oxford meta-analysis by Coleman and colleagues showed a significant, positive effect on bone metastasis-free survival of 34% and overall survival of 17% for postmenopausal patients (including premenopausal patients under ovarian suppression with GnRH analogues; ABCSG-12) [869].

For premenopausal patients (without ovary suppression using GnRH analogues), the meta-analyses did not show a significant advantage with regard to disease-free, bone metastasis-free and overall survival. An evaluation of the secondary endpoint in a subpopulation of premenopausal patients (largely without ovary suppression) showed no effect on the prognosis despite a higher therapy density at the beginning of treatment (AZURE study [856]).

To date, however, no bisphosphonate has been approved for the indication of adjuvant therapy in the European Union, so that treatment can only be carried out outside the approval status (off-label use).

4.143	**Evidence-based Statement**
ST	Adjuvant bisphosphonate therapy prolongs bone metastasis-free survival and overall survival in postmenopausal breast cancer patients as well as in premenopausal patients under ovarian suppression (outside the approval status).
LoE **1**	[868]; [869]
	Strong Consensus

Background 4.143

A preventive effect of Denosumab against the occurrence of bone metastases and the prolongation of overall survival could not be clearly demonstrated so far. Prospective studies with this question are currently being conducted.

4.144	**Evidence-based Recommendation**
GoR **0**	For premenopausal patients without ovary suppression, no recommendation can currently be made for the adjuvant use of bisphosphonates or Denosumab.
LoE **1b**	[856]; [868]; [869]
	Strong Consensus

Background 4.144

Bisphosphonates with evidence of an adjuvant therapeutic benefit (according to meta-analysis by Coleman et al., 2015 [870]):

- Alendronate p.o. 70 mg/w
- Clodronate p.o. 1600 mg/d
- Clodronate p.o. 1040 mg/d
- Ibandronate p.o. 50 mg/d
- Pamidronate p.o. (in oral form not available in D)
- Risedronate p.o. 35 mg/w
- Zoledronate i.v. 4 mg/6 m

4.7.6.3. Bone-directed therapy for patients with bone metastases

In the case of breast carcinoma, metastases are most frequently found in the bones carrying bone marrow. Especially the luminal tumors show an affinity to the skeletal system. The most frequent complications in bone metastases are pain, pathological fractures, vertebral compression syndromes and hypercalcemia [870]. If the above-mentioned symptoms (except for pain) occur, morbidity is significantly increased. Various measures can be taken to prevent these serious complications.

In the interdisciplinary AWMF-S3 guideline 032-054OL "Supportive Therapy in Oncological Patients" the diagnosis and therapy of bone metastases are discussed in detail [871]).

4.7.6.4. Tolerance of bisphosphonates

Possible side effects of bisphosphonates are:

When administered intravenously

- flu-like symptoms ("flu like symptoms") especially with the first i. v. administrations
- Deterioration of renal function, especially in cases of reduced renal function prior to the start of therapy until renal failure develops

For peroral administration

- gastrointestinal complaints (e.g. B. Nausea, vomiting, diarrhoea).

The rate of jaw bone necrosis caused by the bisphosphonates and Denosumab was not increased in the studies on adjuvant use [848], [872]. Only in the AZURE study, which showed a higher dose density in the first 30 months of treatment (see above), were increased rates of jawbone necrosis described [856].

4.145	**Consensus-based Recommendation**
EC	Before the start of adjuvant osteoprotective therapy, a visit to a dentist shall take place. Otherwise, the recommendations of the S3 guideline on "Antiresorptive-associated jaw necrosis" apply.
	Strong Consensus

4.7.7. Lifestyle factors that can be influenced

Exercise therapy and physical activity

4.146	**Evidence-based Recommendation**
GoR **A**	Patients shall be motivated to be physically active and to normalize their body weight (in case of an increased BMI). Assistance shall be provided. It is especially recommended: a) to avoid physical inactivity and return to normal everyday activity as soon as possible after diagnosis (LoE 2a) b) to achieve the goal of 150 minutes of moderate or 75 minutes of strenuous physical activity per week (LoE 1a)
LoE **2a/ 1a**	[873]; [874]; [875]; [876]; [877]; [878]
	Strong Consensus

Background 4.146

Follow-up care should not only focus on the detection of a relapse of the disease, but also on general health maintenance with training and counselling. This includes information about lifestyle, e.g. exercise and nutrition, especially in the case of obesity with a BMI ≥ 30 kg/m². The increasing body weight is related to the mortality due to a breast cancer disease [879]. Retrospective studies have shown that patients with a BMI ≥ 30 kg/m² compared to a BMI

Insufficient physical activity increases the risk of osteoporosis [881]. Initial strategies to reduce morbidity associated with osteoporosis include education about risk factors and a healthy lifestyle. In addition, overweight and obese survivors should be advised to reduce the consumption of high-calorie foods and beverages, promote physical activity and thereby achieve weight loss.

It is recommended that primary health care providers provide the following interventions based on clinical indication against the background of musculoskeletal symptoms, including pain acupuncture, physical activity, recommendation for physical therapy and rehabilitation. Exercise therapy could also reduce the risk of cardiotoxicity and cardiovascular disease [873].

Table 6: Definitions of weight categories according to body-mass-index

Category	BMI (kg/m²)	
massive underweight	< 16,00	
moderate underweight	16,0 -	Underweight
slight underweight	17,0 -	
Normal weight	18,5 -	Normal weight
Preadiposity	25,0 -	Overweight
Obesity grade I	30,0 -	
Obesity grade II	35,0 -	Obesity
Obesity grade III	≥ 40,0	
Source: WHO, 2003		

Meanwhile, numerous systematic reviews and meta-analyses document the many health effects of physical activity in breast cancer patients, including the reduction of treatment-specific symptoms (e.g. fatigue), improvement of quality of life and physical functions. Data from a meta-analysis of 16 studies suggest an average relative risk of 0.72 for physically active breast cancer patients (95% CI, 0.60-0.85) and 0.52 for all-cause mortality (95% CI, 0.42 0.64) [882].

Breast cancer patients should return to normal daily activities as soon as possible after diagnosis and should also be advised to continue regular physical activity. Breast cancer patients should exercise at least 150 minutes of moderate or 75 minutes of

intensive physical activity per week. Exercise therapy should include strength training at least 2 days per week [878], [883], [880]0.

On lifestyle factors in breast cancer there are it's a layman's terms Deciding Wisely Together " -Recommendation based on this guideline.

4.147	**Evidence-based Recommendation**
GoR **B**	Patients should be offered strength training programmes, especially under chemo- and hormone therapy.
LoE **1b**	[873]; [884]; [885]; [886]; [887]
	Consensus

Background 4.147

Movement therapy, including stretching and other methods of movement therapy, show effective effects in the treatment of postoperative musculoskeletal symptoms [888], [889]. Recent data from the Hormones and Physical Exercise Trial, a prospective RCT study, show that participation in an intensive exercise program reduced aromatase inhibitor-associated pain by 20% [886]. To date, apart from acupuncture [890], only exercise therapy shows statistically significant improvements in aromatase inhibitor-associated symptoms according to [886]. This RCT study was able to prove that primarily intensive strength training units led to a reduction of pain and aromatase inhibitor-associated symptoms. Breast cancer patients under radiation also benefit from strength training, which is safe, feasible and an effective method to reduce the fatigue syndrome is [887].

Physical activity reduces pain in breast cancer patients, as shown in a meta-analysis of RCT studies [891].

4.148	**Evidence-based Recommendation**
GoR **B**	Patients should be advised and guided to regular sports therapy and physical activity for the treatment of breast cancer-associated fatigue.
LoE **1a**	[892]; [893]; [894]; [895]
	Strong Consensus

Background 4.148

It is recommended that primary health care providers should advise and guide patients to regular physical activities to treat fatigue. A regular, physical exercise program can reduce fatigue, help survivors to feel better physically and emotionally, and to cope with the disease, as several RCTs show [878], [893], [894].

4.149	**Evidence-based Recommendation**
GoR **B**	In manifest chemotherapy-induced polyneuropathy, exercise therapy should be used to improve functionality. This may include: • Balance exercises, • sensomotoric training, • Coordination training, • Vibration training, • Fine Motor Training
LoE **1a/2a**	[885]; [886]; [891]; [896]
	Strong Consensus

Background 4.149

The following section on polyneuropathy and exercise therapy is based almost entirely on the S3 guideline supportive therapy (http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html).

It is recommended that primary care should offer interventions such as physical activity to treat neuropathy and relieve pain. The effectiveness of non-drug interventions is evaluated in a review by Streckmann et al. [896]. In this review 18 studies on "exercise interventions for neuropathic patients" were analysed. The majority of the studies (11 of 18) refer to diabetes mellitus-induced neuropathy and the others to neuropathy of different etiologies (such as polyneuropathy after liver transplantation, Charcot-Marie-Tooth syndrome and others). Only one study refers primarily to neuropathy in the context of an oncological disease [896].

In this study, a total of 61 patients with lymphoma were randomized to different therapy times. The patients received a combined training of aerobic endurance, strength and sensorimotor training. The study was terminated prematurely due to clear effects in favour of the intervention group regarding quality of life, depth sensitivity, activity level (measured in metabolic equivalent (MET)/week), balance control, lactate values and side effects of oncological therapy (recorded by SGA; HADS and questionnaire of experienced deficits in attention). In further RCTs with breast cancer patients, physical activity showed that arthralgias, neuropathies and neuropathy symptoms improved, but in which "reduction of neuropathy" was not the primary endpoint [885], [886].

In the review, a positive effect for exercise therapy for the treatment of PNP of different genesis is documented [897]. Training methods such as endurance training, balance training, vibration training, Tai Chi, walking and standing training, also using weights, are used. Basically, this review results in an advantage for balance training regardless of the underlying genesis. For CIPN, a combination of endurance, strength and sensomotoric training is found to be effective. Whether a prophylactic effect can also be generated is currently still the subject of several ongoing studies.

For CIPN in comparison to PNP of other genesis a deviating/different pathogenetic mechanism is suspected depending on the aetiology.

This limits the comparability of studies on PNP and should give reason for caution when transferring results from studies on PNP of other aetiology to CIPN.

Based on data from a randomized study on healthy volunteers to improve balance (tested on a one-legged stand), it could be shown that exclusive strength training or also strength and endurance training had no effects, but that sensorimotor training was required [898].

With regard to other therapeutic measures such as occupational therapy or physical therapy/electrotherapy, no randomized studies on the treatment of CIPN are available. In a review from 2011, therapies used in oncological rehabilitation are described as beneficial [899]. In the intervention group, occupational therapy sensitivity training (e.g. exercises in a bean bath, electrotherapy) was used and the course during rehabilitation was evaluated. Success criteria were the reduction of CIPN symptoms and assessment of future performance in working life. The intervention group showed a clear benefit in this respect.

A systematic review of rehabilitative interventions also lists publications that show an improvement in functional limitations. However, these reviews include patients with Guillain-Barré syndrome [900].

In line with this, positive effects of Tai Chi in the training of balance could be achieved with older people [901].

In summary, there are clear indications for the improvement of functional limitations by non-drug methods such as sports therapy, occupational therapy, physiotherapy and physical therapy including electrotherapy. In addition, there is no evidence of a damaging effect of the intervention. Furthermore, there is evidence for the effectiveness of exercise therapy to reduce further side effects in female tumor patients, such as Fatigue [894]. Exercise training, primarily as sensomotoric and balance training, as well as occupational therapy, physiotherapy and physical therapy including electrotherapy under consideration of the contraindications are therefore recommended.

4.150	**Evidence-based Recommendation**
GoR **B**	Patients after surgical treatment of breast cancer and the occurrence of lymphedema should be introduced to supervised, slowly progressive strength training for lymphedema treatment.
LoE **1b**	[876]; [902]; [903]; [904]; [905]; [906]; [907]
	Strong Consensus

Background 4.150

Patients after surgical treatment of breast cancer and the occurrence of lymphedema should be introduced to supervised, slowly progressive strength training for lymphedema treatment. This is safe and effective in reducing arm swelling in high risk breast cancer survivors (five or more lymph nodes). In the past, patients with axillary lymphonodectomy/radiation have been advised to avoid physical activity and heavy lifting with the arm of the affected side. However, one study found that supervised, slowly progressive strength training after breast cancer is safe and effective. In addition, this type of physical activity can reduce the likelihood of arm swelling in high-

risk breast cancer survivors (five or more lymph nodes) and improve symptoms of existing lymphedema [876].

Body Weight

4.151	Evidence-based Recommendation
GoR **A**	Patients shall be advised (a) to achieve and maintain a healthy body weight and (b) in the case of overweight or obesity, to limit the intake of high-calorie foods and beverages and to increase physical activity in order to promote moderate weight loss and maintain it in the long term.
LoE **5**	[873]
	Strong Consensus

Background 4.151

Increased body weight is accompanied by a reduction in life expectancy. As causes of death, cardiovascular diseases are in the foreground, but cancers as a whole also increase the mortality [908]. A more recent analysis by IARC recently confirmed that an increase in fat mass increases the risk of postmenopausal breast cancer and other cancers [909]. In another analysis using the GLOBOCAN database, 10.2% of all postmenopausal breast cancers were due to obesity (population attribute fraction) [910].

If there is a breast carcinoma, the presence of obesity (BMI 30 ≥ kg/m²) increases the overall mortality risk by 75% for women with premenopausal breast carcinoma and by 34% for women with postmenopausal breast carcinoma. Per BMI increase of 5 kg/m² a risk increase for total mortality of 8-17% and for breast cancer-related mortality of 17-29% was observed [911].

In recent years, several weight loss studies have been conducted in obese women with breast cancer. These studies showed that a moderate weight reduction with improvement of various accompanying phenomena (biomarkers, psychosocial parameters, quality of life) is possible with moderately energy-reduced diets and increased exercise, and no particular side effects are to be expected [912]. In a more recent evaluation of the ENERGY trial it was reported that a program with dietary changes and increased exercise improves the quality of life in obese women with breast cancer, but this effect weakened over time starting with [913].

In older persons with obesity (BMI 30 kg/m²) there is only weak evidence that these persons benefit from weight reduction with reduction diet and increased exercise [914].

Nutrition

4.152	Evidence-based Recommendation
GoR **A**	Patients shall be advised to achieve and maintain a diet rich in vegetables, fruits, whole grains and legumes, low in saturated fats and limited in alcohol intake.
LoE **5**	[873]
	Strong Consensus

Background 4.152

So far there are only few nutritional intervention studies in women with breast cancer. These studies were mostly of short duration and almost exclusively recorded surrogate parameters. Two larger intervention studies started more than 20 years ago led to contradictory results, which may be explained by different compliance [915], [916]. In both studies the intervention aimed at a significant reduction of fat intake. The WHEL study also recommended a high consumption of vegetables, fruit and wholemeal products [916].

From prospective cohort studies, similar findings are found for breast cancer as for chronic diseases in general. According to these findings, a western diet rich in fat and sugar also increases the risk of breast cancer, while a health-promoting diet reduces the risk. The WCRF therefore also recommends a balanced mixed diet for cancer patients. Recently, a secondary analysis of the PREDIMED study reported that a Mediterranean diet, supplemented with olive oil or nuts, was associated with a 62% and 34% lower incidence of breast cancer [917].

Concerning the specific role of individual food groups, a number of analyses and meta-analyses have now been published from cohort studies, which essentially show an inverse relationship between dietary fiber consumption and breast cancer risk [918], while a high consumption of meat and processed meat products was associated with an increased risk of breast cancer [919]. In another meta-analysis, the consumption of milk and dairy products was associated with a reduced risk [920]. In sum, it follows that a diet according to the Nutrition Circle of the German Society for Nutrition (DGE) [921] is also recommended for women with breast cancer. Alternatively, a Mediterranean diet or a diet according to the principles of the Mediterranean diet can be recommended.

The recommendations made so far are almost exclusively from prospective cohort studies; controlled intervention studies are largely lacking and are urgently needed in order to be able to make nutritional recommendations with greater evidence.

The data on alcohol consumption in women with breast cancer is contradictory [922]. According to expert panels, alcohol consumption should be limited to a maximum of 10 grams per day [923].

Avoidable toxins

4.153	Evidence-based Recommendation
GoR **A**	Patients shall be advised not to smoke, and smoking cessation programmes should be recommended to women smokers.
LoE **2a**	[873]
	Strong Consensus

Background 4,153

The meta-analysis of various observational studies by Berube et al. [924] shows a 33% increased risk of breast cancer-specific mortality in patients who smoked at the time of initial diagnosis compared to previous smokers. Already during the primary therapy and later also during the aftercare the patients should be influenced by suitable means to keep abstinence from tobacco. In this context, reference is made to the S3 guideline "Screening, diagnosis and treatment of harmful and dependent tobacco consumption" AWMF-Register No. 076-006.

4.154	Evidence-based Recommendation
GoR **B**	To avoid later relapses (> 5 years after initial diagnosis), patients with receptor-positive disease should avoid a daily alcohol consumption of > 12 g pure alcohol.
LoE **2a**	[925]
	Strong Consensus

Background 4,154

While the data on the increase in breast cancer risk for healthy women through regular alcohol consumption can be regarded as robust, there has been inconsistent and contradictory evidence in recent years on the significance of alcohol consumption for the probability of recurrence. In the USA, about 7% of patients with primary breast cancer say that they consume more alcohol [873]. The OAS and DFS of breast cancer patients seems to be unaffected by a daily intake of less than 12g of pure alcohol per day ("one drink" in the US guidelines). However, the pooled analysis of prospective cohort studies in receptor-positive disease with a daily intake of > 12g showed a significant deterioration of DFS after the first 5 years ("late recurrences") [925]. In this context, the authors explain that regular consumption from the time of diagnosis was decisive for the classification into the respective group. Thus, the consumption behaviour 5 years after diagnosis was not decisive.

5. Recurrent or metastatic breast cancer

5.1. Definition and prognosis

5.1.1. Definition

Local or locoregional recurrences are: the recurrence of breast cancer in the ipsilateral breast, on the ipsilateral thoracic wall including the overlying skin, the regional lymph nodes of the axilla, the supra- and infraclavicular region and along the internal mammary vessels.

The local or locoregional recurrence can be isolated or in combination with distant metastases in other organ systems [926], [927].

Early detection of isolated local or locoregional recurrence has a positive influence on survival. Therefore, regular monitoring of local and axillary tumor freedom is an important task of aftercare. Accordingly, local/local-regional recurrences are mainly treated with curative (50-70%) and only about 30% with palliative targeting [928].

5.1.2. Incidence and prognosis

Local relapses after breast-conserving surgery and radiation occur with a frequency of 5-10% (after 10 years). The median 5-year survival rate is 65 (45-79)% [929]. Recurrences on the thoracic wall after mastectomy are observed in 4 (2-20)% and recurrences in the axilla in 1 (0.1-8)%. These patients show a 5-year survival of 50 (24-78)% and 55 (31-77)% respectively on [929]. Locoregional recurrences occurring simultaneously at different sites are observed with a frequency of 16 (8-19)% and are associated with a 5-year survival of 21 (18-23)% [930]. The course and biological behavior of the inbreast recurrence after BET and the local recurrence after MRM do not differ significantly [931], [932], [933], [934]. For both constellations the same prognostic factors for the clinical course are found without differences. In the event of a local recurrence, the primary prognostic factors continue to apply, differences exist only between "early" (2 years) local recurrences. The "early" recurrences can be cured to a lesser extent and are also correlated with a higher rate of secondary recurrence and distant metastasis [935], [936], [937], [938], [939].

Prognostic factors for the occurrence of local/local recurrence after MRM or BET:

- Number of lymph nodes affected
- Tumor size (maximum diameter)
- Grading
- Hormone receptor status
- Resection status (R0/R1/R2)
- Focality (unifocal > multifocal > inflammatory LR)

A local relapse or a locoregional relapse is treated locally. In operable cases, a complete excision of the recurrent tumor should be aimed for. Postoperative radiotherapy after extirpation may improve local tumor control [940]. If local tumor control is achieved with this therapy, long-term survival is possible [931]. In case of inoperability radiotherapy is the therapeutic procedure of choice [940]. Due to the high risk for a subsequent systemic progression a systemic therapy can be considered in addition to the local therapy of the recurrence (surgery and/or radiotherapy) [936]. The effect of systemic chemotherapy has not yet been proven by prospective randomized studies [936].

Prognostic factors for disease progression after local/local recurrence after MRM or BET:

- Resection status of the local relapse (R0, R1, R2)
- Tumor size of the local recurrence
- Localization (scars vs. far away from scars)
- Focus
- Grading
- Hormone receptor status
- Length of the disease-free interval
- primary lymph node status

5.2. Diagnostic for locale or locoregional recurrences

5.1	Evidence-based Recommendation
GoR **B**	Patients should be informed about the clinical signs of a relapse.
LoE **5**	[31]; [873]
	Strong Consensus

5.2	Evidence-based Recommendation
GoR **B**	Further diagnostic methods in addition to those recommended in the follow-up should not be used in asymptomatic patients.
LoE **5**	[31]; [873]
	Strong Consensus

5.3	Evidence-based Recommendation
GoR **A**	Mammography and breast ultrasound shall be used for the imaging clarification in case of suspected local/local recurrence - as in the diagnosis of primary breast carcinoma.
LoE **2a-2b**	[941]; [942]
	Strong Consensus

5.4	Evidence-based Recommendation
GoR **B**	Breast MRI should be used if no sufficiently reliable diagnostic statement can be made with other methods with regard to the risk situation of the woman.
LoE **2b**	[30]; [943]; [944]
	Strong Consensus

5.5	Evidence-based Recommendation
GoR **B**	For the primary histological clarification of a locoregional recurrence, mammary sonography and minimally invasive biopsy methods are suitable.
LoE **2b**	[28]
	Strong Consensus

5.6	Evidence-based Recommendation
GoR **A**	If distant metastases are suspected, they can be excluded by appropriate diagnostic measures. In case of newly diagnosed breast cancer and the clinical suspicion of metastases, imaging staging shall be performed. As staging examinations, a contrast-enhanced CT (thorax, abdomen, pelvis) and a bone scintigram shall be performed.
LoE **2b**	[234]; [28]; [941]
	Strong Consensus

5.7	Evidence-based Recommendation
GoR **B**	A PET-CT should only be used if there is a strong suspicion of remote metastasis in symptomatic patients using other methods and this metastasis cannot be reliably detected or ruled out.
LoE **2b**	[234]; [28]
	Consensus

Background 5.1 to 5.7

The goals of follow-up care are mentioned in Chapter 7. These include the diagnosis of curable local recurrence and locoregional recurrence.

Since there were different definitions of recurrence, an international consensus group was formed to define the different localizations of recurrence [945]:

Local recurrence: Any epithelial invasive breast cancer and any DCIS in the ipsilateral breast or in the skin or subcutaneous tissue in the ipsilateral thorax

Regional recurrence: Occurrence of the recurrence in the ipsilateral lymph nodes of the axilla and around the clavicle

The locoregional recurrence summarizes the local recurrence and the regional recurrence.

In Germany the following constellations are called local or locoregional recurrences according to the previous S3 guidelines for early detection, diagnosis, therapy and aftercare of breast cancer:

The recurrence of breast cancer in the ipsilateral breast, on the ipsilateral thoracic wall including the overlying skin, the regional lymph nodes of the axilla, the supra- and infraclavicular region and/or along the internal mammary vessels.

In case of local and locoregional recurrence without distant metastasis there is usually a curative therapy chance. Factors for a good prognosis of patients with local and locoregional recurrence are age of the patient below 70 years, a finding as small as possible at diagnosis of the recurrence, a longer disease-free interval and the complete removal of the recurrence [946], [947], [948].

Early detection of these recurrences is therefore important. Patients in follow-up care after completion of locoregional primary therapy are therefore offered regular examinations to detect intramammary or locoregional recurrence as early as possible. At the same time the patient must be informed about the typical clinical signs of a local and locoregional recurrence [28], [31], [873].

After a mastectomy, a clinical and sonographic examination should be performed at least annually to monitor the ipsilateral thoracic wall and the regional lymph node stations. After breast-conserving therapy, regular mammography with supplementary mammary sonography is also recommended [28], [941], [949], [950].

Apparative diagnostics (mammography, sonography) to assess the ipsilateral and contralateral thoracic wall and axilla should be performed at least once a year.

Although in principle a stratification of the aftercare with regard to the imaging procedures used and the examination frequency according to individual risk constellation seems to be reasonable, there is no sufficient data available in the literature on this subject [951] Recommendations for the indication and implementation of the various diagnostic and interventional procedures for the primary diagnosis of breast cancer (see Chapter 5.2) can largely be transferred to the aftercare situation. There are differences, however, in that changes in the breast after surgery and radiotherapy can lead to limited assessability in mammography and sonography. If the differentiation between scarred and carcinomatous lesions cannot be made in mammography and sonography when a recurrence after BET is suspected, a magnetic resonance imaging (MRI) examination of the breast should be performed. As in the primary diagnosis of breast cancer, histological confirmation should be sought before determining the therapy in the case of recurrence - if technically feasible using percutaneous minimally invasive biopsy procedures.

If the recurrence is histologically confirmed, a mammography and sonography of the contralateral mamma should be performed as well as a re-staggering [28], [941]. This re-staggering comprises a contrast-enhanced computed tomography of the thorax and abdomen [234] and can be supplemented by a PET-CT if the suspicion of a distant metastasis cannot be confirmed or disproved by other diagnostic methods [234]. This re-staging is justified by the fact that before the start of therapy it must be assessed whether a curative or palliative therapy goal exists [952], [953].

5.3. Treatment of local/locoregional recurrence

5.3.1. Local (intramammary) recurrence

5.8	**Consensus-based Recommendation**
EC	In case of a suspected diagnosis of a locoregional relapse, a histological backup with re-determination of ER, PR and HER2 and a complete re-staging shall be performed first to exclude metastases and to enable the planning of an interdisciplinary therapy strategy.
	Strong Consensus

5.9	**Consensus-based Recommendation**
EC	In the case of intramammary recurrence (DCIS/invasive carcinoma), the secondary mastectomy provides the highest local tumor control.
	Strong Consensus

5.10	**Evidence-based Recommendation**
GoR **0**	If the initial situation is favourable, e.g. DCIS or invasive carcinoma with a long recurrence-free interval and no skin infestation, breast-conserving surgery can be performed again after careful clarification.
LoE **4a**	[954]; [955]; [956]; [957]
	Strong Consensus

5.11	**Consensus-based Recommendation**
EC	Before a new breast-conserving surgery, the possibility of re-radiation (partial breast radiation) shall/should be examined, discussed in an interdisciplinary tumour conference and, if necessary, the patient should be introduced to a radiotherapist.
	Consensus

5.12	**Consensus-based Recommendation**
EC	In the case of breast-conserving surgery, the patient shall be advised of an increased risk of a renewed intramammary recurrence.
	Strong Consensus

Background 5.8 to 5.12

The therapy of intramammary local recurrence consists, if possible, in surgical intervention with the aim of R0 resection. The highest tumor control is achieved by mastectomy [932]. If organ preservation surgery is performed again, there is an increased risk of another intramammary recurrence. A renewed breast-conserving procedure can be performed if the initial position is favorable - DCIS or invasive carcinoma with a long recurrence-free interval or in the absence of skin infestation or a long distance from the primary tumor localization - [958]. The highest local control is achieved if the disease-free interval is over 5 years and if there are clearly negative resection margins during the renewed breast-conserving surgery [956], [959]. In the case of renewed breast-conserving surgery, local flap plasty, such as M. latissimusdorsi plasty, should be performed with restraint and after detailed explanation, since a survival disadvantage cannot be excluded and reduced cosmetic results are achieved. If the axilla is clinically unremarkable, a renewed axillary intervention after primary axillary dissection is not recommended. If no radiotherapy has been performed as part of the primary therapy, postoperative radiotherapy should be followed. After radiotherapy with initial breast-conserving procedure, in the recurrence situation with renewed local excision, repeated external radiation or local brachytherapy may be considered if necessary to reduce recurrence and avoid salvage mastectomy [954], [960], [961], [962].

Survival after local or locoregional relapse varies considerably. Proven independent and significant prognostic factors for survival with or without additional therapy are the disease-free interval and tumor mass of the relapse, multifocality, as well as the initial tumor stage and the time to metastasis [928], [963], [964], [965], [966], [967], [968]. Further prognostic factors are grading, resectability (R0 versus R1 versus R2), hormone receptor status and HER2 oncogene status of the recurrent tumor [928], [967], [969].

Patients should be informed and educated about the possibility of a renewed breast-conserving procedure under appropriate initial conditions. A local recurrence indicates the biology of the disease and the avoidance of salvage mastectomy does not necessarily mean a deterioration in overall survival.

5.3.2. Local recurrence after mastectomy

5.13	**Consensus-based Recommendation**
EC	If possible, an isolated recurrence of the thoracic wall shall be surgically removed completely (R0). If the ribs/intercostal muscles are affected, the decision on therapy should be made in interdisciplinary cooperation with thoracic surgery.
	Strong Consensus

Background 5.13

The incidence of local/local recurrence after mastectomy depending on tumor biology is 9-20% [970], [971]. Among these, in about one third the recurrence is locally limited and - in decreasing frequency - manifested on the thoracic wall, in the supraclavicular region, in the axilla as well as in 10-30% multilocally [939], [964], [972], [973]. The complete excision of the tumor should be aspired. Small scar recurrences can be treated by wide excision in healthy individuals, larger thoracic wall recurrences by chest wall resections. In the case of larger chest wall excisions, covering the defect with skin flaps may be necessary. An interdisciplinary surgical procedure in cooperation with plastic surgery may be necessary. If an R0 resection is achieved, the 5-year survival rate is 40-60%.

If no radiation has been carried out as part of the primary therapy, postoperative radiation should be followed. In the presence of unfavorable risk factors, renewed small volume radiation may also be indicated after recurrent surgery [974], [975].

In the presence of distant metastases, a renewed surgical intervention may be considered as palliative surgery of the local recurrence for pain, ulceration or for psychosocial reasons [976].

5.14	**Consensus-based Recommendation**
EC	In case of symptomatic local recurrence (e.g. ulceration, pain), local therapy (surgical intervention, radiotherapy) can be considered even in the presence of distant metastases with the aim of reducing symptoms.
	Strong Consensus

5.3.3. Axillary lymph node recurrence

5.15	**Consensus-based Recommendation**
EC	In the case of an axillary lymph node recurrence, local control of the disease should be achieved by renewed surgical axillary intervention, if necessary with radiotherapy. Preoperatively, a CT thorax should be performed to extend the lymph node metastasis.
	Strong Consensus

Background 5.15

Axillary recurrence occurs after axillary dissection or sentinel node biopsy in about 1%. The 5-year survival in axillary recurrence after axillary dissection is approximately 55% [929]. In case of recurrence after sentinel node biopsy the 5-year survival is significantly higher [977] with 93%.

For isolated locoregional recurrences, surgical rehabilitation is the method of first choice. If surgical treatment options for locoregional lymph node recurrences (in contrast to local recurrences) are limited or not curatively feasible, radiotherapy in combination with systemic therapy represents the most promising local therapy modality for tumor control, by which the chance of a cure can be maintained [978].

5.3.4. Pharmacological therapy

5.16	**Consensus-based Recommendation**
EC	A systemic therapy after R0 resection of a locoregional recurrence shall be considered for a prolonged disease-free interval as well as a prolonged overall survival.
	Strong Consensus

Background 5.16

In principle, a locoregional recurrence like the primary disease is also to be considered a systemic disease and requires systemic therapy.

An additional systemic endocrine therapy after surgical therapy and R0 situation can extend the disease-free interval in patients with a hormone receptor-positive recurrence; however, the improvement of the survival rate is not proven [979], [980], [981], [982], [983], [984]. In case of hormone sensitive recurrences a postoperative endocrine therapy should be started or the current endocrine therapy should be changed. Possibly this will improve disease-free and overall survival.

The data on chemotherapy after isolated locoregional recurrence and surgical therapy is weak. However, the results of a prospective randomized study [985] are available. In the CALOR study patients with surgically free tumor margins after mastectomy or breast-conserving therapy and free margins were randomized to chemotherapy (n=85) or no chemotherapy (n=77) (1:1). The choice of chemotherapy was in the hands of the study centres, but should include at least two therapeutic agents and be carried out over 3-6 months. In case of positive estrogen receptors, adjuvant endocrine therapy was used. Radiation therapy was carried out on microscopically affected tumour margins. An anti-HER2 therapy was optionally available in case of positive HER2 receptor. The primary study objective was disease-free survival (DFS). Patients with metastases were excluded. After a median follow-up of 4.9 years, a 5-year DFS of 69% (95% CI 56-79) was observed in the group with chemotherapy and 57% (95% CI 44-67) without chemotherapy (HR 0.59, 95% CI 0.35-0.99), p=0.046). The benefit was significant with negative estrogen receptor and greater than with positive estrogen receptor of the local recurrence [ER negative: DFS 67% versus 35%, HR 0.32 (95% CI 0.14-0.73); ER positive: 70% versus 69%, HR 0.94 (95% CI 0.47-1.89)]. In terms of overall survival, the use of chemotherapy also showed a significant benefit for the overall collective. 5-year survival was 88% with chemotherapy versus 76% without chemotherapy [HR 0.41 (95% CI 0.19-0.89), p=0.024)], but there was no significant difference between the ER positive and negative subgroups. Even though the groups are small overall, the study shows a significant benefit from the use of systemic therapy after surgical rehabilitation. Thus, patients should be informed about the data situation, advantages and disadvantages should be weighed and the use of chemotherapy should be considered.

The data on chemotherapy after isolated locoregional recurrence and surgical therapy is clearly arranged. This is particularly true for patients with inadequate adjuvant primary therapy (e.g. trastuzumab-naive, HER2-positive patients, triple-negative patients). In case of a HER2-positive local recurrence a combination of chemotherapy and HER2-targeted therapy can be considered [985], [986].

If, in the course of a locoregional recurrence, R0 resection is unlikely and therefore the local findings are not operable, endocrine therapy should be initiated for endocrine

responsive tumors (based on the immunohistochemistry of the local recurrence). In extensive thoracic wall recurrences, chemotherapy can improve local control. If necessary, surgical repair is possible afterwards. For HER2-overexpressing tumours, HER2-targeted therapy in combination with chemotherapy or anti-hormonal therapy (for Er+) should be considered (http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf Chapter Systemic treatment of recurrent or stage IV-breast cancer. BINV-17 version 3.2012).

5.3.5. Radiation therapy

Radiation after recurrence surgery

5.17	Consensus-based Recommendation
EC	Radiation after recurrence surgery should be discussed and decided on on an interdisciplinary basis. Postoperative radiotherapy should be performed if no previous radiotherapy had been performed or the local recurrence had not undergone radical surgery (R1-2).
	Strong Consensus

Background 5.17

If no radiation has been performed in the course of primary therapy, postoperative radiation can be discussed. In the presence of additional unfavourable risk factors, small-volume radiation may again be indicated even after adjuvant radiotherapy previously performed as part of primary therapy. In the case of inoperability, radiotherapy as well as systemic hormone and chemotherapy can be used as the sole measure or in combination. There is evidence that simultaneous chemotherapy or hyperthermia as radiation-sensitizing procedures can achieve higher response rates.

In the previously irradiated area, lower-dose re-radiation with simultaneous surface hyperthermia can lead to better local tumor control than re-radiation alone. The survival rates are not improved [987], [988].

5.18	Consensus-based Recommendation
EC	In the case of an inoperable local recurrence, palliative radiotherapy, possibly in combination with chemotherapy, can be useful for symptom control.
	Strong Consensus

5.19	Consensus-based Recommendation
EC	In case of an intramammary or thoracic wall recurrence without prior radiation after breast-conserving surgery (R0) or after mastectomy (R0), the indication for adjuvant radiotherapy should be analogous to the recommendations in the primary situation.
	Strong Consensus

5.20	**Consensus-based Recommendation**
EC	In the case of intramammary recurrence after pre-radiation after breast-conserving surgery (R0), the indication for adjuvant radiotherapy should be discussed on an interdisciplinary basis and can be made by the 1st radiotherapy, especially in patients without serious late effects.
	Strong Consensus

5.21	**Consensus-based Recommendation**
EC	In case of a recurrence of the thoracic wall after pre-radiation after mastectomy (R0), a new indication for local control should be discussed interdisciplinary.
	Strong Consensus

5.22	**Consensus-based Recommendation**
EC	In case of a chest wall recurrence after primary mastectomy with subsequent radiotherapy after resection of the recurrence (R0), the indication for a renewed adjuvant radiotherapy should be discussed interdisciplinary in the presence of risk factors (narrow resection, rpN+, G3, lymph vessel invasion). This can be done in patients without serious late effects from the 1st radiotherapy.
	Strong Consensus

5.23	**Consensus-based Recommendation**
EC	In case of a chest wall recurrence after primary mastectomy with subsequent radiotherapy after resection of the recurrence (R0), the indication for a renewed adjuvant radiotherapy should be discussed interdisciplinary in the presence of risk factors (narrow resection, rpN+, G3, lymph vessel invasion). This can be done in patients without serious late effects from the 1st radiotherapy.
	Strong Consensus

5.24	**Consensus-based Recommendation**
EC	For recurrences that are not in a previously irradiated area and have been R1/R2 resected - without the possibility of surgically creating an R0 situation with an acceptable risk - additional radiotherapy shall be recommended in this situation.
	Strong Consensus

5.25	**Consensus-based Recommendation**
EC	In the presence of recurrences after R1/R2 resection and prior radiation without the possibility of creating an R0 situation surgically with an acceptable risk, the indication for renewed radiotherapy should be discussed on an interdisciplinary basis. This can be provided by the 1st radiotherapy in patients without serious late effects.
	Strong Consensus

5.4. Distant metastases

5.4.1. Systemic therapy in pre- and perimenopausal patients and positive hormone receptor status and negative HER2 status.

5.26	**Evidence-based Recommendation**	**modified 2021**
GoR **A**	In pre- and perimenopausal patients, endocrine therapy, possibly combined with targeted therapy, shall be offered if hormone receptor status is positive and HER2 status is negative. Endocrine-only monotherapy is not indicated in patients with the need to achieve rapid remission to avert marked symptoms of the affected organ.	
LoE **1b**	[28]; [989]; [990]; [991]; [992]; [993]; [994]	
	Strong Consensus	

Background 5.26

Endocrine therapy is less toxic than chemotherapy and should therefore always be used as first-line therapy. Especially those patients who have had a long disease-free interval, who have responded to previous anti-hormonal therapy measures, and who do not belong to the small group of patients in whom a very rapid onset of action is necessary (e.g., in cases of shortness of breath in diffuse lung metastasis or threatened liver failure in liver metastasis or possible ileus in peritoneal carcinomatosis), benefit from endocrine therapy. With a positive hormone receptor status, remission is expected in 60% of patients, with a negative hormone receptor status in less than 10%. Endocrine therapy should therefore only be used in exceptional cases of negative hormone receptor status. In rare cases with unknown hormone receptor status, however, the indication for endocrine therapy can be made dependent on the clinical course.

If a patient responds to endocrine therapy, it is continued until progression is achieved. In case of progression, the use of alternative endocrine substances is indicated and justified. Only after all endocrine treatment measures have been exhausted or in case of non-response to endocrine therapy should a switch to cytostatic therapy be made.

In the presence of HER2 overexpression, a worse response to endocrine therapy is to be expected. Studies combining endocrine therapy with HER2-targeted therapy could not show a survival benefit from additional HER2-targeted therapy. Therefore,

chemotherapy in combination with HER2-targeted therapy is recommended for patients with hormone receptor-positive, HER2-positive tumours, see the section Distant Metastases - Chemotherapy [992], [998], [999], [1000], [1001], [1002], [1003], [1004], [1005], [1006], [995], [996], [997]

5.27	Evidence-based Recommendation	checked 2021
GoR **A**	A combined chemo-endocrine therapy is not recommended. Although it can increase remission rates, it also leads to increased toxicity without extending the progression-free interval or overall survival.	
LoE **1a**	[1007]; [1008]	
	Strong Consensus	

5.28	Evidence-based Recommendation	new 2021
GoR **B**	In premenopausal patients, endocrine-based therapy should be with a CDK4/6 inhibitor with ovarian function abolished and in combination with an aromatase inhibitor or with fulvestrant (depending on prior therapy).	
LoE **1b**	[1009]; [1010]; [1011]; [1012]; [1013]; [1014]; [1015]; [1016]; [1017]	

5.29	Evidence-based Recommendation	modified 2021
GoR **0**	In premenopausal patients, ovarian function elimination (GnRH analogs, ovariectomy) may be performed in combination with tamoxifen if tamoxifen therapy was discontinued more than 12 months ago.	
LoE **1b**	[1018]; [1019]; [28]; [992]	
	Strong Consensus	

5.30	Evidence-based Recommendation	modified 2021
GoR **B**	For sequential endocrine therapies, the different endocrine agents should be selected depending on previous therapies, response, and tumor and patient characteristics.	
LoE **1b**	[1020]; [1021]; [28]	
	Strong Consensus	

Background 5.27.

In a meta-analysis of 26 trials involving 3,606 patients with advanced breast carcinoma, Fossati et al [1040] demonstrated that the combination of chemotherapy and endocrine therapy resulted in increased remission rates but not prolonged survival compared with chemotherapy alone. Under combined chemoendocrine therapy, adverse effects such as edema tendency and cardiovascular complications were significantly increased.

Background 5.28.

Data from AMNOG benefit assessments are available on therapy with CDK4/6 inhibitors in addition to endocrine therapy in pre- or perimenopausal patients for a total of three randomized controlled trials (MONARCH-2 [1009], PALOMA-3 [1013] and MONALEESA-7 [1015]) on three substances (abemaciclib, palbociclib and ribociclib) are available. These studies are randomized, controlled, blinded clinical trials (see guideline report for full study assessment details). PALOMA-3 and MONARCH-2 included patients with failure of a prior line of therapy regardless of menopausal status, while MONALEESA-7 included only pre- and perimenopausal patients. Stratification by menopausal status was performed post hoc for PALOMA-3 and MONARCH-3 to meet the requirements of the benefit assessment for the G-BA. The data on abemaciclib and palbociclib presented below are therefore results of subgroup analyses. With non-significant effect estimates, these do not have sufficient test strength to allow a statistically sound interpretation and should therefore be regarded as exploratory results.

The following results were taken from the corresponding benefit assessment procedures, in each case from modules 4 and/or the relevant publications. At the time of the amendment, the active substances abemaciclib and ribociclib are still in additional, ongoing benefit assessment procedures without decisions on the additional benefit by the G BA. The status of the procedure can be viewed on the pages of the G-BA (Abemaciclib: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/535/; Ribociclib: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/526/ und https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/527/).

Overall survival

Regarding overall survival, there were no consistent benefits of treatment with CDK4/6 inhibitors for the group of pre- or perimenopausal patients. There was no significant survival benefit with treatment with abemaciclib or palbociclib compared with placebo (abemaciclib HR: 0.69 [0.38; 1.25], palbociclib HR: 1.07 [0.61; 1.86]) [1009], [1013]. There was a significant survival benefit for premenopausal or perimenopausal patients when treated with ribociclib (HR: 0.71 [0.54; 0.95]), but there were also significant effect differences with respect to ethnicity, lineage of therapy, and age: patients with age <40 years: HR 0.79 [0.48; 1.30] vs. age ≥40 years: HR 0.68 [0.48; 0.98]. Asian female patients: HR 0.40 [0.22; 0.72]) vs. non-Asian female patients: HR 0.91 [0.64; 1.30]) [1015]. Stratified by line of therapy, the first-line HR was 0.68 [0.45; 1.00] and the second- and follow-up-line HR was 0.78 [0.50; 1.21] [1028].

Progression-free survival

In all three studies, there was a clear advantage under therapy with CDK4/6 inhibitors vs. placebo in terms of progression-free survival: HR 0.41 [0.25; 0.70] with abemaciclib (second- and subsequent-line) [1010], HR 0.44 [0.23; 0.83] with palbociclib (second- and subsequent-line) [1011], and HR 0.52 [0.38; 0.70] with ribociclib in the first-line and HR 0.62 [0.44; 0.89] in the second- and subsequent-line, respectively [1016]. No persistent effect modifications in subgroups emerged for any of the three agents

[1010], [1011], [1016], [1027], [1029], [1030], i.e., the advantage of CDK4/6 inhibitors was also evident in the subgroup strata studied.

Health-related quality of life

A generalizing statement on the effect of CDK4/6 inhibitors on health-related quality of life was made for all studies using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the Global Health Status scale. For this purpose, a minimum clinically relevant difference of 10 points was assumed [1031], [1032]. There was no significant, clinically relevant improvement (HR: 0.63 [0.33; 1.20]) for patients treated with abemaciclib [1012]. Under palbociclib, there were also no statistically significant differences compared with placebo (HR: 0.81 [0.47; 1.41]) [1014]. However, clinically relevant benefits with respect to global health status versus placebo were identified under second- and follow-up ribociclib (HR: 0.70 [0.53; 0.92] [1017]. Given the heterogeneous results for the CDK4/6 inhibitors evaluated, no robust evidence of improvement in quality of life can be derived for them.

Adverse events

Treatment with CDK4/6 inhibitors was generally associated with a significantly higher incidence of adverse events. Expressed as hazard ratios for the occurrence of adverse events with Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3, comparable effect estimates were obtained for all agents: HR 5.64 [2.54; 12.55] among abemaciclib, HR 5.90 [2.91; 11.95] among palbociclib, and HR 4.14 [3.28; 5.23] among ribociclib [1012], [1014], [1017]. Among all agents, patients discontinued treatment significantly more often than on placebo: RR 4.18 [0.22; 79.00] under abemaciclib, RR 3.60 [0.19; 67.81] under palbociclib, and HR 1.66 [0.82; 3.38] under ribociclib [1012], [1014], [1017].

Overall, the evidence particularly supports a benefit of treating pre- and perimenopausal patients in second- and subsequent-line therapy with CDK4/6 inhibitors in terms of significant effects on progression-free survival. Results on tolerability of CDK4/6 inhibitors were comparable for all patient populations analyzed and indicated significantly higher event rates compared with placebo. Adverse events can be minimized by careful management of therapy [1033].

Conclusion pre- and perimenopausal patients

CDK4/6 inhibitors in early benefit assessment

For palbociclib, ribociclib and abemaciclib, results of the early benefit assessment according to § 35a SGB are available at the time of guideline preparation (last review: February 2020). The Institute for Quality and Efficiency in Health Care (IQWiG) and the Federal Joint Committee (G-BA) concluded that for palbociclib, ribociclib, and abemaciclib there is no evidence of an added medical benefit compared with the respective appropriate comparator therapy for any therapy line or patient group [1034], [1035], [1036], [1037], [1038], [1039]. This conclusion was mainly based on the observed unfavorable side effect profile in the absence of evidence for benefits in overall survival or quality of life. Effects on progression-free survival (PFS) are only considered in the early benefit assessment if analyses are available that show PFS as a valid surrogate endpoint for overall survival. According to IQWiG, these were not available. Thus, the discrepancy between the results of the early benefit assessment and the guideline recommendation on overall survival data, which were not available at the time of the early benefit assessment, and the consideration of progression-free survival as a benefit parameter can be explained. For abemaciclib and riboclicib,

however, further benefit dossiers are ongoing at the time of the admendment and their final assessments are still pending.

The adverse events shown were generally compared with the placebo or endocrine therapy alone as defined by the G-BA. In clinical practice, however, a comparison to chemotherapy associated with significantly more severe side effects is appropriate. CDK4/6 inhibitors are expected to show a significantly more tolerable side effect profile than placebo compared to available chemotherapeutic agents. In addition, side effects are very well managed with established supportive measures [1033]. A tabular overview in the form of evidence tables of the listed effect estimates can be found in the evidence report for this guideline.

Background 5.29 to 5.31.

Unless CDK4/6 inhibitors are given, the initial therapeutic step is ovarian function elimination (GnRH analogs, ovariectomy, or radiomenolysis) in combination with tamoxifen. If tumor progression occurs or tamoxifen is contraindicated, a third-generation aromatase inhibitor plus GnRH analog can be used, and fulvestrant plus GnRH analog may also be considered. Despite sparse data, therapy should be largely analogous to the treatment of postmenopausal patients while maintaining ovarian suppression [1018], [1021], [1022], [1023], [1024], [1025], [1026].

5.31	Evidence-based Recommendation	modified 2021
GoR **0**	Therapy can be performed while maintaining ovarian suppression in analogy to the treatment of postmenopausal patients. As options can be used in combination with a GNRH analogue depending on the previous therapy: • aromatase inhibitors • fulvestrant • tamoxifen	
LoE **1b**	[1041]; [1042]; [1043]; [1044]; [28]; [989]; [992]; [1000]	
	Strong Consensus	

5.4.2. Systemic therapy in postmenopausal patients and positive hormone receptor status and negative HER2 status.

5.32	Evidence-based Recommendation	new 2021
GoR **A**	In postmenopausal patients, endocrine therapy, possibly combined with targeted therapy, shall be offered if hormone receptor status is positive and HER2 status is negative. Endocrine therapy is not indicated in patients with the need to achieve rapid remission to avert marked symptoms of the affected organ.	
LoE **1b**	[1045]; [1046]; [1047]; [1048]; [1049]; [1050]; [1051]	
	Strong Consensus	

5.33	Evidence-based Recommendation	checked 2021
GoR **A**	Combined chemo-endocrine therapy is not recommended. Although it may increase remission rates, it also leads to increased toxicity without prolonging progression-free interval or overall survival.	
LoE **1a**	[1052]; [1053]	

Background 5.32 and 5.33

See background text to 5.26 and 5.27

5.4.2.1. First-line therapy

5.34	Evidence-based Recommendation	new 2021
GoR **B**	Combination therapies with an aromatase inhibitor or fulvestrant with CDK 4/6 inhibitors should be performed if this group of substances has not yet been used.	
LoE **1b**	[1029]; [1054]; [1055]; [1056]; [1057]; [1058]; [1059]	
	Strong Consensus	

5.35	Consensus-based Recommendation	modified 2021
EC	Treatment with fulvestrant should particularly follow pretreatment with an aromatase inhibitor, but can also be used as a first line of therapy, especially in patients who have not yet undergone endocrine pretreatment.	

Background 5.34

First-line therapy of postmenopausal patients with CDK4/6 inhibitors

For postmenopausal patients, data are available on first-line therapy with CDK4/6 inhibitors in combination with endocrine therapy from a total of five randomized controlled trials of three compounds (abemaciclib: MONARCH-3; palbociclib: PALOMA-1 and PALOMA-2; ribociclib: MONALEESA-2 and MONALEESA-3). MONARCH-3, PALOMA-2, MONALEESA-2, and MONALEESA-3 were randomized, controlled, and blinded clinical trials, whereas PALOMA-1 was conducted as an open label study and thus subject to a higher potential for bias.

Gesamtüberleben

With regard to overall survival, there have been no significant advantages for postmenopausal patients in first-line therapy to date (see evidence tables in the guideline report - section 14.6).

Progressionsfreies Überleben

In contrast, treatment with CDK4/6 inhibitors showed significant advantages over placebo in terms of progression-free survival in all studies. With abemaciclib: HR 0.54 [0.42; 0.70], with palbociclib HR 0.49 [0.32; 0.75] (PALOMA-1), resp. HR : 0.58 [0.46; 0.72] (PALOMA-2) and under ribociclib HR 0.57 [0.43; 0.74] (MONALEESA-2) and HR 0.58 [0.42; 0.80] (MONALEESA-3), respectively) [1029], [1055], [1056], [1058].

Gesundheitsbezogene Lebensqualität

There is no evidence of an effect of treatment with CDK4/6 inhibitors on health-related quality of life in postmenopausal patients in terms of a clinically relevant difference in scores on the EORTC QLQ-C30 or FACT-B questionnaire (see guideline report).

Adverse events

Treatment with CDK4/6 inhibitors was also generally associated with a significantly higher incidence of adverse events for postmenopausal patients: Under abemaciclib, the effect for UE with CTCAE grade ≥3 was HR 3.14 [2.25; 4.39] (MONARCH-3), under palbociclib HR 5.47 [3.15; 9.51] (PALOMA-1) and 5.50 [4.14; 7.31] (PALOMA-2), respectively, and under ribociclib HR 4.21 [3.40; 5.21] [1054], [1055], [1056], [1059]. Patients discontinued treatment significantly more often under abemaciclib and ribociclib than under placebo. With abemaciclib, the hazard ratio was 6.04 [2.18; 16.70]; with ribociclib, first-line HR was 4.23 [2.31; 7.74]; and for any line of therapy, it was 2.73 [1.58; 4.74] [1012], [1014], [1054], [1056], [1059].

Conclusion postmenopausal patients in first-line therapy

Overall, the evidence in postmenopausal patients in first-line therapy with CDK4/6 inhibitors shows a treatment advantage over comparator therapy only for the endpoint progression-free survival. The results for tolerability of CDK4/6 inhibitors were comparable for all patient populations analyzed and indicated significantly higher event rates compared with comparator therapy. Comments on the benefit assessments by IQWiG and the decisions of the G-BA can be found in chapter 5.4.1. A tabular overview in the form of evidence tables of the listed effect estimates can be found in the evidence report for this guideline

5.4.2.2. Second and follow-up line therapy

5.36	Evidence-based Recommendation	modified 2021
GoR **B**	If a CDK4/6 inhibitor had not yet been used in the first-line setting, it should be used in further endocrine-based lines of therapy.	
LoE **1b**	[1009]; [1013]; [1057]	

5.37	**Consensus-based Recommendation**	**modified 2021**
EC	After prior anti-hormonal therapy with a non-steroidal aromatase inhibitor as well as CDK4/6 inhibitors, follow-up therapy with exemestane and the mTOR inhibitor everolimus can be performed.	

5.38	**Consensus-based Recommendation**	**new 2021**
EC	Further steps in the endocrine treatment sequence in postmenopausal patients represent, depending on the pretreatment, the use of alpelisib (if a corresponding PI3KA mutation is detected) or antiestrogens, estrogen receptor antagonists, switching the aromatase inhibitor from a steroidal to a nonsteroidal aromatase inhibitor, or vice versa.	
	Strong Consensus	

Background text 5.36.

Second-line and follow-up therapy of postmenopausal patients with CDK4/6 inhibitors

For postmenopausal patients, data are available on second and subsequent line therapy with CDK4/6 inhibitors in combination with endocrine therapy from a total of three randomized controlled trials on three substances (abemaciclib: MONARCH-2, palbociclib: PALOMA-3; ribociclib: MONALEESA-3). These studies are randomized, controlled, blinded clinical trials. The population of postmenopausal patients in second-line and follow-up therapy was extracted for the MONARCH-2 and PALOMA-3 studies in the form of subgroups in order to be able to represent the patient group required by the G-BA. The data on abemaciclib and palbociclib presented below are therefore the results of subgroup analyses. With non-significant effect estimates, these do not have sufficient test strength to allow a statistically sound interpretation and should therefore be regarded as exploratory results.

Overall Survival

With regard to overall survival, there were advantages for the postmenopausal patients in the second- and follow-up-line therapy. There was a significant survival advantage over placebo here for abemaciclib (HR 0.77 [0.61; 0.98]) and palbociclib (HR 0.73 [0.57; 0.95]) [1009], [1013]. For ribociclib, the hazard ratio for overall survival was just below the significance threshold (HR 0.73 [0.53; 1.00]) [1057]. No subgroup analyses (e.g., with regard to age or ethnicity) are available for the group of postmenopausal patients in second-line or follow-up therapy.

Progression-free Survival

There were significant advantages of treatment with CDK4/6 inhibitors over placebo in terms of progression-free survival in all studies. With abemaciclib: HR 0.58 [0.46; 0.73], with palbociclib: HR 0.41 [0.30; 0.56], and with ribociclib HR 0.58 [0.42; 0.80] [1060], [1061], [1058].

Health-related quality of life

There is no evidence of an effect of treatment with CDK4/6 inhibitors on health-related quality of life in postmenopausal patients in terms of a clinically relevant difference in EORTC QLQ-C30 score (see guideline report).

Adverse events

Treatment with CDK4/6 inhibitors was also generally associated with a significantly higher incidence of adverse events for postmenopausal patients: For abemaciclib, the effect estimate for UE with CTCAE grade ≥3 under any line of therapy was HR 3.34 [2.43; 4.59], for palbociclib HR 4.54 [3.22; 6.41], and for ribociclib HR 4.46 [3.45; 5.77] [1012], [1014], [1059]. Patients discontinued treatment significantly more often with abemaciclib and ribociclib than with placebo. Under abemaciclib, the effect estimate was HR 2.32 [1.03; 5.23] and under ribociclib, HR 2.73 [1.58; 4.74] [1012], [1014], [1059].

Conclusion Second- and Follow-up-Line Therapy of Postmenopausal Patients with CDK4/6 Inhibitors

Overall, the evidence supports a benefit of treating postmenopausal patients in second- and subsequent-line therapy with CDK4/6 inhibitors in the form of significant effect estimates for both progression-free survival and overall survival that have not been achieved in the past. Results on tolerability of CDK4/6 inhibitors were comparable for all patient populations analyzed and indicated significantly higher event rates compared with placebo. Comments on the benefit assessments by IQWiG and the decisions of the G-BA can be found in chapter 5.4.1. A tabular overview in the form of evidence tables of the listed effect estimates can be found in the evidence report for this guideline.

Background 5.37. and 5.38.

First-line drugs are third-generation aromatase inhibitors. Subgroup analyses for three predominantly used aromatase inhibitors (anastrozole, exemestane, and letrozole) show similar survival benefits [1063].

After failure of a nonsteroidal aromatase inhibitor (anastrozole or letrozole), administration of everolimus in addition to exemestane has been shown to prolong progression-free survival. Thus, this approach represents another treatment option.

In case of tumor re-progression, antiestrogens, estrogen receptor antagonists, and finally high-dose progestogens or estrogens can be used [1065], [1066].

Aromatase inhibitor treatment is associated with a significant increase in side effects induced by hormone withdrawal [1067]. During aromatase inhibitor therapy, fewer hot flashes, thromboembolic events, and endometrial cancer occur as side effects compared with tamoxifen, but the rate of arthralgias and myalgias is increased. Furthermore, higher bone density loss and possibly a higher rate of osteoporotic fractures are to be expected. However, these aspects are often not of primary concern in the palliative treatment situation.

A combination of fulvestrant and aromatase inhibitors is not recommended due to controversial
data [1062], [1064], [1068], [1069], [1070], [1071], [1072], [1073], [1074], [1075], [1076].

Summary conclusion on the use of CK4/6 inhibitors in patients with breast cancer

The clinical trial data presented here include results from populations defined a priori in the study protocol as well as results from post-hoc subgroups, some of which were

prescribed by the G-BA. They were listed to ensure a complete reporting of the available evidence.

However, a final interpretation of the subgroup analyses presented is hampered by statistical limitations (multiple testing, insufficient test strength (power). Therefore, the recommendations formulated by the guideline group on the use of CK4/6 inhibitors are based on the analyses of the respective overall populations in the studies (see guideline report).

In these patients, advantages of the CDK4/6 inhibitors were shown with respect to prolonged overall survival, especially for abemaciclib as well as ribociclib [1009], [1015]. In addition, significant prolongation of progression-free survival was observed for all agents [1060], [1061], [1016], [1029], [1058].

These survival benefits outweigh any lack of effects with respect to health-related quality of life as well as the well-treatable side effects

5.4.3. Chemotherapy of metastatic breast cancer

Pre-chemotherapy criteria

5.39	**Consensus-based Recommendation**
EC	Before chemotherapy is administered, the patient's general condition and comorbidity, previous therapies and compliance shall be assessed.
	Strong Consensus

Toxicity assessment

5.40	**Consensus-based Recommendation**
EC	During the therapy, a regular toxicity assessment (subjective and objective) shall be carried out. The dosage as well as the desired time intervals shall be carried out according to generally accepted standard or currently published therapy regimes. After determination of a suitable and representative measurement parameter (symptoms, tumor markers, imaging) before the start of therapy, an evaluation of the therapeutic effect shall be performed at least every 6-12 weeks in accordance with clinical requirements. In the course of time, the imaging intervals can be extended if the remission is persistent and the clinical and laboratory chemical assessment of the disease status is good.
	Strong Consensus

Modification of chemotherapy

5.41	Consensus-based Recommendation
EC	Therapy should be discontinued if clinically relevant progression or intolerable toxicity is observed. A switch to another chemotherapy should not be made without proven progression or intolerable toxicity.
	Strong Consensus

Polychemotherapy/combination therapy

5.42	Evidence-based Recommendation
GoR **B**	If chemotherapy is indicated, patients without high remission pressure should receive sequential chemotherapy.
LoE **1a**	[1077]; [1078]
	Strong Consensus

5.43	Evidence-based Recommendation
GoR **0**	The combination therapy of chemotherapy and bevacizumab in first-line therapy can improve progression-free survival, but with an increased rate of side effects and without impact on overall survival.
LoE **1a**	[1079]; [1080]; [1081]; [1082]; [1083]; [1084]
	Strong Consensus

5.44	Evidence-based Recommendation
GoR **0**	In the case of more severe symptoms and rapid growth or aggressive tumour behaviour, i.e. high remission pressure, polychemotherapy or chemotherapy + bevacizumab can be performed.
LoE **1a**	[1007]; [1077]
	Strong Consensus

Background 5.34 to 5.39

Due to the heterogeneity of the metastases and the individual course of the disease, no uniform therapy strategy can be given. This applies in particular to the cytostatic

treatment of metastasized breast carcinoma. Although monotherapy has lower remission rates than polychemotherapy, this does not have a significant negative impact on survival time. Monotherapies are better tolerated, so that monotherapy should be used whenever possible. Monotherapy should be used in cases of minor symptoms and slow tumour growth or ineffectiveness of endocrine therapy. Polychemotherapy is only indicated for severe symptoms, rapid tumour growth and aggressive tumour behaviour. Cytostatic therapy should be based on the therapeutic index in the case of incurable disease, whereby the effect (e.g. symptom control) and side effects of a therapy must be considered and weighed up. For the majority of patients, the use of subjectively less stressful monotherapies compared to a combination therapy is recommended. This is supported by a Cochrane meta-analysis published in 2015, which showed that there were no significant differences in overall survival and progression-free survival between combination therapy and sequential monochemotherapy when compared with sequential monochemotherapy (OS HR 1.04 95% CI 0.93-1.16; p=0.45 / PFS HR1.11 95% CI 0.99-1.25; p=0.08). In comparison, the response was significantly higher with combination chemotherapy. However, combination chemotherapy also showed a higher toxicity with regard to the rate of febrile neutropenia. Many mainly non-haematological side effects were not described in this meta-analysis. In the meta-analysis, two scenarios of sequential monochemotherapy were described, one change of monochemotherapy with progression or fixed change of monochemotherapy without progression after a few cycles. The results were similar for both scenarios, with the hazard ratios described referring to the total collective. The authors conclude that the results of this meta-analysis support the recommendations for sequential monotherapy compared to combination chemotherapy [1077], except for the cases with rapid tumor progression and high remission pressure.

If the patient has not yet received anthracyclines/taxanes in adjuvant therapy, they can be used primarily.

Before and during chemotherapy the patient's general condition must be assessed regularly. During therapy, the side effects of this treatment must also be evaluated regularly. An evaluation of the therapeutic effect by means of imaging should be performed every 6-12 weeks (interval depending on the spread of the disease, disease dynamics and clinical situation). In the course of time, the imaging intervals can be extended in case of remission and good clinical and laboratory chemical assessment of the disease status. In case of progress or pronounced toxicity, therapy should be discontinued. The therapeutic index (individual patient benefit versus therapy-related side effects) should be positive in the overall assessment of the therapy.

The dosage as well as the intended time intervals of the therapy should be adapted to general guidelines of the therapy, i.e. recognized published protocols. Dose-intensified and high-dose therapies have not yet led to any improvement in effectiveness. Their use is only acceptable in the context of studies (Conchrane: [800]).

A meta-analysis by Ghersi et al. showed that taxane-containing chemotherapies were associated with improved progression-free and overall survival as well as an increased tumor response. However, they also led to an increased risk of neuropathy and a lower risk of nausea and vomiting compared to non-taxan-containing regimens [1085].

5.4.3.1. Bevacizumab in metastatic breast cancer (first line)

The improved efficacy of first-line treatment with paclitaxel plus bevacizumab (P/Bev) compared to paclitaxel monotherapy was demonstrated in a randomized phase III study: In the E2100 study, the combined use of P/Bev doubled the objective response

rate (36.9% vs. 21.2%; p<0.001), was in einer nachfolgenden unabhängigen Auswertung bestätigt wurde (48,9% vs. 22,2%; p<0,0001). Dieses Ergebnis wurde unabhängig vom Hormonrezeptor-Status der Tumore erzielt. Mit P/Bev wurde eine signifikante Verlängerung der progressionsfreien Zeit (PFS) von 11.4 vs. 5.8 Monaten (HR 0,42; 95% CI, 0,34 – 0,52; p<0.001) im Vergleich zur Monotherapie erzielt, die ebenfalls in der Kontrollauswertung bestätigt wurde (11.3 vs. 5.8 Monate; HR 0,48; 95% CI 0.385 - 0.607; p < 0,0001) [1079], [1080]. Ein Vorteil hinsichtlich des medianen Gesamtüberlebens (OS) konnte hingegen nicht belegt werden (26.7 vs. 25.2 Monate; HR 0.88; p=0.16). Blutdruckerhöhungen > Grade 3 (14.8% vs. 0.0%, p < 0.001), Proteinurie (3.6% vs. 0.0%, p < 0.001), Kopfschmerzen (2.2% vs. 0.0%, p = 0.008) und cerebrovasculäre Ischämien (1.9% vs. 0.0%, p = 0.02) traten dabei deutlich häufiger beim Einsatz von P/Bev im Vergleich zur Monotherapie mit Paclitaxel auf [1079].

The efficacy of first-line combination therapy of capecitabine with bevacizumab (cap/ev) has also been demonstrated in several Phase III studies. These studies showed a median PFS for this taxane-free combination of 9.2 (RIBBON-1), 8.8 (CARIN) and 8.1 months (TURANDOT) [1081], [1082], [1083].

In the phase III study TURANDOT, which directly compared P/Bev with Cap/Bev, P/Bev was found to be superior to Cap/Bev with regard to ORR (44% vs. 27%; p grade 3), in particular neutropenia (18%) and peripheral polyneuropathy (14%), while in the Cap/Bev arm hand-foot syndrome (16%), elevated blood pressure (6%) and diarrhoea (5%) were prominent [1083].

In summary, the additional therapy with bevacizumab showed increased remission rates and an improvement of PFS (but without survival advantage, which makes a combination therapy especially suitable in case of higher "remission pressure" and in the absence of a risk constellation regarding side effects (no uncontrolled arterial hypertension, no cerebrovascular ischemia and no deep vein thrombosis in the history).

5.4.3.2. Regimens

Adriamycin 60 / cyclophosphamide 600

Table 7: Adriamycin 60 / cyclophosphamide 600

Day	Substance	Dosage
1	**Adriamycin**	60 mg/m²
1	**Cyclophosphamide**	600 mg/m²

Cycle duration 21 days

Reference: [1089]

Adriamycin liposomal 75 / cyclophosphamide 600

Table 8: Adriamycin liposomal 75 / cyclophosphamide 600

Day	Substance	Dosage
1	**adriamycin liposoma**	75 mg/m²
1	**Cyclophosphamide**	600 mg/m²

Cycle duration 21 days

Reference: [1090]

Adriamycin 50 / docetaxel 75

Table 9: Adriamycin 50 / docetaxel 75

Day	Substance	Dosage
1	**Adriamycin**	50 mg/m²
1	**Docetacxel**	75 mg/m²

Cycle duration 21 days

Reference: [1089]

Capecitabine 2000 / Bevacizumab 15

Table 10: Capecitabine 2000 / Bevacizumab 15

Day	Substance	Dosage	Procedure
1-14	**Capecitabine**	1000 mg/m² KOF	1-0-1
1	**Bevacizumab**	15 mg/kg bw	

Cycle duration 21 days

Reference: [1083]

Capecitabine 2000 / Paclitaxel 175

Table 11: Capecitabine 2000 / Paclitaxel 175

Day	Substance	Dosage	Procedure
1-14	**Capecitabine**	1000 mg/m² KOF	1-0-1
1	**Paclitaxel**	175 mg/m² KOF	

Cycle duration 28 days

Reference: [1091]

Cisplatin 75 / Gemcitabine 1250

Table 12: Cisplatin 75 / Gemcitabine 1250

Day	Substance	Dosage	Carrier solution	Appl.	Inf. duration	Procedure
1	**Cisplatin**	75 mg/m² KOF	NaCl 0.9% 500 ml	intravenously	60 min	Order
1,8	**Gemcitabine**	1250 mg/m² KOF	NaCl 0.9% 250 ml	intravenously	30 minutes	Order

Cycle duration 21 days

Reference: [1092]

Cyclophosphamide 600 / non-pegylated liposomal doxorubicin 75

Table 13: Cyclophosphamide 600 / non-pegylated liposomal doxorubicin 75

Day	Substance	Dosage
1	**Cyclophosphamide**	600 mg/m² KOF
1	**liposomal doxorubicin**	75 mg/m² KOF

Cycle duration 21 days

Reference: [1090]

docetaxel

Table 14: docetaxel

Day	Substance	Dosage
1	**docetaxel**	100 mg/m² KOF

Cycle duration 21 days

Reference: [1093], [1094]

Docetaxel 35, breast cancer

Table 15: Docetaxel 35, breast cancer

Day	Substance	Dosage
1, 8, 15	**docetaxel**	35 mg/m² KOF

Cycle duration 28 days

Reference: [1095]

Doxorubicin 50 / docetaxel 75, breast cancer

Table 16: Doxorubicin 50 / docetaxel 75, breast cancer

Day	Substance	Dosage
1	**Doxorubicin**	50 mg/m² KOF
1	**docetaxel**	75 mg/m² KOF

Cycle duration 21 days

Reference: [1089], [1096]

Doxorubicin 60 / cyclophosphamide 600

Table 17: Doxorubicin 60 / cyclophosphamide 600

Day	Substance	Dosage
1	**Doxorubicin**	60 mg/m² KOF
1	**Cyclophosphamide**	600 mg/m² KOF

Cycle duration 21 days

Reference: [1089]

Epirubicin 60 / cyclophosphamide 600

Table 18: Epirubicin 60 / cyclophosphamide 600

Day	Substance	Dosage
1	**Epirubicin**	60 mg/m²
1	**Cyclophosphamide**	600 mg/m²

Cycle duration 21 days

Reference: [1097]

Epirubicin 75 / cyclophosphamide 600

Table 19: Epirubicin 75 / cyclophosphamide 600

Day	Substance	Dosage
1	**Epirubicin**	75 mg/m² KOF
1	**Cyclophosphamide**	600 mg/m² KOF

Cycle duration 21 days

Reference: [1097]

Epirubicin 75 / docetaxel 75

Table 20: Epirubicin 75 / docetaxel 75

Day	Substance	Dosage
1	**Epirubicin**	75 mg/m² KOF
1	**docetaxel**	75 mg/m² KOF

Cycle duration 21 days

Reference: [1096]

Epirubicin 60 / Paclitaxel 175

Table 21: Epirubicin 60 / Paclitaxel 175

Day	Substance	Dosage
1	**Epirubicin**	60 mg/m²
1	**Paclitaxel**	175 mg/m²

Cycle duration 21 days

Reference: [1097]

Epirubicin 60 / Paclitaxel 175

Table 22: Epirubicin 60 / Paclitaxel 175

Day	Substance	Dosage
1	**Epirubicin**	60 mg/m²

Day	Substance	Dosage
1	**Paclitaxel**	175 mg/m²

Cycle duration 21 days

Reference: [1097]

eribulin 1,23

Table 23: eribulin 1,23

Day	Substance	Dosage
1, 8	**Eribulin**	1, 23 mg/m² KOF

Cycle duration 21 days

Reference: [1098], [1099]

everolimus 10 / exemplestan 25, postmenopausal

Table 24: everolimus 10 / exemplestan 25, postmenopausal

Day	Substance	Dosage
1-28	**Everolimus**	10 mg
1-28	**Copy**	25 mg

Cycle duration 28 days

Reference: [1088], [1100]

Fulvestrant 500, postmenopausal

Table 25: Fulvestrant 500, postmenopausal

Day	Substance	Dosage
1	**Fulvestrant**	500 mg

Cycle duration 28 days

Reference: [1101][1102]

Gemcitabine 1000 / Carboplatinum 4

Table 26: Gemcitabine 1000 / Carboplatinum 4

Day	Substance	Dosage
1, 8	**Gemcitabine**	1000 mg/m² KOF
1	**Carboplatinum**	4 AUC

Cycle duration 21 days

Reference: [1103]

Lapatinib 1250 / Capecitabine 2000

Table 27: Lapatinib 1250 / Capecitabine 2000

Day	substance	Dosage	Procedure
1-21	**Lapatinib**	1250 mg	1-0-0
1-14	**Capecitabine**	1000 mg/m² KOF	1-0-1

Cycle duration 21 days

Reference: [1104]

NabPaclitaxel 125 / carboplatinum

Table 28: NabPaclitaxel 125 / carboplatinum

Day	Substance	Dosage
1, 8	**NabPaclitaxel**	125 mg/m²
1, 8	**Carboplatinum**	AUC 2

Cycle duration 21 days

Reference: [1105]

Nab-paclitaxel 100 / carboplatin 2 / bevacizumab 10, (triple negative)

Table 29: Nab-paclitaxel 100 / carboplatin 2 / bevacizumab 10, (triple negative)

Day	Substance	Dosage
1, 8, 15	**Nab paclitaxel**	100 mg/m² KOF

Day	Substance	Dosage
1, 8, 15	**Carboplatinum**	AUC 2
1, 15	**Bevacizumab**	10 mg/kg bw

Cycle duration 28 days

Reference: [1106]

Nab-paclitaxel 125 / Trastuzumab (4/2)

Table 30: Nab-paclitaxel 125 / Trastuzumab (4/2)

Day	Substance	Dosage
1, 8, 15	**Nab paclitaxel**	125 mg/m² KOF
1	**Trastuzumab**	4 mg/kg bw
8, 15, 22	**Trastuzumab**	2 mg/kg bw

Cycle duration 28 days

Reference: [1107]

Nab-paclitaxel 125 weekly

Table 31: Nab-paclitaxel 125 weekly

Day	Substance	Dosage
1, 8, 15	**Nab paclitaxel**	125 mg/m² KOF

Cycle duration 28 days

Reference: [1107], [1108]

Paclitaxel 90 / Bevacizumab 10

Table 32: Paclitaxel 90 / Bevacizumab 10

Day	Substance	Dosage
1, 8, 15	**Paclitaxel**	90 mg/m² KOF

Day	Substance	Dosage
1, 15	**Bevacizumab**	10 mg/kg bw

Cycle duration 28 days

Reference: [1079], [1080], [1083], [1109], [1110]

Paclitaxel 175 / Capecitabine 2000

Table 33: Paclitaxel 175 / Capecitabine 2000

Day	Substance	Dosage
1	**Paclitaxel**	175 mg/m²
1-14	**Capecitabine**	2000 mg/m²

Cycle duration 21 days

Reference: [1091]

paclitaxel 175 / gemcitabine 1250

Table 34: paclitaxel 175 / gemcitabine 1250

Day	Substance	Dosage
1	**Paclitaxel**	175 mg/m² KOF
1-14	**Gemcitabine**	1250 mg/m² KOF

Cycle duration 21 days

Reference: [1092], [1111]

Palbociclib 125 / Fulvestrant 500

Table 35: Palbociclib 125 / Fulvestrant 500

Day	Substance	Dosage
1-21	**Palbociclib**	125 mg (every 4 weeks)
1, 15, 29	**Fulvestrant**	500 mg (only in 1st cycle, from 2nd cycle every 4 weeks)

Cycle duration 28 days

Reference: [1086][1087], [1112]

Pertuzumab 840 / Trastuzumab 8 / Docetaxel 75, (HER2+) cycle 1

Table 36: Pertuzumab 840 / Trastuzumab 8 / Docetaxel 75, (HER2+) cycle 1

Day	Substance	Dosage
1	**Pertuzumab**	840 mg
1	**Trastuzumab**	8 mg/kg bw
1	**docetaxel**	75 mg/m² KOF

Cycle duration 21 days

Pertuzumab 420 / Trastuzumab 6 / Docetaxel 75, (HER2+) cycle 2+

Table 37: Pertuzumab 420 / Trastuzumab 6 / Docetaxel 75, (HER2+) cycle 2+

Day	Substance	Dosage
1	**Pertuzumab**	420 mg
1	**Trastuzumab**	6 mg/kg bw
1	**docetaxel**	75 mg/m² KOF

Cycle duration 21 days

Reference: [1113]

Trastuzumab (8) 6 / Docetaxel 100, (HER2+)

Table 38: Trastuzumab (8) 6 / Docetaxel 100, (HER2+)

Day	Substance	Dosage
1	**Trastuzumab**	(8) 6 mg/kg bw
1	**docetaxel**	100 mg/m² KOF

Cycle duration 21 days

Reference: [1114]

Trastuzumab 6 / letrozole 2.5, HER2+/HR+

Table 39: Trastuzumab 6 / letrozole 2.5, HER2+/HR+

Day	Substance	Dosage
1	**Trastuzumab**	6 mg/kg bw
1-21	**Letrozole**	2.5 mg

Cycle duration 21 days

Reference: [1115]

Trastuzumab (8) 6 / vinorelbine 30, breast carcinoma (HER2+)

Table 40: Trastuzumab (8) 6 / vinorelbine 30, breast carcinoma (HER2+)

Day	Substance	Dosage
1	**Trastuzumab**	(8) 6 mg/kg bw
1, 8	**Vinorelbine**	30 mg/m² KOF

Cycle duration 21 days

Reference: [1114]

Trastuzumab Emtansin 3,6, (HER2+)

Table 41: Trastuzumab Emtansin 3,6, (HER2+)

Day	Substance	Dosage
1	**trastuzumab emtansin**	3,6 mg/kg bw

Cycle duration 21 days

Reference: [1116][1117]

trofosfamide 150

Table 42: trofosfamide 150

Day	Substance	Dosage	Procedure
1-10	**Trofosfamide**	150 mg	1-1-1

Cycle duration 28 days

Reference: [1118]

trofosfamide 50

Table 43: trofosfamide 50

Day	Substance	Dosage	Procedure
1-28	**Trofosfamide**	50 mg	1-1-1

Cycle duration 28 days

Reference: [1118]

vinorelbine 30

Table 44: vinorelbine 30

Day	Substance	Dosage
1-28	**Vinorelbine**	30 mg/m² KOF

Cycle duration 21 days

Reference: [1119], [1120], [1121]

vinorelbine 70 oral

Table 45: vinorelbine 70 oral

Day	Substance	Dosage
1, 3, 5, 8, 10, 12, 15, 17, 19	**Vinorelbine**	23.3 mg/m² KOF

Cycle duration 28 days

Reference: [1122]

5.45	Consensus-based Recommendation
EC	The following substances, for example, can be used as monotherapy: alkylanciens, anthraquinones, anthracyclines (also in liposomal form), eribulin, fluoropyrimidines, platinum complexes, taxanes and vinorelbine. In polychemotherapy, these substances can be combined with each other or with other substances. However, only combinations that have been verified in studies should be used.
	Strong Consensus

Background 5.40

Due to the heterogeneity of the metastases and the individual courses of disease, no uniform therapy strategy can be specified. This applies in particular to the cytostatic treatment of metastasized breast carcinoma. Although monotherapy has lower remission rates than polychemotherapy, this does not have a significant negative impact on survival time. Monotherapies are better tolerated, so that monotherapy should be used whenever possible. Polychemotherapy is only indicated for severe symptoms, rapid tumor growth and aggressive tumor behavior.

If the patient has not yet received anthracyclines/taxanes in the adjuvant therapy, these can be used primarily.

Cytostatic therapy should be based on the therapeutic index in cases of incurable disease, whereby the effect (e.g. symptom control) and side effects of a therapy must be considered and weighed up. The use of subjectively less stressful monotherapies or combination therapies is recommended. This is supported by a Cochrane meta-analysis published in 2015, which showed that there were no significant differences in progression-free survival and overall survival between combination therapy and sequential monochemotherapy when compared with sequential monochemotherapy. The response was significantly higher with combination chemotherapy compared to sequential monochemotherapy. However, combination chemotherapy also showed a higher toxicity with regard to the rate of febrile neutropenia. Many mainly non-haematological side effects were not described in this meta-analysis. In the meta-analysis, two scenarios of sequential monochemotherapy were described, one change of monochemotherapy with progression or fixed change of monochemotherapy without progression after a few cycles. The results were similar for both scenarios, with the described results referring to the first scenario [1077].

Before and during chemotherapy, the patient's general condition must be assessed regularly. During therapy, the side effects of this treatment must also be evaluated regularly. An evaluation of the therapeutic effect by means of imaging should be performed every 6-12 weeks (interval depending on the spread of the disease, disease dynamics and clinical situation). In the course of time, the imaging intervals can be extended in case of remission and good clinical and laboratory chemical assessment of the disease status. In case of progress or pronounced toxicity, therapy should be discontinued. The duration of therapy depends on the therapeutic index, whereby tumor response and therapy-related side effects should be included in the overall assessment and therapy should only be continued if the assessment is positive.

The dosage as well as the intended time intervals of the therapy should be adapted to general guidelines of the therapy, i.e. recognized published protocols. Dose-intensified and high-dose therapies have not yet led to any improvement in effectiveness. Their use is only acceptable in the context of studies (Cochrane: [800]).

5.4.4. Metastatic HER2-positive breast cancer

5.46	Evidence-based Recommendation
GoR **B**	Metastatic HER2-positive breast carcinomas should be treated with anti-HER2 therapy, provided that there are no cardiac contraindications.
LoE **1a**	[1123]; [1124]
	Strong Consensus

5.47	Evidence-based Recommendation
GoR **B**	In the case of a metastasized HER2-positive breast carcinoma, a dual blockade with trastuzumab / pertuzumab and a taxane should be used in first-line therapy.
LoE **1b**	[1123]
	Consensus

5.48	Evidence-based Recommendation
GoR **B**	In the case of a metastasized HER2-positive breast carcinoma, therapy with T-DM1 should be used in second-line therapy.
LoE **1b**	[1123]
	Consensus

5.4.5. Specific metastatic localization

5.4.5.1. Basic management of distance metastases

5.49	Consensus-based Recommendation
EC	The indication for surgical or local ablative therapy of distant metastases should be determined individually and in an interdisciplinary consultation.
	Strong Consensus

Background 5.44

In individual cases, patients with oligometastasis (staging), good performance status and a long interval between initial therapy can benefit from local therapy [1125]. However, the prognostic relevance compared to an adequate systemic therapy is unclear, since only retrospective studies with strictly preselected patients are available.

In the following chapter, recommendations of the S3 guideline Supportive Therapy of Oncology Patients (Version 1, 2016) are listed at several points. The guideline group is of the opinion that these recommendations can be applied directly to patients with breast cancer. A renewed consensus on the recommendations by the breast cancer guideline group was not reached.

Caution: If this recommendation in the S3 guideline Supportive Therapy of Oncological Patients (current version at http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html) is changed, for example in the context of an update, these recommendations also lose their validity at this point.

5.4.5.2. Specific management of bone metastases

For the diagnosis and therapy of skeletal metastases, please refer to the S3 guideline Supportive Therapy in Oncology Patients (http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html).

Osseous metastases occur very frequently (> 50%) in patients with breast cancer. Associated skeletal complications / skeletal related events (SREs) such as pathological fractures, pain with increased analgesic consumption, spinal compression syndromes or hypercalcemia require effective and often interdisciplinary therapy. In symptomatic tumor patients, a bone scintigraphy is suitable for diagnosis to assess the spread of osseous involvement. If there is a risk of fractures in particular, an x-ray-based procedure (native x-ray / CT) should be performed. An MRI should be performed if soft tissue is involved or in the case of neurological deficits, especially myelocompression. In case of detection of a newly occurring osseous manifestation, a new spread diagnosis is necessary. These different imaging techniques have different sensitivities and specificities in the diagnosis of bone metastases [1126].

Depending on the urgency and the aim of the therapy, the proposal of a therapy should be determined on an interdisciplinary basis by the surgeon, radio-oncologist, nuclear medicine specialist, internal oncologist, oncology specialist, pain therapist and, if necessary, representatives of other specialist disciplines.

The following treatment options are available for patients with osseous manifestations:

- Medicated pain therapy
- Local radiation
- Surgical intervention
- Systemic tumour therapy
    - Cytostatic drugs, hormone therapy, targeted substances, immunomodulating therapy, etc.
    - Radionuclides
    - Bisphosphonates or RANK ligand antibodies

In the case of painful bone metastases, the first priority is consistent medicinal analgesia. For stable osseous manifestations including stable vertebral body manifestations without evidence of myelon compression, conservative therapy (e.g. systemic tumor therapy, radiotherapy, radionuclide therapy, bisphosphonates/RANK ligand antibodies) is indicated. For patients with myelon compression and neurological symptoms, surgery followed by radiotherapy or radiotherapy alone is available. Therapy recommendations should be made on an interdisciplinary basis, with special

consideration of the underlying disease, operability and the chances of neurological recovery. In the combined therapy (surgery + radiotherapy), the surgical intervention should be performed first. Surgery and radiotherapy are available for patients with a risk of stability in case of osseous manifestation (with or without fracture already occurred). Surgery is to be preferred if it is feasible and a positive effect on quality of life and/or lifetime can be expected.

5.4.5.2.1. Indications for radiation therapy

5.50	Consensus-based Statement
ST	**from Guideline Supportive Treatment (Version 1, 2016)** Indications for local percutaneous radiotherapy for bone metastases are • local pain symptoms, • Restricted movement, • Reduction of stability (risk of fracture), • Condition after surgical stabilization, threatening or existing neurological symptoms (e.g. spinal cord compression).
	Strong Consensus

Background 5.45

For the reasons for this recommendation, see S3 guideline Supportive therapy in oncological patients (http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html).

The indication should always be interdisciplinary, especially in consideration of a potential surgical intervention.

For pain therapy of uncomplicated bone metastases (without already occurred spinal cord compression or fracture), a single time radiation with 1 x 8 Gy achieves an equally good reduction as fractional radiation series (5 x 4 Gy or 10 x 3 Gy). After fractionated radiation, however, re-radiation is less frequently necessary [1127]. The overall prognosis of the patient should be taken into account when selecting the radiation scheme for bone metastases. Fractionated radiation concepts (e.g. 5 x 4 Gy or 10 x 3 Gy) should be preferred in patients with a more favorable prognosis. Recalcification of an osteolytic metastasis is expected at the earliest about 3 months after radiation therapy [1127]. With modern radiation techniques a renewed palliative radiation of skeletal metastases can usually be performed after pre-radiation and achieves a good pain response in about half of the cases [1128]. Radiation therapy of osseous metastases can be performed in parallel to therapy with antiresorptive substances (bisphophonates, RANK ligand antibodies) [1129]. Radionuclide therapy with Samarium-153 can be performed in patients with multifocal osseous metastases of solid tumors to reduce pain symptoms [1130].

In patients with acutely occurred, functionally relevant spinal cord injury (e.g. leg paresis, bladder and rectum dysfunction) in good general condition and sufficient survival prognosis an emergency decompression should be performed to minimize permanent neurological deficits [1131] Surgical decompression should be followed by postoperative fractional radiotherapy. After surgical decompression in myelon compression, radiotherapy should be started within 14 days in dry wound conditions. After intralesional and marginal surgical procedures on osseous manifestations, local

radiation therapy should be performed. Postoperative radiotherapy after stabilising procedures should be carried out after completion of wound healing. No preoperative radiotherapy should be performed on the extremities or the spinal column in the surgical area.

5.4.5.2.2. Indications for surgical tretment

5.51	**Consensus-based Recommendation**
EC	**from Guideline Supportive Treatment (Version 1, 2016)** Indications for surgical therapy of osseous manifestations may be: • Myelon compression with neurological symptoms, • pathological fracture, • imminent fracture (fracture risk e.g. via Mirel Score, Spinal Instability Neoplastic Scale (SINS)), • solitary late metastasis, • radiation-resistant osteolysis, • therapy-resistant pain.
	Strong Consensus

Background 5.46

For the justification of this recommendation, see S3 guideline Supportive therapy in oncological patients (http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html).

A biopsy under established conditions [1132] is to be performed in cases of osseous manifestations:

- First-time imaging evidence of possible (also multiple) skeletal metastasis in a long-past primary tumour
- Isolated bone lesion with potential curative therapy approach without further metastases
- Radiological and/or clinical findings are not consistent with the diagnosis of bone metastasis (differential diagnoses must be considered)

The indication for a surgical intervention should be interdisciplinary, in particular in consideration of a potential radiotherapeutic intervention.

Pathological fractures that have already occurred or are imminent represent the main indication for surgical therapy in the area of the extremities. In the presence of a pathological fracture of the lower extremities of a previously mobile patient, there is an indication for surgical therapy. When choosing the appropriate surgical procedure for osseous manifestations in the extremities, the patient's prognosis must be taken into account in addition to the entity and radiation sensitivity of the tumor.

In stable vertebral body metastases or manifestations without evidence of myelon compression, conservative therapy (systemic tumor therapy, radiotherapy, radionuclide therapy, bisphosphonate / RANK ligand antibodies) is preferable to surgery.

In the case of therapy-refractory pain with imminent or actual compression fracture of one or more vertebral bodies in the thoracic spinal canal and lumbar spine without invasion of the tumor into the spinal canal, rapid pain reduction can be achieved by percutaneous cement augmentation with vertebroplasty or kyphoplasty [1133], [1134].

Patients with acutely occurred, functionally relevant compression-related spinal cord injury (e.g. proximal leg paresis, bladder and rectum dysfunction) in good general condition and sufficient survival prognosis should undergo emergency decompression to minimize permanent neurological deficits. Surgical decompression should be followed by postoperative radiotherapy with 10 x 3 Gy. After surgical decompression in myelon compression, radiotherapy should be started within 14 days in dry wound conditions [1131].

5.4.5.2.3. Bone protective therapy

5.52	Evidence-based Recommendation
GoR **B**	**from Supportive Guideline (Version 1, 2016)** To prevent complications in osseous manifestations, an osteoprotective therapy with bisphosphonates/denosumab should be performed.
LoE **1a**	[871]
	Strong Consensus

Background 5.47

For the reasons for this recommendation see S3 guideline Supportive Therapy in Oncological Patients (http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html).

Therapy with bisophosphonates/RANK ligand antibodies in osseous manifestations can delay or prevent the occurrence of skeletal-related events (SREs) [1135], [1136]. To prevent complications in osseous manifestations an osteoprotective therapy with bisphosphonates/denosumab should be performed. In patients with osseous metastases in breast cancer and after one year of zoledronate therapy in 4-weekly intervals the subsequent administration of zoledronate should be every 12 weeks [1137].

In patients with osseous metastases of breast cancer, the administration of denosumab compared to zoledronate leads to a numerically small, statistically significant reduction of SREs [1138]. For other outcome parameters (e.g. pain, QoL, spinal compression, mortality, AE maxillary osteonecrosis) there is no evidence for a difference. Data on the comparison of Denosumab versus the other bisphosphonates are not available. In order to prevent osteonecrosis of the jaw, a dental examination and any necessary dental rehabilitation should be carried out before the administration of bisphosphonates or Denosumab, and the patient should be instructed and motivated to maintain above-average (careful and regular) oral hygiene. In addition, regular risk-adapted dental examinations should be performed [1139].

5.4.5.3. Treatment of brain metastases

5.53	Evidence-based Recommendation
GoR **B**	Singular or solitary brain metastases should be resected with a favourable prognostic constellation if the metastasis localisation is accessible for resection and the risk of postoperative neurological deficits is low. Subsequently, local fractionated radiation or radiosurgery of the tumor bed should be performed.
LoE **1b** **5**	[1140]; [1141]; [1142]; [1143]; [1144]; [1145]; [1146]; [1147]; [1148]; [1149]
	Strong Consensus

5.54	Evidence-based Statement
ST	For patients with single metastases, radiosurgery is an alternative to resection if the metastases are not larger than 3 cm and there is no midline shift in the sense of space-consuming cerebral pressure symptoms.
LoE **1b** **5**	[1140]; [1141]; [1142]; [1143]; [1144]; [1145]; [1146]; [1147]; [1148]; [1149]
	Strong Consensus

5.55	Evidence-based Recommendation
GoR **B**	Infratentorial metastases should be primarily resected if occlusive hydrocephalus is imminent.
LoE **1b** **5**	[1140]; [1141]; [1142]; [1143]; [1144]; [1145]; [1146]; [1147]; [1148]; [1149]
	Strong Consensus

5.56	**Evidence-based Recommendation**
GoR **A**	In the presence of a limited number of brain metastases (in the order of 2 - 4), which do not exceed a total irradiatable volume, initial radiosurgery shall be preferred due to the lower negative effects on neurocognition compared to whole brain radiation, the shorter treatment duration and the higher control rate. If surgery or radiosurgery cannot be considered due to other, negative prognostic criteria, sole whole brain radiation shall be used. For patients with multiple brain metastases, sole whole brain radiation should be used.
LoE **1b** **5**	[1140]; [1141]; [1142]; [1143]; [1144]; [1145]; [1146]; [1147]; [1148]; [1149]
	Strong Consensus

5.57	**Evidence-based Recommendation**
GoR **0**	The combination of resection or radiosurgery with whole-brain radiation improves brain-specific progression-free survival compared to surgery or radiosurgery alone, but not overall survival. It can be considered in individual cases.
LoE **5**	[1140]; [1141]; [1142]; [1143]; [1144]; [1145]; [1146]; [1147]; [1148]; [1149]
	Strong Consensus

5.58	**Consensus-based Recommendation**
EC	There is no indication for combining whole brain radiation with radiosensitizing drugs.
	Strong Consensus

Background 5.48 to 5.53

Drug therapy: Drug therapy of tumors plays an increasingly important role in the treatment of brain metastases. It can be used in primary therapy in addition to radiotherapy or radiosurgery or as the sole therapy modality [1151]. The blood-brain barrier, which under physiological circumstances prevents the penetration of cytostatic drugs into the brain, is often permeable in cerebral metastases, so that cytostatic drugs can reach cerebral therapeutic levels [1150]. The response rate in the sole drug therapy of brain metastases can reach the response rate in other organ metastases and is up to 50% in breast cancer. The vast majority of brain metastases in breast cancer are parenchymatous metastases. 11-20% of brain metastases are leptomeningeal metastases. Diagnostics should include a cranial MRI in addition to clinical examination. A cytological detection of malignant cells in the CSF puncture is the gold

standard for the diagnosis of a leptomeningeal metastasis. In the case of a negative CSF puncture if leptomeningeal metastasis is still suspected, the CSF puncture should be repeated [1152]. In general, the treatment of patients with solid brain metastases [1153] and leptomeningeal metastases [1152] is based on the premise that the systemic therapy should be based on the primary tumor and its molecular characteristics. In a systematic review of the therapy of leptomenin-geal metastases in breast cancer Scott et al. could show in 36 studies with a total of 851 patients with meningeosis carcinomatosa that 87% had been treated with intrathecal chemotherapy and the median overall survival was 15 weeks [1154]. In addition to 18 retrospective studies and 13 case collections, 5 prospective randomized studies were included in this current review. In the only prospective randomized study that exclusively included breast cancer patients, 35 patients with breast cancer and meningeosis carcinomatosa were randomized to systemic therapy + radiotherapy with and without additional intrathecal chemotherapy (ITC) [1155]. The systemic therapy was based on hormone receptor status, previous therapies and general condition. Radiotherapy was performed as whole brain radiation if clinically indicated. Systemic therapy and radiotherapy were well balanced between both therapy arms. ITC was performed with methotrexate and applied via an ommaya reservoir. Neurological stabilisation or improvement was described in 59% (ITC) vs. 67% (no ITC). Median time to progression 23 (ITC) vs. 24 (no ITC) weeks. Overall survival was 18.3 weeks vs. 30.3 weeks (no ITC) (p=0.32) for those patients who were additionally treated with ITC. Therapy related neurological complications were found in 47% (ITC) vs. 6% (no ITC) (p=0.0072). The authors concluded that intrathecal chemotherapy in addition to adequate systemic therapy and possibly radiotherapy in breast cancer patients with meningeosis carcinomatosa does not prolong survival but leads to an increased risk of therapy-related neurological complications.

In breast cancer, more than a third of patients with HER2-positive tumours develop brain metastases when treated with targeted therapies. One reason could be that these tumours preferentially metastasise to the brain, where they are protected from the action of antibodies by the blood-brain barrier. Antibody-based therapy is also effective for existing brain metastases in HER2-positive patients, and trastuzumab has been shown to penetrate brain metastases. The EGFR/HER2 inhibitor lapatinib is also effective in the treatment of brain metastases, but cannot prevent the occurrence of brain metastases. In monotherapy the substance has an objective response rate of only 6% [1156]. In combination with capecitabine the response rates are up to 38% [1157], [1158], [1159]. Even higher response rates of more than 60% were reported in non-irradiated patients treated with lapatinib and capecitabine [1160]. The occurrence of brain metastases as the first progression event in metastatic HER2-positive breast cancer was comparable between lapatinib / capecitabine vs. trastuzumab / capecitabine (3% vs. 5%) - while progression-free survival (HR 1.30) was prolonged under trastuzumab / capecitabine [1161]. In a retrospective analysis of the EMILIA study, the cerebral progression rate between trastuzumab emtansine (T-DM1) vs. capecitabine / lapatinib was comparable (without cerebral metastases at baseline 2% vs. 0.7%; with previously known cerebral metastases 22.2% vs. 16.0%). Overall survival in patients with cerebral metastases at baseline was significantly extended by T-DM1 compared to capecitabine / lapatinib (HR 0.38; 26.8 vs. 12.9 months) [1162].

Overall, it must be emphasized that even after the occurrence of brain metastases, a continuation of the HER2 blockade may be useful to keep systemic metastases under control [1163], [1164].

Breast carcinoma is the second most common cause of CNS metastases (after lung carcinomas). Data on the actual incidence vary in the literature between 15-20%; in

autopsy collectives up to 40% [1150], [1165]. In recent years an increasing incidence of brain metastasis in patients with breast cancer has been observed. The increasing incidence is attributed to longer survival due to better control of the underlying disease and extracranial metastases as well as improved diagnostic measures (MRI) and their greater use. Patients with triple-negative histology and HER2-positive status were identified as risk factors in subgroup analyses [1166]. A single metastasis in the brain with simultaneously detectable metastases in other organs is described as singular, while singular cerebral metastasis is described as the only (detected) metastasis in the organism.

The overall prognosis is limited with a median survival time of 2 to 25 months. However, individual patients survive several years without relapse. Particularly in the case of isolated brain metastases occurring late in the course of the disease, intensified therapy seems justified. By means of a recursive partition analysis of the Radiation Therapy Oncology Group (RTOG) on a collective with brain metastases (predominantly from lung cancer) in the USA, 3 prognosis classes (RPA Class I - III) based on whole brain radiation were defined as therapeutic measures according to simple prognostic criteria (age 70, systemic disease controlled). With the help of these three classes, the median survival between less than 2 or longer than 7 months can be estimated [1167]. Based on more recent data, a new score, the so-called Graded Prognostic Assessment (GPA), was proposed in 2012 [1168], again based on whole brain radiation, which was supplemented by primary tumor-specific indices specifically for breast cancer. Using the breast carcinoma-specific score (allocation of points for Karnofsky index, histological subtype, age), the median survival times for GPA 0-1: 3.4 months, for GPA 1.5-2: 7.7 months, for GPA 3: 15 months and for GPA 3.5-4: 25.3 months.

In addition to the above-mentioned prognosis factors, the therapy strategy depends on the number, location and size of the brain metastases. The main therapy modalities include resection, radiosurgery, fractional radiotherapy, e.g. as stereotactically guided, localized radiotherapy or as whole brain radiation, and drug therapy of tumors. When assessing the effect of local therapies in clinical trials, it should be noted that median survival time is not only influenced by the effectiveness of the treatment of brain metastases, but also by the consequences of systemic tumor progression.

Surgery: Surgery has a safe value in the therapy of brain metastases [1140]. The median survival improves by 6-9 months compared to whole brain radiation alone when resecting single metastases and subsequent whole brain radiation. In symptomatic large metastases the palliative effect of the resection is important. Two of 3 randomized studies concluded that resection of single or solitary metastases followed by whole brain radiation is superior to sole whole brain radiation [1141], [1142], [1143]. A third study did not prove the value of surgery [1169]. However, this discrepancy can be explained by later surgery in the radiotherapy arm and an overall prognostically unfavorable patient population. Numerous retrospective analyses also speak in favor of resection of single or solitary metastases [1170]. However, the local recurrence rates after sole resection are relatively high at 60% [1148]. Local as well as distant recurrences are reduced if whole-brain radiation is followed by surgery [1143], [1148]. Whether whole-brain radiation can be replaced by a hypofractionated, circumscribed postoperative follow-up radiation of the postoperative tumor bed to avoid the negative effects of whole-brain radiation is the subject of ongoing studies. In all the studies cited, the group of breast cancer patients represented a relevant subgroup; data exclusively on the therapy of brain metastases in breast cancer do not exist.

Radiosurgery: The percutaneous stereotactic application of single high radiation doses (radiosurgery) is a standard therapy in the treatment of brain metastases. The high

radiation dose often leads to good tumor control, while the surrounding healthy tissue is well protected by the steep dose drop to the periphery. Radiosurgery thus represents an alternative to neurosurgical resection. At present, radiosurgery is mostly used as primary treatment of single or multiple lesions with a diameter of up to 30 mm (or 15 ml) or as recurrence treatment in patients who show a recurrence in a previously conventionally irradiated region. Local control rates range from 73-94%. Retrospective cohort studies indicate an equivalence of radiosurgery and neurosurgical resection. Comparative studies have not yet been published. However, it must be emphasized that local control seems to be better after radiosurgery. In EORTC study 22952-26001 the cumulative incidence of local progression was 59% after resection compared to 31% after radiosurgery [1148].

The decision depends on clinical circumstances (per surgery: histological backup, mass effect, per radiosurgery: applicability in any localization, even in functionally non-resectable lesions such as brainstem).

Radiation therapy for limited (1-4 brain metastases) and multiple metastases, significance of whole brain radiation: On the question of the combination of radiosurgery alone or with additional whole-brain radiation, there are now data from 6 randomized studies [1144], [1145], [1146], [1147], [1148], [1149]. Here, too, the size of the randomized breast cancer patients was almost 20%, in addition to patients with lung cancer as the largest group. The first two studies unanimously showed an increased local metastasis control and "in-brain-control" (prevention of new intracranial metastases) in combination with radiosurgery and whole brain radiation [1144], [1145]. In the three subsequent studies [1146], [1147], [1148], higher control rates were also shown due to the resulting dose escalation through the combination of radiosurgery and whole-brain radiation, but this was not accompanied by a survival advantage of the whole collective and the neurocognitive endpoints showed a substantial deterioration through the addition of whole-brain radiation. In two more recent studies, neurocognitive endpoints were placed in the foreground of the evaluation [1147], [1149]. Due to the deterioration of neurocognition with simultaneous lack of survival advantage, current recommendations of the American professional societies are to initially withhold or postpone whole brain radiation in favor of radiosurgery, despite the improved tumor control proven in all studies (using regular follow-up MRIs). Since modern radiosurgical techniques are now available to perform this also in the case of multiple brain metastases (up to 10), the side effects of whole-brain radiation are increasingly questioned even in the case of multiple metastases [1171]. In this respect, initial radiosurgery may be preferred in the case of more than 4 lesions (taking into account the pattern of infection and localization) in order to avoid the negative effects of whole-brain radiation on neurocognition or to provide whole-brain radiation as a salvage option.

Which patients will benefit from additional whole brain radiation in the future due to prognosis or infestation pattern, also with the help of the technically possible hippocampal sparing in order to avoid negative effects on neurocognition, is the subject of currently ongoing studies.

Whole brain radiation: The sole fractionated whole brain radiation (usually fractionated with 10 x 3 Gy) remains the therapy of choice for patients with multiple brain metastases, limited prognosis group and reduced general condition, in addition to the alternative of refraining from therapy (best supportive care). In this clinical constellation, whole brain radiation improves the median survival time from 2 months with purely supportive therapy to 3-6 months. It leads to an improvement in tumour-related neurological symptoms and quality of life. If favourable prognostic factors are present, treatment should be performed normo-fractionated with 5 fractions per week,

2 Gy per fraction up to a total dose of 36-44 Gy in order to avoid neurotoxic late effects of radiation therapy and to achieve an extension of the neurological remission time. Since the hippocampus is considered a sensitive region with regard to the occurrence of neurocognitive late effects, it is currently being investigated whether modern radiation techniques (intensity-modulated radiotherapy, IMRT) allow bilateral sparing of the hippocampus ("hippocampal sparing") without compromising cerebral tumor control.

5.59	**Consensus-based Recommendation**
EC	In the case of cerebral metastases, systemic therapy (chemotherapy / endocrine therapy / anti-HER2 therapy) should be used in addition to local therapy (surgery / radiotherapy).
	Strong Consensus

5.4.5.4. Treatment of liver metastases

5.60	**Evidence-based Recommendation**
GoR **0**	If liver metastases are present, in individual cases a resection or possibly another local therapy (RFA, TACE, SBRT, SIRT) may be indicated: • no disseminated metastases • controlled extrahepatic metastasis
LoE **3b**	[1172]; [1173]; [1174]; [1175]; [1176]; [1177]; [1178]; [1179]; [1180]; [1181]; [1182]; [1183]
	Strong Consensus

Background 5.55

If a limited number, especially isolated liver metastases occur in the liver, a metastasis resection can be performed. Alternatively, radiofrequency ablation, transarterial chemoembolization (TACE) [1184] or stereotactic radiation (SBRT) may be considered, although even less data are available. Factors that positively influence the decision to resect are Time interval after primary treatment > 12 months, good response to systemic therapy and estrogen-receptor-positive disease. Systemic therapy should be followed after surgical therapy. A prerequisite for local liver metastasis therapy is usually the exclusion of extrahepatic metastases as well as a local/local/regional recurrence and secondary carcinomas. As a locoregional therapy method, the Yttrium-90-Radioembolization (SIRT) [1185] can be considered for hepatic metastases that exceed the possibilities of local procedures in terms of number and size. All in all, the data required for SIRT are lacking to prove a patient-relevant benefit.

In individual cases, liver resection or interventional liver therapy may be indicated within the framework of the overall oncological concept even in the case of multiple or bilateral liver metastases or also in the case of limited but stable extrahepatic tumors [1186], [1187], [1188], [1189]. Even if a curative approach cannot always be pursued with the mentioned procedures, a progression-free time may be achieved under certain circumstances.

For the symptomatic treatment of upper abdominal pain, nausea and other complaints of the patient until the expected effect of a metastasis-specific therapy has set in, in the absence of this effect or if the patient refuses tumour therapy, reference is made to the S3 guideline "Palliative medicine for patients with incurable cancer" (AWMF register number 128/001OL).

5.4.5.5. Treatment of lungmetastases

5.61	Evidence-based Recommendation
GoR **0**	In the presence of pulmonary metastases, in individual cases a resection or possibly another local therapy (RFA, stereotactic radiotherapy) may be indicated: • No disseminated metastases, • controlled extrapulmonary metastasis.
LoE **4**	[1190]; [1191]; [1192]; [1193]; [1194]
	Strong Consensus

Background 5.56

A metastasis resection is only indicated in the presence of a very limited, particularly solitary pulmonary metastasis after exclusion of extrapulmonary metastases. Factors that positively influence the decision to resect are: longer time interval after primary treatment > 24-36 months, good response to systemic therapy, solitary metastasis and estrogen-receptor-positive disease. Systemic therapy should be followed after surgical therapy. A prerequisite for lung metastasis resection is the exclusion of local/local recurrence, secondary carcinoma and, as a rule, extrapulmonary metastasis. For curative resection of pulmonary metastases a 5-year survival rate of 40 to 80% is given.

5.4.5.5.1. Malign pleural effusion

5.62	Evidence-based Recommendation
GoR **A**	If a pleural carcinosis with symptomatic effusion formation occurs, the patient shall be offered a pleurodesis.
LoE **1a**	[1195]
	Strong Consensus

Hintergrund 5.57

Wenn maligne Pleuraergüsse symptomatisch sind und sonstige Manifestationen nicht im Vordergrund stehen, ist eine Pleurodese indiziert (Talkum, Tetrazyklin oder Bleomycin oder/und Einlage einer Thorax-Verweil-Drainage). Diese wird bevorzugt thorakoskopisch durchgeführt.

Zur symptomatischen Therapie von Dyspnoe, Schmerzen u. a. Beschwerden der Patientin bis zum Einsetzen der erwarteten Wirkung einer metastasenspezifischen Therapie, bei Ausbleiben dieser Wirkung oder wenn die Patientin eine Tumortherapie ablehnt, wird auf die S3-Leitlinie „Palliativmedizin für Patienten mit einer nicht heilbaren Krebserkrankung" (AWMF-Registernummer 128/001OL) verwiesen.

5.4.5.6. Cutaneous and soft tissue metastases

5.63	Consensus-based Recommendation
EC	If skin and soft tissue metastases occur, surgical excision or other local therapy (e.g. radiotherapy) may be considered.
	Strong Consensus

Background 5.58

Circumscribed skin metastases and metastases of soft tissue can be excised in healthy individuals or locally irradiated percutaneously. If the findings are not very extensive, topical procedures can be discussed [1196], [1197], [1198]. If necessary, electrochemotherapy can also be used [1199], [1200], [1201].

Exulcerative tumor growth / Cancer en Cuirasse:

Breast carcinoma is the malignant tumor which most frequently develops skin metastases, which already in curable stages of the disease lead to considerable symptom burden with impairment of the patient's quality of life [1202] Cancer en Cuirasse is a distinct, aggressive, nodular plate-like, partly exulcerated manifestation with consecutive lymphedema. It is often accompanied by pain, itching, bleeding and foetal odor. Due to the thick fibrotic manifestation with reduced vascularization of the carapace-like skin metastases, the causal therapy options are limited. As a rule, exudative skin metastases or Cancer en Cuirasse are non-curative stages of the disease. Patients are severely affected by the physical disfigurement, limited movement, pain, weeping of the wound and the sometimes very unpleasant odour. Palliative care aims to relieve all these symptoms. This requires complex interventions (wound care plus psychosocial support) [1198], [1202], [1203], [1204], [1205].

5.5. Palliative medicine

5.64	Consensus-based Recommendation
EC	In the palliative situation, all necessary measures shall be geared to the patient's individual therapy and life goals.
	Strong Consensus

5.65	Consensus-based Statement
ST	The right time to supplement regular care with palliative care depends primarily on the patient's needs and individual disease-related requirements.
	Strong Consensus

5.66	**Consensus-based Statement**
ST	Palliative care is characterised by a multi-professional and interdisciplinary approach.
	Strong Consensus

5.67	**Consensus-based Recommendation**
EC	The following principles shall be applied in the palliative care of patients with an incurable breast cancer disease: • consideration of and response to the patient's needs in all four dimensions (physical, psychological, social, spiritual) • the consideration of patients' preferences • the determination of realistic therapy goals • Knowledge of the organizational forms of palliative care • the creation of conditions that respect the intimacy of the patient
	Strong Consensus

5.68	**Consensus-based Statement**
ST	Palliative care includes medical symptom control, palliative care and psychosocial support until death. It is provided as general or specialised palliative care according to need.
	Strong Consensus

Background 5.59 to 5.63

Palliative medicine/palliative care (synonym: palliative care) pursues the goal of improving the quality of life of patients with a life-threatening disease and their relatives. This is achieved by prevention and alleviation of suffering, by early recognition and treatment of physical, psychological, social and spiritual problems [1207], [1208], [1209], [1210], [1211], [1206], [1212], [1213], [1214], [1215], [1216], [1217], [1218], [1219], [1220]. This is done by preventing and alleviating suffering, by early recognition, careful assessment and treatment of pain and other distressing symptoms of a physical, psychosocial and spiritual nature [1207], [1208], [1209], [1210], [1211], [1206], [1212], [1213], [1214], [1215], [1216], [1217], [1218], [1219], [1220], [1221].

The recommendation is based on the consensus of the technical experts involved. Otherwise, the guideline group refers to the overarching interdisciplinary S3 cross-sectional guidelines "Palliative Care for Patients with Non-Curable Cancer" (AWMF Registry Number 128/001OL), the guideline "Supportive Therapy for Oncological Patients" (AWMF Registry Number 032/054OL) and the guideline "Psycho-oncological Diagnosis, Counselling and Treatment of Cancer Patients" (AWMF Registry Number 032/051OL) as well as the corresponding chapters in this guideline.

Palliative care

Palliative care includes medical symptom control, palliative care and psychosocial support until death [1208], [1209], [1210], [1211], [1206], [1212], [1213], [1214], [1215], [1216], [1217], [1218], [1219], [1220], [1222]. In the palliative situation, all necessary measures are oriented towards the individual therapy and life goals of the patient [1208], [1214]. Graduated palliative care is the necessary prerequisite for varying the intensity of treatment according to the symptom burden and at the same time ensuring continuity of palliative support [1223], [1224]. Symptom control, palliative care and psychosocial support stand for three dimensions of palliative treatment which must be included in every qualified palliative care offer, regardless of the level of specialization of the offer [1209]. Palliative care is provided in addition to (a) disease-modifying therapies with the primary therapeutic goal of prolonging life *(palliative therapy),* (b) prophylaxis or treatment of side effects associated with the disease or with these therapies *(supportive therapy*) [1207], [1214], [1216], [1220], [1225], [1226], [1227], [1228] and (c) the needs-based psychosocial and psycho-oncological care. Specialised co-treatment is advisable for patients in whom a high level of physical, psychosocial or spiritual stress persists despite general palliative medical measures. This is characterised by the fact that a team (a) with specialised training (e.g. palliative care nursing training or additional medical designation palliative medicine), (b) which (b) is mainly and primarily entrusted with palliative care, (c) is involved in the treatment of the patient in addition to routine care (S3 guideline AWMF register number 128/001OL). Routine integration of specialized palliative care into local therapy standards is aimed at in accordance with current international guideline recommendations [1208], [1214], [1229] in the sense that palliative care is integrated into treatment and no longer whether this should be done. In Germany, Gärtner et al. have developed disease-specific indicators for palliative medical counselling and, if necessary, co-care. These include (1.) metastasized and inoperable breast cancer, (2.) locally advanced and inoperable breast cancer, or (3.) recurrent disease situations in which intravenous chemotherapy is administered [1230].

For further information on the question of care structures, reference is made to the S3 guideline on oncological palliative care in the Oncology guideline program (AWMF register number 128/001OL).

5.5.1. Patients' needs

The highest therapeutic goal in palliative care - the individual quality of life - can only be evaluated and defined by the patient herself [1231], [1232]. The therapy goal must be measured against the patient's ideas, priorities and wishes [1233]. The patient's physical, psychosocial, spiritual and existential burdens can be [1208], [1209], [1210], [1211], [1206], [1212], [1213], [1214], [1215], [1216], [1217], [1218], [1219], [1220]. Patients with breast cancer have a high need for medical information and psychological support [1234], [1235], [1236]. It should be noted that the interindividual needs may be the same, but priorities may be weighted differently. In order to identify unconsidered needs, a short assessment is routinely performed when palliative care is called in, which includes the multidimensional needs of the patients according to their self-assessment [1237]. A validated single-item questionnaire is the "NCCN Distress Thermometer", while the "Palliative Outcome Scale (POS)" asks for special stresses and needs in more detail [1238], [1239], [1240]. A structured recording of the physical symptoms (e.g. Edmonton Symptom Assessments Scale (ESAS)) may also be helpful [1241]. For all three assessment instruments there are validated versions for Germany [1242], [1243], [1244]. Recording the patient load improves the need orientation in the care of patients [1245].

A prerequisite for the treatment of patients and a component of palliative basic values is the high appreciation of patient autonomy and participation [1206], [1215], which, in addition to the above-mentioned routine recording of the patient's self-assessment of quality of life and symptom burden, also includes the active inclusion and comprehensive/adequate information/education of the patient in the decisions for certain therapy options [1208], [1214]. In principle, the patient has the possibility to include close relatives in the discussions according to her wishes. In order to enable the patient to have her confidants be able to represent the presumed will of the patient as well as possible in the case of possible disturbances of consciousness in the course of the disease, there is the offer of consultation for writing a "power of attorney for medical matters" [1233]. Regarding further aspects of palliative care independent of the underlying diagnosis, reference is made to the S3 guideline "Palliative Care for Patients with Non-Curable Cancer" of the Oncology Guidelines Program (AWMF Register Number 128/001OL). It discusses questions of symptom control, palliative care, psychosocial support and care structures in detail and across all organs.

5.5.2. Family carers' needs

A central point of palliative care is the involvement of those close to the patient. In addition to family members, this means above all those persons who are important for the patient in the current situation, regardless of the degree of kinship. In principle, the patient has the possibility to include the persons she wishes in the discussions. However, the wishes and fears of the close relatives themselves as well as their needs, for example for information, also play an important role. With regard to further aspects of care for close relatives, reference is made to the S3 guideline "Palliative care for patients with incurable cancer" of the Oncology Guidelines Programme (AWMF register number 128-001OL).

6. Treatment, support and continuing care

6.1. General concept

The chapters in Section 6 - Treatment, Care, Accompaniment of our patients - have been redefined and restructured due to the significant development of diagnostic and therapeutic options in recent years. For example, the start of aftercare has so far referred to the completion of primary treatment (if necessary, no later than 6 months after surgery). The definition of this period has changed with the introduction of neoadjuvant therapies, adjuvant long-term therapies with antibodies and (anti-)hormones and the modified forms of radiation therapy. Consequently, the content and timing of the term "aftercare" must be adapted. In addition, there are overlaps between the various subject areas that exist at different points in time in the care chain for patients with breast cancer.

The chapter "Treatment, care and support" covers the psychosocial aspects and psycho-oncology and supportive therapies. Both chapters deal thematically with treatment situations that begin in the context of primary treatment, but which also seamlessly move on to long-term support. The chapter on rehabilitation covers the period following the completion of primary local therapy. This point in time is usually the end of primary treatment by means of surgery (also after previous neoadjuvant chemotherapy) or radiotherapy (also after previously carried out adjuvant chemotherapy).

Following the completion of the primary local therapy, in particular the completed radiotherapy, the newly defined aftercare will then follow, focusing on the earliest possible detection of locoregional or intramammary recurrences, contralateral breast carcinoma, the targeted search for metastases in the event of symptoms or justified suspicion, as well as the diagnosis and therapy of side effects and late effects of the primary and long-term therapies.

The final sections in this restructured chapter are palliative care, which will be discussed due to its increasing importance, and the not unimportant complementary medicine.

The tasks of the treating physicians have changed due to the increasing complexity of the diagnosis and therapy options or the time periods. Although data from prospective randomised trials with regard to individual aspects such as adverse effects, long-term toxicity or the use of supportive measures are available, the definition of the investigations, both in terms of the interval and the type of investigations, is defined on a study-specific basis. Summarising overall data from prospective randomised studies for the corresponding evidence-based recommendations for action within the framework of this changed range of tasks are not available. A generalisation for everyday clinical practice can therefore only be made after an evaluation of the study data and the combination of individual aspects. It must also be taken into account that since 2004, no new prospective randomized studies have been published to test new methods or time intervals for the diagnosis of locoregional recurrence or distant metastases. Short-term, almost annual variations in therapy recommendations therefore make it impossible to change the recommendations on intervals and the type of diagnosis. Prospective randomized studies to test this have been initiated, so that the data situation may improve in the near future.

6.2. Psycho-oncological aspects

6.2.1. Basic principles of psycho-oncological care

Today, psycho-oncology is a separate discipline whose task is to scientifically research the various psychosocial aspects in the development, treatment and course of cancer in children, adolescents and adults and to apply the relevant findings to the care and treatment of patients [29], [1246], [1247], [1248]. Psycho-oncology is an integral part of the care of patients with breast cancer. In Germany, further education and training curricula are offered by corresponding professional associations to ensure professional qualification. The addressees of these further training courses are doctors, psychologists and social pedagogues, who are referred to in the following as psycho-oncology specialists. An additional psycho-oncological qualification is a prerequisite for recognition as a psycho-oncological specialist [1249]. The psycho-oncological care of breast cancer patients should be implemented in an interdisciplinary manner between all professional groups involved in the treatment. This implies that a psycho-oncological specialist is integrated into the treatment team in the respective care setting (inpatient and outpatient treatment, inpatient rehabilitation, outpatient aftercare) and is in regular contact with the medical staff. This exchange should be regulated and structured in the form of case discussions or ward conferences [1250], [1251], [1252] Detailed aspects of psycho-oncological care can be found in the S3 guideline for psycho-oncological diagnostics, counselling and treatment of cancer patients [29].

Psycho-oncological support

6.1	Evidence-based Statement
ST	Psycho-oncological measures are part of the overall concept of oncological therapy.
LoE 1b	[1253]; [28]; [29]; [873]
	Strong Consensus

6.2	Consensus-based Recommendation
EC	All patients and their relatives shall be informed early on about the possibilities of psycho-oncological support.
	Strong Consensus

6.2.2. Psycho-oncological care strategies and interventions

Psycho-oncological care of patients with breast cancer includes patient-oriented information and counselling [37], [1254], [1255], [1256], [1257], [1258], [1259], a qualified psychological diagnosis and determination of needs [29], [1260], [1261], [1262] as well as a targeted psycho-oncological treatment to support the management of the disease and treatment consequences [1263]. The relatives must be included in the psycho-oncological care [1264], [1265].

6.3	Consensus-based Recommendation
EC	All patients shall receive screening for psychosocial stress. Psycho-oncological screening should be carried out as early as possible, at appropriate intervals if clinically indicated, or repeatedly as the disease progresses if the patient's condition changes (e.g. recurrence or progression of the disease).
	Strong Consensus

Background 6.3

The diversity and complexity of possible psychological impairments in breast cancer in different disease and treatment phases require that the need for psychosocial treatment be determined individually and that a psycho-oncological specialist be involved as needed, as well as a reference to the support services offered by self-help. This is the only way to adequately address the different problems and burdens of breast cancer patients.

- Target areas of psycho-oncological interventions in breast cancer are:
- Anxiety, depression, stress experience [1267], [1268] [873]
- Disease processing, disease settings [1265], [1269], [1270], [1271]
- Health-related quality of life and functional status [1253], [1272]
- Body image and self-concept [1273], [1274], [1275] [873]
- social relations, communication [1276], [1277], [1278]
- Sexuality [873], [1255], [1273], [1274], [1275]

- Fatigue [873], [1239], [1279], [1280], [1281], [1282], [1283]
- Pain [1284], [1285]
- neuropsychological impairments (attention, memory, concentration) [873], [1286]; see also Chapter 7.5.

Within the framework of a systematic literature review the following psycho-oncological interventions for breast cancer patients could be identified as evidence-based [1266]:

Individual psychotherapeutic interventions [1255], [1259], [1266], [1287], [1288]

- psychoeducative individual or group intervention as well as supportive expressive group therapy [1249], [1289], [1290], [1291], [1292]
- Relaxation method [1293], [1294], [1295], [1296], [1297]
- Couple Counselling or Couple Therapy [1274], [1298], [1299], [1300], [1301]

The publication [1266] summarizes the results for all diagnosis groups. Since studies with breast cancer patients accounted for about 50% of all included publications, a subanalysis was conducted for the target group of breast cancer patients, which yielded an identical evaluation of the evidence base.

Without systematic research, randomised studies, in some cases meta-analyses, are available for the following interventions:

- Neurocognitive Training [300], [1286], [1302], [1303] ; see also Chapter 7.5
- artistic therapy methods (art, music and dance therapy) [1304], [1305], [1306], [1307], [1308]

A systematic literature search has shown that relaxation techniques, psychoeducational interventions, individual psychotherapeutic interventions and psychotherapeutic group interventions show significant improvements with regard to the target variables anxiety, depression, psychological well-being and quality of life. In some studies, only significant effects on depressiveness could be achieved for the couple interventions, while no effects could be demonstrated for the other target parameters.

6.4	**Evidence-based Recommendation**
GoR **A**	The psycho-oncological interventions listed below shall be offered to patients after the individual needs have been determined using validated measuring instruments: • Relaxation method • psychoeducational interventions • individual psychotherapeutic interventions • psychotherapeutic group interventions • psychotherapeutic couple interventions
LoE **1a**	[1266]
	Strong Consensus

Background 6.4

In addition to the clinical picture, validated measuring instruments such as the psycho-oncological basic documentation (PO BaDo), the German version of the Hospital Anxiety

and Depression Scale (HADS), the Hornheider questionnaire or the distress thermometer [1309] can be helpful for individual assessment of needs.

6.5	Consensus-based Recommendation
EC	In order to ensure continuity of psycho-oncological care after inpatient treatment, patients shall be informed about further outpatient and aftercare offers by professional helpers and self-help.
	Strong Consensus

Background 6.5

It has proven to be helpful to include quality of life in addition to the classical parameters for the assessment and planning of diagnostics and therapeutic measures. For the assessment of quality of life, structured and standardized questionnaires (such as the EORTC QlQ C30 or FACT G) [1311], [1312], [1310], [1316] can be used in addition to the medical consultation. These questionnaires can be used to evaluate the patients' well-being in somatic (intensity and frequency of physical symptoms, functional limitations), psychological (anxiety, depression, cognitive limitations) and social (family life, work, sexuality) areas [1313]. They have been tested in elaborate studies with regard to their measurement quality (reliability, validity and sensitivity) [1263]. Randomized studies on the use of quality of life instruments in routine care are available [1314], [1315].

6.6	Consensus-based Recommendation
EC	The patient's quality of life should be assessed using validated methods (e.g. EORTC QlQ C30) at appropriate intervals when clinically indicated or when there are changes in the disease status.
	Consensus

Background 6.6

For a sufficient supply, the validated recording of the quality of life is necessary for the identification of previously unrecognized secondary problems such as fatigue or insufficiently adjusted pain. In the case of identification of quality of life problems, appropriate measures for their treatment or alleviation must be initiated.

Necessary for adequate therapy is the establishment of a regional network of all health care professions in the inpatient and outpatient sector and specific treatment according to agreed recommendations for each area of intervention.

The evaluation of validated questionnaires and the visualisation of existing deficits (e.g. by means of a profile showing inroads in the above options) is a prerequisite for individual therapy and a helpful instrument for improved communication between doctor and patient [1319]. The EORTC QlQ C30 [1318], for example, is a suitable questionnaire for recording quality of life. The distress thermometer [1317] can also be considered with the additional questions as an instrument for recording general stress.

6.3. Supportive therapy

This chapter with the respective marked statements and background texts is partly based on the S3 guideline "Supportive therapy in oncological patients" [871].

The following sections with background texts are partly taken literally from the S3 guideline "Supportive therapy in oncological patients":

- Definition
- Drug-induced nausea and vomiting
- Radiotherapy induced nausea and vomiting
- Neutropenia, febrile neutropenia (FN), infections
- Anemia
- Neurotoxicity

Some of the background texts have been significantly shortened and focused on relevant content for the care of patients with breast cancer. For more detailed information on the background and data, please refer to the S3 guideline "Supportive Therapy for Oncological Patients" [871].

The remaining sections were updated by the chapter authors based on the previous version.

6.3.1. Definition

Supportive therapy is understood to be supportive measures that optimize the safety and tolerability of cytostatic therapies and other drug treatments, surgical interventions or radiotherapy for the treatment of the underlying malignant disease. Supportive measures are an indispensable part of the oncological treatment concept, the prevention and treatment of complications and side effects of cancer therapy. A major goal of supportive therapy is to maintain or improve the patient's quality of life and to be able to implement modern therapy strategies without abortion, dose reduction or extension of intervals.

Supportive therapy includes all supporting measures to avoid or treat side effects of the cancer disease or therapy. These can relate to the management of physical, psychological symptoms or to side effects throughout the entire treatment process and course of disease, starting with diagnosis, through tumor therapy, to aftercare (from S3 guideline "Supportive therapy in oncological patients" as defined by the international supportive organization MASCC; www.mascc.org/about-mascc, accessed 02-10-2016). Supportive therapy and palliative medicine or palliative care are not synonymous. Whether "side effects of cancer" are part of supportive or palliative medical therapy is disputed (from AWMF S3 guideline Palliative Medicine for Patients with Non-Curable Cancer; [1320]).

6.3.2. Significance and qualification of side effects

In the case of concomitant symptoms of cytostatic therapies, a distinction must be made between objectively measurable side effects or damage on the one hand and subjectively perceived impairment on the other. These effects are often evaluated differently by doctors and patients - for example, nausea and alopecia are experienced by the patient as very stressful, while the doctor's attention is directed more towards objectively measurable organ toxicities (e.g. myelosuppression) that may be life-threatening.

For better understanding and documentation, it is recommended to indicate the severity of adverse effects according to a generally accepted classification, e.g.

according to the Common Terminology Criteria for Adverse Events of the American National Cancer Institute - currently version 4.03 (NCI-CTCAE) [1321] - or the toxicity scales of the WHO.

6.3.3. Principle of supportive therapy

Supportive therapy in oncology or senology comprises an interdisciplinary spectrum of measures that serve to improve the conditions for the feasibility of a therapy, reduce side effects, achieve treatment results that meet the objectives and maintain or improve the patient's quality of life.

In principle, foreseeable toxicities should be anticipated and, if possible, primarily avoided. The individual situation and comorbidities of the patients must always be taken into account when selecting and dosing e.g. drug-based cancer therapy. If side effects cannot be avoided, prophylaxis is generally more advantageous than treatment of the already manifest toxicity. In everyday clinical practice, therefore, concomitant diseases and risk factors for side effects should be systematically recorded before the start of cytostatic treatment and the therapy protocol should be adapted accordingly.

The patient should be informed early and in detail about expected side effects, general measures to avoid them and treatment options. Preventive medication should be prescribed. The drug prophylaxis of nausea and vomiting as well as the avoidance of neutropenia in certain chemotherapies are oncological standards which must be adhered to according to the current guidelines listed below.

In the course of therapy, undesirable effects must be specifically and promptly queried and documented in order to be able to react accordingly with modifications of the treatment protocol (e.g. dose reduction) as well as indicated measures for the treatment of any toxicities that have occurred. This includes among others

- Detection and treatment of infections,
- Detection and treatment of symptomatic anaemia,
- Detection and treatment of skin toxicities,
- Detection and treatment of lymphedema.

6.7	**Evidence-based Recommendation**
GoR **A**	Patients shall be advised to be physically active during oncological therapy, as this has a positive effect on the physical fitness of the patient and thus facilitates the performance of daily activities (ADL).
LoE **1a**	[1322]; [892]
	Strong Consensus

6.3.4. Medication-induced nausea and vomiting

Nausea and vomiting induced by chemotherapy and/or targeted therapy are among the most stressful side effects of drug treatment, whereby vomiting can be effectively prevented in the vast majority of cases with adequate antiemetic prophylaxis. More problematic is the nausea, which is often still subjectively impairing.

Avoiding nausea and vomiting, which can be caused by chemotherapy or other oncological preparations, is an essential supportive measure in oncology and thus for the doctors in charge.

The symptom complex includes nausea, gagging and vomiting. The intensity of nausea and vomiting is classified internationally according to the Common Terminology Criteria for Adverse Events (CTCAE) into 4 degrees of severity [1321].

Table 46: Common Terminology Critera for Adverse Events (CTCAE, Version 4.03)

Criterion	Grade 0	Grade 1 Mild	Grade 2 Moderate	Grade 3 Mainly	Grade 4 Life-threatening
Nausea	No nausea	Something, food intake not restricted	Moderate, food intake restricted	Strong, no food intake	
Vomiting	No vomiting	1-2x/day	3-5x/day	≥ 6x/day	Life-threatening

Nausea and vomiting are divided into 3 forms according to the time of symptomatology in accordance with the S3 guideline "Supportive therapy in oncological patients":

- Acute: Occurs within 24 hours after the start of tumour therapy,
- delayed: Occurs later than 24 hours after the start of tumour therapy and lasts up to 5 days,
- anticipatory: consequence of a classical conditioning triggered by external factors such as smell, taste and visual impressions, by psychological factors such as fear and tension or characterized by nausea and vomiting during a previous tumor therapy

6.3.4.1. Diagnostics

The general occurrence, frequency and intensity are recorded in a conversation before and after each therapy cycle, before the start of a new therapy cycle and at regular intervals in the case of long-term therapy. It is also possible to use patient diaries to document the occurrence between two cycles.

In addition, numerous other causes of nausea and vomiting are possible in oncological patients, which should be considered and clarified by differential diagnosis, especially if there is no temporal connection between the occurrence and application of the tumour therapy or a new occurrence during ongoing therapy. These are described in detail in the S3 guideline "Supportive therapy in oncological patients" [871].

6.3.4.2. Prophylactic pharmacotherapy

In principle, antiemetic prophylaxis is based on the emetogenic potential of the drugs (see Table 10). Table 10 shows the substances which are of importance for patients with breast cancer. An overview of all antineoplastic substances can be found in the current S3 guideline "Supportive Therapy in Oncological Patients" [871].

With regard to the emetogenic risk of drug therapy, the following factors play an essential role according to the S3 guideline "Supportive Therapy in Oncological Patients":

- Type of therapy: higher for cytostatic drugs than for anti-hormonal therapy and targeted therapies (e.g. antibodies or kinase inhibitors),
- Dosage: higher with increasing dosages,
- Therapy regimen: higher for dose-dense therapy regimens,
- Combination: higher in combination with other emetogenic drugs and in combination with radiotherapy.

The cytostatic drug with the highest emetogenic potential determines the classification in the group "high, moderate, low or minimal". Here, the emetic risk in the absence of antiemetic prophylaxis is considered. For oral therapies the emetogenic potential is given for a complete therapy cycle. No additive effect on the emetogenic potential is to be expected from other cytostatic drugs, e.g. in combination chemotherapy. An exception is the anthracycline/cyclophosphamide-based chemotherapy for patients with breast cancer [1323], [1324], [1325].

Table 47: Emetogenes Potenzial der beim Mammakarzinom verwendeten einzelnen Zytostatika, aktualisiert 5/2012 [1323], [1326]

High: Risk of vomiting without antiemetic prophylaxis > 90 %	
Anthracycline in combination with cyclophosphamide	Cyclophosphamide (> 1500 mg/m2)
Cisplatin	
Moderate: risk of vomiting without antiemetic prophylaxis 30-90 %	
Carboplatin*\footnote {* Cave: Carboplatin is a special group; see recommendations below.}	Doxorubicin
Cyclophosphamide (	Epirubicin
Cyclophosphamide, per os	Mitoxantrone (> 12 mg/m2)
Low: risk of vomiting without antiemetic prophylaxis 10-30 %.	
Capecitabine	Methotrexate
docetaxel	Mitoxantrone (
Eribulin	Nab paclitaxel
everolimus	Paclitaxel
5-fluorouracil	Pertuzumab
Gemcitabine	
Ixabepilon	Topotecan
Lapatinib	Trastuzumab emtansin

High: Risk of vomiting without antiemetic prophylaxis > 90 %	
liposomal doxorubicin	
Minimal: risk of vomiting without antiemetic prophylaxis	
Anastrozole	Letrozole
Bevacizumab	Methotrexate, per os
Bleomycin	Tamoxifen
Copy	Trastuzumab
Fulvestrant	Vinorelbine
GnRH Analogues	

According to the S3 guideline "Supportive Therapy in Oncological Patients" [871] belongs to the patient-specific risk factors:

- Gender: higher for women,
- Age: higher in younger patients,
- Travel sickness / morning sickness: higher in patients with this condition,
- History of nausea and vomiting: higher in patients with previous exposure to chemotherapy,
- Alcohol consumption: lower in patients with chronic heavy alcohol consumption,
- Anxiety: higher in anxious patients,
- and the negative expectation

If necessary, the antiemetic prophylaxis should be adjusted if patient-specific risk factors are present.

Other factors may include the time of day of treatment, the environment/ environment and other emetogenic drugs, e.g. opiates.

In order to keep the side effects of the therapy low, to reduce the strain on the patient and to optimise the feasibility and acceptance of the therapy, antiemesis must always be carried out as prophylaxis during tumour treatment. Before each new therapy cycle, the effectiveness of the previous prophylaxis must be evaluated and adjusted if necessary. For the planning and implementation of supportive antiemetic therapy, the following aspects must be considered:

- antiemetic prophylaxis before the start of therapy according to the cytostatic drug protocol,
- detailed knowledge of the emetogenic risk of the respective therapy,
- Knowledge of individual patient risk,
- Reserve medication for the case of need,
- Education of the patient before therapy about prophylaxis and emergency medication,

- Radiation of peace and security,
- regular airing of the room,
- sufficient hydrogenation,
- Provide for distraction/relaxation.

The administration of antiemetics must always be carried out as a prophylaxis before the start of chemotherapy application. The oral administration of antiemetics is equivalent to the i.v. administration. Prophylaxis must be taken on the 1st day of chemotherapy application (acute phase) and on days 2 to 3 or 4 (delayed phase). In the case of chemotherapy lasting several days, prophylaxis for the acute phase should be repeated every day and prophylaxis for the delayed phase should be continued for two subsequent days.

The American Society of Clinical Oncology (ASCO) and the Multinational Association of Supportive Care in Cancer (MASCC) have developed guidelines for the prevention and control of nausea and vomiting which, together with the current data situation, form the basis of the recommendations of the S3 guideline "Supportive Therapy in Oncology Patients", which are presented in the following [1324] [1325] Background and detailed information on the data and literature of the individual drugs as well as dosages can be found in the current S3 guideline "Supportive Therapy in Oncology Patients" [871].

6.3.4.3. Highly emetic cancer chemotherapy

The following statement was taken from the S3 guideline "Supportive therapy in oncological patients":

6.8	**Evidence-based Recommendation**
GoR **A**	**Acute phase:** In the case of a one-day drug therapy with a risk of vomiting > 90%, prophylaxis with 5-HT3-RA, NK1-RA and dexamethasone shall be administered before the drug therapy. **Delayed phase:** In a one-day drug therapy with a risk of emesis > 90%, prophylaxis with dexamethasone shall be continued for another 2-4 days after the end of the highly emetogenic therapy. If the NK1- RA aprepitant was part of the primary prophylaxis, it shall be administered for 2 further days with 80 mg daily. Fosaprepitant or netupitant/palonosetron is only administered on day 1 of the drug therapy. Abbreviation: 5-HT3-RA - 5-hydroxytryptamin3-receptor antagonist, NK1- RA - neurokinin-1-receptor antagonist
LoE **1a**	[871]
	Strong Consensus

6.3.4.4. Anthracycline/Cyclophosphamide (AC)-based chemotherapy specifically for patients with breast cancer

In all international guidelines as well as in the S3 guideline "Supportive Therapy in Oncological Patients" AC-based chemotherapy is now classified as highly emetogenic [1323], [1324], [1325]. In analogy to the approval studies of highly emetogenic chemotherapy, aprepitant was applied for 3 days in the so-called Warr study of AC-based chemotherapy, but the combination with ondansetron and dexamethasone was only given on day 1. Patients in the control arm received ondansetron and dexamethasone on day 1 and ondansetron for 2 additional days. The primary endpoint was also the complete response. In this study, the additional administration of aprepitant in the overall phase of AC-based chemotherapy resulted in a 9% higher CR (p = 0.015) [1327]. In contrast to the highly emetogenic chemotherapy no significant effect of aprepitant in the delayed phase (day 2-5) of vomiting could be achieved. It is worth mentioning that the response rate in the delayed phase of 55% (control arm 49%) was significantly lower than in phase III studies with cisplatin-containing chemotherapy (complete response 75-76%), so that a reclassification of AC-based chemotherapy as highly emetogenic chemotherapy is logical.

In another large phase III study (n = 1449) in AC-containing chemotherapy, the efficacy of NEPA (netupitant/palonosetron) and dexamethasone day 1 versus palonosetron and dexamethasone day 1 was tested [1328]. No further antiemetic prophylaxis was given beyond day 1. The complete response on days 1-5 was 66.6% in the control arm and 74.3% in the experimental arm (p = 0.001).

6.3.4.5. Moderately emetic cancer chemotherapy

The following statement was taken from the S3 guideline "Supportive therapy in oncological patients":

6.9	Evidence-based Recommendation
GoR **A/B/0**	**Acute phase:** In the case of drug therapy of tumours with an emesis risk > 30-90% (except carboplatin, see next recommendation), prophylaxis with 5-HT3- RA and dexamethasone shall be carried out before chemotherapy. **Delayed phase:** In the case of a drug therapy with known emetogenic potential in the delayed phase (oxaliplatin, doxorubicin, cyclophosphamide and bendamustin (for bendamustin: EC recommendation)), dexamethasone should be administered on days 2 to 3. Other drug therapies with a moderate risk of vomiting do not require antiemetic prophylaxis on days 2-3. (recommendation grade 0) Abbreviation: 5-HT3-RA - 5-hydroxytryptamine3 receptor antagonist
LoE **1a/5**	[871]
	Strong Consensus

Background 6.9

Since the use of carboplatin is increasing in patients with breast cancer, especially in triple-negative carcinomas in neoadjuvant and BRCA mutation-associated metastatic carcinomas, the corresponding recommendation from the S3 guideline "Supportive Therapy in Oncological Patients" is presented below

6.10	Evidence-based Recommendation
GoR **A/B/0**	**Acute phase:** In the case of carboplatin-containing chemotherapy (from AUC ≥ 4), prophylaxis with a 5-HT3 receptor antagonist and dexamethasone shall be carried out before application. In addition, an NK1-RA can be administered. **Delayed phase:** In the case of carboplatin-containing chemotherapy (from AUC ≥ 4), antiemetic prophylaxis with dexamethasone should be administered on days 2-3. If the NK1- RA aprepitant was part of the primary prophylaxis, it shall be administered for another 2 days with 80 mg daily. Fosaprepitant or netupitant/palonosetron is administered only on day 1 of carboplatin therapy Abbreviation: 5-HT3-RA - 5-hydroxytryptamin3 receptor antagonist, NK1- RA - neurokinin-1 receptor antagonist
LoE **1a**	[871]
	Strong Consensus

6.3.4.6. Low emetic cancer chemotherapy

The following statement was taken from the S3 guideline "Supportive therapy in oncological patients" [871]:

6.11	Consensus-based Recommendation
EC	**Acute phase:** In the case of drug therapy of tumours with a risk of vomiting 10-30%, antiemetic prophylaxis can be omitted or carried out with dexamethasone, 5-HT3- RA or metoclopramide. (recommendation grade 0) **Delayed phase:** In case of tumor therapy with a risk of vomiting 10-30%, no primary antiemetic prophylaxis shall be taken on days 2-3. (recommendation grade A)
	Strong Consensus

6.3.4.7. Minimally emetic cancer chemotherapy

In accordance with the S3 guideline "Supportive Therapy in Oncological Patients", no prophylaxis is recommended for minimal risk, analogous to MASCC/ESMO and ASCO

LL in first-line therapy [1324], [1325]. Randomized studies do not exist in this setting. In case of nausea and vomiting prophylaxis is indicated from the next therapy course on.

6.3.4.8. Anticipatory nausea ad vomiting

Anticipatory ("learned") vomiting is triggered by classical conditioning after nausea and vomiting during previous therapies, as a consequence of patient-specific and therapy-related factors and fear and negative expectations, and is difficult to control with classical antiemetics [1329]. In cases of anticipatory nausea and vomiting a behavioral therapy including desensitization and hypnosis and benzodiazepines can be used.

6.3.4.9. Nausea and vomiting despite optimal prophylaxis

The emetic risk of the therapy is to be re-evaluated, as well as disease status, concomitant diseases and medication. Differential diagnoses of nausea and vomiting should be excluded. It should be ensured that the optimal regime is used. According to the S3 guideline "Supportive Therapy in Oncological Patients" [871], an alternative antiemetic regimen should be applied in the follow-up cycle. There should be no dose increase of 5HT3-RA/NK1-RA beyond the recommended daily dose. Furthermore, the administration of an antiemetic of the same substance class should not be performed.

In cases of nausea and/or vomiting despite optimal antiemesis, the following drugs can be used as rescue antiemesis with a strong consensus of the S3 guideline "Supportive therapy in oncological patients":

- Neuroleptics and other dopamine receptor antagonists:
  - Olanzapine, initial 1 x 5 mg p.o.,
  - Haloperidol, initial 1-3 x 1 milligrams p. o,
  - ...metoclopramide, 3 x 10 mg p. o. (maximum daily dose 0.5 mg/kg bw to a maximum of 30 mg) over 5 days,
  - Levomepromazine, initial 3 x 1-5 mg p.o. Alizapride, initial 3 x 50 mg.
- benzodiazepines:
  - Lorazepam, initially 1 x 1-2 mg p.o,
  - Alprazolam, initial 1 x 0.25-1.0 mg p.o.,
- H1 blocker:
  - Dimenhydrinate, initially 3 x 50-100 mg p.o. or 1-2 x 150 mg rectally.

The antiemetic effect of neuroleptics (e.g. haloperidol) is much less pronounced than with metoclopramide. As with benzodiazepines, the desired psychological distancing is more important. Phenothia-zines, the so-called low-potency neuroleptics (e.g. levopromazine) have a stronger sedative effect than butyrophenones (high-potency neuroleptics: haloperidol). On the other hand, the extrapyramidal side effects (parkinsonoid) of phenothiazines are much less pronounced than those of butyrophenones.

Olanzapine should be preferred to metoclopramide as a rescue antiemesis. This is an off-label use. In addition, the sedating component [1330] should be considered.

In exceptional cases cannabinoids may be considered.

6.3.4.10. Nonpharmacological treatment options

Non-drug interventions for the treatment of chemotherapy-induced nausea and vomiting are recommended in the guideline of the Oncology Nursing Society in combination with pharmaceutical measures [1331]. Various procedures such as

acupuncture and acupressure, relaxation techniques and massages can be used as an accompanying measure and in individual cases support drug therapy options.

In anticipatory vomiting as a cognitive process, primarily psychological interventions are discussed, such as progressive muscle relaxation, systemic desensitization, hypnosis and cognitive distraction [1332].

Acupuncture or acupressure are also used for the prophylaxis of nausea and vomiting under drug therapy of tumors. In the published studies, acupuncture was investigated in combination with drug prophylaxis. Some positive results have been described, but so far no statistically significant improvements in adults have been reported in randomised trials.

6.3.5. Radiotherapy-induced nausea and vomiting

Nausea and vomiting are among the most stressful side effects of radiotherapy in terms of localization. Intensity and duration of the symptoms depend, among other things, on the type of radiotherapy used, the dose, the irradiated area (volume) and the combination with chemotherapy [1333].

The emetogenic potential of radiotherapy of the breast is estimated to be minimal [1323], [1326]. General routine antiemetic prophylaxis is therefore not recommended.

Dopamine receptor antagonists or 5-HT3-serotonin receptor antagonists can be used as rescue medication. The potentiating effect of dexamethasone has been proven [1334].

In the case of radiation of osseous metastasis, cerebral metastasis or soft tissue metastasis the emetic risk should be assessed according to the localization and prophylaxis should be initiated, if reasonable, according to the criteria mentioned below.

In contrast to the more aggressive chemotherapies, vomiting under radiotherapy is relatively less pronounced in incidence and intensity. However, the emetic episodes can become subjectively just as stressful due to the usually several weeks of treatment. Observational studies suggest an incidence of emesis under radiotherapy of about 7-28%. The rate of nausea is much higher at about 40%. The incidence of nausea in patients with upper abdominal radiation is even given as 66% [1333], [1335].

The dominant risk factor for the occurrence of nausea and vomiting is the radiotherapy itself. In addition, patient-specific risk factors increase the risk of vomiting (see also tumour therapy related nausea and vomiting).

The intensity of these side effects is influenced by several factors, which are summarized in Table 4.

Table 48: Strahlentherapiespezifische Faktoren des emetogenen Risikos

Localization of the radiotherapy
Radiotherapy volume
Single and total radiation therapy Dose/fractionation
Radiotherapy Technology

Table 49: Zusammenfassung der antiemetischen Prophylaxe

Emesis risk	Irradiated body region	Antiemetic prophylaxis
High	Full body radiation	5-HT3-RA and dexamethasone
Moderate	Upper abdomen, BWS/LWS , neuro axis depending on the technique	5-HT3-RA and dexamethasone can be used for dexamethasone
Low	Pelvis, cranium, ENT	5-HT3-RA or rescue therapy
Minimal	Extremities, chest	No routine prophylaxis

In the case of combined radiochemotherapy, antiemetic prophylaxis is based on the highest achieved risk class of radiotherapy or chemotherapy. For example, in the case of combined radiochemotherapy with cisplatin, the emetogenic potency of cisplatin is decisive for antiemetic prophylaxis. In this case prophylaxis with a 5-HT3-RA, dexamethasone and NK1-RA is recommended [1336], [1337].

6.3.6. Neutropenia, febrile neutropenia (FN), infections

Febrile neutropenia (FN) and neutropenia-associated infections are a significant factor in morbidity and mortality after cytotoxic therapy. In addition, they can lead to a dose reduction of chemotherapy and/or cycle delays [1338]. Granulocyte colony stimulating factors (G-CSF) are approved for the reduction of the incidence of febrile neutropenia and duration of neutropenia in malignant diseases with cytotoxic chemotherapy.

6.12	**Consensus-based Statement**
ST	The sole presence of afebrile neutropenia after tumor therapy does not justify the administration of G-CSF.
	Strong Consensus

6.13	**Evidence-based Statement**
ST	The prophylactic administration of G-CSF depends on the risk of developing febrile neutropenia according to the individual risk factors and the cytotoxic therapy used.
LoE **1b**	[871]
	Strong Consensus

6.14	**Consensus-based Recommendation**
EC	Patient-specific risk factors shall be evaluated before the start of each chemotherapy cycle to estimate the overall risk of febrile neutropenia.
	Strong Consensus

6.15	**Consensus-based Statement**
ST	No individual risk factor can be clearly identified. The following factors, especially when they occur in combination, are likely to increase the risk of febrile neutropenia: • Age > 65 years • Low performance status (low Karnofsky Index, high ECOG) • Comorbidities (COPD, heart failure NYHA III-IV, HIV disease, autoimmune disease, significantly impaired kidney function) • Very advanced, symptomatic tumor disease • Past history of chemotherapy... • Laboratory parameters (anemia, lymphocytopenia Other study endpoints such as infection-related mortality were also included in the evaluation.
	Strong Consensus

6.16	**Consensus-based Statement**
ST	Based on the risk of developing febrile neutropenia under the respective tumor therapy protocol, the classification is made into 5 categories: 1. Risk ≥ 40% for one FN 2. Risk ≥ 20% and 3. Risk 4. < 20 % und ≥ 10 % für eine FN 5. < 10 % für eine FN
	Strong Consensus

6.17	**Evidence-based Recommendation**
GoR **A**	**Recommendation for G-CSF prophylaxis depending on the febrile neutropenia risk** Patients with solid tumors who receive tumor therapy with a febrile neutropenia risk ≥ 40% shall be given prophylactic G-CSF.
LoE **1a**	[871]
	Strong Consensus

6.18	**Evidence-based Recommendation**
GoR **B**	In patients with solid tumors who have undergone tumor therapy with a febrile neutropenia risk ≥ 20% and
LoE **1a**	[871]
	Strong Consensus

6.19	**Evidence-based Recommendation**
GoR **B**	In patients with solid tumors who have a febrile neutropenia risk of <20% and > 10% and have individual risk factors, prophylactic G-CSF sould be administered.
LoE **1a**	[871]
	Strong Consensus

6.20	**Evidence-based Recommendation**
GoR **B**	In patients with solid tumors who have a febrile neutropenia risk of < 20% und ≥ 10% without individual risk factors, no prophylactic G-CSF should be administered.
LoE **1a**	[871]
	Strong Consensus

6.21	**Consensus-based Recommendation**
EC	Patients with solid tumors who have a febrile neutropenia risk < 10% shall not receive prophylactic G-CSF administration.
	Strong Consensus

6.22	**Evidence-based Recommendation**
GoR **A**	Prophylactic administration of G-CSF shall take place no earlier than 24 hours and no later than 3 days after completion of chemotherapy, unless otherwise specified in the protocol.
LoE **1a**	[871]
	Strong Consensus

6.23	**Evidence-based Recommendation**
GoR **A**	Patients receiving pegfilgrastim shall be administered 24 hours after completion of chemotherapy unless otherwise specified in the protocol.
LoE **1b**	[871]
	Strong Consensus

6.24	**Consensus-based Recommendation**
EC	In therapy situations where dose-dense (increased frequency) or dose-intensified (increased dose) tumor therapies show a survival benefit, the prophylactic administration of G-CSF shall be carried out according to the established therapy protocol.
	Strong Consensus

6.25	**Evidence-based Recommendation**
GoR **B**	In case of febrile neutropenia after tumor therapy, G-CSF should not be administered routinely.
LoE **1a**	[871]
	Strong Consensus

6.3.6.1. Infections in neutropenia

Fever in chemotherapy-associated neutropenia is due to infection in over 95% of cases. Nevertheless, no pathogen can be detected in 50 - 70% of patients. The immediate use of broad-spectrum antibiotics is therefore necessary in order to prevent further development into a potentially life-threatening infection or to treat [1339], [1340], [1341], [1342] immediately and effectively. Infections are the most frequent therapy-related causes of death in cancer patients. The risk of febrile neutropenia or life-threatening infections correlates with the severity and duration of neutropenia [1343]. The mortality due to infections in chemotherapy-induced neutropenia is 2.8% and early mortality is 5.7% [1344]. Documented infections in neutropenia have a significantly worse prognosis than febrile neutropenia [1339], [1344], [1345]. Multivariate analysis revealed the following risk factors for a fatal course of FN: gram-negative sepsis (relative risk: 4.92), invasive aspergillosis 3.48, invasive candidiasis 2.55, lung disease 3.94, cerebrovascular disease 3.26, kidney disease 3.16, liver disease 2.89, pneumonia 2,23, gram-positive sepsis 2.29, hyptension 2.12, pulmonary artery embolism 1.94, heart disease 1.58, leukemia 1.48, lung cancer 1.18, age > 65 years 1.12 [1344].

The diagnosis and therapy of infections in neutropenia are presented in a differentiated manner in special recommendations and guidelines, which are explicitly referred to here.

1. German Society for Hematology and Medical Oncology (DGHO), Onkopedia Guidelines, https://www.onkopedia.com/de/onkopedia/guidelines/infektionen-bei-haematologischen-und-onkologischen-patienten-uebersicht/@@view/html/index.html
2. European Society of Medical Oncology (ESMO): http://www.esmo.org/Guidelines/Supportive-Care/Management-of-Febrile-Neutropaenia
3. National Comprehensive Cancer Network (NCCN) https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf

6.3.7. Cancer therapy-induced anemia

Patients with a tumor disease often suffer from anemia that can cause clinical symptoms. The cause can be the tumor disease itself as well as chemotherapy or radiotherapy/radiochemotherapy.

Chemotherapy can trigger or intensify anemia. When treating anaemia, it is therefore necessary to consider the possible causes, including multiple causes. Depending on the clinical constellation, blood transfusions, erythropoiesis-stimulating agents (ESA) or, in the case of functional iron deficiency, the substitution of intravenous iron, also in combination with ESA, can be considered. In these cases, an accurate and individual risk-benefit assessment is necessary.

In this S3 guideline, the forms of anaemia are defined as follows:

Tumour anaemia (anaemia in chronic disease): This form of anaemia results from the activation of the immune system (by tumour, infection, autoimmune disease) with complex effects on haematopoiesis, iron metabolism and its regulation.

Tumor therapy induced anemia: Anemia caused by chemotherapy (including "new substances") and/or radiotherapy and/or radiochemotherapy.

Chemotherapy-induced anaemia: anaemia caused by chemotherapy

6.3.7.1. Definition of anemia

Anaemia is a reduction in the number of erythrocytes, characterized by a decrease in hemoglobin concentration (Hb) and/or hematocrit in peripheral blood.

The lower reference value of haemoglobin is defined (WHO) as 12 g/dl (7.45 mmol/l) in central European adults, depending on age, in non-pregnant women and 13 g/dl (8.07 mmol/l) in men.

6.3.7.2. Anemia in cancer, anemia of chronic disease (ACD)

Symptomatic anemia is frequent in cancer patients and, depending on the type and stage of tumor, amounts to approx. 31-50% already at diagnosis of solid tumors without therapy. The prevalence is even higher in hematological neoplasias [1346], [1347].

Anemia in cancer without therapeutic influence is caused by the activated immune system. This form of anaemia is called anaemia of chronic disease (ACD) [1348]. In the foreground are disorders mediated by inflammatory cytokines (tumor necrosis factor-α, interleukin-1-α and -ß, interleukin-6, interferon-γ). They concern homeostasis of iron metabolism, inhibited proliferation of erythroid precursor cells, insufficient synthesis of and reduced response to erythropoietin (EPO) in relation to anemia, and a shortening of erythrocyte survival [1348], [1349], [1350].

Hepcidin, a type II acute phase peptide produced in the liver, inhibits intestinal iron absorption, iron release from enterocytes, iron mobilization from the reticulohistiocyte system (RHS) and iron uptake into the erythropoietic progenitor cells [1351]. Hepcidin binds to the single cellular iron exporter ferroportin and causes its degradation. There is a reduced haemoglobin synthesis in the case of iron overload of the organism. Despite increased storage iron, haematopoiesis results in insufficient iron being available, corresponding to a functional iron deficiency.

With increased erythropoietic activity, the precursor cells of erythropoiesis in the bone marrow, the proerythroblasts, form the molecule erythroferrone, which inhibits the formation of hepcidin in the liver and thereby promotes the absorption and distribution of iron from the storage cells [1352]. In reduced or suppressed hematopoiesis, erythroferrone production is therefore reduced and hepcidin production is increased.

6.3.7.3. Incidence of cancer therapy-induced anemia

Under tumor therapy anemia occurs in about 75% of all patients, most frequently in gynecological tumors (81-88%) and in patients with lung cancer (77-83%) [1347].

With radiotherapy alone, anemia is reported in about 38% of patients, with rates of 51% in patients with lung cancer, 35% in patients with breast cancer, 49% in tumors of the gastrointestinal tract, 54% in gynecological tumors and 42% in malignant lymphomas [1347], [1353]. In prostate carcinoma the anemia rate is about 32% [1346].

In combined radio- and chemotherapy the overall anemia rate is about 62% [1347].

6.3.7.4. Diagnostics

6.3.7.4.1. Laboratory parameters

The following values may be elevated in chronic anemia: Ferritin, free transferrin-iron binding capacity (transferrin saturation decreased), BSG, fibrinogen, CRP and haptoglobin, zinc protoporphyrin (ZPP), soluble transferrin receptor in serum, erythropoietin in serum (but not sufficient, i.e. inadequately increased).

Table 50: Anemia workup [676]

Diagnostics for anaemia	
exclusion of additional causes of anaemia, clinical examination	
absolute and functional iron deficiency Bleeding Vitamin B12 (cobalamin) and folic acid deficiency Hemolysis	Renal dysfunction haematological systemic disease other internal diseases (infection, chronic inflammatory disease)
Laboratory Diagnostics	
Basic diagnostics	additional laboratory diagnostics
Blood count with Hb, Hk, MCV, MCH quantitative reticulocyte count Differential blood count	Erythropoietin levels hypochromic erythrocytes
Iron status: ferritin, transferrin Transferrin saturation	Reticulocyte hemoglobin (CHr) Zinc protoporphyrin (ZPP), soluble transferrin receptor (sTfR)
Holo-trans-cobalamin (vitamin B12), folic acid	Hemolysis parameters: LDH, haptoglobin, Coombs test
Routine laboratory with liver and kidney function parameters: bilirubin, transaminases, albumin, creatinine	Bleeding diagnosis: thromboplastin time (Quick, INR), stool on blood, urine status

6.3.7.4.2. Therapy options in cancer therapy-induced anemia

Anemia therapy is indicated for clinical complaints (see above). The tolerance of anemia varies greatly from individual to individual. The lowered Hb value alone is not sufficient to establish an indication.

Depending on the severity of the anemia, there are several options for the treatment of tumor therapy induced anemia. The listed therapeutic approaches are erythropoiesis-stimulating agents, iron replacement and transfusions with different degrees of recommendation.

6.3.7.4.3. Erythropoiesis-stimulating agents (ESA) in chemotherapy-induced anemia

The use of ESA in oncology is subject to a strict indication. The recommendations in this chapter therefore only refer to chemotherapy-induced anaemia.

Currently, ESAs with an Hb value ≤ 10 g/dl (6.2 mmol/l) are approved for the treatment of symptomatic, chemotherapy-induced anaemia in tumour patients to increase the haemoglobin value to a maximum of 12 g/dl (7.5 mmol/l).

The de novo research of the Cochrane Haematological Malignancies Group was based on the fundamental work of Tonia et al. [1354] and the subsequently published RCTs in the sense of an update research [1355], [1356], [1357], [1358].

6.26	Evidence-based Recommendation
GoR **0**	Erythropoiesis-stimulating agent administration can be considered for the therapy of chemotherapy-induced anaemia.
LoE ⊕⊕⊖⊖	[871]
	Consensus

6.27	Evidence-based Recommendation
GoR **A**	When considering the use of erythropoiesis-stimulating agents, patients shall be informed about the benefits (potential increase in quality of life and reduction in transfusion frequency) and risks (thromboembolic complications and hypertension).
LoE ⊕⊖⊖⊖	[871]
	Strong Consensus

6.3.7.4.4. Iron substitution

The chapter on iron replacement also only refers to patients with chemotherapy-induced anaemia.

6.3.7.4.5. Differential diagnosis and diagnostic workup

An iron deficiency often occurs in tumor patients on [1359]. Depending on the severity, 3 stages are distinguished: storage iron deficiency, iron deficient erythropoiesis and iron deficiency anaemiaTable 7). Thus, a negative iron balance initially leads to iron deficiency without affecting erythropoiesis. In the stage of iron-deficient erythropoiesis (functional iron deficiency, FID) the supply of the erythropoietic precursors in the bone marrow is insufficient, but the hemoglobin is still normal [1360]. Only when the hemoglobin level falls below the hemoglobin level is iron deficiency anemia (absolute iron deficiency, AID) present.

When making a diagnosis, it should be borne in mind that ferritin can show false normal or elevated values in inflammatory and malignant diseases and thus mask an existing iron deficiency. On the other hand, transferrin saturation can be lower in chronic diseases despite normal iron stores. Here, the determination of the soluble transferrin receptor (sTfR), zinc proto-porphyrin (ZPP), hypochromic erythrocytes or reticulocyte hemoglobin can be helpful.

Table 51: Stages and diagnostic workup of iron deficiency [676]

Stages and diagnostics of iron deficiency
1. lack of storage iron
Ferritin for men in females
2. iron deficiency erythropoiesis, corresponds to functional iron deficiency or Functional Iron Deficiency (FID)
Transferrin saturation (TSAT) Ferritin > 30-800 ng/ml + If necessary, sTfR (transferrin receptor) or ZPP (zinc protoporphyrin) or hypochromic erythrocytes or reticulocyte hemoglobin
3. iron deficiency anemia, corresponds to absolute iron deficiency or Absolute Iron Deficiency (AID)
Hb Transferrin saturation (TSAT) For patients with tumor disease: serum ferritin value (With otherwise healthy people: Serum ferritin value

6.28	**Evidence-based Recommendation**
GoR **0**	In the case of a therapy with erythropoiesis-stimulating agents, if there is a functional iron deficiency, in order to achieve an increase in Hb, the accompanying therapy can be carried out with i.v. iron. Analyses of overall survival have not been performed in the respective studies.
LoE **1b**	[871]
	Strong Consensus

6.29	**Evidence-based Statement**
ST	The available evidence from the RCTs is not sufficient to make a recommendation for or against i.v. iron therapy alone due to methodological deficiencies.
LoE **1b**	[871]
	Strong Consensus

6.3.7.4.6. Transfusion of packed erythrocytes

Evidence-based recommendations on the indication can be found in greater detail in the guidelines of the AABB (formerly "American Association of Blood Banks"), last published in 2012 [1361], especially for the intensive care sector also from Great Britain [1362], and in detail in the "Cross-sectional guidelines (BÄK) for therapy with blood components and plasma derivatives", (last 4th edition, updated 2014, [1363]).

According to the cross-sectional guideline of the BÄK, transfusion is not indicated in chronically anaemic patients without cardiovascular diseases, even at haemoglobin concentrations of up to 8.0-7.0 g/dl (HK 24-21 % = 5.0-4.3 mmol/l), as long as no symptoms attributable to the anaemia occur. Exceptions allow even deeper triggers, on the one hand if the symptom burden is low or tolerable, on the other hand in special therapeutic situations.

Aspects of quality of life must be weighed against the risks of transfusions (especially iron overload), which are usually necessary in chronic anaemia.

In addition to the BÄK cross-sectional guidelines, it should be mentioned that in the presence of cardiovascular risk factors only triggers of 8 g/dl versus 10 g/dl have been randomly compared to [1364], without finding disadvantages for the restrictive strategy. Patients with infarcts within the last 30 days were not included. Due to the occasional coincidence of neoplastic and cardiovascular diseases at an older age, it should be taken into account that randomized studies on the range of < 7g/dl as a possible trigger.

6.30	**Consensus-based Statement**
ST	In a variety of clinical contexts, a restrictive indication for transfusion is not associated with clinical disadvantages for patients with acute anemia. By analogy, a similar situation can also be assumed in the absence of data on tumour therapy-induced anaemia.
	Strong Consensus

6.31	**Consensus-based Statement**
ST	In addition to the clinical condition and the severity of the anaemia symptoms, the decision to transfuse is based on the Hb value (or haematocrit), the acute nature of the blood loss and the patient's compensation options and risk factors.
	Strong Consensus

Table 52: Recommendations for RBC transfusion in acuute anemia as pre cross-sectional guidelines (BÄK) for therapy with blood components 2014 [676]

For the indication of an erythrocyte transfusion, individual consideration of the criteria Hb concentration, compensatory capacity and risk factors of the patient is recommended:

Hb area	**Compensability/risk factors**	**Transfusion**	**Evaluation *****
< 6 g/dl (<3,7 mmol/l)	/	yes *	1 C+
> 6-8 g/dl (> 3.7 - 5.0 mmol/l)	Adequate compensation, no risk factors	no	1 C+
	Compensation limited, risk factors present (e.g. CHD, heart failure, cerebrovascular insufficiency)	yes	1 C+
	Indications of anemic hypoxia (physiological transfusion triggers: e.g. tachycardia, hypotension, ECG ischemia, lactic acidosis)	yes	1 C+
8-10 g/dl (5.0 - 6.2 mmol/l)	Indications of anemic hypoxia (physiological transfusion triggers: e.g. tachycardia, hypotension, ECG ischemia, lactic acidosis)	yes	2 C

For the indication of an erythrocyte transfusion, individual consideration of the criteria Hb concentration, compensatory capacity and risk factors of the patient is recommended:			
> 10 g/dl (> 6.2 mmol/l)	/	no **	1 A

Notice!

Haemoglobin concentration alone is not an adequate measure of O2 supply.

In hypovolaemia, the hematocrit does not correctly reflect erythrocyte deficiency.

Individual factors may require indications that deviate from the recommendations.

* In individual cases, with adequate compensation and without risk factors, lower Hb values can be tolerated without transfusion.

** In individual cases a transfusion to Hb values > 10 g/dl may be indicated.

*** Assessment level of the BÄK

1A: Strong recommendation that applies to most patients, based on randomized controlled trials without significant methodological limitations

1C +: Strong recommendation that applies to most patients, no randomized controlled trials, but clear data

2C: Very weak recommendation, depending on the individual case, a different procedure may be indicated; based on observational studies, case descriptions

6.32	**Consensus-based Statement**
ST	In patients with long-term tumour therapy-induced anaemia, a transfusion is recommended if the Hk is below 24 - 21% or the haemoglobin concentration is less than 8 - 7 g/dl (< 5,0 – 4,3 mmol/l), after considering and weighing the overall situation.
	Strong Consensus

6.33	**Consensus-based Recommendation**
EC	In hospitalized patients with chronic anemia, whose clinical condition and laboratory parameters are closely monitored, only one red cell concentrate should be administered if the trigger is slightly undershot.
	Strong Consensus

Background 6.32 and 6.33

The recommendation to always give only one red cell concentrate and only in exceptional cases two preparations, because more transfusions would not be beneficial

for the patient, comes from a setting with intensive monitoring of patients and daily controls of the blood count [1365], [1366], The strategy is not evaluated in terms of safety for a setting with longer control intervals.

The reduction of the transfusion frequency is part of the North American initiative "Choosing wisely" to optimize the medical measures [1367]. There the recommendation was chosen to "transfuse the minimum number of units necessary to relieve the symptoms of anemia or to bring the patient into a safe Hb range (7-8 g/dL in stable, non-cardiological inpatients)". The background text also recommends avoiding transfusion of two units where one unit would be sufficient. On the other hand, in order to improve the quality of life (reduced fatigue, better mobility in everyday life and sports, reduction in the frequency of visits to the doctor), it may be useful, for example in outpatients, to transfuse two red cell concentrates even at Hb values around 8 g/dl, depending on the planned interval until follow-up. The aspects of transfusion medical care (blood supply time and logistics) must also be taken into account.

6.3.8. Neurotoxicity

The neurotoxicity associated with the treatment of the patient with a breast cancer is usually chemotherapy-induced peripheral neuropathy (CIPN). This is a peripheral neuropathy which can be motor or sensory. The symptoms are manifold. Often it is limited to mild paresthesia, hypaesthesia and hyperaesthesia, mostly affecting hands and feet, sometimes a superficial, burning or stabbing neuropathic pain may occur. An impairment of the sensation of vibration and the sense of position (depth sensitivity) can also occur. Furthermore, the neuropathic pain can significantly impair the patient's quality of life. Motor neuropathy of the proximal muscle group is rarely seen.

After completion of the therapy, symptoms usually disappear within a few months.

Risk factors include an existing neuropathy (e.g. diabetic, alcohol toxic, renal insufficiency), increased age, combination therapies with platinum derivatives (e.g. cisplatin > 300 mg/m², grade I-II 14-63%, grade III-IV 7-21%), eribulin (grade I-IV up to 35%, grade III-IV up to 8%) and the taxanes, which are of fixed importance in the therapy of breast cancer [1368]. With regard to the taxanes docetaxel, paclitaxel and nab-paclitaxel are used. Thus, the supportive therapy of neurotoxicity is particularly relevant for breast cancer patients.

6.3.8.1. Taxane-associated neuropathy

Typically, neuropathy is more frequent under paclitaxel than under docetaxel (sensory neuropathy grade III/ IV: 2-33% versus 1-9%; motor neuropathy grade III/ IV: 0-14% versus 1-9%) [1369]. It occurs less frequently under the weekly administration of paclitaxel than under the three-weekly administration (grade III/ IV: 19% versus 12%, p=0.001) [1370]. Sensory neuropathy occurs more frequently under nab-paclitaxel than under standard paclitaxel. In a study by Gradishar et al. a third degree sensory neuropathy was observed significantly more frequently with 10% than under paclitaxel with 2% (p<0,001) [1371]. Es zeigte sich jedoch auch eine rasche Erholung der Neuropathie auf Grad I oder II mit einem Median von 22 Tagen. Nach 28 Tagen war die Anzahl der Patientin mit einer sensorischen Neuropathie dritten Grades in beiden Armen identisch. Motorische Neuropathien und sensorische Neuropathien vierten Grades wurden nicht beobachtet. In Bezug auf das Auftreten der sensorischen Neuropathie ist auch die hö-here Dosierung des nab-Paclitaxels im Vergleich zum konventionellen Palcitaxel zu berücksichtigen. In einer Phase-II-Studie wurde die Dosierung von 175 m/m² nab-Paclitaxel bei 43 Patientinnen mit einem metastasierten Mammakarzinom untersucht [1372]. Es trat keine Neuropathie Grad III oder IV auf. In

Bezug auf die wöchentliche Therapie mit nab-Paclitaxel untersuchten Gradishar und Kollegen 302 nicht vorbehandelte Patientinnen mit einem metastasierten Mammakarzinom mit Docetaxel 100 mg/m², q21d, nab-Paclitaxel 300 mg/m², q21d, oder nab-Paclitaxel 150 mg/m² oder 100 mg/m², q7d [1373]. Die Inzidenz der sensorischen Neuropathie zeigte sich zwischen Docetaxel und allen drei nab-Paclitaxel-Armen gleich ($p > 0.1$). Within the nab-paclitaxel arms, the rate of sensory neuropathy was higher at the dosages of 300 mg/m², q21d, and 150 mg/m², q7d. Sensory neuropathy recovered more rapidly under nab-paclitaxel than under docetaxel. The time to recovery on ≤ 2nd degree was 22, 22 and 19 days for the doses 300 mg/m², 100 mg/m² and 150 mg/m². In the docetaxel arm this took 37 days. In the publication of the study with the final analysis of overall survival no significant difference in the incidence of neuropathies was observed between the four arms (p=0.83) [1374]. Recovery time to grade II and below was 20-22 days for nab-paclitaxel and 41 days for docetaxel. In further studies, patients with progression under taxane therapy in the metastatic situation or metastasis within 12 months after adjuvant taxane therapy were treated with 100 mg/m² (n=106) or 125 mg/m² nab-paclitaxel, d1, 8, 15, q28d, [1108]. The median number of cycles was 5.3 and 4.7. In the cohort with 100 mg/m², 9 patients (8%) developed a grade III sensory neuropathy, whereas three patients already had a pre-existing grade I neuropathy. Under the 125 mg/m² dose, 19% (n=14) of the patients showed a grade III sensory neuropathy, with three patients also having a grade I neuropathy before the start of therapy. Of the 23 patients with a grade III neuropathy, 15 patients were able to continue the therapy with a reduced dosage after a 1-2 week therapy break. The study did not show any grade IV neuropathy, while 17% (n=18) developed grade II neuropathy under the 100 mg/m² dose and 32% (n=24) under the 125 mg/m² dose.

6.3.8.2. Diagnostics

According to the S3 guideline "Supportive Therapy for Oncological Patients" [871], CIPN is diagnosed on the basis of the patient's medical history and clinical findings. In case of special questions electrophysiological examinations may be necessary. It is essential that these are carried out before the start of therapy and before each cycle. To prevent a higher degree of chemotherapy-induced polyneuropathy, its early detection is crucial. In order to ensure an early diagnosis of CIPN, patients need to be instructed in the documentation of neurotoxic symptoms and reliable methods of CIPN recording, which are presented in detail in the S3 guideline "Supportive therapy in oncological patients" [871]. The world's leading scale for quantitative assessment of peripheral neurotoxicity is based on the National Cancer Institute-Common Toxicity Criteria (NCI-CTC).

The following statement was taken from the S3 guideline "Supportive therapy in oncological patients":

6.34	**Consensus-based Recommendation**
EC	An examination of the neurological status shall be carried out before initiating a potentially neurotoxic tumour therapy to determine the initial findings and identify patients at risk. Before each cycle, a detailed anamnesis shall be taken with special consideration of possible neurotoxicities, including a repetition of the neuro status if necessary.
	Strong Consensus

6.3.8.3. Patient education

It is essential to inform the patient in detail about the background of neurotoxicity, the risks and behavioural measures before therapy. As a result of possible sensory-motor failures, there is a risk of burns and frostbite (e.g. use thermometers when bathing and rinsing), falls and injuries with subsequent wound infections and in some cases limited fitness to drive. Patients should have regular examinations for pressure points and injuries, good skin care on hands and feet and regular gripping exercises with hands and feet.

6.3.8.4. Prophylaxis of CIPN

There is currently insufficient data from RCTs for the prophylaxis of function loss through CIPN using non-drug methods. Nevertheless, the expert consensus of the S3-guideline "Supportive Therapy in Oncological Patients" recommends regular exercise training, especially of finger and toe functions, because in the context of CIPN-related sensory limitations, consecutive additional motor disorders are to be expected.

With regard to drug therapy, there is no effective prophylaxis of chemotherapy-induced polyneuropathy. Standardized prophylactic measures or causal therapy approaches are not yet available for CIPN according to the S3 guideline "Supportive Therapy in Oncological Patients" [871]. Therefore, prevention and early detection of CIPN have the highest priority [1375]. According to the S3 guideline "Supportive Therapy in Oncological Patients", prophylaxis of chemotherapy-induced polyneuropathy with the following substances is not recommended:

- Alpha lipoic acid (recommendation level A, level of evidence 1b),
- Amifostine (recommendation grade B, level of evidence 1a),
- Calcium and magnesium (recommendation grade B, level of evidence 1a),
- Carbamazepine (recommendation level B, level of evidence 1b),
- diethyldithiocarbamate (DDTC),
- Glutathione (recommendation level A, level of evidence 1a),
- and vitamin E (recommendation level B, level of evidence 1a).

6.3.8.5. Therapy of CIPN

In principle, a dose reduction can be considered in patients with known diabetic or alcohol-induced neuropathy or in patients with the development of severe neuropathy, but this must be weighed against the potential loss of efficacy of oncological therapy.

The data available on the treatment of CIPN with non-drug interventions are limited to date. The effectiveness of non-drug interventions has been evaluated in a review by Streckmann et al. [1376]. In this review 18 studies on "exercise interventions for

neuropathic patients" were analysed. The review described a positive effect for exercise therapy to treat PNP of different etiologies. Training methods such as endurance training, balance training, vibration training, Tai Chi, walking and standing training, also using weights, were used. Basically, this review results in an advantage for balance training regardless of the underlying genesis. For CIPN, a combination of endurance, strength and sensorimotor training has been found to be effective, which led to the following statement in the S3 guideline "Supportive Therapy in Oncological Patients":

6.35	**Consensus-based Recommendation**
EC	In manifest chemotherapy-induced polyneuropathy, exercise therapy should be used to improve functionality: This may include: • Balance exercises • sensomotoric training • Coordination training • Vibration training • Fine Motor Training
	Strong Consensus

Background 6.35

With regard to the initiation of symptomatic drug therapy, the decision and selection of drugs should be made on the basis of a risk-benefit analysis. The latter includes, in particular, sedative effects that often occur at the beginning of the therapy when the dosage is administered, and which require special consideration also for impairment of driving ability.

In general, CINP shows a poor response to pain therapy drugs. There is a choice of selective serotonin-noradrenalin-reuptake inhibitors (SSNRI), e.g. venlafaxine, duloxetine, tricyclic antidepressants, e.g. amitriptilin, clomipramine, imipramine or doxepin, for shooting pain carbamazepine, gabapentin, pregabalin.

According to the S3 guideline "Supportive Therapy in Oncological Patients" [871], the following drug therapies can be considered in the case of chemotherapy-induced polyneuropathy:

- SSNRI venlafaxine (expert consensus),
- Amitriptyline (recommendation level 0, level of evidence 1b),
- Gabapentin (recommendation level 0, level of evidence 1b),
- Pregabalin (expert consensus).

In case of pain in chemotherapy-induced polyneuropathy, therapy with duloxetine should be considered (recommendation level B, level of evidence 1b) [1377]. This is an off-label use. The effect is greater in platinum-induced neuropathy than in taxane-induced neuropathy. The recommendation is consistent with the ASCO guidelines [1375]. In the case of neuropathic pain, opioids are also available as effective drugs (expert consensus). However, data on opioid therapy in CIPN and neuropathic pain are still limited [897], [1378]. In addition, side effects and tolerance development can limit the application. Non-opioid analgesics (NSAID, paracetamol and metamizole) have only a low effectiveness in neuropathic pain and are to be viewed very critically due to the potential side effects (e.g. gastrointestinal ulcers, renal insufficiency, cardiovascular

side effects, very rarely agranulocytosis in metamizole) in accordance with the S3 guideline "Supportive therapy in oncological patients".

6.3.8.6. Other toxicities

Other toxicities associated with different systemic therapies of the patients and with different frequencies depending on the therapy are diarrhoea, mucositis and stomatitis and skin toxicities. Since these can significantly reduce the quality of life of a patient with a therapy for breast cancer, prophylactic as well as therapeutic measures are essential if they occur. Extensive supportive therapies are available for these side effects which, together with the handling of extravasations, are reflected in the S3 guideline "Supportive Therapy in Oncological Patients" [871].

6.4. Follow-up and long-term care

6.4.1. Objectives

Aftercare in the narrower sense includes structured examinations of locoregional or intramammary recurrence and contralateral breast carcinoma, examinations for distant metastases and the monitoring of long-term therapies with diagnosis and therapy of consequences and side effects. It begins due to the variation of the therapy regimen following the completion of the primary locoregional therapy [1379].

Patients with a completely different starting position are treated within the scope of aftercare. These include, for example, patients after neoadjuvant or adjuvant chemotherapy, targeted therapy, endocrine system therapy or complementary and alternative therapy procedures (CAM). They also include patients who have been treated within the framework of studies. Patients who have received radiation therapy must be regularly and specifically examined for radiogenic late effects.

An individualized risk-adapted aftercare would be necessary. While therapy decisions are made according to risk classifications (TNM stage, steroid hormone receptors, growth factor receptors, age, etc.), there are no larger valid studies that have investigated individualized risk-adapted follow-up. Survival comparisons of the different tumour stages show that survival rates are stage-dependent, so that stage-adapted risk stratification could be carried out. There are no criteria for modifying the structured aftercare established to date. Thus, patients with a high risk of locoregional recurrence and a risk of distant metastasis are accompanied and treated in the same way in structured follow-up as those with a low risk of recurrence.

At the same time, it is also apparent that a time limit of 5 years for aftercare is not sufficient given the different risk constellations of the patients. Thus, even without direct study funding, the time frame for follow-up care has been extended from currently 5 years to a period of 10 years [1380]. It should be noted that therapy monitoring should be continued for at least 10 years.

There are no new prospective randomised studies that take into account different risk constellations, adapted aftercare schedules or integration of newer diagnostic methods. The currently practiced aftercare concept supported by prospective randomized studies is to be seen as an orientation, although it should be adapted to the individual situation of the affected woman due to the symptoms.

6.36	**Consensus-based Statement**
ST	Aftercare for patients with breast cancer begins with the completion of locoregional primary treatment. It consists of an anamnesis, physical examination, medical consultation, care and support as well as imaging diagnostics to detect local and locoregional recurrence and contralateral breast carcinoma. In case of abnormal findings, the follow-up care should be designed in a symptom-oriented manner.
	Strong Consensus

Background 6.36

In contrast to the situation in metastatic breast carcinoma patients with an intramammary or locoregional recurrence have a curative therapy chance.

For the early detection of distant metastases and their treatment there are no large prospective randomized studies available that have shown a significant survival benefit. A further distinction must be made here between patients who are undergoing long-term therapy and those who have metastasized after a therapy-free interval [1384], [1386].

The basis of the aftercare is the attention and the conversation. Central concerns are the reduction of anxiety and the improvement of the patient's quality of life. This is supplemented by a physical examination, which includes in particular the local findings and the contralateral mamma. The invitation to participate in the recommended early cancer detection examinations, especially in the genital area, should be made [1379].

6.37	**Consensus-based Statement**
ST	If necessary, the individual follow-up care of breast cancer patients should include oncologically experienced specialists and other professional groups, for example psycho-oncologists, physiotherapists, lymphologists, oncological nurses, breast care nurses, etc. Depending on individual needs, the patient should be provided with information about the possibilities of further counselling and care, including offers of self-help.
	Strong Consensus

6.4.2. Examinations to detect locoregional and in-breast recurrences or contralateral breast cancer

A local/local recurrence after mastectomy and/or axilla dissection can usually be diagnosed by clinical examination. Palpation of the thoracic wall and the lymph drainage areas is therefore a central part of the follow-up examinations [1390]. Local/locoregional or intramammary recurrences in patients with breast-conserving surgery are in most cases curatively treatable. They should therefore be diagnosed as early as possible. Aftercare should therefore include a mammography at least once a year and, if possible, a complementary mammary sonography of the affected breast.

6.38	**Evidence-based Recommendation**
GoR **B**	Imaging diagnostics for the detection of local and locoregional recurrences and contralateral carcinomas should include annual mammography and quality-assured sonography.
LoE **2c**	[1391]; [1392]
	Strong Consensus

Background 6.38

The time of the start of mammography in the context of follow-up care must also depend, among other things, on the type of radiation (e.g. intraoperative radiation, postoperative brachytherapy, etc.) and the local findings of the breast.

Since the scar region frequently changes postoperatively and the differential diagnosis between scarring changes and recurrence is difficult, mammography and sonography of the affected side may be necessary at shorter intervals during the first 3 years after surgery [929]. If the findings are difficult to assess (scar, DD recurrence) an MRI is necessary for further diagnosis [1393], [1394]. The patient with breast carcinoma should therefore not be integrated into the mammography screening with a 2-year examination interval.

A previous breast carcinoma is a strong risk factor for contralateral breast carcinoma. The contralateral breast and axilla must be palpated at every follow-up examination and sonographic checks must be performed. Mammography controls and sonography are to be performed [1395].

MRI examinations can provide additional information for high-risk patients [1293][1395], [1396].

6.39	Evidence-based Recommendation
GoR **B**	The established quality-assured ultrasound examination in follow-up care, the recall and biopsy rates increase. Most commonly, patients report (82%) that they derive positive psychological aspects from the increased attentiveness and the associated safety; rarely, some (< 6%) feel a psychological burden due to insecurity and anxiety. Imaging diagnostics should therefore only be performed to supplement mammography
LoE **2c**	[1391]; [1392]
	Consensus

Background 6.39

The question of the significance of ultrasound in aftercare was addressed in the context of the S3 guidelines (see evidence report SF 4.6-1 Ultrasound Aftercare). A total of 54 publications were identified for the period 2005 to 2016. According to methodological inclusion and exclusion criteria, only 2 studies could be included in the evaluation. According to the study by Riebe et al. 2007 (LoE 3a), the clinical examination and mammography alone show a sensitivity of 81.8% and a PPV of 37.5%. The addition of the ultrasound examination (thoracic wall + axilla bds.) increased the sensitivity to 100% and the PPV to 41%. In the prospective cohort study by Wojcinski et al. 2011 (LoE 2c) with n = 735 patients, the addition of ultrasound (according to DEGUM Level I) showed a significantly increased local recurrence detection rate from 3.7% (95%CI: 2.3-5.0) to 4.5% (95%CI: 3.0-6.0) p=0.041, accompanied by an increase in the recruitment rate from 3.3% to 5.9% (p<0.0001) und der Biopsierate von 9.0% auf 11.8% (p<0.0001). Alle Patientinnen mit Lokalrezidiv wiesen keine Fernmetastasierung auf. Die Patientinnen bewerteten die psychischen Aspekte der zusätzlichen Untersuchungen in 82% (95%CI: 79.3-84.8) positiv als „sicherer und aufmerksam kontrolliert“, psychisch belastet als „verunsichert und ängstlich“ nur 5.9% (95% CI: 4.2-7.6).

6.4.3. Men with breast cancer

6.40	Consensus-based Recommendation
EC	Men with breast cancer, like women, shall receive annual imaging diagnostics, especially since there is a higher risk of contralateral carcinoma.
	Consensus

Background 6.40

Men with breast cancer have a higher risk than women with breast cancer for contralateral breast cancer. A study with data from the Surveillance, Epidemiology, and End Results database with follow-up of n=1,788 patients showed a 30-fold increased risk for contralateral breast cancer (SIR [standardized incidence ratio] 29.64, 95% CI: 15-52) compared to the general male population, while women with breast cancer have only a 2-4-fold increased risk [1397].

6.4.4. Examination for metastases

The 3 most frequent metastasis sites in patients with breast cancer are the lung, liver and bones. Within the framework of the primary therapy, a stage-dependent diagnosis of the spread of the disease is carried out. The currently available prospective randomized studies have shown that an intensified follow-up at fixed intervals with lung x-ray, bone scintigraphy, upper abdomen sonography, tumor marker or CT diagnostics in symptom-free patients does not result in a survival advantage [1384], [1386], but rather shortens recurrence-free survival. However, the studies in question were conducted so long ago that it is currently impossible to assess, against the background of new therapeutic procedures, whether a corresponding survival advantage can be achieved today. Prospective randomized studies with risk adaptation of a diagnostic aftercare program or the integration of procedures such as PET, SPECT/CT, short-term tumor marker controls, examination for circulating tumor cells, risk determination according to gene chips or tissue micro arrays, etc. are currently not available. In addition, it is possible that metastases in patients with breast cancer may be detected between the intervals of follow-up visits due to their symptoms. Therefore, it is all the more important to inform the affected person about the self-observation of persistent symptoms or the self-examination of the operated region.

6.41	Evidence-based Recommendation
GoR **A**	An intensified apparatus and laboratory diagnostics with x-ray thorax, bone scintigraphy, CT, PET or MRT as well as blood count, serum biochemistry or tumor marker determination are part of metastasis diagnostics, not of standard aftercare, and are only indicated in case of clinical abnormalities.
LoE **1a**	[1381]; [1389]; [1398]; [1399]; [1400]; [1401]
	Strong Consensus

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

Among other things, the examinations in the context of aftercare are intended to check and document the success of the primary therapy. The overriding principle is to help patients overcome their fear of a recurrence of the disease. With a favourable tumour constellation (pT1 N0 M0), the 10-year survival probability is over 90%.

Therapy consequences and toxicities of local therapies such as surgery and radiation and of systemic therapies such as chemotherapy, targeted therapy, endocrine therapy, osteooncological therapy or complementary and alternative methods (CAM) can be recognized and treated if necessary. Since more and more breast cancer patients are being treated curatively, but the necessary therapies are carried out over a longer period of time, the support of long-term therapies and the treatment of concomitant symptoms or late effects are becoming increasingly important. It is important to distinguish between early and late effects, between local and systemic side effects and between long-term side effects of already completed therapies or acute side effects of current therapies.

The patient should be informed about therapy-specific short and long-term side effects and late effects. Targeted diagnostic and therapeutic measures should be recommended to her if necessary, or these should be performed on her.

Local therapy side effects are edema, sensitivity disorders, pain in the chest wall or in the chest with breast-conserving therapy, movement restrictions and a lymphedema [1402].

Consequences (acute and late toxicity) of the systemic drug therapy can be myelotoxicity, hepatotoxicity, alopecia, nephrotoxicity, ototoxicity, pulmotoxicity, cardiotoxicity, infections, thromboembolic events as well as osteoporosis, sterility, the climacteric syndrome, the occurrence of second cancers, cognitive impairment and many more [1400].

It is not possible to provide a complete overview of all problem areas, so only the most common ones are presented:

6.4.5.1. Lymphedema

The secondary lymphedema of the arm in breast cancer is with an incidence of 20-30% a frequent problem after axillary dissection [1379], [1380]. However, due to the routine use of sentinel lymph node excision, lymphedema has become significantly less frequent. The morbidity includes functional limitations, increase in circumference and associated impairment of quality of life.

6.42	Evidence-based Recommendation
GoR **A**	All patients with axillary lymphadenectomy shall be informed about the options for detection, prophylaxis and treatment of postoperative lymphedema.
LoE **1b**	[1403]; [1404]; [1405]; [1406]; [1407]; [1408]; [1409]; [1410]; [1411]; [1412]; [28]
	Strong Consensus

Background 6.42

The main influencing factors are:

- the extent of the surgical intervention in the armpit
- the number of lymph nodes removed correlates significantly with the occurrence of lymphedema (p
- radiation of the axillary lymph drainage area (RR 1.35; 95 % CI 1.00-1.83).

3 randomized studies prove the individual benefit of morbidity reduction with reduced surgical radicality by sentinel lymph node biopsy (SLN): absolute risk reduction for loss of sensitivity 8% (5% SLN versus 11% ALND), for arm lymphedema symptoms 20% (11% SLN versus 31% ALND) [1413], [1414], [1415], [1416].

Sentinel lymph node biopsy without further axillary lymphadenectomy is a primary prophylaxis of arm lymphedema for breast cancer patients. These patients must be informed about normal use of the arm postoperatively and should consult their specialist or family doctor if they experience functional disorders or signs of lymphedema.

Primary prophylaxis of lymphedema by lymphatic drainage in asymptomatic patients is not recommended.

Physiotherapeutic exercises can improve the mobility of the arm [1417], [1418], [1419].

6.4.5.2. Cardiotoxicity

Cardiotoxicity must be considered when using anthracyclines and trastuzumab [1420]. The simultaneous combination of both substance classes significantly increases the risk and is not recommended. Predisposing factors are age, obesity, pre-existing heart failure, arterial hypertension, diabetes mellitus, condition after myocarditis or infarction and left-sided radiation. In the development of acute and chronic myopathies with heart failure, a distinction is made between the acute and sub-acute dose-independent early form, the chronic form (within one year) and the late form. The extent ranges from a reduction of the left ventricular ejection fraction (LVEF) to clinically relevant heart failure (CHF). General reduction in performance or reduction in the physical capacity of the affected person should be clarified. Early clarification of cardiac damage is necessary to initiate appropriate supportive measures such as targeted therapy of heart failure etc., to improve the patient's quality of life and not to worsen the life prognosis [843], [1421], [1422].

6.4.5.3. Leukemia

Leukaemia is the most common chemotherapy-induced second malignancy. The highest risk for secondary leukaemias is in the first ten years. The most frequent type of leukaemia is acute myeloid leukaemia when using the anthracyclines [1423], [1424].

6.4.5.4. Menopausal syndrome

The climacteric syndrome comprises the vegetative (hot flushes, sweating, dizziness, headache, tachycardia etc.), the psychological (insomnia, depression, abandonment anxiety, neurotic behavior, irritability, nervousness, lack of drive, lack of concentration etc.) and the organic climacteric syndrome (organ involution, metabolic changes etc.) [1425]. These physiological changes can be intensified by the therapies or by therapy-specific side effects. These include vaginal bleeding, thromboembolic events, muscle and joint pain, dry mucous membranes, etc. The climacteric syndrome can be induced

in pre/perimenopausal patients or in postmenopausal patients by chemotherapy or endocrine system therapy [1426].

The perception of symptoms varies subjectively and depends, among other things, on the onset and duration of amenorrhoea or the duration of therapy, especially endocrine therapy. The treatment of the symptoms of climacteric syndrome is symptom-oriented. Hormone therapy after breast cancer is contraindicated. Therefore, it can only be discussed in extremely exceptional cases, with the greatest restraint, and only be considered if the quality of life is seriously impaired. In hormone receptor-positive breast cancer patients, hormone therapy is contraindicated in the current data situation [1427].

6.4.5.5. Antibody therpay

Reference can be made here to Chapter 5.7.5.

6.4.5.6. Thromboembolic events

Thromboembolic events can occur as a paraneoplastic syndrome during primary therapy. They are often indications of a more extensive tumor or a metastasis [1428]. In endocrine systemic therapies, thromboembolic events are possible, especially in the context of long-term therapies [1429]. The diagnosis and therapy of thrombosis or pulmonary artery embolism and its prophylaxis are defined in interdisciplinary S2 or S3 guidelines of other professional societies (AWMF 065/002).

6.4.5.7. Osteoporosis

One of the main factors regulating bone metabolism is oestrogen. Physiologically, the reduction of bone substance at the beginning of the menopause is physiological. This can be intensified by triggering the premature menopause in premenopausal patients by chemotherapy or endocrine system therapy or in postmenopausal patients by the use of aromatase inhibitors. In patients with a significantly increased risk of developing osteoporosis or with known osteoporosis, appropriate medication should be recommended. In patients who are not yet ill, attention should be drawn to behavioural measures such as physical activity, modification of the diet or substitution with vitamin D and calcium [1400], [1430], [1431]. Detailed information about osteo-oncological medication options should be given.

In any case, it is important to diagnose bone stability at an early stage with a bone densitometry before and during a possibly necessary anti-hormonal therapy and a planned chemotherapy.

6.43	**Evidence-based Recommendation**
GoR **B**	Bone densitometry should be recommended for breast cancer patients under aromatase inhibitor therapy, premenopausal patients under tamoxifen and/or GnRH therapy and patients with chemotherapy-induced premature menopause. Depending on the result and other risk factors, the bone density measurement should be repeated at regular intervals. Under prophylactic osteoprotective therapy, regular monitoring is not necessary.
LoE **2a**	[873]
	Consensus

6.4.5.8. Fatigue

Patients with chronic exhaustion and fatigue syndrome (Fatigue) after treatment of breast cancer should be informed about physical training strategies and psychosocial support [1432], [1433].

6.4.5.9. Reprodction

Premenopausal breast cancer patients who wish to have children should be informed about the possibilities of further family planning after successful completion of the primary therapy of breast cancer [1434]. The originally anticipated increase of the risk of recurrence due to endocrine changes during pregnancy has not been confirmed in any study [1435]. However, the survival advantage of patients who became pregnant in the years following successful treatment of breast cancer, as postulated in some studies, is probably based on a "healthy mother effect" [1434], [1436]. As a general rule, the decision for or against the realisation of the desire to have children after completion of primary therapy for breast cancer should follow personal considerations of lifestyle and less vague medical hypotheses.

If there is an indication for contraception, either for medical reasons such as endocrine therapy, or because of personal lifestyle considerations, it should generally not be performed hormonally. The risks of hormonal contraception must be carefully weighed up.

6.4.6. Frequency of follow-up examinations

Follow-up examinations should be performed quarterly for the first 3 years, semi-annually for the 4th and 5th year and annually from the 6th year onwards.

Due to the tumor biology of the breast carcinoma, a follow-up phase of at least ten years should be considered [1379], [1437]. The therapy monitoring should be continued for at least 10 years.

A patient with breast cancer can no longer be included in normal mammography screening. However, it is possible to extend the aftercare intervals after a longer period of time, depending on the risk, and if necessary, to perform imaging at longer intervals.

6.44	Consensus-based Recommendation
EC	Follow-up examinations should be carried out quarterly in the first 3 years after local primary therapy, half-yearly in the 4th and 5th year, and annually from the 6th year onwards. Annual screening examinations should be included.
	Strong Consensus

Background 6.44

Other cancer screening tests should also be offered to patients.

The follow-up plan should be discussed with the patient. If risk factors are present, an appropriate allocation should be made.

Table 53: Follow-up examinations in breast cancer

Years after primary therapy	Aftercare		Early detection
	1st - 3rd year	4th and 5th year	6 and further years
Medical history Physical examination Reconnaissance/Information	quarterly	half-yearly	annually
Laboratory examinations, examinations using imaging techniques (exception: mammography and mammary sonography)	only in case of clinical suspicion of recurrence and/or metastases		

Table 54: Follow-up examinations for breast cancer – Breast diagnostics after BCT or mastectomy

Years after primary therapy	1st - 3rd year	from the fourth year
Ipsilateral breast (BET): mammography, mammary sonography Mastectomy: Sonography	at least once a year	annually
contralateral breast: mammography, sonography if necessary	annually	annually

If the risk of relapse is low, **after** 10 years of follow-up, the X-ray frequency of mammography can be extended to 2 years. For normal as well as higher risk patients, follow-up is continued at annual intervals according to the table above.

Patients often ask for or request more intensive aftercare. They expect detailed information about their own risk and want to comply with this risk by intensifying aftercare [1438]. It turns out that the belief in the effectiveness of aftercare examinations is high and often unrealistic [1438].

More than two thirds of the patients believe that early diagnosis of metastasis and the associated earlier use of therapy is more likely to lead to healing. Most patients therefore wish for additional diagnostic measures. About 50% of patients also prefer a lifelong follow-up [1438] without a time limit. On the other hand, only 67% of patients actually use the annual mammography after the primary surgery [1439], [1440], [1441], [1442]. While 80% of patients have a mammography in the first year of follow-up, only 63% do so in the fifth year of follow-up. Only 33% of patients use a mammography in each of the first five years after surgery [1439]. Since the detection of recurrence is the central task of aftercare, it is therefore necessary to inform patients specifically about using the established examination measures (see above) at the recommended intervals.

6.45	**Consensus-based Recommendation**
EC	Patients shall be motivated to be physically active (> 2-3 h/week) and to normalize their body weight (in the case of an increased BMI) as part of aftercare. Support should be provided.
	Strong Consensus

Background 6.45

Follow-up care should not only focus on the detection of a relapse of the disease, but also on general health maintenance with training and counselling. This includes information about lifestyle, e.g. exercise and nutrition, especially in the case of obesity with a BMI ≥ 30 kg/m². The increasing body weight is related to the mortality due to a breast cancer disease. Retrospective studies have shown that patients with a BMI ≥ 30 kg/m² have a significant 4% increased risk of developing distant metastases within the first ten years compared with those with a BMI < 25 kg/m², and a 38% higher risk of death from breast cancer 10 or more years after primary diagnosis [877]. Continued physical activity and the maintenance of body weight within the normal range produce a significant improvement in quality of life, less fatigue and greater physical function [874]. There is indeed evidence that regular exercise confers a survival benefit [878]. Notwithstanding, an improved outcome as a result of exercise interventions as part of follow-up care has not yet been demonstrated in prospective studies. [879].

6.46	**Consensus-based Statement**
ST	An essential part of the aftercare is the constant motivation of the patient to regularly take the drugs prescribed for adjuvant therapy, especially the endocrine therapy (e.g. tamoxifen or aromatase inhibitors). The patient must be asked in detail about tolerability or side effects of the therapy. Complaints are to be treated with suitable measures. A premature discontinuation of therapy can be prevented by changing the endocrine treatment.
	Strong Consensus

Background 6.46

Endocrine therapies in the adjuvant situation of patients with hormone receptor-positive breast cancer (e.g. tamoxifen or aromatase inhibitors) are highly effective. The disadvantage is that these preparations must be taken continuously for at least five years. Since these therapies have side effects on the one hand, and the necessity of long-term continuous intake is not adequately accepted by patients on the other, long-term compliance is not sufficient for this therapy. After the first year of use, 40-50% of patients stop taking the prescribed medication. This reduces the disease-free and survival rates, so that it is necessary to repeatedly point out the compliance with the therapy in the follow-up care.

Predictors for a discontinuation of endocrine therapy are a younger (< 50 years) and older age (≥ 75 years), breast-conserving treatment (versus mastectomy), the presence of comorbidities (≥ 2), the prescription of smaller pack sizes, and higher top-up payments for medications (particularly among the elderly) [1394]. Predictors of reliable adherence are married life and previous administration of chemotherapy and radiotherapy. The aftercare consultation should address in detail the need for compliance with endocrine therapies, taking into account the predictors of compliance, and the possible reasons for discontinuation, such as side effects.

For the documentation of adjuvant therapy, it is important that not only the planning of the therapy is documented, but also the actual start and end as well as the adequate implementation.

6.5. Rehabilitation

The multimodal therapy of patients with breast cancer can lead to somatic and psychosocial secondary disorders that result in functional impairment in the sense of participation in everyday life. Medical rehabilitation measures to reduce or eliminate functional disorders are available to patients according to SGB IX if there is a need for and ability to rehabilitate and a positive rehabilitation prognosis can be given. The ICF (International Classification of Functioning, Disability and Health) is used to assess the functional disorders.

Pursuant to § 4 SGB IX, benefits for participation include social benefits (i.e. in this context, in particular medical rehabilitation benefits) in order, irrespective of the cause of the disability

- to avert or remove the disability, to prevent its aggravation or to mitigate its consequences,
- To avoid restrictions of the earning capacity or a need for care,
- to ensure participation in working life according to aptitudes and skills,
- to promote personal development in a holistic way to enable or facilitate independent participation in social life.

The cost units for rehabilitation measures are in particular the statutory health insurance funds, the statutory pension insurance funds and the social administration. According to § 19 SGB IX, rehabilitation can be provided in inpatient or outpatient form, taking into account personal circumstances. According to § 26 SGB IX, medical rehabilitation services include medical and nursing treatment, drug therapy, physiotherapy and use of aids, functional occupational therapy and psychosocial services.

For the medical rehabilitation of patients with breast cancer, the German Pension Insurance Association (DRV Bund) has drawn up rehabilitation therapy standards and

updated them in 2016, in which evidence-based therapy modules are summarised (see http://www.deutsche-rentenversicherung-bund.de).

6.47	Consensus-based Recommendation
EC	The tumor disease and its treatment through surgery, radiotherapy and systemic therapy can lead to disorders of varying severity, which require specific rehabilitative measures in the somatic and psychosocial field. Patients shall be informed at an early stage about the possibilities of outpatient and inpatient rehabilitation measures as well as other claims arising from social law. The wishes of the patients should be taken into account when determining the indication and recommending the type of rehabilitation.
	Strong Consensus

6.48	Evidence-based Recommendation
GoR **A**	Exercise programmes with strength and endurance training shall be offered with the aim of reducing therapy-related limitations in physical performance, reducing fatigue and improving the quality of life of breast cancer patients.
LoE **1a**	[1443]; [1444]; [873]
	Strong Consensus

Background 6.47 and 6.48

Fatigue in tumour diseases describes a persistent, multidimensional appearance, which includes subjectively perceived increased fatigue and physical exhaustion and can be associated with psychological stress. The symptoms often represent the greatest burden for the patient and restrict the quality of life and the ability to cope with stress in everyday life in the long term [1445], [1446]. In order to diagnose a tumor-associated fatigue and to assess the degree of its severity, a multidimensional approach is required in accordance with the clinical picture: a fatigue-related anamnesis, recording with the support of validated questionnaires, and somatic diagnostics. Since 1998, the American Fatigue Coalition has had a catalogue of criteria for the diagnosis of tumour-associated fatigue, which records the various dimensions of fatigue [1447]. A tumor-associated fatigue is considered to be accepted if at least 6 of the 11 criteria apply [1448]. The indication for treatment should be based on the National Comprehensive Cancer Network (NCCN) algorithm for the assessment of tumor-associated fatigue [1449].

An improvement of the symptoms of fatigue is mainly achieved by an exercise therapy individually adapted to the patient's capacity. There is a benefit for strength and endurance training. Five meta-analyses and one Cochrane analysis are available. 16-72 studies were included in the meta-analyses. With regard to the reduction of fatigue, the meta-analyses showed a moderate, significant improvement [1450], [1451], [1452], [1453], [1454]. The Cochrane analysis included 56 randomised trials and also showed a significant benefit for exercise therapy with regard to the improvement of fatigue. Both the NCCN Guideline and the Guideline of the American Society of Clinical Oncology (ASCO) therefore recommend exercise therapy for the treatment of fatigue [894],

[1449]. In addition, three meta-analyses of psychosocial and behavioural therapy approaches also established their benefit [1281], [1455], [1456]. A small benefit could also be shown for relaxation methods such as yoga [1457]. Movement interventions can lead to an improvement in cancer-related fatigue [1450], [1458]. Training forms such as endurance and strength training or a combination of both seem particularly suitable. The question of the training frequency cannot be answered unambiguously, on average intervals of 2 - 3 times a week for 8 - 12 weeks are examined [871], [1377], [1457], [1459], [1460], [1461], [1462], [1463], [1464], [1465], [1466], [1467], [1468]. An important factor is the problem that it is always difficult to keep patients in line when it comes to movement interventions. However, additional cognitive interventions were not able to demonstrate clear results here [1461], [1465], [1467], [1469].

Recent studies show that there are differences in the benefit of physical training to improve fatigue for patients during primary therapy and for cancer survivors. A series of systematic reviews show that physical training after chemo- or radiotherapy is more effective with regard to fatigue than during therapy [532], [1470], [1471], [1472], [1473], [1474], [1475].

6.49	Evidence-based Recommendation
GoR **A**	Post-operative physiotherapy to mobilize the shoulder joint shall begin early.
LoE **1a**	[1417]; [1476]; [1477]; [888]
	Strong Consensus

Background 6.49

After a surgical intervention for breast cancer, physiotherapeutic treatment aims in particular to regain mobility and strength in the arm and shoulder, to avoid movement restrictions and relieving postures after breast surgery and to overcome contractures.

Multifactorial physiotherapy and active exercise therapy bring positive results in terms of shoulder mobility and pain, as two systematic reviews show.

6.50	Evidence-based Recommendation
GoR **B**	(Only) for lymphedema, a complex decongestive therapy (KPE) consisting of skin care, manual lymph drainage, exercise therapy and compression treatment should be performed.
LoE **1b**	[1418]; [1478]; [1479]
	Strong Consensus

Background 6.50

The removal of the lymph nodes or subsequent radiation can lead to lymphedema in the upper extremities. The diagnosis of lymphedema is made by a precise clinical examination using the "skin fold test according to Stemmer" (lifting of tissue between

thumb and forefinger), which is always carried out in a side by side comparison. With the help of a measuring tape, the circumference of the arms can be checked over the course of the procedure - it is always advisable to do this at the same places and without pulling on the measuring tape. The date and time of day should also be noted, as fluctuations in oedema occur throughout the day or depending on the season (summer/winter). Both arms should be measured before the surgery and regularly afterwards. Favourable measuring times are, for example, the oncological aftercare appointments. A combined physiotherapy consisting of skin care, manual lymph drainage, exercise therapy and compression is the most suitable treatment method here. However, this should only be used if lymphedema really exists. The use of treatment methods such as manual lymph drainage to prevent lymphedema has no effect. The exercise programme (e.g. for shoulder mobilisation) does not represent an increased risk for the occurrence of lymphoedema, but has a positive effect on mobility and quality of life. Compression with bandages appears to be more effective than pneumatic compression, although kinesio-tape may be an alternative to conventional bandages. The results summarised here are similarly reflected in the various international treatment recommendations.

6.51	Consensus-based Recommendation
EC	In the case of chemotherapy-induced polyneuropathy (CIPN), the extent of the damage (symptoms, localisation) should be documented and the affected patients should be informed about the range of therapies available (pain, physiotherapy, occupational therapy).
	Strong Consensus

Background 6.51

Cytostatic drug-induced polyneuropathy (CIPN) is increasingly proving to be a significant long-term toxicity in modern cytostatic therapy. The incidence is stated in the literature to be about 38% and depends on the substances used, the combination of cytostatic drugs and the type of application [1459]. CIPN manifests itself as sensory neuropathy with paresthesia in hands and/or feet. The symptoms usually begin with distally emphasized, stocking and glove-like dysesthesias, numbness and tingling paresthesias which may be accompanied by considerable pain sensations and proximal spread [1460]. Since chemotherapy in the treatment of patients with breast carcinoma usually contains a taxane, this long-term side effect is often to be expected.

In 80% of the patients the symptoms are spontaneously completely reversible, but in about 20% of the patients the symptoms are long-term. In addition, the symptoms can still worsen 2-6 months after the end of chemotherapy and 40% of these patients need another 6-8 months before a noticeable improvement occurs [1461]. In addition to anamnesis and clinical-neurological examination, the measurement of the nerve conduction velocity is diagnostically necessary to objectify the symptoms [1462], [1463]. Therapeutically, neuropathic pain can be treated with the combined serotonin-noradrenalin-reuptake inhibitor duloxetine [1377]. Therefore, the patient should be offered a therapeutic trial with this substance. In the context of rehabilitation often occupational therapy methods are used, but their effectiveness is unclear because no data are available. For magnetic field therapy, positive effects were shown in a phase II study [1464]. This was confirmed in a randomized placebo-controlled double-blind phase III study [1465]. Other stimulation therapies such as acupuncture and electrostimulation also show some benefit [1466], [1467]. For the stimulation

procedures with rapeseed or hedgehog ball, which are often used in rehabilitation, no data on the effectiveness are available. Sports and exercise therapy may also have a positive effect on CIPN. In a randomized study, but with a small number of cases and in lymphoma patients, a significant improvement could be achieved [896]. Further information on cytostatic-induced polyneuropathy can also be found in the S3 guideline supportive medicine [871].

Cognitive performance limitations

6.52	Evidence-based Recommendation
GoR **B**	Patients should be asked about cognitive performance limitations (concentration, executive functions, short-term memory) and, if necessary, further diagnostic clarification should be initiated.
LoE **1b**	[1302]; [1303]; [300]; [873]
	Consensus

Background 6.52

Cognitive dysfunction (CD) in oncological diseases is a short-term, long-term or even permanent functional disorder of the:

- Attention
- Ability to concentrate
- Thinking processes
- Memory performance (especially short-term memory)
- Learning ability
- Ability to perform complex tasks

The term KD dates back to the 1980s and was first described in patients with tumors of the central nervous system and in pediatric tumors. It was not until the 1990s that this clinical symptomatology received scientific attention and was perceived as an independent functional disorder [1468]. Depending on the tumor disease investigated, the prevalence of KD varies between 12% - 68% [1469], [1480]. According to subjective patient data, this number can increase up to 80% [1470] 6 months after chemotherapy. A KD after oncological therapy is described by patients up to 20 years after cancer therapy [532]. However, these studies are mostly small inhomogeneous collectives without control groups [1471].

Pathophysiologically, KD is most likely a multifactorial event. In addition to the actual tumor disease itself, genetic conditions and anti-tumor therapy play an important role. The interaction of these three components ultimately determines the severity of the cognitive dysfunction. In particular, drug therapy of tumors is associated with inflammatory processes and secondary changes such as vascular damage, hormonal and metabolic changes [1472] On the other hand, the world's largest multicenter study with 477 patients with early or locally advanced breast cancer showed that the administration of chemotherapy has no significant influence on the development of a KD. Rather, the symptoms of latent depression are associated with significantly increased rates of cognitive dysfunction [1486].

Therapy- or tumor-associated KD should be distinguished from a possible pre-existing dementia brain disorder. This can be achieved by means of a targeted collection of the

patient's own and/or the patient's medical history. If this is not sufficient, the dementia test DemTect can be used [1473].

A systematic diagnosis of KD is not standardized and a gold standard does not exist yet. Neuropsychological test batteries have not found widespread application in clinical routine, as they are associated with high personnel and time expenditure (2-3 hours per patient, execution by psychological psychotherapist). They can therefore only be considered if a KD needs to be further examined in individual cases and there are consequences, e.g. for socio-medical assessment. If this is the case, a test battery should be chosen which includes the qualities attention, reaction time, memory and executive functions [1481]. To simplify the diagnosis of KD in oncological patients, the d2 test, the CogPack® test or the NeuroCog FX® test can be used [1475]. The latter computer-aided test contains all the qualities of a neuropsychological test battery and has been validated in patients with breast cancer [see above]. A psychometric test procedure that is also manageable in terms of time is the syndrome short test according to Erzigkeit (SKT), which tests the qualities of memory performance and attention [1474]. The DemTect or mini-mental test procedures commonly used in geriatrics and dementia diagnostics are not suitable for the diagnosis of oncological oncology patients. The classification into three degrees of severity can be made according to the Common Terminology Criteria for Adverse Events (CTCAE Version 4.0) of the National Cancer Institute (NCI) [1321].

There are no effective drug treatments for KD. The data on the use of Modafinil are inconstant. Therefore, its use outside of studies cannot be recommended at present [300]. Indications for the benefit of computer-assisted concentration and memory training are available from one phase II and three randomized phase III studies prior to [300], [1302], [1303], [1482]. Positive data on the benefit of behavioral therapy approaches are available from a case-control study prior to [1483]. For sports and exercise therapy, three randomized studies are currently available with a majority of patients with breast cancer. While one study examined walking and fitness training [1484], two other studies examined the use of yoga [1485], [1486]. All three studies found a significant improvement in cognitive function. A limiting factor, however, is that it was a heterogeneous therapy program over different therapy periods [873].

Therefore, patients with moderate and severe PD should be offered treatment with computer-assisted training programs in combination with psychotherapeutic interventions, exercise therapy and yoga according to the classification of NCI-CTCAE.

The application for oncological rehabilitation is usually submitted to the statutory health or pension insurance. The statutory health insurance company bears the costs for its insured persons (§ 40 SGB V). The pension insurance institutions provide oncological rehabilitation services for their insured persons (according to § 15 SGB VI) as well as for insured persons, pension recipients and their relatives (§ 31 para. 1 no. 3 SGB VI). Immediately after completion of the primary therapy, the application is submitted via the social services of the last hospital treating the patient, otherwise via the treating physician. Medical rehabilitation can be repeated if serious functional disorders persist due to the disease itself or the tumour therapy.

After completion of the oncological rehabilitation (see above) a socio-medical evaluation of the rehabilitated person is performed. On the basis of continuing functional deficits and available resources, it is assessed which restrictions or possibilities of participation in social life/working life arise for the affected person and by which measures restrictions can be counteracted if necessary. On the basis of socio-medical assessments, further benefit decisions are often made and benefits provided by the social service providers. These can be, for example, assistance with career

advancement, measures to secure maintenance (reduced earning capacity pensions) or measures of secondary and tertiary prevention.

6.6. Complementary medicine

6.53	Consensus-based Recommendation
EC	All patients should be asked whether they use complementary and/or alternative therapies. Patients who use such procedures should be informed about possible risks and, where appropriate, about interactions with standard therapies.
	Strong Consensus

Background 6.53

It is important to note that there is no universally accepted definition of complementary and alternative medicine in oncology. In most cases, it is contrasted with so-called conventional medicine, without a clear definition of the boundaries being possible.

Complementary medicine is subject in its evaluation to the basic principles of evidence-based therapy. It is used in **addition** to the standard clinical therapy [1487]. On the other hand, alternative therapy methods are offered as a supposed substitute for an evidence-based therapy. The resulting therapy competition represents the greatest danger of the alternative therapy.

The integration of complementary measures to support evidence-based therapy is also known as "integrative oncology" [1488].

According to literature data, breast cancer patients seem to use complementary therapy methods in 50-90% of cases [1489], [1490], [1491], [1492].

Medical advice on the topic of complementary medicine can

- Strengthen the feeling of self-responsibility and control
- from dubious offers,
- Protect against damage caused by side effects or interactions,
- encourage the development of personal initiative (e.g. exercise, diet)

One risk of complementary therapies is that patients and therapists have so much confidence in the effectiveness of these complementary measures that they abandon conventional breast cancer therapy in favor of these measures. These are alternative procedures and should not be used because of the obvious risks to the patient's health.

The particular problem in the evidence evaluation of complementary procedures lies in their often less well defined effect spectra, complex mechanisms of action and interaction possibilities, as well as the lack of conventionally conducted studies on remedies that provide clear indications of effectiveness and benefit-risk ratio.

As part of the Oncology Guidelines Programme, complementary and alternative medical procedures in oncology will be evaluated in a separate S3 Guidelines process in the future (http://leitlinienprogramm-onkologie.de/Projekte.6.0.html).

In order to better describe the existing evidence at this point in time, the guideline report lists evidence tables of an American working group [1493], which has compiled studies on the effectiveness of complementary medicine procedures in patients with breast cancer.

The following Table 12 gives an overview of the most common complementary methods and substances used by patients with breast cancer and the possible interactions. These interactions can both attenuate and enhance (toxicity) the effect of an existing breast cancer therapy. Some of the methods and substances listed are discussed in further subchapters.

Table 55: Use of complementary methods, observed side effects, potential interactions

Substance/method	Propagated use	Side effects	Interactions
beta-carotene	Prevention of recurrence, improvement of the tolerability of chemotherapy	Increased incidence of tumours in smokers	as antioxidant possible attenuation of chemo- and radiotherapy
vitamin C	Prevention of recurrence, improvement of the tolerability of chemotherapy	in high dosage kidney damage possible	as antioxidant possible attenuation of chemo- and radiotherapy
High-dose vitamin C (infusions)	Antitumoral action	Vitamin C can promote tumour growth in vitro.	as antioxidant possible attenuation of chemo- and radiotherapy
vitamin D	Prevention of osteoporosis Improvement of the forecast	not known at normal dosage	not known generally worse prognosis with low serum values
vitamin E	Prevention of recurrence, improvement of the tolerability of chemotherapy, reduction of menopausal complaints	not known	In vitro data with indications of attenuation of the effects of tamoxifen
Selenium	Prevention of recurrence, improvement of the tolerability of chemotherapy	short-term, even high-dose use without side effects, long-term use only under mirror control	No evidence of a reduction in the effect of anti-tumour therapies in preclinical or clinical data
Zinc	Prevention of recurrence,	Zinc is important for tumor cell	not known

Substance/method	Propagated use	Side effects	Interactions
	improvement of the tolerability of chemotherapy	growth in vitro, a promotion of tumor growth cannot be excluded.	
Curcumin	antitumoral action	From 8 g/d increased gastrointestinal complaints	in vitro isolated indications of antagonistic effects to chemotherapy
EGCG (green tea)	antitumoral effect, prevention of recurrence	in high dosage caffeine-like side effects	In-vitro data predominantly speak for synergies
Omega-3 fatty acids	Effect against cachexia	None	None
Enzymes	Prevention of recurrence, improvement of the tolerability of chemotherapy	rarely upper abdominal discomfort	None
Mistletoe therapy	antitumoral effect, prevention of recurrence, improvement of the tolerability of chemotherapy	Allergies, in vitro in 2 studies Indications of increased tumor growth	It is unclear whether immune stimulation can lead to an increased risk of hypersensitivity reactions to antitumoral drugs.
Thymus therapy	antitumoral effect, prevention of recurrence, improvement of the tolerability of chemotherapy	not known	not known, enhancement of immunological reactions possible
medicinal mushrooms	antitumoral effect, synergy with chemotherapy, improvement of the tolerability of chemotherapy	not known	not known, enhancement of immunological reactions possible

Substance/method	Propagated use	Side effects	Interactions
Immunostimulants (organopeptides, complex polysaccharides)	antitumoral effect, synergy with chemotherapy, improvement of the tolerability of chemotherapy	not known	Not known, enhancement of immunological reactions possible
Herbs of TCM	antitumoral effect, synergy with chemotherapy, improvement of the tolerability of chemotherapy	not known, insufficient data situation	not known, insufficient data situation
Acupuncture/Acupressure	improvement of side effects (nausea, pain, hot flushes)	in one study evidence of an increase in oestradiol in non-tumour menopausal patients - no confirmatory data	not known
Homeopathy	Reduction of side effects, improvement of quality of life	none	preparations with higher potency cannot have interactions, these cannot be excluded in mother tinctures and low potencies
Soya extract	Reduction of hot flushes	Conflicting in vitro and in vivo data - breast cancer growth demonstrated in a number of studies	Reduction of the effect of anti-hormonal therapy in vitro and in vivo
Grape Silver Candle	Reduction of hot flushes	not known	not known

6.6.1. Diagnostics

6.54	Consensus-based Recommendation
EC	The diagnostic measures offered within the framework of complementary and alternative therapy concepts, which are based on scientifically unproven concepts and/or misinterpretations of correlations between bodily functions, should not be recommended.
	Strong Consensus

Background 6.54

Some diagnostic measures offered within the framework of complementary or alternative therapy concepts, such as iris diagnostics, dark field microscopy, bioresonance, so-called allergy diagnostics, etc., are based on scientifically unproven concepts and/or misinterpretations of interrelationships of bodily functions and should therefore not be recommended.

6.6.2. Complementary medical interventions for anxiety/anxiety disorders/depression

With regard to some complementary medical approaches for the treatment of anxiety disorders, reference is made to the S3 guideline Psycho-oncological Diagnosis, Counselling and Treatment of Adult Cancer Patients (see http://leitlinienprogramm-onkologie.de/Psychoonkologie.59.0.html).

There, the following interventions are commented on:

- Yoga/ massages
- Artistic therapies
- Music Therapies
- Relaxation method and imaginative method

The recommendations there also apply to patients with breast cancer.

In addition, patients with anxiety disorders or depression are referred to the corresponding S3 guidelines:

- Anxiety disorders: http://www.awmf.org/leitlinien/detail/ll/051-028.html
- Depression: http://www.versorgungsleitlinien.de/themen/depression/

In the review by Greenlee et al. 2014 [1493] a randomized study with 302 female volunteers [1494] was identified, in which acupuncture therapy showed a reduction of anxiety disorders (HADS [scale from 0-21]: -1.83 pts, 95% KI -2.69 -0.97) compared to standard therapy (no sham acupuncture).

6.6.3. Complementary medical interventions for fatigue

Regarding the therapy of fatigue syndrome by means of exercise therapy in patients with breast cancer, reference is made to the chapter on lifestyle factors that can be influencedChapter 5.7.7) and rehabilitationChapter 7.5) as well as to the S3 guideline Psycho-oncological Diagnosis, Counselling and Treatment of Adult Cancer Patients (see http://leitlinienprogramm-onkologie.de/Psychoonkologie.59.0.html).

In the review by Greenlee et al. 2014 [1493], randomized studies with breast cancer patients and partially positive effects were identified for the following interventions:

- Hypnosis [1495] and Ginseng [1496] during therapy
- Acupuncture [1497] and Yoga [1498] after therapy

Studies on acetyl L-carnitine [1499] and guarana [1500] were also identified, but they did not show any positive effects with regard to fatigue.

6.6.4. Complementary medical interventions for the prophylaxis of chemotherapy-induced nausea and vomiting

The complementary use of different procedures such as acupuncture, acupressure, relaxation techniques, massages or ginger for the prophylaxis of chemotherapy-induced nausea and vomiting is discussed in the chapter Supportive TherapyChapter 7.3) or in the corresponding S3 guideline on Supportive Therapy in oncological patients.

A further overview of the studies available on this subject with breast cancer patients is provided in the review by Greenlee et al. 2014 [1493].

6.6.5. Complementary medical interventions for the prophylaxis and treatment of oral mucositis

The S3 Guidelines for Supportive Therapy in Oncological Patients comment on complementary medical procedures/approaches for the therapy or prophylaxis of oral mucositis.

6.6.6. Complementary medical interventions for the treatment of acute radiation-induced skin reactions

The S3 guideline on supportive therapy in oncological patients comments on complementary medical procedures for the prevention and therapy of acute radiogenic skin reactions.

6.6.7. Food supplements

6.55	Consensus-based Recommendation
EC	During chemo-, hormone or radiation therapy, dietary supplements (micronutrients), such as vitamins and trace elements, should be supplied via the natural diet and according to the physiological requirements. Proven deficiencies should be compensated.
	Strong Consensus

Background 6.55

Dietary supplements are preparations of vitamins and trace elements, amino acids, fatty acids and secondary plant substances, some of which are offered as single substances or mainly as combination preparations. The composition varies considerably, only a few preparations are based on the actual physiological requirements.

The use of antioxidants can impair the effect of simultaneously administered chemo- and/or radiotherapy [1501], [1502], [1503]. These include vitamin C, E and beta-carotene. Folic acid can influence the effect of 5-fluorouracil in particular. Up to now

there are only a few clinical studies with a sufficient number of patients which could clearly characterize the side effects and the effects of the antioxidants, so that one should be rather cautious with recommendations for such a therapy.

Vitamin D protects against the development of osteoporosis and should therefore be used prophylactically in time. Patients at increased risk of osteopenia or osteoporosis include patients on aromatase inhibitors, young patients who have become postmenopausal as a result of chemotherapy, patients who have taken or need to take corticosteroids long-term or repeatedly, or immobilised patients. In this context, the recommendations of the Dachverband Osteologie DVO e.V. should be referred to.

Vitamin E has occasionally been used prophylactically to protect against the development of neurotoxicity under cisplatin and taxol therapy.

As there are no sufficient data on efficacy and influence on survival available to date, the use of vitamin E outside of studies is not recommended [1504] [1505]. Furthermore, there are apparently biological differences in the effects of the various vitamin isomers and forms. In particular, alpha-tocopherol could have an inherent pro-carcinogenic effect under certain conditions (prostate carcinoma) [1506].

The clinical studies on the administration of selenium published to date have been presented in a review of the Cochrane Collaboration (Cochrane: Dennert et al. 2006 [1507]). While deficiencies should be compensated, the data do not show sufficient evidence for the general supportive use of selenium (Cochrane: Dennert et al. 2006 [1507]). There are no meaningful studies specifically on the use of selenium in breast cancer. Long-term selenium administration should only be carried out under consecutive serum level control. Overdoses must be avoided. A Cochrane review of 2014 did not yield consistent data on cancer prevention by selenium intake [1508].

For a number of secondary plant compounds such as curcumin, quercetin, EGCG, experimental preclinical data are available which indicate an antitumoral effect of these substances. However, these data in no way justify the use of these substances outside clinical studies. Since little is known about interactions of these plant substances with standard clinical therapy, their parallel use should be avoided. In general, natural substances have a considerable potential for interference. The uptake of secondary plant substances via a healthy fruit and vegetable rich diet is desirable [1509].

6.6.8. Mistletoe therapy

6.56	Consensus-based Statement
ST	Mistletoe therapy does not prolong the survival of patients with breast cancer, and an improvement in quality of life is questionable according to current data.
	Strong Consensus

Background 6.56

Both the Cochrane analysis by Horneber et al. (2008) [1487] and the systematic review by Ernst et al. 2003 [1510] come to the conclusion that most of the studies on mistletoe therapy published to date are not of sufficient quality. Methodologically robust studies show no effect of mistletoe therapy on relevant endpoints such as survival. A review on quality of life [1511] shows indications of an improvement in quality of life under mistletoe therapy, but the data are based on studies of significantly lower quality.

6.6.9. Traditional Chinese medicine (TCM)

6.6.9.1. Treatment with herbal products

The use of plant mixtures according to Traditional Chinese Medicine has been shown to have positive effects on quality of life and individual immune functions. Although two Cochrane reviews show positive effects for this therapy with regard to quality of life (Cochrane: Taixiang et al. 2005 [1512]; Cochrane: Zhang et al. 2007 [1513]), it became known after the reviews were prepared that randomised clinical trials from China could not fulfil the internationally recognised criteria of randomisation on a large scale. In addition, little information is available on interactions and side effects. There are a number of reports on impurities (heavy metals, pesticides, corticoids and coumarins) with sometimes fatal consequences. Some preparations contain phytoestrogens which should not be used uncritically in patients with hormone-dependent breast cancer.

Green tea

A meta-analysis of epidemiological studies suggests that green tea could reduce the risk of disease [1514]. Likewise, a meta-analysis that took into account two non-randomized studies (n=123, n=133) showed a lower risk of recurrence with increased consumption of green tea [1509]. A systematic review found possible positive interactions between green tea and tamoxifen and no negative interactions between green tea and aromatase inhibitors or fulvestrant [1416][1515]. Thus, green tea seems to be an interesting approach for recurrence prevention in breast cancer, especially since problematic side effects or interactions are not known.

Due to the bias potential of previous studies on relapse prevention (retrospective observational studies, mainly Asian collectives, partly not adjusted for known confounders (e.g. smoking)), further (prospective) studies are necessary until clear recommendations can be made.

Soy products

Since soya contains phytoestrogens that might interact with tamoxifen, soya could be a healthy or harmful food for women affected by breast cancer. Accordingly, soya is the subject of controversial discussion.

Two meta-analyses investigated the effects of soy. These included 9514 and 11206 patients from observational studies [1516], [1517]. In the analysis by Nechuta et al. (2012) a significantly reduced risk of recurrence was found based on three cohorts (HR: 0.75; 95 % CI: 0.61, 0.92). Chi et al (2013) found a better overall survival based on 5 cohorts, especially in ER-negative, ER+/PR+ and postmenopausal patients. It remains unclear whether this is particularly or exclusively valid for Asian women. Since the underlying studies are observational studies in which the compared populations differ in terms of socio-demographic parameters (ethnicity, education, age) and no data are available on known confounders (e.g. smoking), these results are not evidence of the effect of soy products in women after treated breast cancer. Further (prospective) studies are also necessary until clear recommendations can be made.

Cimicifuga (grape silver candle)

According to preclinical and clinical data, Cimicifuga is not a phytoestrogen, but has a SERM-like mechanism. Therefore, its use in breast cancer seems possible [1518], [1519], [1520], [1521], [1522], [1523], [1524], [1525]. So far there are only two studies on the reduction of hormone withdrawal symptoms in patients with breast cancer under

anti-hormonal therapy. Here, an improvement of the symptoms was found with only moderate effect strength [1493], [1526], [1527].

Homeopathy

A therapeutic benefit - of homeopathy - in terms of improving progression-free or overall survival in breast cancer has not been proven.

6.57	Consensus-based Statement
ST	There is no evidence for an improvement in progression-free and overall survival in breast cancer through the use of homeopathic drugs.
	Strong Consensus

6.6.10. Meditation and mindfulness-based stress reduction

The terms meditation, "mindfulness based meditation", as well as "mindfulness based stress reduction" cover different therapeutic approaches. What they have in common is the attempt to increase the (self-)attentiveness of the patient and thus to achieve a better handling of the disease situation.

For the evaluation of such therapies, reference is made to the S3 guideline Psycho-oncological diagnosis, counselling and treatment of adult cancer patients.

In the review by Greenlee et al. 2014 [1493] several studies with breast cancer patients were identified, which show an improvement of quality of life through meditation. Mostly, the so-called MBSR, mindfulness-based stress reduction, or mindfulness-based stress reduction, is used as a meditation program. Crane-Okada et al. (2012) [1528] and Nidich et al. (2009) [1296] showed in two randomized controlled trials with less than 50 and 150 subjects, respectively, an improvement of quality of life in older breast cancer patients through meditation programs. In two randomized-controlled studies by Henderson et al. (2012 and 2013, respectively) [1529], [1530] with less than 200 subjects each, breast cancer patients in early stages between 20 and 65 years of age benefited in terms of quality of life. After 24 months no significant benefit could be demonstrated. A positive effect was also demonstrated in patients who received radiotherapy treatment during the program. A randomized controlled trial with more than 200 subjects [1531] showed the efficacy of MBSR after surgery, chemo- and radiotherapy until 12 weeks after the intervention. Overall, the small number of cases and the short follow-up time should be noted, long-term effects could not yet be shown.

6.6.11. Complementary medical interventions for the treatment of sleep disorders in breast cancer patients

An updated S3 guideline on sleep disturbances/non-restful sleep is expected to be available in October 2017. This also addresses complementary medical approaches: http://www.awmf.org/leitlinien/detail/anmeldung/1/ll/063-003.html

6.58	Consensus-based Recommendation
EC	Stress management techniques can be considered for the treatment of sleep disorders.
	Strong Consensus

Background 6.58

The randomized studies of Garssen et al. (2013) [1532] and Andersen (2012) [1533] with a small number of cases can demonstrate a significant effect on the improvement of fatigue and sleep quality through psychological short intervention and MBSR. However, the effects last only briefly in acute cases. No long-term effects could be observed.

Light Yoga

Studies with patients with breast cancer and sleep disorders were identified in the review by Greenlee et al. 2014 [1493] on light yoga [1498], [1534], [1535], [1536].

Two studies from 2010 and 2012 with very small case numbers n< < 100 showed an improvement in quality of life and vitality of breast cancer patients through various yoga regimens. The study by Danhauer et al. [1487] is not considered important due to the small number of cases. Worth emphasizing is the work by Mustian et al. (2013) [1488] with n=410 case numbers. A four-week yoga course with two units per week, consisting of pranayama, hatha yoga, asanas and meditation had a significant benefit on sleep problems. In general, it is important to note that the studies used different yoga regimens, meaning various techniques over different times.

6.6.12. Complememntary medical interventions for the treatment of pain in breast cancer patients

The therapy of tumor pain is addressed in the S3 guideline for palliative care:

In the review by Greenlee et al. 2014 [1493], studies with breast cancer patients were identified for the following complementary medicine interventions:

Massage/healing touch [1537]: A randomized study from 2003 with 230 participants who received therapeutic massages could show, among other things, a reduction of pain.

Emotion And Symptom-focused Engagement (EASE)-Intervention [1538]: A major study (n=292) investigated the influence of a telephone intervention/conversation with rules of conduct by an oncologically trained nurse in patients undergoing chemotherapy. With regard to the secondary endpoint "pain" there was as little evidence of a benefit of the programme as for the primary endpoints fatigue, sleep quality and functional status.

Music therapy to reduce pain associated with surgery [1539], [1540]: Two randomized studies with small case numbers (n=120, n=30) from 2011 investigated the influence of music on postoperative pain after mastectomy and were able to show lower pain in the music intervention group compared to the control groups.

A Cochrane review is also available on music therapy interventions in cancer patients in general. In a total of 7 studies (n=528), a significant reduction in pain was determined (SMD: -0.91, 95% CI -1.46 to -0.36), although the quality of the evidence was rated as low [1304].

Training programs for the relief of pain associated with breast surgery [1541], [1542]: Two small randomized studies (n=66, n=44) showed significant improvements in neck and shoulder pain after an 8-week water sports intervention and an 8-week multidimensional program, respectively.

Hypnosis for the relief of complaints associated with surgery [1543], [1544]: Two studies by Montgomery et al. from 2002 and 2007 showed that patients who received short hypnosis before a mammary PE had less propofol and lidocaine consumption and reported lower pain intensity, less nausea and fatigue postoperatively.

Acupuncture or electro-acupuncture for short-term treatment of aromatase inhibitor-associated musculoskeletal complaints: In two small randomized studies [890], [1545] (n=21, n=38) there was evidence of a positive effect of acupuncture treatment on aromatase inhibitor-associated musculoskeletal pain. In a further study (n=47) [1546] no advantages could be determined compared to a sham acupuncture.

As for acupuncture [1547], [1548], only studies with small case numbers exist on the influence of electroacupuncture on aromatase inhibitor-associated pain. An improvement of pain was observed in one of the studies (n=67) [1548], but here it was compared with a waiting list group and not with sham acupuncture.

6.6.13. Complementary medical approaches for the treatment of taxane-induced neuropathy

6.59	Consensus-based Recommendation
EC	Acetyl l-carnitine shall not be recommended for the prevention of taxane-induced neuropathy due to the risk of damage.
	Strong Consensus

6.60	Consensus-based Statement
ST	There is no sufficient data base to evaluate the effectiveness of vitamin E or omega 3 fatty acids.
	Strong Consensus

Background 6.59 and 6.60

Smaller studies by Ghoreishi et al. 2012 [1549] (n=69) and Argyriou et al. 2006 [1504] (n=37) provided evidence for a positive effect of omega-3 fatty acids and 300 mg vitamin E (versus placebo or "standard therapy") regarding the prophylaxis of paclitaxel-induced peripheral neuropathy in patients with breast cancer. Since there are no larger, randomized studies that could confirm these effects, the evidence base for these interventions is considered insufficient to make a recommendation (see also Greenlee et al. 2014 [1493]).

Acetyl-L-carnetine (ALC) is a natural substance involved in neuronal protection. While some previous studies had suggested that the use of ALC would be suitable for the prevention and therapy of taxane-induced peripheral neuropathy, a prospective placebo-controlled study by Hershman et al (2013) [1499] showed that after 12 weeks there was no effect of ALC on neuropathy, but after 24 weeks peripheral neuropathy

was significantly increased. Since a risk without demonstrable benefit could be established by taking this food supplement, ALC should not be used for the purpose of neuroprotection in chemotherapy.

6.6.14. 6.6.14. Complementary medical approaches for the treatment of hot flushes/vasomotor symptoms

Hot flushes and other vegetative regulation disorders are a relevant problem in clinical care. They occur particularly severely in pre- and perimenopausal patients after ovarian failure due to chemotherapy or ovarian dysfunction in the context of endocrine therapy. However, postmenopausal women also suffer an increased recurrence of these symptoms in the course of anti-oestrogenic therapy, especially with tamoxifen. Since causal therapy with estrogens is not possible, especially in hormone-responsive breast cancer, non-hormonal interventions are of particular clinical relevance. In this context, reference is made to the chapter "Gynaecological problems" in the collection of recommendations of the AGO's Breast Commission.

6.61	Evidence-based Recommendation
GoR **B**	Soya supplements should not be recommended for the treatment of hot flushes in breast cancer patients due to their lack of efficacy.
LoE **2b**	Guidelines adaptation : Greenlee et al. 2014
	Strong Consensus

Background 6.61

Three placebo-controlled studies from the years 2000 to 2005 with an average of about 120 test subjects showed no efficacy of soy products at the selected dosage and form of application. Due to the lack of efficacy and the fundamental problem of exposure to a food containing phytoestrogens, the use of soy products for the purpose of hot flush therapy should be avoided. In breast cancer a daily intake of less than 100 mg isoflavonoids seems to be of little concern [1550]. For the interventions Cimicifuga Racemosa, flaxseed, homeopathy, hypnosis, magnet therapy, meditation, peppermint, vitamin E the authors around Greenlee [1493] could not find sufficient evidence to make a recommendation.

6.6.15. Alternative medical methods

6.62	Consensus-based Recommendation
EC	Alternative therapies shall not be recommended to patients. In an empathetic counselling situation, the patient should be informed neutrally, competently and comprehensively about the damage and benefits of such a therapy.
	Consensus

Background 6.62

Patients encounter many unfounded offers in their search for help. Some of these are based on the honest efforts of doctors to help and support their patients, especially in hopeless situations. In addition, however, there are numerous providers of alternative therapy concepts, for which economic aspects seem to be the main focus. It becomes dangerous if patients are deprived of effective standard therapies within the framework of these alternative methods (therapy competition). It is therefore important to protect patients from these offers by providing sufficient information.

Among the frequently used alternative therapy methods are Ukrain, vitamin B17 (apricot kernels, bitter almond), insulin potentiated therapy, vitamins according to Dr. Rath®, Germanic New Medicine®, autologous blood cytokines, zapper, various cancer diets, such as the Breuss cure and cell symbiosis therapy.

Some of the methods used are based on traditional empirical medicine. However, adaptations of modern branches of research (e.g. hyperthermia) or our own interpretations of carcinogenesis and immunological correlations (dendritic cells) are also used, which are difficult to recognise as dubious even for doctors specialising in oncology.

6.7. Documentation, care coordination and quality management

6.7.1. Documentation

6.63	Consensus-based Recommendation
EC	The course of disease of patients with breast cancer/DCIS shall be reported by all health care providers involved in the care process in accordance with the requirements of the German Cancer Early Detection and Registry Act. The evaluation of the data from the cancer registries and the annual reports of the DKG/DGS-certified breast cancer centres shall be available to service providers, the public and health policy-makers.
	Strong Consensus

Background 6.63

The recommendation is based on the knowledge and experience of the experts involved. Today, it is possible and also necessary to present the implementation of guidelines and the results achieved with them in a transparent manner over the long term. Overall survival, disease-related survival, local recurrences, regional recurrences, metastases and secondary malignancies provide evidence of success and failure of oncological care, depending on the constellation of findings and treatment. Long-term results (longitudinal data) are the basis for institutional, regional, national and international comparisons. Such correlations must be made transparent on a regular basis, both overall and for the specialist areas involved, with evaluations. A prerequisite is the systematic collection of relevant data available in interdisciplinary and intersectoral care. The data thus become a reflection of the patient-related network of the doctors and clinics involved. Data quality and care-related documentation of all service providers are two sides of the same coin and require an up-to-date information

infrastructure. From the point of view of each individual health care provider, a specialty or a single physician involved in the supply chains of various centres, this data use can only be achieved with efficient cooperation in a regional cancer registry.

Each specialist area should make its own contribution to the cancer register. In part, this is done by transmitting findings and treatment reports from pathologies and radiotherapy, independently of other individual care providers. Particularly urgent is the establishment and expansion of a valid database of drug therapy, which should at least be provided by large centers.

The cancer registries must correctly combine the data from the various sources and make valid and integral data available to the service providers through multi-layered checks. The most important parameters for process and outcome quality must be prepared for each institution and for comparison for the entire catchment area. Prospectively collected clinical data from population-based cancer registries are particularly valuable for science, the public and health policy-makers because they can show changes in disease and care over time. Regional and international comparisons are also part of transparency and can provide impetus for improvements.

In the annual reports of the DKG/DGS-certified breast cancer centres, the implementation of the work in accordance with the guidelines is evaluated annually on the basis of the quality indicators [1551].

The reports (see https://www.krebsgesellschaft.de/jahresberichte.html) also include evaluations of the cooperation between the partners of the oncological network (e.g. presentation rates in interdisciplinary tumour conferences, study activities, etc.) as well as the expertise of the treatment partners over a period of 5 years and based on data from over 50,000 patients per year [1552]. This allows developments of the therapies carried out over time and between different treatment networks. The anonymised and individualised annual reports provide the individual networks with feedback on their results and are suitable for identifying concrete measures if certain results show potential for improvement.

The objectives described above have received a decisive impetus from health policy. Since April 2013, the Act on the Further Development of Cancer Early Diagnosis and Quality Assurance through Clinical Cancer Registries Cancer Early Diagnosis and Registry Act (KFRG) has been in force, according to which "the Länder establish clinical cancer registries to improve the quality of oncological care" (§ 65c, SGB V). "Clinical cancer registration is based on the nationwide uniform data set of the Association of German Tumour Centres and the Society of Epidemiological Cancer Registries in Germany for basic documentation for tumour patients and modules supplementing it, covering the entire country and as complete as possible" (§ 65c, SGB V).

The range of tasks for the clinical cancer registries also provides feedback to the service providers, which will range from differentiated evaluations to access to disease progression with recurrence, metastasis and date of death. The aim is to ensure that certified centres in particular and each participating specialty have access to their own data and that it is possible to maintain and update them.

In addition, regional conferences are required in which the data of certified and non-certified centres and the participating disciplines are analysed and discussed. The need for action can range from completeness and comprehensiveness to the improvement of care.

A further task that is important by law is to contribute to daily care and to fulfil the tasks of "promoting interdisciplinary, directly patient-related cooperation in cancer treatment" and "cooperation with centres in oncology" (§ 65c, SGB V). The "exchange

of data with other regional clinical cancer registries" as well as with evaluation centres for clinical cancer registration at the state level" (§ 65c, SGB V) is intended to support the aforementioned care processes.

The objective of "transparency of care in a region" is to be achieved by increasingly improving interdisciplinary and intersectoral communication.

6.7.2. Care coordination and quality management

6.7.2.1. Structural elements of good care coordination

6.64	Consensus-based Statement
ST	Essential structural features for quality-assured, interdisciplinary and intersectoral care of breast cancer patients are • the nationwide implementation and further development of early detection measures (such as mammography screening, recording of genetic risk) with evidence-based and quality-assured information, • the certification of interdisciplinary breast cancer centres according to DKG e.V. and DGS e.V, • the implementation of the S3 guideline "Diagnosis, therapy and aftercare of breast cancer", • improving communication in the supply chain for cross-sectoral patient aftercare • the integration of social services, psycho-oncology, rehabilitation, physiotherapy, palliative medicine and self-help into the care concepts.
	Strong Consensus

Background 6.64

The recommendation is based on the knowledge and experience of the experts involved. The diagnosis, therapy and aftercare of breast cancer requires a multidisciplinary concept. Not only the experience of the individual practitioner is important, but also the smooth organisation between the individual treatment disciplines.

Quality-assured early detection, professional imaging diagnostics, histopathological confirmation of findings, excellent surgical procedures, consistent radiation treatment, drug therapy using the latest therapeutic methods and professional aftercare, throughout the entire duration of therapy and beyond, must be part of an overall concept. This concept can only be sustainable through interdisciplinary and cross-sectoral cooperation.

Only the qualitative optimisation of this supply chain is suitable for reducing the morbidity and mortality of breast cancer. Thus, all measures to improve the care of women with breast cancer must not only relate to individual aspects, but always to the entire care chain.

All measures must be quality-assured and transparent. Structural, process and outcome quality must be queried and the relevant care data must be reported to cancer registries.

Annual audits and recertification at three-year intervals with presentation of patient and referring physician satisfaction, compliance with quality objectives, fulfilment of quality indicators and presentation of treatment quality are prerequisites for adequate quality management.

Those responsible in our health system are called upon to overcome particular interests and to make every effort to strive for and achieve optimal treatment conditions and results for the benefit of our patients.

Institutions that do not operate with quality assurance should be excluded from the care of breast cancer patients.

7. Breast cancer during pregnancy and lactation, pregnancy after breast cancer, fertility preservation

7.1. Pregnancy after breast cancer

7.1	**Evidence-based Recommendation**
GoR **A**	Pregnancy shall not be discouraged after a breast carcinoma. This applies regardless of the hormone receptor status.
LoE **3a**	[1553]; [1554]; [1555]
	Strong Consensus

7.2	**Evidence-based Statement**
ST	The timing of the onset of pregnancy after breast cancer does not correlate with a worse prognosis.
LoE **3a**	[1553]
	Strong Consensus

7.3	**Consensus-based Recommendation**
EC	The risk of recurrence depends on the biology and stage of the disease. This shall be taken into account in the consultation about a subsequent pregnancy.
	Strong Consensus

7.4	**Consensus-based Recommendation**
EC	The longer an endocrine therapy is carried out, the better the chances of recovery (reference to Chapter Chapter 5.7.2). If pregnancy is desired before the end of the planned endocrine therapy period, endocrine therapy should be continued after delivery and lactation.
	Consensus

Use of reproductive medical measures

7.5	Evidence-based Recommendation
GoR **0**	After a breast carcinoma, pregnancy can be achieved with the help of reproductive medical procedures.
LoE **4**	[1556]; [1557]; [1558]
	Strong Consensus

7.6	Evidence-based Statement
ST	The chances of success for an intact pregnancy or child are lower with autologous egg cell use in breast cancer patients than in non-cancer patients.
LoE **2c**	[1559]
	Strong Consensus

Background 7.1 to 7.6

A subsequent pregnancy after breast cancer should not be advised against. The evidence from prospective studies is missing, these are currently being collected. Retrospective studies show that pregnancy should not be discouraged for fear of worsening the prognosis.

In a multicenter cohort study, 333 women who became pregnant after breast cancer disease were compared in a 1:3 ratio with a non-pregnant breast cancer control cohort to investigate the influence of pregnancy on disease-free and overall survival. There was no difference in disease-free survival for both ER-negative (HR = 0.75; 95%-CI, 0.51-1.08, P = 12) and ER-positive (HR = 0.91; 95%-CI, 0.67-1.24, P = 0.55) tumors. However, overall survival was significantly better for the group that became pregnant without interaction with ER status (HR = 0.72; 95%-CI, 0.54-0.97, P = 0.03; P interaction = 0.11). The outcome of the pregnancy and the interval between disease and pregnancy did not play a role.

In women with hormone receptor-positive breast cancer, if endocrine therapy has not yet been administered for 5 years, it should be continued after the desire for children has been fulfilled, but at the latest after 2 years, and continued for 5-10 years depending on the risk of relapse. For the connection between the duration of endocrine therapy and the chances of recovery, please refer to the chapter on endocrine therapy (see chapter 4.7.2. Endocrine therapy).

After breast cancer, pregnancy can be achieved with the help of reproductive medical procedures.

The chances of success for an intact pregnancy or child are lower with autologous egg cell use in breast cancer patients than in non-cancer patients.

In a retrospective study, 198 women were included, 25 of whom underwent a reproductive examination. These women were older at diagnosis, at conception and suffered more miscarriages. In both groups the rate of full-term pregnancies was equal to 77% and 75%. There was no difference in prognosis between the two groups. Necessary stimulation therapy can be used to obtain oocytes in the case of hormone receptor-positive breast carcinoma with anti-hormonal concomitant treatment (e.g. aromatase inhibitors or tamoxifen) (see also S3 guideline Fertility maintenance).

In a population-based register of 53,426 women, 441 women with a previous carcinoma were identified within the last 5 years. One third of the women had a breast carcinoma. In women with au-tologous oocytes, there were significant differences in live birth rates between women with and without cancer (47.7% without carcinoma versus 24.7% with previous carcinoma, p = 0.0001) and between the different tumor types (from 53.5% for melanoma to 14.3% for breast cancer, p = 0.0001). With donor oocytes these differences did not exist. In breast cancer patients, the probability of a live birth was only 11.7% if the ART was performed within 6 months of the breast cancer diagnosis, compared to 23% if it was beyond 6 months. Overall, only with melanoma and ovarian cancer was the probability of a live birth after ART as high as without cancer. For breast, cervical and endometrial carcinoma the probability was up to 80% lower. However, there was no difference in the birth rate after successful conception.

7.2. Breast cancer during pregnancy

7.7	**Consensus-based Recommendation**
EC	The treatment (system therapy, surgery, RT) of breast cancer (of pregnant patients) during pregnancy shall be as close as possible to the standard treatment of young, non-pregnant patients with breast cancer.
	Strong Consensus

7.8	**Evidence-based Recommendation**
GoR **0**	Standard chemotherapy with anthracyclines and taxanes can be administered in the 2nd and 3rd trimester.
LoE **2b**	[1560]; [1561]; [1562]
	Strong Consensus

7.9	**Evidence-based Recommendation**
GoR **A**	Anti-HER2 therapy shall not be administered during pregnancy.
LoE **3a**	[1560]; [1561]; [1563]
	Strong Consensus

7.10	**Consensus-based Recommendation**
EC	Endocrine therapy shall not be administered during pregnancy.
	Strong Consensus

Background 7.7 to 7.10

Breast cancer diagnosed during pregnancy has no worse prognosis if it is treated according to its stage and biology. Surgery including sentinel node biopsy can be performed at any time during pregnancy. Chemotherapy can be administered from the beginning of the 2nd trimester. The data on anthracyclines including cyclophosphamide are better than those on taxanes. Both standard therapies can be administered during pregnancy. Due to the higher transplacental transition of platinum salts, more caution is required. The data on platinum salts is less good. Anti-HER2 therapy should be avoided during pregnancy, as the development of an oligo-anhydramnion has been described here under therapy with a fatal outcome. Likewise, endocrine therapy is not indicated during pregnancy.

Radiotherapy should only be performed in exceptional cases and then only in the 1st and beginning of the 2nd trimester.

Supportive therapy should be carried out as for non-pregnant women.

It is important for patients with breast cancer in pregnancy that the pregnancy is closely monitored ultrasonographically and clinically. This is a high-risk pregnancy and should be managed as such.

The inclusion of patients in prospective registries, e.g.: that of the German Breast Group, is recommended as this is the only source of evidence (http://www.gbg.de/de/studien/bcp.php).

7.11	**Consensus-based Recommendation**
EC	The surgery can be performed as if it were performed outside the pregnancy.
	Strong Consensus

7.3. Fertility preservation

7.12	**Consensus-based Recommendation**
EC	Breast carcinoma patients of childbearing age shall receive counselling on fertility and fertility maintenance before starting therapy.
	Strong Consensus

7.13	**Evidence-based Recommendation**
GoR **0**	The administration of GnRH analogues before the start of chemotherapy can be considered for all women who wish to maintain ovarian function/fertility.
LoE **1b**	[1564]; [1565]; [1566]; [1567]; [1568]; [1569]; [1570]
	Strong Consensus

Background 7.12 and 7.13

Women of childbearing age should be advised on the potential gonadotoxicity of the planned systemic therapy and any fertility-sustaining measures.

GnRH on the possible preservation of ovarian function

281 premenopausal patients with hormone receptor-positive or -negative breast cancer, were randomized to triptorelin vs. observation. Triptorelin was started at least 1 week before the start of (neo)adjuvant chemotherapy and then administered every 4 weeks until the end of chemotherapy. Twelve months after the end of the last chemotherapy cycle, the rate of premature menopause (defined as absence of menstruation and postmenopausal levels of FSH and estradiol 1 year after the end of chemotherapy) was 8.9% in the group with triptorelin and 25.9% in the group without triptorelin for chemotherapy. The absolute difference was -17% (95% confidence interval, -26 to -7.9%; P < 0,001. Die Odds Ratio zur therapieinduzierten Menopause betrug 0,28 (95%-CI; 0,14–0,59; P < 0,001).

In December 2015, the long-term data were published after a median follow-up of 7.3 years from the study. Overall, 72.6% (95%-CI, 65.7-80.3%) of the 148 patients in the GnRH group and 64.0% (95%-CI, 56.2-72.8%) of the 133 patients in the control group menstruated again (1.28 [95%-CI, 0.98-1.68]; P = 0.07; age-adjusted HR, 1.48 [95%-CI, 1.12-1.95]; P = 0 ,006). A total of 8 pregnancies occurred, 5 (cumulative 5-year incidence 2.1% [95%-CI, 0.7-6.3%]) with GnRH and 3 (cumulative 5-year incidence, 1.6% [95%-CI, 0.4-6.2%]) in the control group (HR, 2.56 [95%-CI, 0.68-9.60]); P = 0.14; age adjusted HR, 2.40 [95%-CI, 0.62-9.22]; P = 0.20). The 5-year DFS was 80.5% (95%-CI, 73.1-86.1%) in the GnRH group and 83.7% (95%-CI, 76.1-89.1%) in the control group (GnRH vs. control HR, 1.17 [95%-CI, 0.72-1.92]; P = 0.52).

The POEM study included 214 patients with HR-negative breast cancer and randomized them to standard chemotherapy with or without GnRH to maintain ovarian function. This was defined in the study as resuming menstruation 2 years after the end of therapy. The amenorrhea rate was 8% with and 22% without GnRH analogue (odds ratio,

OR 0.3; 95%-CI 0.1-0.87, p = 0.03). Birth and pregnancy rates were significantly higher in the group with GnRH than in the group without (21% vs. 11%; OR 2.45 p = 0.04). The women who had a child were significantly younger than the others. They may also have been more motivated to contribute to the success of the study. In addition, the study showed a significantly better disease-free and overall survival for the GnRH group in patients with HR-negative breast cancer. Overall, the primary endpoint could only be determined in less than 50% of the patients, and the study was terminated prematurely. The study therefore has clear deficiencies.

A meta-analysis of the various studies on the subject also comes to a positive effect of GnRH therapy, at least as far as ovarian function is concerned.

As far as fertility maintenance is concerned, reference is made primarily to the methods of reproductive therapy, which will not be discussed here (reference to S2/3 guideline on this).

8. Breast cancer in elderly patients

8.1. General

8.1	Consensus-based Recommendation
EC	Therapy decisions for older patients should take into account the biological age, life expectancy, patient preference and risk-benefit ratio based on the current standard recommendation.
	Strong Consensus

8.2. Geriatrics

8.2	Evidence-based Recommendation
GoR B	In patients older than 75 years of age, a geriatric assessment or a screening/geriatric assessment algorithm should be performed, especially if chemotherapy or surgery under general anesthesia is planned, to improve treatment adherence, chemotherapy tolerance and possibly survival.
LoE 2a	[1571]; [1572]; [1573]; [1574]
	Strong Consensus

Background 8.2

Numerous articles show that various parameters of geriatric assessment are related to outcome. Interventional evidence is also increasing in this area: Only recently, a large study on the adaptation of therapy in frail patients showed a significant improvement in functionality and reduction in mortality by means of a geriatric frailty assessment prior to surgery, although no breast cancer patients were included.

In a non-randomised study it was also shown that in the intervention group with a CGA (comprehensive geriatric assessment) fewer therapy modifications were necessary and the planned therapy could be completed with fewer toxicities. Overall survival in this group has not yet been investigated [1571], [1572], [1573], [1574].

8.3	Evidence-based Recommendation
GoR **B**	Geriatric assessment and management should include therapy-relevant geriatric domains (in particular functionality-associated parameters such as activities of daily living, mobility, cognition, falls and morbidity-associated parameters such as multimedication, nutrition, fatigue and number of comorbidities) in order to adapt the choice of therapy accordingly and initiate supportive measures.
LoE **2a**	[1575]; [1576]; [1577]; [1578]; [29]
	Strong Consensus

Background 8.3

Increasingly, geriatric assessment parameters are used in observational studies and in randomized studies, which are subsequently available for (mostly secondary) analyses. For example, the ELDA study showed that the number of comorbidities and activities of daily living (ATL) (in addition to age and therapy with docetaxel) was associated with severe non-hematological toxicities [1579].

Hamaker was also able to show that the number of geriatric syndromes from a complete geriatric assessment was associated with the occurrence of grade 3-4 toxicities. In contrast, the results of the Groningen Frailty Indicator showed no association with the occurrence of grade 3-4 toxicities in this cohort. Polymedication was the best predictor of Grade 3-4 toxicity after chemotherapy [1580].

Hurria has associated different geriatric and non-geriatric parameters with toxicity in different studies in patients with different neoplasms, as well as Cough-Gorr et al. These include falls, mobility, hearing, creatinine clearance, comorbidities, cognition, social status. CGA, especially cognition and functionality, was also associated with 7-year survival [1575], [1581].

8.3. Local therapy

8.4	Consensus-based Recommendation
EC	The surgical therapy of the older patient is not fundamentally different from that of the younger patient.
	Strong Consensus

8.5	Evidence-based Recommendation
GoR **B**	In patients with ER/PR-positive breast cancer: Primary endocrine therapy should be carried out if surgery is not performed in cases of frailty (including comorbidity and increased risk of anaesthesia) or if surgery is refused. When choosing a therapy, the drug-associated specific side effects, in particular the risk of thrombosis/embolism (tamoxifen) or bone fracture (aromatase inhibitors), must be taken into account.
LoE **1b**	[1582]
	Strong Consensus

8.6	Consensus-based Recommendation
EC	For patients with ER- and PR-negative breast cancer: If surgery under general anesthesia is not performed due to frailty (including comorbidity and increased risk of surgery) or refusal to undergo surgery, surgical therapy under local anesthesia, primary radiotherapy or purely palliative medical care may be considered.
	Strong Consensus

Background 8.4 to 8.6

The indications for breast-conserving surgery or mastectomy are basically no different for older patients than for younger patients. However, co-morbidities such as cardiac diseases should be taken into account, which may make follow-up radiation of the mamma impossible and thus also influence the decision on the type of surgery. SNB (sentinel node biopsy) is also the therapy of choice for older patients with clinically negative axilla. Even in affected SLN, the ACOSOG-Z0011 study was able to show that under certain conditions (BET, T1/2 and 1-2 positive sentinels, systemic therapy) axillary lymphonodectomy can be dispensed with, without negative influence on locoregional and systemic control. In the case of a primarily clinically positive axilla, axilla dissection is indicated as in the younger patient. The renunciation of axilla staging can be considered in individual cases depending on age and comorbidities.

Based on the Cochrane review by Morgan et al. (2014) of 7 studies in women aged 70 and older with endocrine positive breast cancer, no benefit was found for surgery or primary endocrine therapy with tamoxifen in terms of breast cancer mortality (HR 0.98, 95% CI 0.81 to 1.20, P = 0.8, follow-up up to 12 years, low heterogeneity). An improved local control was observed in operated patients [1582].

8.4. Adjuvant endocrine therapy

8.7	**Evidence-based Recommendation**
GoR **0**	Endocrine therapy is recommended for hormone receptor-positive disease. In patients with a very favourable tumour stage or very favourable biology or a very frail patient, endocrine therapy can be dispensed with in individual cases.
LoE **2b**	[1577]; [1583]
	Consensus

Background 8.7

At a very favourable stage and with a favourable biology, e.g. pT1 pN0 ER and PgR positive, G1-G2 has a low benefit of endocrine therapy due to the low risk of recurrence. In a Danish cohort study, the absence of endocrine therapy in patients aged 60-74 years showed no difference in survival compared to the normal population for pT1a,1b pN0 tumors G1 ductal or G1 or 2 with lobular histology.

8.5. Adjuvant chemotherapy

8.8	**Consensus-based Statement**
ST	With increasing age and frailty, reduced physical reserves and altered pharmacokinetics can reduce the tolerability of chemotherapy and increase the rate of treatment-related side effects.
	Strong Consensus

Background 8.8

There are numerous age-associated factors that can influence the pharmacokinetics of chemotherapeutic agents. These include absorption through reduced gastric secretion and motility. The distribution volume of fluids may change due to increased body fat content, decreased intracellular water and reduced albumin concentrations. Metabolism in the elderly is also altered by reduced liver flow, reduced liver size and also changes in the microsomal P-450 system. Pharmacodynamically important with increasing age is the reduced glomerular filtration rate and thus impaired renal function.

8.9	**Evidence-based Statement**
ST	Chemotherapy may be associated with a significant decrease in cognitive performance in older women > 70 years of age.
LoE **2b**	[1584]; [533]
	Strong Consensus

Background 8.9

The most recent and largest study on this subject at least suggests this, especially for docetaxel [533], even though the meta-analysis (without this new study from 2015) had not yet found any evidence for this [1584].

8.10	**Evidence-based Recommendation**
GoR **B**	Anthracycline and/or taxane based combination or sequence regimes should be preferred. An increased cardiotoxicity risk and MDS/AML risk for anthracyclines should be considered.
LoE **2b**	[1579]; [1585]; [1586]; [1587]; [1588]; [1589]; [1590]; [1591]; [790]
	Strong Consensus

Background 8.10

In most chemotherapy studies, older women were either not included or were underrepresented. The available data are therefore often only derived from subgroup analyses of older patients who were not included in these studies. Based on the available evidence and according to the SIOG task force, anthracycline taxane containing sequence regimens, e.g. 4 x EC followed by 12 x paclitaxel weekly, 4 x docetaxel/cyclophosphamide and 4 x epirubicin/cyclophosphamide, are recommended regimens. The CMF regimen may also be an option in individual cases, was superior to capecitabine monotherapy in a randomized trial and was as effective as docetaxel weekly, but with significantly fewer non-hematological side effects and better quality of life. For taxanes, weekly paclitaxel doses are preferable to (weekly) docetaxel. Primary prophylaxis with growth factors should be considered in older patients. The intensity of the therapy should depend on the tumour stage, the tumour biology and the general condition of the patient.

The increased risk of cardiotoxicity should also be considered in older patients with anthracycline therapy. In a retrospective study of 630 patients with doxorubicin-based therapy, age was a risk factor for cardiac side effects, independent of performance status and comorbidities. In a further retrospective study of 40 000 66-80 year old women in the SEER database who received adjuvant chemotherapy, a steadily increasing rate of cardiac impairment of varying degrees was found up to 10 years after completion of adjuvant therapy.

Older patients under therapy with anthracyclines also have a higher risk of developing MDS or AML than younger patients. In a recent study by Freedman, however, the

absolute risk remained low with about 1% of patients treated in patients between 65 and 70 years of age (<65% 0.4%). The hazard ratio (HR) of = 5 (with large CI) for anthracycline was, however, the strongest predictive factor for developing AML/MDS syndrome.

8.11	Evidence-based Statement
ST	Monochemotherapy alone is less effective.
LoE **1b**	[1586]
	Strong Consensus

Background 8.11

633 women with early breast cancer stage I-III and older than 65 years (65% ≥70 years) were randomized to 6 x CMF / 4 x AC (depending on the investigator's preference) or 6 cycles of Capecitabine. In hormone receptor-positive disease, endocrine therapy was started after the end of chemotherapy. Disease-free and overall survival was significantly higher in the CMF/AC group (85% vs 68% and 91% vs 86%) compared to the capecitabine group.

8.6. Anti-HER2-Therapy

8.12	Evidence-based Statement
ST	Treatment is analogous to the younger patient with trastuzumab in combination with a sequential anthracycline-taxan-containing chemotherapy. The increased cardiotoxic risk must be taken into account. (Expert consensus) Carboplatin-docetaxel or docetaxel-cyclophosphamide can be used as anthracycline-free combinations. (1b)
LoE **1b/5**	[1578]; [1592]; [1593]; [1594]
	Strong Consensus

Background 8.12

The proportion of HER2-positive breast cancer patients is not exactly known. However, on the basis of retrospective studies it can be assumed that it is similarly high in older women as in younger women (10% to 20%) [1592].

The tumor biological behavior does not differ from that in younger women.

Since the drug treatment of breast carcinoma should be based on tumor biological factors, there is no reason to deviate from the therapy recommendations for younger women [1578], [1593].

However, age-related changes (higher proportion of cardiac comorbidities, reduction of the bone marrow reserve) must be included in the therapy concept.

Anthracycline-free chemotherapy regimens in combination with trastuzumab showed an identical efficacy on [1595]. In a randomized phase III study, the combination of docetaxel-cyclophosphamide with doxorubicin-cyclophosphamide was superior to [1594]. Due to the expected myelotoxicity, granulocyte stimulating factors (GCSF) should be used prophylactically according to the ESMO guidelines.

8.13	Evidence-based Recommendation
GoR **0**	Paclitaxel weekly (12 weeks) with trastuzumab can be used for T1-2 (up to 3cm) pN0 tumors.
LoE **2b**	[1596]; [1597]
	Strong Consensus

Background 8.13

The Pase-II study of CALBG by Tolaney et al. showed excellent 3-year survival (98% survival rate) for hormone receptor-positive, HER2-positive, nodal-negative tumors.

In this study, patients were treated for 12 weeks with weekly paclitaxel therapy in combination with trastuzumab. After 12 weeks, treatment with trastuzumab was continued for a total of 1 year and endocrine therapy was started. In this study one third of the women were older than 60 years. Due to the reduced toxicity of this combination, it appears to be particularly suitable as an adjuvant treatment option for patients with cardiac comorbidities [1596] and HER2-positive breast cancer.

9. Breast cancer in men

The diagnosis and treatment of breast cancer in men should be interdisciplinary and requires gynaecological and oncological expertise due to the tumor biological characteristics and similarity to breast cancer in women. Interdisciplinary cooperation between breast centers, practicing gynecologists, urologists and andrologists is particularly recommended for the treatment of sexual dysfunction by tamoxifen therapy, for men with BRCA mutations [1598] with an associated increased risk of prostate cancer, and for men with breast cancer for whom treatment of benign prostate syndrome should be performed [1599].

9.1	Consensus-based Recommendation
EC	Early medical consultation shall be encouraged by informing men about the disease, especially about symptoms and changes in the breast, and by encouraging self-observation.
	Strong Consensus

9.2	Consensus-based Recommendation
EC	The basic diagnostics shall be carried out in case of suspected malignant findings by anamnesis, clinical examination, mammography and ultrasound diagnostics of the breast and the lymph drainage regions. No data are available on the diagnostic use of KM-MRI.
	Consensus

9.3	Consensus-based Recommendation
EC	Further diagnostics and staging/spreading diagnostics shall be carried out for breast and axilla findings according to the recommendation for women, although no data are available on the diagnostic use of KM-MRI.
	Consensus

9.4	Consensus-based Recommendation
EC	The surgery aims at the complete removal of the tumour and should be performed as a mastectomy. If the size ratio between tumour and breast is favourable, breast preservation should be considered.
	Strong Consensus

9.5	Consensus-based Recommendation
EC	In the case of clinically unremarkable axilla (cN0), sentinel lymph node removal should be performed according to the same rules as in women.
	Consensus

9.6	Consensus-based Recommendation
EC	In the case of larger tumours (≥ 2cm), in the case of axillary lymph node involvement and in the case of a negative hormone receptor, adjuvant radiotherapy of the chest wall and, if necessary, of the lymph drainage channels (indication as for women) shall be carried out independently of the surgical procedure.
	Strong Consensus

9.7	Consensus-based Recommendation
EC	Adjuvant chemotherapy as well as antibody therapy (anti-HER2) shall be indicated and carried out according to the same rules as in women.
	Consensus

9.8	Consensus-based Recommendation
EC	Patients with hormone receptor-positive breast cancer shall receive adjuvant endocrine therapy with tamoxifen, usually for 5 years. No data are available for treatment beyond 5 years. As with female breast carcinoma, this may be considered in individual cases.
	Strong Consensus

9.9	Consensus-based Recommendation
EC	a) Therapy for metastatic disease should follow the same rules as for women. b) It is unclear whether aromatase inhibitors are sufficiently effective without suppression of testicular function in men. Therefore aromatase inhibitors should be given in combination with suppression of testicular function.
	Strong Consensus

9.10	Consensus-based Recommendation
EC	Participation in studies/registers should be offered and made possible for men with breast cancer.
	Consensus

9.11	Consensus-based Recommendation
EC	Genetic counseling shall be recommended to all men with breast cancer.
	Consensus

9.12	Consensus-based Recommendation
EC	The design of aftercare, including imaging diagnostics, shall be analogous to the approach taken by women.
	Strong Consensus

9.13	Consensus-based Recommendation
EC	Qualified and relevant gender-specific information (print and Internet) should be made available to the patient by the treating professionals and access to the special offers of the self-help groups should be made possible.
	Strong Consensus

Background 9.1 to 9.13

Male breast cancer has an incidence of approximately 0.5 - 1.0% of all diagnosed breast cancer cases. In Germany every year about 600 new cases of breast cancer are diagnosed in men [43]. Factors that increase the risk of breast cancer in men are shown in table 20 [1600]. The median age at first diagnosis is 67 years [43]. No special screening procedures or early detection measures are recommended for men. Most breast cancer cases are detected by men themselves. The initial diagnosis is made 40% in advanced stages UICC III and IV [43], [1601]. The reasons for this are a lack of knowledge about the disease on the part of the patients, with a resulting delay in the medical presentation. In addition, there are also knowledge deficits on the medical side regarding the possibilities of imaging diagnostics and clarification as well as the coordination of care through the care in certified breast centers [1602], [1603], [1604].

Table 56: Risikofaktoren für Männer, an einem Mammakarzinom zu erkranken

Age	unimodal age distribution with the highest incidence in 71 years of age
Origin	Increased risk in African and Caribbean men, usually also in advanced stages at initial diagnosis
Germ line mutations	2.5 times the risk of disease in the case of a positive family history of both sexes; BRCA2 mutations can be detected in 4 % - 40 % of all cases; RAD51B gene alteratons increase the risk by 50
Endocrine causes	exogenous oestrogen exposure e.g. through hormone therapy for transsexuals, treatment of prostate cancer, occupational exposure
	increased endogenous estrogen synthesis: Klinefelter syndrome, obesity
	decreased androgen levels: orchidectomy, undescended testicles, mumps-associated orchitis, liver cirrhosis
Environment	Lifestyle: obesity, lack of exercise, excessive alcohol consumption
	radiation exposure: nuclear weapons, radiotherapy, diagnostic radiology
	occupational exposure: high temperatures, petroleum, exhaust fumes

There is very little evidence from randomized studies on specific diagnostics, biological parameters and therapy of male breast cancer. Currently, the data are mainly based on epidemiological data, retrospective case reports, retrospective small cohorts and inhomogeneous study collectives. There are no treatment standards that could refer to larger randomized studies.

At present, the recommendations for the treatment of men with breast cancer are mainly based on the recommendations for the diagnosis, treatment and aftercare of the disease in postmenopausal women [1604], [1605]. Well knowing that the disease

in men has other biological potentials that have to be considered in the care of patients [1606], [1607], [1608]. There is an international consensus to increase the knowledge base on breast cancer in men by participating in registry studies [1605], [1609], [1610].

In male breast cancer patients a similar breast cancer mortality rate is found as in older postmenopausal women. A genetic disposition is more frequent in men, especially mutation BRCA1 and BRCA2 [1611]. Furthermore, men with breast cancer have an up to 20% increased risk constellation for second malignancies [1612].

Over 90% of patients are diagnosed with ER-positive invasive ductal carcinoma. The HER2 overexpression is inconsistently reported in the literature as 12-37%. A recent study found 97% ER-positive and only 10% HER2-positive tumors in a unicentric cohort of 61 invasive mammary carcinomas in men [1613]. 39-95% of the cases showed androgen receptor expression. In contrast to the histopathological similarities to breast cancer in women, molecular biological examinations show significant differences in [1607], [1608], [1610], [1613].

Most men have so far been treated by mastectomy and axillary lymphonodectomy (ALND) and possibly with chest wall radiation [1601], [1614], [1615] Current data suggest in particular less radical surgical measures with the aim of reducing therapy-related morbidity [1616], [1617], [1618], [1619].

Men with breast cancer with lymph node involvement benefit from adjuvant chemotherapy with improved prognosis (disease-free survival, overall survival) [1620]. When deciding on adjuvant therapy, comorbidities and tolerance as well as patient preferences must be considered. The substances and regimens commonly used in women including anti-HER2-therapy are used if indicated. Tamoxifen is currently the standard therapy for hormone receptor-positive breast cancer. The side effects such as sexual dysfunction lead to a high therapy discontinuation rate [1621]. The use of aromatase inhibitors in adjuvant therapy is not recommended; aromatase inhibitors were associated with a significantly increased mortality in a retrospective analysis of German cancer registries [1622].

There is no evidence from clinical studies on the treatment of HER2-positive breast cancer in men; however, there is consensus that, following the successes in HER2-positive breast cancer in women, men with HER2-positive breast cancer should also be treated adjuvantly with trastuzumab [1623].

In metastasis, aromatase inhibitors can be used second-line, most likely in combination with drug suppression of the gonadal function [1624], [1625], [1626], [1627], [1628].

In advanced metastatic disease, studies show treatment options for fulvestrant, aromatase inhibitors and eribulin from [1625], [1626], [1628], [1629], [1630].

Rehabilitation and aftercare, including imaging diagnostics, are carried out in accordance with the recommended aftercare for women. Aftercare for men focuses on the specific risks, comorbidities, short and long-term side effects to be considered and includes psychosocial as well as psycho-oncological aspects [1387], [1631].

10. Quality Indicators

Quality indicators (QI) are measured variables whose collection serves to assess the quality of the underlying structures, processes or results [1632]. Quality indicators are an important instrument of quality management. The aim of their use is the continuous improvement of care by presenting the results of care, reflecting them critically and improving them if necessary. The present selection of quality indicators was prepared according to the methodology of the Oncology Guidelines Programme [1633]. For the derivation process a working group "Working Group Quality Indicators" was constituted. This group created the final set of quality indicators based on the existing quality indicators of the 2012 guideline and the new strong recommendations (strength of recommendation A, "should") of the updated guideline. The compilation took into account the results of the existing quality indicators from the certified breast cancer centers of the German Cancer Society and the German Society for Senology [1551], the quality indicators of the external inpatient quality assurance [1634] and the results of the research for existing national and international QIs. The results of the guideline-based quality indicators, which are measured and evaluated in the certification procedure, were already presented at the kick-off meeting of the present update in order to be able to make changes to recommendations and background texts based on the results from the care system, if necessary. Changes were made for some of the recommendations underlying the existing indicators. The changes are mainly due to new study results. The exact procedure for selecting potential QIs and the composition of the working group is described in the guideline report (http://leitlinienprogramm-onkologie.de/index.php?id=67ype=0).

After a face-to-face meeting, a written evaluation of the indicators positively prioritized there and a concluding conference call of the working group, 2 new indicators were adopted (supplement for QI 5 "Indication for sentinel lymph node biopsy" and QI 6 "Therapy of axillary lymph drainage areas in pN1"). The already existing QI 5 "Indication for sentinel lymph node biopsy" will in future be calculated separately for female (5 a)) and male patients (5 b)) on the basis of the data of the QA procedure for breast surgery of the Institute for Quality Assurance and Transparency in Health Care (IQTIG), so that only 1 QI will be added to the already existing QI. Of the 12 QIs from Guideline 2012, 4 QIs were deleted and 2 QIs (QI 2: Intraoperative preparation radio/sonography, QI 4: Endocrine therapy as the first therapeutic option in steroid-receptor-positive metastatic breast cancer) were adjusted in the numerator or denominator. The justifications are described in detail in the Methods Report. The final set thus consists of 9 quality indicators.

Based on the recommendation "3.9 Diagnosis and care chain breast cancer early detection", the Working Group QI has defined a QI that is intended to record and improve the further treatment of patients secured in screening in certified breast cancer centres.

Table 57: Quality Indicator definitions

Enumerator	Number of patients receiving treatment in a certified breast cancer center (DKG/DGS, NRW)
Denominator	All patients with histologically confirmed invasive breast cancer u/o DCIS

The data required for this QI are exclusively available to the Mammography Screening Cooperative and cannot be generated by the cancer registries or the certified centres. In this respect, the members of the Working Group QI could not positively evaluate criterion 5 to be evaluated "The data are routinely documented by the service provider or an additional survey requires a justifiable effort" for this QI, since the group members can only access data from certified centres, cancer registries and IQTIG. However, there was consensus in the group to include the QI in the list of QIs and to name and contact the Mammography Cooperative as the addressee of the recording of this QI.

The WG did not derive any new quality indicators for the field of palliative care, but referred to the existing QIs of the guideline on palliative care, especially the QI "Foresighted care planning" and "Screening using MIDOS and IPOS" of the guideline. The latter QI is recorded in the oncological centers of the German Cancer Society.

In the case of QIs that consider small populations, the detailed processing of cases, e.g. within the framework of on-site audit procedures, should be more important than a quantitative evaluation. This is to prevent conspicuous QI results, which are mainly caused by small populations ("small number problem"), from leading to a negative evaluation. In these cases, the QI's main aim is to identify conspicuous developments, to address these specifically and to initiate improvement measures, e.g. through on-site auditing. Due to the small population, no valid data in the sense of a defined reference value can be provided.

The numerator is always a partial quantity of the denominator. The quality indicators apply to female and male patients unless otherwise described.

Table 58: Quality Indicators

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
QI 1: Further treatment of breast cancer detected by mammographic screening in certified breast cancer centers		
Enumerator Number of patients treated in a certified breast cancer center (DKG/DGS, NRW) **Denominator** All patients detected during mammographic screening with histologically confirmed invasive breast cancer and/or DCIS	**3.13** In order to ensure the best possible treatment, further therapy of breast cancer detected in screening shall be carried out in certified breast centres. Continuous quality assurance is to be ensured by communication and data acquisition between the	**Quality objective:** As often as possible, further treatment of the breast carcinomas and/or DCIS detected in screening in a certified breast cancer centre

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
The QI can be evaluated with data from the Mammography Cooperation Group.	screening centre and the certified breast centre.	
QI 2: Pretherapeutic histological confirmation (since 2012, formerly: Breast CA 1)		
Enumerator Patients with pretherapeutic histological confirmation of diagnosis by core needle biopsy or vacuum-assisted biopsy **Denominator** Patients with primary intervention and histology “invasive breast cancer (primary tumor) or DCIS" as primary disease	**4.14** The histological clarification of findings shall be carried out by punch biopsy, vacuum biopsy and, in exceptional cases which must be justified, by open excision biopsy.	LOE 3a, recommendation level A **Quality objective**: As many patients as possible with pre-therapeutic histological confirmation by punch or vacuum biopsy in case of initial intervention and primary disease invasive breast cancer and/or DCIS
QI 3: Intraoperative specimen radiography/sonography (since 2012, formerly: Breast CA 2)		
Enumerator Surgeries using intraoperative specimen X-ray or intraoperative specimen ultrasound **Denominator** Surgeries with preoperative wire marking guided by mammography or ultrasound	**4.25** Pre-operative or intraoperative marking shall be carried out using the method that allows the findings to be clearly visualized, especially in the case of non-palpable changes. Proof of adequate resection must be provided intraoperatively by means of specimen radiography or specimen sonography. If MR-guided marking has been performed, an MR control should be performed within 6 months in case of histologically unspecific benign findings.	**Quality objective:** As often as possible intraoperative preparation sonography or radiography after preoperative marking
QI 4: Axillary lymph node biopsy in DCIS (since 2012, formerly: Breast CA 3)		
Enumerator Patients who have undergone axillary lymphadenectomy	**4.23** An axillary dissection shall not be performed in DCIS. A	LOE 1b, recommendation level A

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
(primary axillary dissection or SLNB) **Denominator** Patients with "DCIS" histology who have completed surgical treatment for their primary disease after breast-conserving treatment Quality objective <5%	sentinel node biopsy shall only be performed if a secondary sentinel node biopsy is not possible for technical reasons, e.g. in the case of a mammary ablatio.	**Quality objective:** As few patients as possible with primary axilla dissection or sentinel node biopsy (SNB) in DCIS with breast-conserving therapy
QI 5: Endocrine therapy as the first therapeutic option for steroid-receptor-positive metastatic breast cancer (since 2012, formerly: Breast CA 11)		
Enumerator Patients who have received endocrine therapy as first-line therapy in the metastatic stage **Denominator** All patients with steroid-receptor-positive breast cancer and HER2- negative breast cancer and primary diagnosis of metastasis	**5.26** In pre- and perimenopausal patients, endocrine therapy, possibly combined with targeted therapy, shall be offered if hormone receptor status is positive and HER2 status is negative. Endocrine-only monotherapy is not indicated in patients with the need to achieve rapid remission to avert marked symptoms of the affected organ.	LOE 1b, recommendation level A **Quality objective:** To perform endocrine-based therapy as a first-line therapy as often as possible for Pat with breast cancer, positive hormone receptor status, negative HER2 status and initial diagnosis of metastasis.
QI 6: Indication for sentinel lymph node biopsy (since 2012, formerly: Breast CA 4)		
Enumerator Patients with sentinel node biopsy alone **Denominator** Patients with primary disease of invasive breast cancer and negative pN staging and without preoperative tumor-specific therapy *The quality indicator should be calculated separately for female and male patients* (see introduction)	**4.51** The axillary staging is intended to be a component of the surgical therapy of invasive breast cancer. **4.52** This shall be carried out with the help of sentinel lymph node removal (SLNB) for lymph node status that is inconspicuous on palpation and sonography.	**Quality objective:** As many patients as possible with sentinel node biopsy in lymph node negative (pN0) invasive breast cancer without preoperative tumour-specific therapy

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
QI 7: Therapie der axillären Lymphabflussgebiete bei pN1mi (neu 2017)		
Enumerator Anzahl Pat. mit Therapie (= Axilladissektion o. Radiatio) der axillären Lymphabflussgebiete **Denominator** Alle Pat. mit Primärerkrankung invasives Mammakarzinom, pN1mi Qualitätsziel <5%	**4.56** In the case of exclusive micrometastasis, a targeted therapy of the lymph drainage areas (surgery, radiotherapy) shall be avoided.	LoE 1b, Empfehlungsgrad B **Qualitätsziel:** Möglichst selten Therapie der axillären Lymphabflussgebiete bei Mikrometastasierung
QI 8: Radiotherapy performed after BCT (since 2012, formerly: Breast CA 6)		
Enumerator Patients with invasive cancer and BCT who have undergone radiation of the breast **Denominator** Patients with primary disease of invasive breast cancer and BCT	**4.87** After breast-conserving surgery due to invasive carcinoma, radiation of the affected breast shall be performed. For patients with clearly limited life expectancy (<10 years) and a small (pT1), node-negative (pN0), hormone receptor-positive HER2-negative tumor receiving endocrine adjuvant therapy, conditional upon free excision margins and taking an increased risk of local recurrence into account. *Note for all recommendations: All individual items are "or" combinations. "And" links are represented by an "and".*	LOE 1a, recommendation level A **Quality objective:** Adequate rate of radiation after BET in patients with the first disease invasive breast cancer.
QI 9: Endocrine therapy in patients with receptor-positive findings (since 2012, formerly: Breast CA 7)		
Enumerator	**4.109**	LOE 1a, recommendation level A

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
Patients who have received adjuvant endocrine therapy. **Denominator** Steroid-receptor-positive patients with invasive breast cancer as primary disease	Patients with estrogen- and/or progesterone receptor-positive (°) invasive tumors shall receive endocrine therapy. ° (>/=10% progesterone receptor-positive tumor cell nuclei)	**Quality objective:** Endocrine therapy should be carried out as often as possible in receptor-positive patients with the first disease invasive mammary carcinoma
QI 10: Trastuzumab therapy in patients with HER2-positive findings (since 2012, formerly: Breast CA 8)		
Enumerator All patients who have received (neo)adjuvant treatment with trastuzumab for one year **Denominator** All HER2-positive (immuno-histochemical score 3+ and/or ISH-positive) patients with invasive breast cancer as primary disease ≥ pT1c	**4.133** Patients with HER2-overexpressing tumours with a diameter of ≥ 1 cm (immunohistochemical score 3+ and/or ISH-positive) should receive (neo-)adjuvant treatment with anthracycline followed by a taxane in combination with trastuzumab. Trastuzumab should be administered over a total period of one year.	LOE 1b, recommendation level A **Quality objective:** Trastuzumab therapy as often as possible over 1 year in HER2-positive patients with first diagnosis of invasive breast cancer >= pT1c

11. Appendices

11.1. Clinical algorithm of the diagnostic chain for the early detection of breast cancer

Algorithm Diagnosis for clarification of symptoms and findings

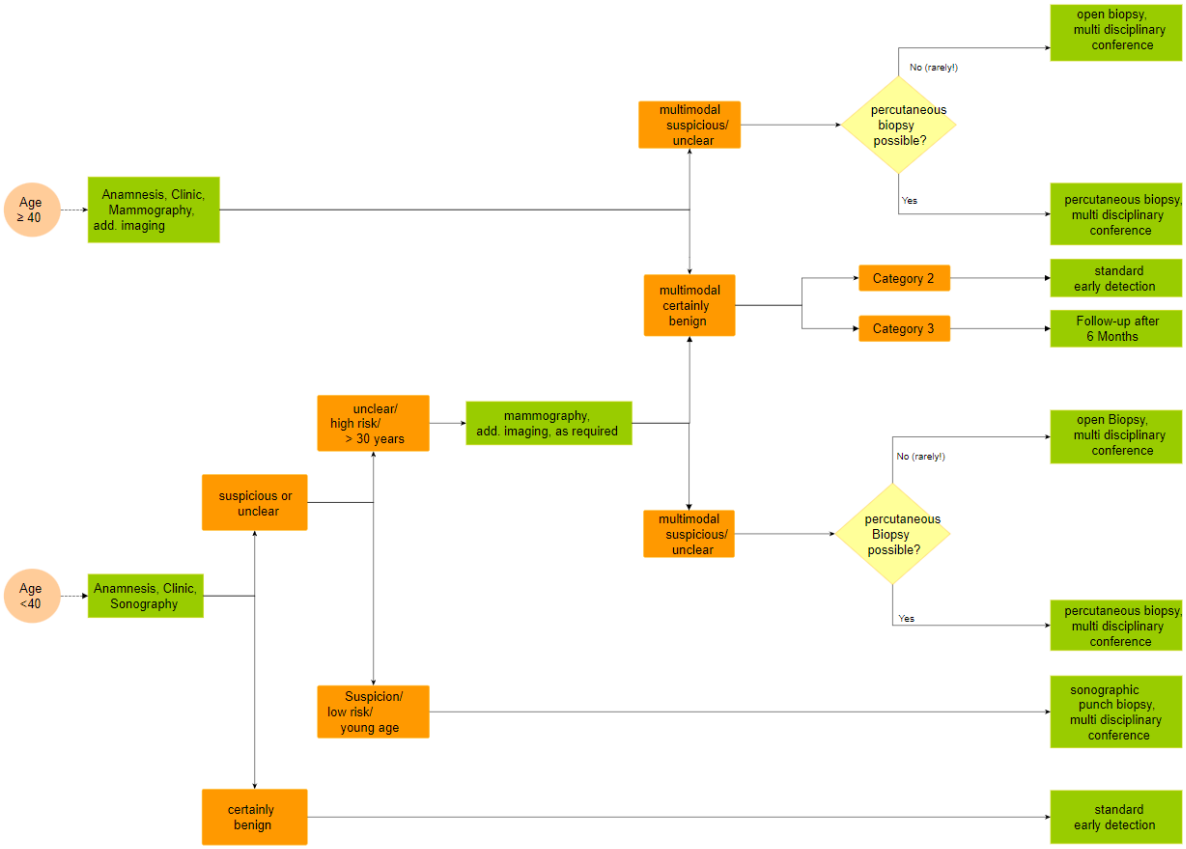


Figure 5: Algorithm for symptoms and findings (woman and man)

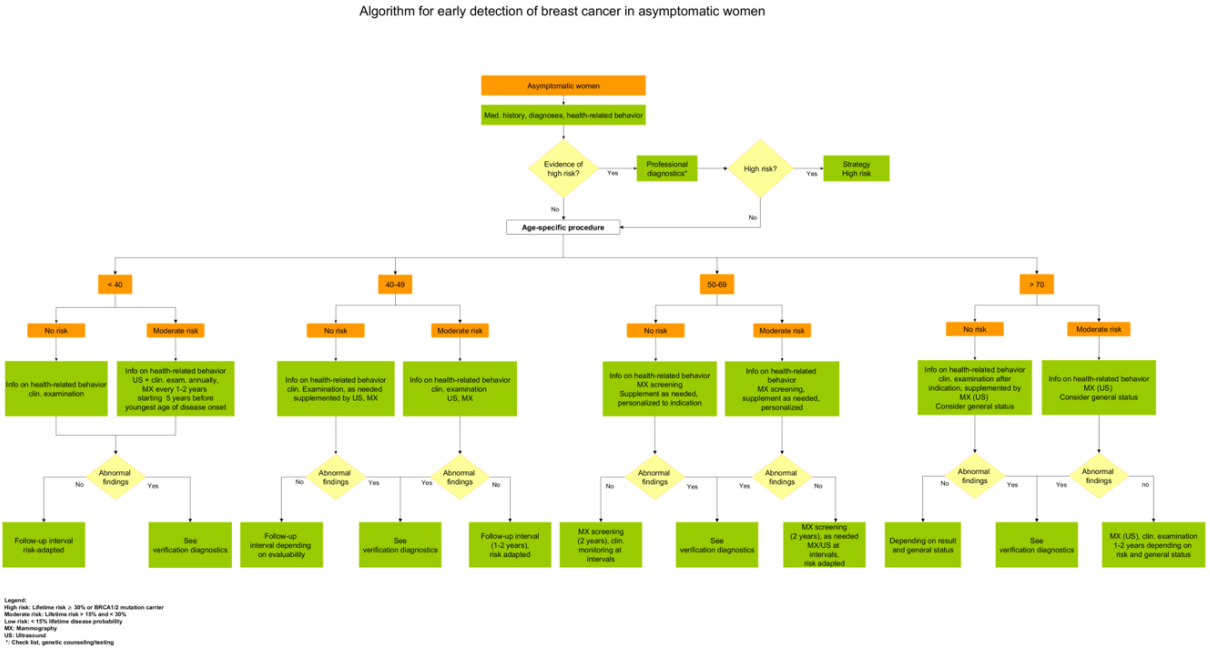


Figure 6: Algorithm for early detection of breast cancer in asymptomatic women

11.1.1. Options and indications for plastic reconstruction

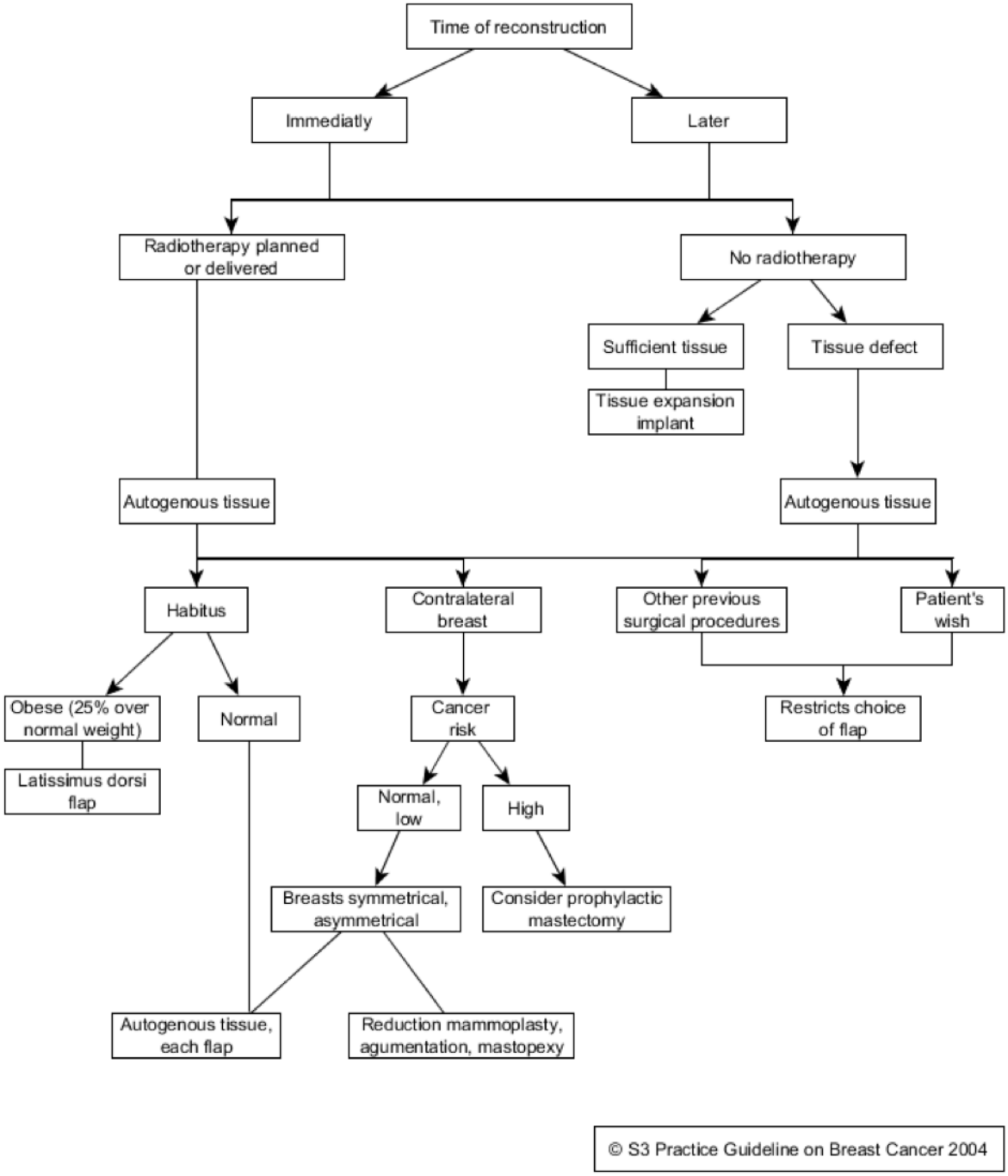


Figure 7: Options and indications for breast reconstruction.

11.1.2. Classification of procedures

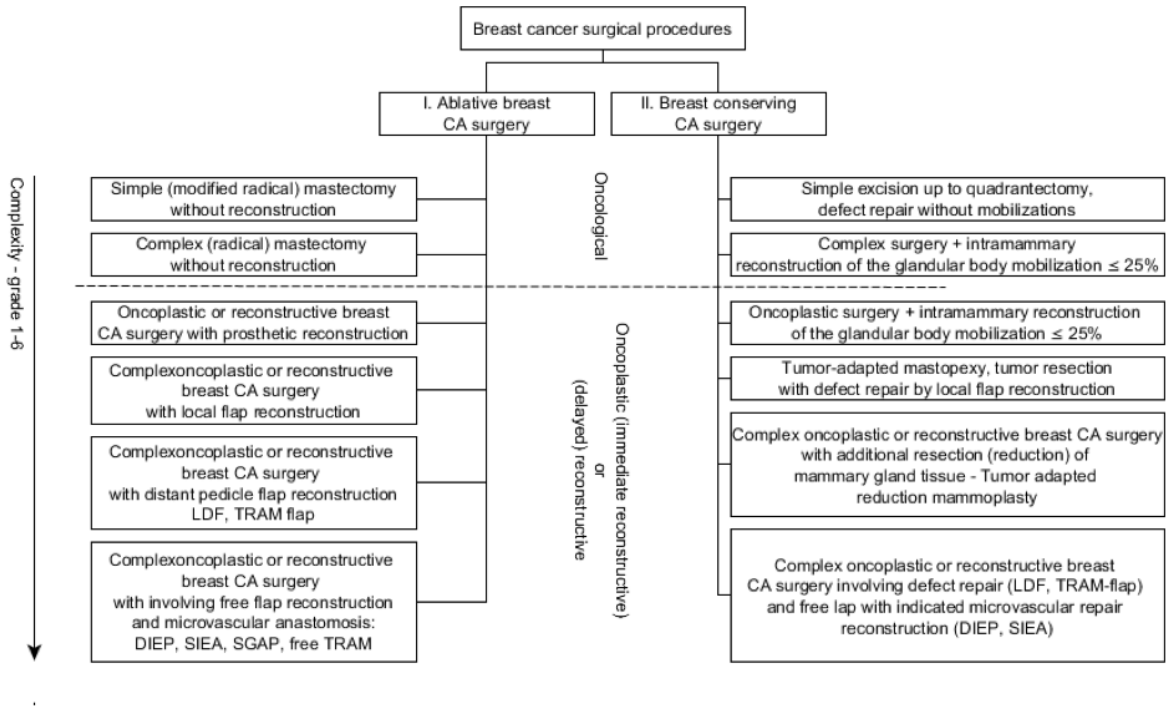


Figure 8: Classification of breast cancer surgery by grade of complexity

11.2. Pathomorphological examination

(to Chapter 5.5 Pathomorphological examination)

The appendix includes excerpts from common classifications and graduation systems referred to in the guideline, as well as proposed forms for the "Begleitschein zur Einsendung" and the "Dokumentation der verachterlichen diagnostischen Begutachtung" (see Figure 9 to Figure 11). The current nomenclature of benign breast lesions is also taken into account. In addition, the appendix contains supplements for the interpretation of the hormone receptor determination. In addition, special aspects of the assessment after neoadjuvant systemic therapy are explained.

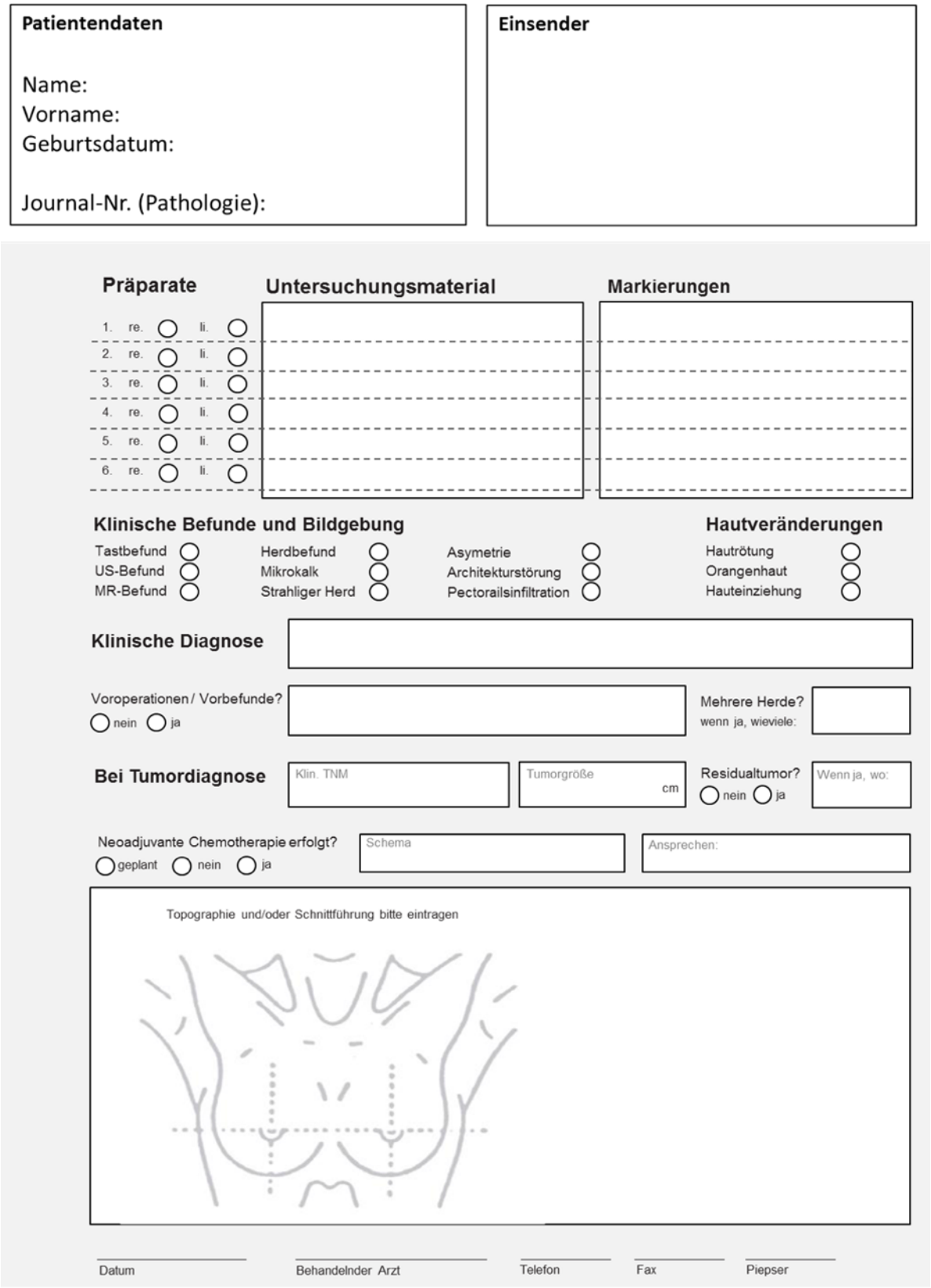


Figure 9: Standardized form 1 – Pathology Request Form

Einsender	Patientendaten Name: Vorname: **Geburtsdatum:** **Journal-Nr.:** **Berichtsdatum:**

Vorgehen, makroskopische Beschreibung:
□ Stanzbiopsie Gesamtlänge der Stanzzylinder: _____ cm
□ Vakuumbiopsie

Anzahl der Stanzen: ____ Präparatradiogramm gesehen □ ja □ nein
Verkalkungen > 100 µm □ ja □ nein
wenn ja: □ lamellär □ amorph

Histopathologische Diagnose:

□ **Nicht verwertbar**
□ **Normalgewebe**

□ **Benigne Läsionen**
- □ Adenose mit Kolumnarzellmetaplasie
- □ Fettgewebsnekrose
- □ Fibroadenom/tubuläres Adenom
- □ Fibrös-zystische Mastopathie
- □ Hamartom
- □ Sonstige benigne Läsionen:
- □ Papillom, vollständig erfasst
- □ Periduktale Mastitis/Duktektasie
- □ Pseudoangiomatöse Stromahyperplasie (PASH)
- □ Sklerosierende Adenose/apokrine Adenose

□ **Benigne Läsionen mit unsicherem biologischem Potential oder malignitätsverdächtig**
- □ Atypische duktale Hyperplasie (ADH)
- □ Flache epitheliale Atypie (FEA)
- □ Klassische lobuläre Neoplasie (LN)
- □ Radiäre Narbe/komplexe sklerosierende Läsion
- □ Sonstige benigne Läsionen mit unsicherem Potential:_____
- □ Intraduktales Papillom
  - □ nicht sicher vollständig erfasst
  - □ mit Atypie
- □ Phylloides-Tumor, benigne/Borderline-Kategorie

□ **Maligne Läsion, nicht invasiv (DCIS, LN-Varianten: mit Komeonekrosen, plemorph, floride/extended)**
DCIS
Kerngrading/WHO-Grad □ Low Grade □ Intermed. Grade □ High Grade
Komedonekrosen □ vorhanden □ nicht vorhanden
LN-Variante
Variante □ Klassisch mit Komedonekrosen □ Pleomorph
□ mit Komedonekrosen
□ ohne Komedonekrosen
□ floride/extended

□ **Maligne Läsion, invasiv**
- □ invasiv, NST M8500/3
- □ invasiv lobulär M8520/3
- □ tubulär M8211/3
- □ muzinös M8480/3
- □ Mischtyp: _____
- □ sonst. Mamma-Ca: _____
- □ nicht beurteilbar

Begleitende in-situ Komponente: □ Ja □ Nein
Histolog. Differenzierungsgrad □ G1 □ G2 □ G3 □ nicht beurteilbar

□ **Sonstige maligne Neoplasie:** _____

□ **Unkl. Läsion**
- □ unklar, ob invasiv oder nicht-invasiv
- □ unklar, ob lobuläre Neoplasie oder DCIS

B-Klassifikation
- □ B1a: nicht verwertbar
- □ B1b: ausschl. Normalgewebe
- □ B2: benigne
- □ B3: benigne mit unsicherem biologischen Potenzial
- □ B4: malignitätsverdächtig
- □ B5: maligne
  - □ B5a: in situ □ B5b: invasiv
  - □ B5c: Nicht zu entscheiden, ob invasiv oder in situ
  - □ B5d: Malignom anderer Histogenese/Metastase

Bei Nachweis von Mikrokalk: Assoziation mit der diagnostizierten Läsion?
□ nein
□ ja, mit: □ invasivem Ca □ DCIS □ ADH □ Sonst.:
□ unsicher

Hormonrezeptoren: ER: __ % positive Tumorzellen PR: __% positive Tumorzellen
HER2: IHC-Score: ____
ISH: □ amplifiziert □ nicht amplifiziert □ zweifelhaft/borderline
Ki-67: __ % positive Tumorzellen
Kommentar/Zusätzliche Informationen:

Datum: _____ Unterschrift: _____

Figure 10: Standardized form 2A – Pathology report for core or vacuum-assisted biopsy

Einsender	**Patientendaten** Name: Vorname: Geburtsdatum: Journal-Nr.: Berichtsdatum:

Seite:		□ Rechts	□ Links		
Präparat topographisch markiert:		□ Ja	□ Nein		
Präparat eingeschnitten übersandt		□ Ja	□ Nein		
Art der Probe:		□ Exzision/Segmentresektion			
		□ Mastektomie/skin-sparing Mastektomie			
		□ Lymphknoten:	□ Sentinel		
			□ Axilläres Dissektat, Level:_____		
			□ Sonstige; welche _____		
		□ Sonstige; welche_____			
Gewicht der Probe:	_____g				
Größe der Probe	_____ mm	X	_____ mm	x	_____ mm
Präparatradiographie der Probe gesehen?		□ Ja	□ Nein		
Bildgebende Anomalie in der Probe?		□ Ja	□ Nein		
		□ Unsicher			
Im Falle einer Vorbiopsie:					
Biopsiehöhle bei OP erfasst?		□ Ja	□ Nein		
		□ Unsicher			

Histopathologische Diagnose

□ **Normalgewebe**

Benigne Läsion (evtl. auch begleitend bei Malignom)

□ Adenom der Mamille	□ Fibös-zystische Mastopathie
□ Adenose mit Kolumnarzellmetaplasie	□ Periduktale Mastitis/Duktektasie
□ Fettgewebsnekrose	□ Pseudoangiomatöse Stromahyperplasie (PASH)
□ Fibroadenom/tubuläres Adenom	□ Sklerosierende Adenose/apokrine Adenose
□ Sonstige:_____	

Proliferative (Risiko-)Läsion ohne Malignität

□ Atypische duktale Hyperplasie (ADH)	□ Phylloides-Tumor, benigne oder borderline
□ Flache epitheliale Atypie (FEA)	□ Radiäre Narbe/komplexe sklerosierende Läsion
□ Lobuläre Neoplasie, klassischer Typ (ALH, LCIS)	□ Sonstige: _____
□ Papillom, solitär/duktales Adenom/Adenomyoepitheliom	
□ Papillom, multiple	

ICD-O-Code

Maligne Läsion, nicht-invasiv (DCIS, LN/LCIS-Varianten)

□ **DCIS**	Größe: _____ mm				*8500/2*
Kerngrad/WHO-Grad:	□ Low Grade	□ Intermed. Grade	□ High Grade		
Komedonekrosen	□ Vorhanden	□ Nicht vorhanden			
M. Paget	□ Vorhanden	□ Nicht vorhanden			
□ **LN/LCIS-Variante**	Größe: _____ mm				*8520/2*
Variante	□ Klassisch mit Komedonekrosen	□ Pleomorph □ mit Komedonekrosen			
	□ Extended/floride	□ ohne Komedonekrosen			

□ **Kombination aus DCIS und LN/LCIS**

Figure 11: Standardized form 2B – Pathology report on surgical specimen

Patient: _____ **Journal-Nr.:** _____

Invasives Karzinom ☐ **Vorhanden** ☐ **Nicht vorhanden**

Histologischer Typ:

☐ Invasiv NST	*8500/3*		
☐ Invasiv lobulär	*8520/3*	☐ Tubulär	*8211/3*
☐ Muzinös	*8480/3*	☐ Mischtyp: _____	
☐ Sonstiges primäres Mammakarzinom:		_____	

Begleitende in situ-Komponente: ☐ vorhanden ☐ nicht vorhanden

Histologischer Differenzierungsgrad: ☐ G1 ☐ G2 ☐ G3 ☐ Nicht zu beurteilen

☐ **Sonstiger maligner Mammatumor:** _____

Tumorgröße

Maximaler Durchmesser des invasiven Karzinoms: _____ mm ☐ Nicht zu beurteilen

Größe des assoziierten DCIS: _____ mm ☐ Nicht zu beurteilen
(bei extensiver intraduktaler Tumorkomponente)

Peritumorale Gefäßinvasion ☐ Vorhanden ☐ Nicht gesehen

Multifokalität ☐ Vorhanden ☐ Nicht vorhanden
Multizentrizität (nach Faverly et al, 1994) ☐ Vorhanden ☐ Nicht vorhanden

Resektionsränder

DCIS unmittelbar am Rand ☐ Ja ☐ Nein
Wenn ja, Angabe wo: _____

Invasives Karzinom unmittelbar am Rand ☐ Ja ☐ Nein
Wenn ja, Angabe wo: _____

Wenn nein; nächstgelegener Rand:
Angabe wo: _____
☐ DCIS ☐ Invasives Karzinom
Sicherheitsabstand: _____

☐ Nicht beurteilbar

Sentinel-Lymphknoten
Zahl untersuchte LK: _____
Zahl befallene Lymphknoten: _____
Maximale Tumorausdehnung: _____ mm

Non-Sentinel-Lymphknoten
Zahl untersuchte LK: _____
Zahl befallene Lymphknoten: _____
Maximale Tumorausdehnung: _____ mm

pTNM-Klassifikation: ___ pT ____ pN ____ (____ / ____) __ M ____ L ____ V _____ R _____

Hormonrezeptoren: ER: ____ % pos. Tumorzellen PR: ____ % pos. Tumorzellen

HER2: IHC-Score: _____
FISH: ☐ Amplifiziert ☐ Nicht amplifiziert
☐ Zweifelhaft (borderline)

Ki-67: ____ % pos. Tumorzellen

Kommentar/zusätzliche Informationen:

Datum: _____ **Unterschrift:** _____

Figure 12: Standardized form 2B – Pathology report on surgical specimen

Histological classification

The nomenclature and grouping of lesions of the breast is based on the WHO classification of tumors of the breast [118] and additionally on the "European Guidelines for Quality Assurance in Pathology in Mammography Screening" [420], [428] as well as recommendations from other internationally recognized guidelines [424], [425].

In the following, only selected points are presented which are of particular importance in terms of differential diagnosis, pathological-radiological correlation or clinical significance. In addition, individual terms of the current WHO classification are explained and commented on.

Normal findings and benign lesions (varia)

"Normal tissue" includes minor age-related changes such as fibrosis, lobular involution, microscopic dilatation of azini and ducts, and mild microcystic adenosis. These minimal changes are usually not sufficient to explain conspicuous clinical or radiological findings.

Fibrocystic mastopathy refers to changes associated with pronounced, macroscopically visible cyst formation, apocrine metaplasia and fibrosis.

This is distinguished from the **solitary cyst,** which is usually larger than 1 cm and is lined by a flat or apocrine epithelium.

Periductal mastitis (ductectasia, plasma cell mastitis) affects larger and mid-sized ducts, which are usually subareolar. The chronic inflammatory reaction in the vicinity of the ducts, which is often rich in plasma cells, may contain a large number of histiocytes and have a granulomatous aspect. It can be accompanied by pronounced periductal fibrosis. Calcifications are possible.

Benign epithelial proliferations

The **sclerosing adenosis** is rather cell-rich in the early phase. The fibre content increases with time. It is recommended that sclerosing adenosis is only mentioned in the documentation of the expert opinion if it is a prominent finding [420], [425]. Calcifications may be present.

Sclerosing adenosis must be distinguished from tubular carcinoma, microglandular adenosis and radial scarring by differential diagnosis.

If neighbouring lobules are affected, a mammographically or palpationally conspicuous tumour may develop, which is called an **adenosetumour**.

Adenoses with pronounced apocrine metaplasia, which occupies at least 50% of the adenosis, are documented as **apocrine adenoses**.

In contrast to sclerosing adenosis, **microglandular adenosis** does not show a lobulocentric organoid pattern. The round glandular structures are lined by a single-row epithelium without atypia. Myoepithelia are missing. However, an intact basal membrane can be shown.

The **radial scar** consists of a central, fibro-elastoid zone with ducts proliferating radially outwards. The lesion is rarely larger than 1 cm. The epithelium is bilayered or

has ductal hyperplasia. Tubules may be trapped, distorted and tilted in the central hyaline fibrosis.

The **complex sclerosing** lesion simulates an invasion. It has all the characteristics of the radial scar, but is larger than 1 cm and more irregularly structured, often with nodular proliferations in the periphery. The lesion may be accompanied by changes such as papillomas, apocrine metaplasia or sclerosing adenosis. The most important differential diagnosis for both radial sclerosing lesions is tubular carcinoma, in which myoepithelium and an intact basement membrane in the border of the tubules are missing.

The diagnosis of a radial scar or complex sclerosing lesion in the punch and vacuum biopsy usually means a classification of the alteration in the B3 category [420] and the indication for a surgical excision. Excluded from this are small radial scars, which are completely recorded in a vacuum biopsy and represent a histological random finding (without mammographic correlate). These do not require excision and can be classified as B2 according to the European guidelines for mammography screening.

The reason for the assignment to the B3 category is that atypical ductal hyperplasia and carcinomas (in situ and invasive) are relatively often detectable in the periphery of mammographically detected radial scars and complex sclerosing lesions, especially in lesions with a size > 0.6 cm and in women > 50 years [118]. DCIS or invasive carcinoma is present in 4-32% of excidates after punch biopsy diagnosis of a radial scar, especially if ADH has already been registered in the punch biopsy.

The changes, which are called **"ductal adenoma"**, have a variable appearance. Characteristic is a well defined benign glandular proliferation, which at least partially expands intraductally. There is overlap with other benign changes such as the papilloma or the complex sclerosing lesion, which is why such lesions are also called sclerosing papillomas.

Papillomas

The papilloma can occur solitary and multiple. The solitary papilloma is usually located centrally **(central papilloma),** in subareolar ducts, while the multiple papillomas are found more peripherally in the area of the terminal ductulo-lobular units (TDLE) **(peripheral papillomas)**. Peripheral papillomas are not only more common with common ductal hyperplasia (UDH), but also with atypical ductal hyperplasia (ADH), DCIS or invasive carcinoma. Therefore, the presence of this change requires extensive tissue embedding.

The term "papillomatosis" should be avoided, as it has been used for both UDH and multiple papillomas.

Papillomas with **atypical ductal hyperplasia (ADH) or ductal carcinoma in si-tu (DCIS), low-grade**, are characterized by the occurrence of a focal proliferation of uniform cells with the cytological and architectural features of a low-grade neoplasia [118] Myopithelia may be reduced. Epithelial proliferation usually does not express basal cytokeratins and is homogeneously ER-positive. In the past, both the extent and the proportion of atypical epithelial proliferation have been **used** as quantitative criteria to distinguish between a **papilloma with ADH** and a **DCIS in the papilloma**. On the one hand, atypical epithelial proliferations of less than 3 mm in size were classified as ADH [1635], on the other hand, atypical epithelial proliferations that occupy less than 30% or 90% of the papilloma cross-section [361], [1636]. Flocks above this were classified as DCIS in a papilloma.

For pragmatic reasons, the WHO expert group recommends the use of the size criterion (limit value 3 mm) to differentiate between a papilloma with ADH and a low-grade DCIS in the papilloma and also points out that in the case of epithelial proliferation with intermediate or high core degree, the diagnosis of a DCIS in the papilloma should be made independent of the extent [118].

The B classification of papillary lesions is based on the epithelial component. Since the epithelial changes within the papillary lesion can be heterogeneous and the punch biopsy usually does not completely capture the lesion, most papillary lesions fall into the B3 category (uncertain biological potential). This excludes small papillomas which have been extensively sampled and are presumably completely removed by the punch/vacuum biopsy. These can be classified as B2. A higher B category is appropriate if the epithelial proliferates have atypia that justify either the suspicion of malignancy (B4) or the reliable diagnosis of a DCIS in the papilloma or an intraductal papillary carcinoma (B5).

Myoepithelial lesions

While **myoepitheliosis** is a mostly multifocal, microscopic process, **adenomyoepitheliomas** impress as circumscribed nodal formations, which can be multilobulated. They are characterized by their biphasic cellular differentiation: The myoepithelial, partly clear cell compartment usually surrounds the tubular component with a luminal epithelial lining. There are essentially 3 different morphological variants: lobulated, tubular and spindle cell/myoid. The differential diagnosis includes not only papilloma and adenosis (each with a fluid transition) but also the tubular adenoma (sharply defined in contrast to the tubular variant of adenomyoepithelioma) and the invasive carcinoma (no biphasic cellular structure).

The majority of adenomyoepitheliomas behave benignly. However, they are considered to have a low malignant potential and should therefore be classified as B3 in the punch/vacuum biopsy and a complete excision is recommended.

Significantly less frequent than benign adenomyoepithelioma are malignant forms (malignant adenomyoepitheliomas) in which the epithelial and/or myoepithelial component may be degenerated.

Fibroepithelial tumours

Fibroadenomas are benign biphasic tumours that are mostly diagnosed in women of childbearing age. Epithelial (ductal) hyperplasia is not unusual in fibroadenoma. In any case, ADH or DCIS in a fibroadenoma must be reported separately. In this case, when punch biopsy is used for diagnosis, the B category is increased from B2 to B3, B4 or B5 depending on the degree and extent of the atypia.

The fibroadenoma must be distinguished from the **phylloides tumour**, which has a stroma richer in cells. For its dignity assessment on the resected tissue, a sufficient number of tissue sections is necessary (rule of thumb: 1 tissue block per cm tumor diameter) to representatively record the characteristic stromal features (cellularity, pleomorphy, mitotic activity, distribution pattern) and the relationship to the surrounding tissue.

In principle, fibroepithelial tumors that suggest the presence of a phylloidal tumor (PT) in the punch or vacuum biopsy due to their cell-rich stroma, the predominance of the stromal component or an increased mitotic activity of the stromal cells are classified

as B3. Cell-rich fibroepithelial lesions in which a phylloides tumour cannot be excluded should also be classified as B3.

Intraductal proliferative lesions

In the current WHO classification [118], this group includes various int-raductal proliferations that have a common point of origin: the terminal ductulo-lobular unit (TDLUs). They are associated with an increased risk for the development of invasive breast carcinoma, although to a significantly different extent.

The **common ductal hyperplasia** (UDH) comprises all cases of intraluminal epithelial proliferation without atypia. A colorful, flowing cell picture is common. If secondary lumina are formed, they are slit-shaped, rounded and irregularly shaped with tangential alignment of the nuclei in the limiting epithelial cells. One of the most important indicators of UDH is the presence of a mixture of at least 2 cell types (luminal and basal/myoepithelial and/or metaplastic apocrine cells). It is associated with only a very slightly increased risk (1.5-fold) of developing breast cancer. It is usually accompanied by diffuse or mosaic-like expression of the basal cytokeratins (including CK5, CK14).

The term **flat epithelial atypia** (FEA) was introduced into the WHO classification in 2003. This rather descriptive category includes lesions that are neoplastic by current standards and are also known as "clinging carcinoma" of the monomorphic type, atypical cystic lobules, atypical lobules type A, columnar cell metaplasia with atypia or columnar cell hyperplasia with atypia. Characteristic is the replacement of the original epithelium by a single layer of a slightly atypical epithelium, which often shows apical "snouts" or 3-5 layers of a monotonously atypical cell population of prismatic cells or columnar cells. The cell nuclei are round, relatively uniform and contain small nucleoli. Micropapillae or more complex structures like arcades are missing. The affected extended lobules often contain secreted material and microcalcifications.

If an FEA is diagnosed in the punch or vacuum biopsy, this change must be assigned to category B3 (see also Chapter 5.3.3 Risk lesions).

As described above, FEA is usually a columnar cell alteration with or without hyperplasia, with low to moderate cytological atypia. This should be distinguished from **columnar cell hyperplasia with architectural atypia**, in which micropapillae or bridges are preferably formed, with only slight cytological atypia. These changes are now classified as ADH or low-grade DCIS depending on the type and extent of the cytological and structural atypias.

It should also be noted that columnar cell proliferations are homogeneously ER-positive and usually CK5-negative. Immunohistochemical imaging of basal cytokeratins is often not helpful in the differential diagnostic differentiation between columnar cell hyperplasia without and with atypia, since the characteristic mosaic-like reaction pattern of UDH in columnar cell hyperplasia without atypia may be absent.

Atypical ductal hyperplasia (ADH) is also considered neoplastic intraductal epithelial proliferation. It is characterized by an intraductal proliferation of evenly distributed, uniform cells which can form micropapillae, arches, solid or cribriform patterns [118]. Roundish, rigid secondary lumina appear together with irregularly shaped ones. Cytologically, the cells of an ADH thus correspond to a low-grade DCIS. However, in an ADH the characteristic cells mix with non-uniform cells within a TDLU (s) or only a limited number of corridors of a TDLU are colonized.

In individual cases, the differentiation between ADH and low-grade DCIS can be difficult. Immunohistochemical imaging of basal cytokeratins does not help in

differential diagnosis, since the proliferating epithelia in both lesions do not express them.

Nowadays, quantitative criteria are primarily used to distinguish ADH from low-grade DCIS. The most commonly used quantitative criteria are those that are used to diagnose a low-grade DCIS when at least two duct structures are completely and homogeneously colonized by neoplastic epithelial proliferation or the lesion is > 2 mm. The expert group of the current WHO classification was not in a position to favor either of the two criteria [118]. It was rather pointed out that these quantitative criteria are primarily helpful to avoid overtherapy of very small neoplastic lesions by not diagnosing these lesions as DCIS. Therefore, a conservative approach is recommended in the differential diagnosis between ADH and low-grade DCIS, especially in punch and vacuum biopsies. The diagnosis of ADH or an atypical intraductal proliferative lesion should be sufficient to induce surgical excision of the change. Depending on the degree of atypia and the extent of the lesion, the result is a B3 or B4 category.

The final diagnostic classification is then made on the surgical specimen (see also Chapter 5.3.3 Risk lesions).

Lobular neoplasia (LN)

According to the current WHO classification [118], the term lobular neoplasia (LN) is used to describe the entire spectrum of atypical epithelial proliferations originating from TDLUs and characterized by the proliferation of mostly small and non-cohesive cells - with or without pagetoid involvement of the terminal ducts. The terms atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) reflect the extent of the change. A classic LCIS is diagnosed when more than half of the azini of a TDLU are colonized and dilated by the characteristic neoplastic proliferation. A less pronounced infestation corresponds to an ALH. The determination of the extension and thus the differentiation between ALH and LCIS is usually only possible on surgical specimens but not on punch biopsies.

As a special feature of the LN, its frequent multicentric (46-85 %) and bilateral occurrence (30-67 %) must be noted. In principle, the LN is, according to current opinion, an indicator lesion for an increased carcinoma risk. The relative risk of a patient is bilaterally increased by a factor of 4-12 after the diagnosis of an LN, whereas the risk after the diagnosis of ALH is half as high as after an LCIS.

According to the WHO, different variants of the LCIS are increasingly frequently diagnosed due to their association with microcalcification:

Classical LCIS with comedonecroses

Pleomorphic LCIS with/without apocrine properties and comedonecroses

Even though individual reports suggest that these variants may have a different course than the classic LCIS, the clinical significance and adequate therapy is not yet clear [118].

If a classic LN is diagnosed in the punch or vacuum biopsy as part of mammography screening, this corresponds to a B3 category. If it is not possible to decide on the punch or vacuum biopsy material whether small cell epithelial proliferation in TDLUs and/or ducts should be classified as LN or DCIS, a higher B category: B4 or B5 is recommended. The variants of the LN (especially pleomorphic variant and classical LN with comedonecroses) are classified as B5a. With regard to the management of the LN, see also Chapter 5.3.3 Risk lesions.

Ductal carcinoma in situ (DCIS)

In the current WHO classification, ductal carcinoma in situ (DCIS) is defined as a neoplastic intraductal lesion characterized by subtle to severe cellular atypia and an inherent but not necessarily obligatory tendency to progression to invasive carcinoma [118]. In small low-grade or non-high-grade DCIS a differentiation from ADH is necessary (see above).

Artefacts at the preparation margin, the retrograde expansion of a DCIS into terminal ductulo-lobular units (so-called lobular carcinoma) or a ductal sclerosis with inclusion of atypical epithelial complexes must not be misinterpreted as microinvasion (pseudoinvasion). The preparation of additional incisions and the use of immunohistochemistry to visualize the epithelial-stroma boundary often allow clarification of the diagnosis. Markers for the detection of myoepithelia (especially p63) and basement membrane components (e.g. type IV collagen) have proven to be particularly helpful.

With regard to clinical, risk and management aspects see Chapter 5.3.2 DCIS

Grading and classification

(see also Chapter 5.5.2.6)

For correlation with imaging and further therapy planning, the grading of DCIS should be performed not only on the excidate but also on the punch or vacuum biopsy material. However, grading may vary between punch/vacuum biopsy and the final surgical preparation due to intratumoral heterogeneity.

The core grading should follow the recommendations of the "Consensus Conference on the Classification of DCIS in Philadelphia, 1997" [453] (see Table 15).

Table 59: Nuklear Grading of DCIS [455]

Core degree	Core form	Core size	Chromatin	Nucleoli	Mitoses
1 Low	monotone and isomorphic	1.5-2 Erythrocyte or gangetic epithelium nucleus diameter	usually diffuse, fine grained	infrequent	rarely
2 Intermediary	neither core degree 1 nor 3				
3 High	clearly pleomorphic	usually > 2.5 erythrocyte or gangetic epithelial cell nucleus diameter	usually vesicular or irregular	prominent, often multiple	possibly conspicuous

The grading is based on the WHO [118] grading scheme (see Table 16).

Table 60: WHO grading of DCIS [118]

Degree	Cytology/nuclear degree (KG)	Necroses	Calcifications	Architecture
low grade	small, monomorphic cells, low nucleus degree (KG 1) with uniform nuclei, regular chromatin pattern, inconspicuous nucleols	-/+	often psammomatous	arches, cribriform, solid and/or micropapillary
intermediate degrees	low to moderate cell size and shape variability, intermediate nucleus degree (KG 2) with variable coarse chromatin, prominent nucleols	-/+	psammomatic or amorphous	solid, cribriform, micropapillary
high grade	high-grade cell atypes, high nucleus degree (KG 3) with pleomorphic nuclei, coarse, clumped chromatin and prominent nucleoli	-/+	amorphous	a cell layer, micropapillary, cribriform or solid

Determination of hormone receptor expression

The evaluation and interpretation of immunohistochemistry is based on the guidelines for invasive breast cancer (see below).

Invasive breast carcinomas

Histological typing

(see also Statement 4.26.)

For all invasive breast carcinomas a histological typing according to the current WHO classification must be performed (see Table 17 [118]). In the case of preoperative diagnostics, this should be done on the punch or vacuum biopsy material. This serves both for correlation with imaging and for therapy planning. As a result of intratumoral heterogeneity there can rarely be deviations between the punch/vacuum biopsy and

the surgical specimen. The findings on the surgical specimen are decisive for the final assignment of the histological type. Some special histological types take a demonstrably more favourable course. These include the tubular, invasive cribriform, mucinous and adenoid-cystic carcinoma. Some authors also include the well differentiated mucinous, tubulo-lobular and papillary carcinoma in this group. In addition to these usually ER-positive carcinomas, certain carcinomas also show a favourable course, which are triple-negative, i.e. ER-, PR- and HER2-negative. These include the adenoid-cystic carcinoma and the low grade fibromatosis-like metaplastic carcinoma. These carcinomas usually grow locally aggressively and have a low tendency to (systemic) metastasis.

Table 61: WHO classification of invasive breast carcinomas [118]

Histological type	ICD-O Code
Invasive carcinoma, no specific type (NST)	8500/3
Pleomorphic carcinoma	8022/3
Carcinoma with osteoclast-like giant cells	8035/3
Carcinoma with chorionic carcinoma-like features	
Carcinoma with melanotic characteristics	
Invasive lobular carcinoma	8520/3
Classical lobular carcinoma	
Solid lobular carcinoma	
Alveolar lobular carcinoma	
Pleomorphic lobular carcinoma	
Tubulolobular carcinoma	
Mixed lobular carcinoma	
Tubular carcinoma	8211/3
Cribriform carcinoma	8201/3

Histological type	ICD-O Code
Mucinous carcinoma	8480/3
Carcinoma with medullary properties	
Medullary carcinoma	8510/3
Atypical medullary carcinoma	8513/3
Invasive carcinoma NST with medullary properties	8500/3
Carcinoma with apocrine differentiation	#
Carcinoma with sigmoid ring cell differentiation	#
Invasive micropapillary carcinoma	8507/3*
Metaplastic carcinoma, no specific type	8575/3
Low-grade adenosquamous carcinoma	8570/3
Fibromatosis-like metaplastic carcinoma	8572/3
Squamous cell carcinoma	8070/3
Spindle cell carcinoma	8032/3
Metaplastic carcinoma with mesenchymal differentiation	
Chondroid differentiation	8571/3
Osseous differentiation	8571/3
Other mesenchymal differentiation	8575/3
Mixed metaplastic carcinoma	8575/3
myoepithelial carcinoma	8982/3
Rare types:	
Carcinomas with neuroendocrine properties:	
Neuroendocrine tumor, well differentiated	8246/3
Neuroendocrine carcinoma, poorly differentiated (small cell carcinoma)	8041/3

Histological type	ICD-O Code
Carcinoma with neuroendocrine differentiation	8574/3
Secretory carcinoma	8502/3
Invasive papillary carcinoma	8503/3
Azinus cell carcinoma	8550/3
mucoepidermoid carcinoma	8430/3
Polymorphic carcinoma	8525/3
Oncocytic carcinoma	8290/3
Lipid-rich carcinoma	8314/3
Glycogen-rich clear cell carcinoma	8315/3
Sebaceous carcinoma (carcinoma of the sebaceous glands)	8410/3
adenoid-cystic carcinoma	8200/3
Adenomyoepithelioma with carcinoma	8983/3*
Encapsulated papillary carcinoma with invasion	8504/3
Solid papillary carcinoma, invasive	8509/3
ICD-O= International Classification of Diseases for Oncology # ICD-O coding is done according to the primary invasive type *new ICD-O code (approved by the IARC/WHO Committee on ICD-O)	

Prognostically relevant is the differentiation of carcinomas of a "pure" special type from mixed types.

According to the WHO classification, a carcinoma is classified as a "pure" type if at least 90% of the tumour shows the characteristic pattern (e.g. tubular carcinoma). A mixed-type carcinoma is defined as a carcinoma where the proportion of a particular type exceeds 50% but 10-49% of the tumour has no specialised pattern; i.e. mixed invasive carcinoma NST (no particular type) and particular type (e.g. mucinous, lobular).

In the following, only certain histological types will be explained in more detail, which are either particularly frequent or for which strict adherence to diagnostic criteria is of particular relevance for correct typing, as this determines the estimation of the prognosis (see also [1637]).

Invasive carcinoma, no special type (NST) is by far the most common type of tumour, accounting for 50-80 % of all tumours. It comprises a heterogeneous group of tumours that do not have sufficient characteristics to be assigned to a specific histological type (e.g. lobular or tubular carcinoma). In order to be classified as invasive carcinoma NST, a tumour must, after careful examination of representative sections, show a non-specialised pattern in more than 50 % of its mass (to distinguish "pure" invasive ductal carcinoma from mixed forms, see also above).

The prognosis of invasive carcinoma NST is equal or slightly worse compared to the prognosis of the total group of all breast cancers. The prognosis is mainly influenced by the established parameters: nodal status, tumor size, grading, etc. Therapeutically relevant is the steroid hormone receptor expression in about 70-80% of invasive ductal carcinomas. HER2 overexpression or amplification is present in about 15 % of cases.

Invasive lobular carcinomas account for about 5-15% of invasive breast carcinomas. The classic appearance of invasive lobular carcinoma is mainly characterized by its small cell size, its dissociated infiltrating growth. From the classic type, different morphological variants are distinguished (solid, alveolar, pleomorphic, tubulo-lobular and mixed) with a partly better (alveolar and tubulo-lobular variants), partly worse prognosis (solid and pleomorphic). The classic form of invasive lobular carcinoma is in most cases associated with lobular neoplasia, but occasionally also with DCIS or carcinoma in situ with ductal and lobular phenotype.

A comparison of the long-term prognosis of ILC and NST carcinomas shows a lower risk of progression of ILC in the first years, but an overlap of the survival curves after about 10 years with a worse long-term survival of ILC. However, invasive lobular carcinomas are characterized by multifocality (9-31%), bilateralism (5-19%) and a different pattern of metastasis. Bones, meninges, gastrointestinal tract and peritoneum are more frequently affected by distant metastases. Lung metastases, on the other hand, are observed less frequently than in the ductal type.

The invasive lobular carcinomas usually express steroid hormone receptors. Among the variants, the ER-positivity rate is highest for the alveolar variant and lowest for the pleomorphic variant. HER2 overexpression or amplification is very rare in classic invasive lobular carcinoma. The pleomorphic variant (G3) is more likely to show HER2 overexpression and gene amplification.

The **tubular carcinoma** is characterized by the presence of neoplastic rounded-oval tubules with a single-row cubic epithelial lining in a dense collagenous connective tissue. The tubules may be angled or folded with a drop-like shape. The epithelium often exhibits "apical snouts". The nuclei are slightly hyperchromatic and should have only small inconspicuous nucleoli. Mitoses are rare. The diagnosis of a (pure) tubular carcinoma requires that the tumour consists of > 90% tubular structures with the described structural and cytological criteria. The (pure) tubular carcinoma accounts for about 2% of all breast carcinomas, but seems to be found more frequently with subtle radiological diagnosis. Its proportion of tumours less than 1 cm in diameter is at least 8%, in pure screening populations even 8-27%.

Strict adherence to the above criteria is crucial for the assessment of the prognosis. Pure tubular carcinoma has an excellent prognosis. The disease-free 10-year survival rate is well over 90%. Even the rare presence of axillary lymph node metastases (6-19%) has no influence on the survival rate.

The tubular carcinomas are usually ER- and PR-positive and HER2-negative.

In **mucinous carcinomas**, islands of relatively uniform cells lie in lakes of extracellular mucus. The classification as (pure) mucinous carcinoma requires, as with the other

special types, that the characteristic morphology is developed in > 90% of the tumour. This applies to max. 2% of invasive breast carcinomas. Here, too, strict adherence to diagnostic criteria serves the purpose of identifying tumours with a favourable prognosis, especially those occurring in older patients. The 10-year survival rate is 80-100 %.

Mucinous carcinomas are usually ER- and PR-positive. HER2 overexpression or gene amplification is very unusual.

In the current WHO classification, it is recommended to leave the terms "medullary carcinoma", "atypical medullary carcinoma" and "invasive carcinoma NST with medullary characteristics" and instead to group tumours with all or some of the following characteristics in the category of "**carcinomas with medullary characteristics**": sharp limitation, synzytial growth pattern, high-grade nuclei and prominent lymphoid cell infiltrate. The background is the insufficient reproducibility of the criteria for distinguishing the classic medullary carcinoma, which accounts for less than 1% of all breast carcinomas, from the other tumours with medullary characteristics. However, a superordinate ICD-O code is missing so far, so that a tumour has to be assigned to one of the older categories for ICD-O coding after all.

Patients diagnosed with a carcinoma with medullary characteristics are on average younger (45-52 years) than those diagnosed with other invasive carcinomas. As these tumours are usually relatively well-defined, low stroma tumours, they can be clinically and imaging benign. Carcinomas of this group are mostly ER-, PgR- and HER2-negative (triple-negative). Basal cytokeratins (CK5/6, CK14), sm-actin, EGFR1, P-cadherin, p53 and caveolin-1 are variably expressed.

The majority of breast carcinomas with medullary characteristics show a basal-like gene expression profile. A common feature is also genomic instability associated with p53 mutations in about 2/3 of the tumors. Remarkably, patients with germline mutations of the BRCA1 gene are more likely to have carcinomas with medullary characteristics.

In the findings report, therefore, the possibility of a hereditary background should be pointed out in the presence of a triple-negative invasive G3 carcinoma with medullary characteristics (see Statement 3.16.).

The classic medullary carcinoma has a more favourable prognosis than a low differentiated NST carcinoma. The relatively favourable prognosis of these tumours is attributed to the presence of the prominent lympho-plasmacellular infiltrate or, at the molecular level, to a B-cell/plasmacell metagen. However, when the overall group of BRCA1-associated breast carcinomas is considered, they show a similar prognosis to sporadic breast carcinomas.

Histological grading

(see also statement 4.27.)

For all invasive breast carcinomas a grading has to be performed [118]. In the case of preoperative diagnostics, this should already be done on the punch or vacuum biopsy material.

Table 62: Criteria for grading breast cancer [510]

Features	Criteria	Score values
Tubule training	> 75 %	1
	10–75 %	2

Features	Criteria	Score values	
	< 10	3	
Nuclear polymorphism	Low medium strong	1 2 3	
Mitosis rate*	0-5/10 HPF 6-11/10 HPF > 12/10 HPF	1 2 3	
	Total score	3-9	
Total score	Degree of malignancy	G Group	Definition
3, 4, 5 6, 7 8, 9	Low moderate high	G1 G2 G3	well differentiated moderately differentiated poorly differentiated
*HPF = high power field; consideration of the individual visual field size for the assignment of score values according to Elston and Ellis [510]. The criteria given here apply to a field of view diameter of 0.45 mm corresponding to a simple light microscope with field number 18 without large field tube.			

The histological grading is performed after a modification of the grading proposed by Bloom and Richardson according to Elston and Ellis [510]. Histological grading should generally be performed on primarily fixed and paraffin-embedded material. The histo- and cytological criteria that are assessed semi-quantitatively are tubule formation, nuclear pleomorphy and mitosis rate (see Table 18).

When quantifying the mitosis rate, the individual visual field size must be taken into account in order to avoid blurring (see Table 19). It is determined in 10 consecutive high power fields (= 400-fold magnification in the microscope) in the area of the highest mitotic activity of the tumour. Only distinct mitotic figures are counted.

Table 63: Assignment of scores for mitotic count as a function of field diameter [510]

Field of view diameter (mm)	Mitosis number*		
	score 1	Score 2	Score 3
0,40-0,41	≤ 4	5-9	≥ 10

Field of view diameter (mm)	Mitosis number*		
	score 1	Score 2	Score 3
0,42-0,43	≤ 5	6-10	≥ 11
0,44-0,45	≤ 5	6-11	≥ 12
0,46-0,47	≤ 6	7-12	≥ 13
0,48-0,49	≤ 6	7-13	≥ 14
0,50-0,51	≤ 7	8-14	≥ 15
0,52	≤ 7	8-15	≥ 16
0,53-0,54	≤ 8	9-16	≥ 17
0,55-0,56	≤ 8	9-17	≥ 18
0,57	≤ 9	10-18	≥ 19
0,58-0,59	≤ 9	10-19	≥ 20
0,60	≤ 10	11-20	≥ 21
0,61	≤ 10	11-21	≥ 22
0,62-0,63	≤ 11	12-22	≥ 23
0,64	≤ 11	12-23	≥ 24
0,65-0,66	≤ 12	13-24	≥ 25
0,67	≤ 12	13-25	≥ 26
0,68	≤ 13	14-26	≥ 27

Field of view diameter (mm)	Mitosis number*		
	score 1	Score 2	Score 3
0,69	≤ 13	14-27	≥ 28
* in 10 fields of vision			

If the detected tumor area in the punch and vacuum biopsies is less than 10 HPFs, the mitosis rate can be approximately determined by counting the total number of mitoses in the available HPFs. The number obtained is divided by the number of HPFs evaluated and multiplied by a factor of 10.

An overview of the evaluation criteria with image examples for the assessment of nuclear pleomorphism and a table for the allocation of the mitosis score in relation to the individual visual field size is provided by a poster of the NHS Cancer Screening Programme, UK (Appendix I in [1638]).

Nottingham-Prognose-Index

In addition, the Nottingham prognosis index (see Table 20) for invasive carcinomas is given here, which includes tumor size, grading, and lymph node status and is considered to have a high prognostic value [1639], [1640], [1641]. Its specification is optional.

Table 64: Nottingham Prognostic Index [1642]

Feature	Criterion	Score value
Grading (Elston, CW et al. 1991)	G1	1
	G2	2
	G3	3
Lymph node status	pN0	1
	1-3 LK positive	2
	≥ 4 LK positive	3
Index value = size (in cm) x 0.2 + score value grading + score value LK status		
Index value	Forecast	15-year survival rate
≤ 3,4	Well	80 %
3,41–5,40	intermediary	42 %
> 5,40	bad	13%

Special additional examinations

(see also Statements 4.28. with text)

In the case of invasive breast cancer, the estrogen and progesterone receptor status and the HER2 status must be determined in the primary diagnosis, preferably already on the punch biopsies [185], [265], [421], [426].

Hormone receptor status: allred score and immunoreactive score

For the immunohistochemical determination of the estrogen and progesterone receptor status, the percentage of positive tumor cell nuclei and the average staining intensity must be indicated in each case. The evaluation as ER- or PR-positive requires at least 1% positive tumor cell nuclei.

In addition, scores can be given that take into account the percentage of positive cells and the staining intensity: Allred-Score [479] or the immunoreactive score (IRS) according to Remmele and Stegner [480]. Their calculation bases are shown in Table 21.

Table 65: Immunohistochemistry scores for hormone receptor assessment

Percentage of positive cell nuclei (PP)		dyeing intensity (FI)		Score
Immunoreactive score (IRS) [480]				
No positive nuclei < 10 % positive Kerne 10-50 % positive cores 51-80 % positive cores > 80 % positive cores	0 points 1 point 2 points 3 points 4 points	no colour reaction weak dye reaction moderate dye reaction strong colouring reaction	0 points 1 point 2 points	PP x FI= IRS (0-12 points)
Allred-Score (AS) [479]				
No positive nuclei < 1 % positive Kerne 1-10 % positive cores 11-33 % positive cores 34-66 % positive cores > 66 % positive cores	0 points 1 point 2 points 3 points 4 points 5 points	no colour reaction weak dye reaction moderate dye reaction strong colouring reaction	0 points 1 point 2 points 3 points	PP + FI= AS (0-8 points)

Further special examinations

Fresh material for additional molecular investigations or for tissue agerivation in a tumour bank can only be taken if it is ensured that sufficient and representative material is available for an adequate histopathological examination. The removal of fresh material from surgical specimens for such examinations is exclusively under the control of the pathologist (see Statement 4.24. and text).

Special aspects in the processing and reporting of surgical specimens after primary (neoadjuvant) chemotherapy

The pathomorphological examination of surgical preparations after neoadjuvant chemotherapy (NACT) provides objective information on the effect of the therapy and the prognosis. The recommendations of an international working group, which emerged from the cooperation of the Breast International Group (BIG) and the North American Breast Cancer Group (NABCG) [1643], provide support for the standardization of the pathological processing and characterization of tumor residuals.

For histological diagnosis the following **information** should be sent from the clinic to the pathologist:

The information that a NACT has occurred

Whether this was done in a study and whether a specific grading system is recommended in the study for the response to therapy

Results of a pre-therapeutic punch biopsy, especially if it was performed externally

Lymph node status pre-NACT and method of determination

The localization of the tumor/tumor bed, whether a clip marker was used

The clinically determined size of the tumor pretherapeutic and posttherapeutic

The processing of the surgical specimens is essentially analogous to the procedure for primary surgical therapy (see sections 4.5.6-4.5.8). Special features result from the varying degrees of tumor regression during cutting and the assessment of the size of the residual tumor and the resection margins.

In the case of a **tumour that can be clearly delimited macroscopically**, the embedding is carried out in the same way as for palpable tumours in primary surgical therapy.

If **macroscopically no clear tumor focus** or tumor bed can be delimited, a systematic examination of the former tumor bed should be performed to document the response to preoperative chemotherapy. For this purpose, the extent and location/quadrant of the original tumor should be clinically indicated or marked. If the tumor bed is then recognizable as a blurred fibrosis area in this clinically indicated area, the extent of the cut is based on the clinically indicated preoperative tumor size. At least one cross-section of the largest tumour diameter should be embedded, taking into account the resection margins (as a guideline, at least one block per cm of the pretherapeutic tumour size). In addition, fibrosed areas suspected of being tumour-suspicious should be examined from the vicinity of the tumour bed and from the area of the resection edges.

If macroscopically **no clear tumor bed** can be identified even when taking into account the clinical information, it is advisable to embed smaller diagnostic excidates primarily completely. In the case of larger resectates, an orienting cut from fibrosed areas should

be made first. The extent of the cutting depends on the pre-therapeutic tumor size and the size of the preparation. As a rule of thumb it is recommended to take at least one block per 2 cm of the largest preparation diameter as well as samples from the resection margins (at least one block per dimension). In the case of microscopic detection of residual tumours or inflammatory/regressive changes, tissue from this area should then be examined in an expanded section, taking into account the resection margins, and if necessary the entire former tumour bed.

In the case of a pronounced resorptive inflammatory reaction, the differentiation between regressively altered tumor cells and histiocytes can be difficult. This is where immunohistological examinations with pancytokeratin antibodies help.

In order to be able to diagnose pathological complete remission (pCR) with sufficient certainty, it is recommended to embed one complete cross-section of the tumour bed per cm of the former tumour size or, in the case of very large tumours, 5 representative blocks of a cross-section per 1-2 cm of the former tumour size (max. 25 blocks) [1643].

In the pTNM classification after primary systemic therapy the prefix y should be prefixed [429].

The determination of residual tumor size post-NACT is often difficult. Tumor residuals can be scattered as small tumor foci in the area of the former tumor bed. Since the 7th edition of the TNM Classification (AJCC/UICC), the ypT classification should be based on the largest coherent tumor focus without inclusion of fibrosis areas. If several tumor foci are present, this is indicated by the suffix "m" (e.g. ypT1b(m)). However, it is also pointed out by the BIG-NABCG working group that this recommendation of the AJCC/UICC leads to a systematic artifactual downgrading of those tumors that respond to therapy with tumor thinning and multifocal scattered tumor residuals. In the view of the experts of the BIG-NABCG working group, the largest extension of tumor residuals (including possible intermediate fibrosis areas) is a better indicator of tumor response than the largest diameter of a contiguous tumor focus and should therefore also be reported in the findings report.

Various histopathological classification systems are under discussion for the graduation of tumor regression. The system recommended by the BIG-NABCG working group for quantification of the residual tumor burden, the Residual Cancer Burden (RCB) System, takes into account not only the maximum tumor extent (2-dimensional) but also the tumor cellularity as well as the DCIS fraction and the number and maximum size of lymph node metastases [1644]. A calculator for the calculation of the 4-stage RCB system is freely available on the Internet on the website of the MD Anderson Cancer Center: http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

In various studies, the CPS+EG score [1645], [1646], [1647] has also proven to be prognostically relevant in the meantime. This takes into account the clinical stage (according to AJCC) before NACT (CS), the post-therapeutic pathological stage (PS) as well as the oestrogen receptor status (E) and the core grading (G) at the pre-therapeutic biopsy (see Table 22). The level of the resulting score correlates with the disease-specific survival of patients after neoadjuvant therapy. It is therefore recommended to document the pre- and post-therapeutic relevant pathomorphological parameters in the findings report.

Table 66: CPS+EG-Score [1648]

Clinical stage (pre-NACT; AJCC)		Pathological stage (post-NACT; AJCC)		Tumor marker (biopsy pre-NACT)	
I	0	0	0	ER-negative*	1
IIA	0	I	0	Core degree 3	1
IIB	1	IIA	1		
IIIA	1	IIB	1		
IIIB	2	IIIA	1		
IIIC	2	IIIB	1		
		IIIC	2		

CPS+EG score (0-6) = score values for pre-therapeutic clinical stage (CS) + pathological stage post-NACT (PS) + ER status (E) + core degree (G)

*ER-positive: >10% ER-positive tumor cells

11.3. TNM and pTNM Classification and UICC Staging

(8th ed. [1649], [1650],[1651], [1652], [1653], [1654])

Rules for classification

The classification only applies to carcinomas of both the male and female breast.

In case of multiple simultaneous breast tumours, the tumour with the highest T-category is classified. Simultaneous bilateral breast carcinomas should be classified separately in order to allow for the possible assignment of tumors to different histological types.

TNM: Clinical classification

T-primary tumor

Table 67: T-primary tumor

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ

TX	Primary tumor cannot be assessed
Tis (Paget)	M. Paget's nipple without detectable tumor

Note:

Tis (Paget) is not combined with an invasive carcinoma and/or DCIS or LCIS Breast carcinomas combined with Paget's disease are classified according to the size and characteristics of the carcinoma in the mammary parenchyma, but the presence of Paget's disease of the nipple should be noted.

The AJCC does not include Tis of type LCIS [517].

Table 68:

T1	Tumour maximum 2 cm in the largest diameter
T1mi	Microinvasion 0,1 cm or less in the largest diameter
T1a	exceeding 0,1 cm up to a maximum of 0,5 cm in the largest diameter
T1b	greater than 0,5 cm to a maximum of 1 cm in the largest diameter
T1c	greater than 1 cm to a maximum of 2 cm in the largest diameter
T2	Tumour larger than 2 cm up to a maximum of 5 cm in the largest diameter
T3	Tumour larger than 5 cm in the largest diameter
T4	Tumour of any size with direct extension to the chest wall or skin, as described under T4a-T4d
T4a	Extension to chest wall (ribs, intercostal muscles, anterior serratus muscle, but not pectoralis muscles)
T4b	Oedema (including 'peau d'orange') or ulceration of the skin of the breast or satellite nodules of the skin of the same breast
T4c	Criteria 4a and 4b
T4d	Inflammatory (inflammatory) carcinoma

Remarks:

Microinvasion is understood to be the penetration of carcinoma cells beyond the basement membrane into the adjacent tissue. No point of invasion may measure more than 0.1 cm in the largest extension. If multiple microinvasion foci are present, only

the extent of the largest foci is used for classification. A sum of the size of all micro-invasion foci must not be calculated. The presence of multiple micro-invasion foci should be recorded in the same way as for multiple larger carcinomas (e.g. pT1mi (m), pT2 (m)). The size indications of the T-classification are applied.

The inflammatory carcinoma of the breast is characterized by a diffuse brown induration of the skin with an erysipelas-like border, usually without a palpable tumor mass underneath. If the skin biopsy is negative and no localised measurable primary tumour is found, this corresponds to clinical inflammatory carcinoma (T4d), in the pathological classification pTX.

Retraction of the skin or nipple or other skin lesions other than those listed under T4b and T4d may occur in T1, T2 or T3 without affecting the T classification.

N - Regional lymph nodes

Regional lymph nodes are ipsilateral axillary (including intramammary and interpektoral "Rotter lymph nodes"), infraclavicular, supraclavicular and internal mammary artery lymph nodes. All other lymph nodes are classified as distant metastases.

Table 69: Regional lymph nodes are ipsilateral axillary (including intramammary and interpektoral "Rotter lymph nodes"), infraclavicular, supraclavicular and internal mammary artery lymph nodes. All other lymph nodes are classified as distant metastases.

Nx	Regional lymph nodes cannot be assessed (e.g. bioptically removed before clinical classification)
N0	No regional lymph node metastases
N1	Metastasis(s) in mobile ipsilateral axillary lymph nodes of level I and II
N2	Metastasis(s) in ipsilateral axillary lymph nodes of level I and II, fixed to each other or to other structures or in clinically recognizable* ipsilateral lymph nodes along the internal mammary artery in the absence of clinically recognizable axillary lymph node metastases
N2a	Metastasis(s) in ipsilateral axillary lymph nodes, fixed among themselves or to other structures
N2b	Metastasis(s) in clinically recognizable ipsilateral lymph nodes along the internal mammary artery in the absence of clinically recognizable axillary lymph node metastases
N3	Metastasis(s) in ipsilateral infraclavicular lymph nodes (level III) with or without involvement of level I and II axillary lymph nodes or in clinically recognizable ipsilateral lymph nodes along the internal mammary artery in the presence of level I and II axillary lymph node metastases or metastasis(s) in ipsilateral supraclavicular lymph nodes with or without involvement of the axillary lymph nodes or lymph nodes along the internal mammary artery
N3a	Metastasis(s) in ipsilateral infraclavicular lymph nodes

Nx	Regional lymph nodes cannot be assessed (e.g. bioptically removed before clinical classification)
N3b	Metastasis(s) in ipsilateral lymph nodes along the A. mammaria interna in the presence of axillary lymph node metastases
N3c	Metastasis(s) in ipsilateral supraclavicular lymph nodes

Comments:

Clinically detectable metastases are those diagnosed by clinical examination or by imaging techniques (excluding lymph scintigraphy) and which are highly suspect of malignancy or a suspected pathological metastasis detected by fine needle aspiration and cytological examination. Confirmation of a "clinically detectable" metastasis by a fine needle biopsy or a punch biopsy with cytological or histological examination, but without excisional bioptic confirmation, is marked with the suffix "f" for clinical classification, e.g. cN3a(f) (supplement punch biopsy: C. Wittekind, personal communication).

An excisional biopsy of a lymph node or a biopsy of a sentinel lymph node in the absence of a pT category (e.g. prior to neoadjuvant chemotherapy) is clinically classified, i.e. cN1. A pathological classification (pN) in the excision of a sentinel lymph node can only be used in the presence of a pT category.

M remote metastases

Table 70: M remote metastases

M0	No remote metastases
M1	Remote metastases

pTNM: Pathological Classification

pT primary tumor

The pathological classification requires the examination of the primary tumor without macroscopically recognizable tumor at the resection margins. A case can be classified according to pT if only histological tumor is detected at the resection margins.

The pT categories correspond to the T categories. In the pT classification, only the invasive component is measured to determine the tumor size.

pN-regional lymph nodes

The pN classification requires the resection and examination of at least the lower axillary lymph nodes (level I). Usually 6 or more lymph nodes are histologically examined.

If the lymph nodes examined are tumour-free, but the number of lymph nodes normally examined is not reached, pN0 should be classified and the number of lymph nodes examined should be added in brackets

pNX Regional lymph nodes cannot be assessed (not removed for examination or removed earlier)

pN0 No regional lymph node metastases

Note:

Cases with isolated tumor cells (ITC) in regional lymph nodes are classified as pN0. Isolated tumor cells are defined as single tumor cells or small clusters of cells not larger than 0.2 mm in the largest dimension, which can usually be detected by immunohistochemical or molecular methods and sometimes verified in HE staining. As an additional criterion it has been proposed to include a cluster of less than 200 cells (in a histological section). Lymph nodes containing only isolated tumor cells are not considered in the counting of lymph node metastases. However, they should be included in the counting of the total lymph nodes examined.

Table 71: Cases with isolated tumor cells (ITC) in regional lymph nodes are classified as pN0. Isolated tumor cells are defined as single tumor cells or small clusters of cells not larger than 0.2 mm in the largest dimension, which can usually be detected by immu

pN1	Micrometastases; metastasis(s) in 1-3 ipsilateral lymph nodes and/or microscopic metastases in sentinel lymph nodes along the ipsilateral A. mammaria interna (not clinically detectable)
pN1mi	Micrometastasis(s) (> 0,2 mm and/or more than 200 tumour cells, but not exceeding 0,2 cm)
pN1a	1-3 axillary lymph node metastasis(s), at least one > 2 mm
pN1b	Lymph nodes along the A. mammaria interna with microscopic metastasis(s)
pN1c	Metastases in 1-3 axillary lymph nodes and lymph nodes along the A. mammaria interna
pN2	Metastasis(s) in 4-9 ipsilateral axillary lymph nodes or in clinically recognizable lymph nodes along the internal mammary artery without axillary lymph node metastases
pN2a	Metastases in 4-9 axillary lymph nodes, including at least one > 2 mm
pN2b	Metastases in clinically recognizable lymph nodes along the A. mammaria interna without axillary lymph node metastases
pN3	metastases as described below:
pN3a	Metastasis(s) in ≥10 ipsilateral axillary lymph nodes (at least one > 2 mm) *or* in ipsilateral infraclavicular lymph nodes
pN3b	Metastasis(s) in clinically recognizable lymph nodes along internal mammary artery with at least one axillary lymph node metastasis *or* lymph node metastases in more than 3 axillary lymph nodes and in lymph nodes along internal mammary artery, as determined by examination of the sentinel lymph node(s), but not clinically recognizable

pN1	Micrometastases; metastasis(s) in 1-3 ipsilateral lymph nodes and/or microscopic metastases in sentinel lymph nodes along the ipsilateral A. mammaria interna (not clinically detectable)
pN3c	Metastasis(s) in ipsilateral supraclavicular lymph nodes

Table 72: Stadium mammary tumors

Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0, T1*	N1mi	M0
Stage IIA	T0, T1*	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0, T1*, T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	N0, N1, N2	M0
Stage IIIC	All T	N3	M0
Stage IV	All T	All N	M1
* (includes T1 mi)			

Note:

The current edition of the AJCC Cancer Staging Manuals (8th ed.) contains not only the anatomical staging but also a prognostic grouping for tumors of the mamma [517].

11.4. Follow-up and long-term care

Table 73: Side effects and long-term effects of treatment in women and men with breast cancer: Aligned to ASCO Guideline Survivorship (guideline adaptation)

Side effects and long-term effects	Measures of prevention and therapy (adapted from Runowicz et al. 2015 [31])
bone loss - Osteopenia/ Osteoporosis	It is recommended that general practitioners/specialists in private practice arrange for an initial bone density measurement for postmenopausal patients with breast cancer. Then, repeated bone density measurements every 2 years should be recommended for breast cancer patients on aromatase inhibitor therapy, premenopausal patients on tamoxifen and/or GnRHa therapy and patients with chemotherapy-induced premature menopause. (see Chapter 5.7.6.1; Chapter 5.7.6.2; DVO Guideline Osteoporosis)
Pain - Arthralgia - Myalgia - Polyneuropathy	It is recommended that general practitioners regularly ask for musculoskeletal symptoms including pain. They should recommend one or more of the following interventions: Acute puncture, physical activity, referral to physical therapy or rehabilitation. It is recommended that general practitioners in private practice ask about pain using pain scales. They should offer interventions such as taking acetaminophen, NSAIs, physical activity and/or acupuncture. They should also refer you to a suitable specialist. They should also ask about peripheral neuropathies, especially numbness and paraesthesias in the upper and lower extremities, and offer therapeutic measures such as physical activity or drug therapy such as duloxetine. (see Chapter 7.5Chapter 7.5)
Cardiovascular diseases - Cardiotoxicity (heart failure/cardiac arrhythmia/cardiomyopathy)	It is recommended that general practitioners monitor both lipid levels and cardiovascular status, and breast cancer patients are educated about healthy lifestyles, cardiac risk factors and relevant symptoms (dyspnea, fatigue) so that they are reported in a timely manner. (see Chapter 7.4)
Specific symptom - Hot flushes/ sweats	It is recommended that general practitioners offer selective serotonin noradrenalin reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), gabapentin, lifestyle interventions to alleviate vasomotor symptoms of premature menopause.
Lymphedema	It is recommended that general practitioners educate breast cancer patients about the prevention or reduction of lymphedema,

Side effects and long-term effects	Measures of prevention and therapy (adapted from Runowicz et al. 2015 [31])
	including weight reduction in obese patients. Patients with clinical symptoms or swelling should be referred to a therapist who is familiar with the diagnosis and treatment of lymphedema, e.g. physiotherapists, lymphedema specialists. (see Chapter 7.5)
Infertility	It is recommended that general practitioners refer breast cancer patients of reproductive age with unfulfilled desire for children to a specialist in endocrinology and reproductive medicine as soon as possible.
Sexual health: Dysfunction - Urogenital Postmenopausal Syndrome - Partnership	It is recommended that general practitioners a) assess signs and symptoms of sexual dysfunction or problems of sexual intimacy (b) should assess and treat risk factors for sexual dysfunction, where appropriate c) non-hormonal, water-based lubricants and moisturisers for vaginal dryness should be offered (d) refer patients to psychoeducational support, group therapy, sexual counselling, marriage guidance or intensive psychotherapy, as appropriate
Cognitive Dysfunction	General practitioners should ask patients about cognitive impairment. Reversible factors that can affect cognitive performance should be identified and treated as well as possible. Patients with signs of cognitive dysfunction should receive neurocognitive assessment and rehabilitation with group training, if available. (see Chapter 7.5)
Fatigue	General practitioners should ask for signs of fatigue and treat any causative factors (anaemia, thyroid dysfunction, cardiac causes). In patients where no underlying cause can be found, other factors that promote fatigue, such as mood swings, sleep disturbances and pain, should be treated. Patients should be advised on regular physical activity and referred to cognitive behavioural therapy if necessary.
Psychosocial stress - Anxiety/depression/ distress - Body image - Emotional perception	General practitioners should evaluate patients for signs of distress, depression or anxiety. Patients with a higher risk of depression (young patients, those with psychiatric illness, low socioeconomic status) should be assessed more precisely. Clinical signs of distress, depression or anxiety should be assessed by counselling and/or pharmacotherapy and/or referral to psycho-oncologists and appropriate mental health facilities.

Side effects and long-term effects	Measures of prevention and therapy (adapted from Runowicz et al. 2015 [31])
- Social role perception - Financial burdens	(see Chapter 7.2)
Secondary malignancies - intestine, skin - (Gynaecological/prostate) - Leukemia	Gynaecologists in private practice should offer the regular check-ups of other departments and perform an annual gynaecological examination in postmenopausal patients under SERM therapy.
Health behaviour - Overweight - Physical mobility - Nutrition/alcohol - Smoking cessation	Aftercare physicians should advise patients in their aftercare regarding weight loss and maintaining a normal body weight. Overweight or obese patients should be advised as follows: high-calorie foods and beverages should be avoided and physical activity increased. Aftercare physicians should advise patients to be physically active on a regular basis (according to ACS guidelines). More specifically, patients should avoid physical inactivity and resume normal daily activities as soon as possible after diagnosis. Patients should be physically active for at least 150 minutes per week at moderate levels or 75 minutes at high levels. Training should include strength training at least 2 days per week. Patients who have received adjuvant chemotherapy or hormone therapy should pay particular attention to strength training. After-care physicians should advise patients on a healthy diet. This should include plenty of vegetables, fruit, wholemeal products, legumes and low saturated fats and alcohol. Aftercare physicians should advise patients to stop smoking and offer smokers supportive measures and programmes.
Aftercare plan, family and relatives, need for information	Aftercare physicians should be in contact with the treating oncological colleagues and receive information about the therapy carried out and other planned measures. Aftercare physicians should support the involvement of (spouses) partners and caregivers in aftercare. Follow-up physicians should ask about patients' needs for information regarding breast cancer, therapies, side effects, other health aspects and support services and should try to meet these needs.

11.5. 2012 Guideline Working Groups

Table 74: 2012 Guideline Working Groups

Chapter/topic complex		Speaker, (Reviewer), Working Group
Chapter 3 General		
3.1	Patient information and education	**Albert, (*Wöckel*)**, Ernst, King, Kreienberg, Naß-Griegoleit, Schulte, Weis
3.2	Early detection, mammography screening	**Schreer, *(Albert),*** Tree, Bick, Degenhardt, Angel, Heywang-Köbrunner, Hölzel, King, Madjar, Schmutzler
3.3	Women with increased risk of breast cancer	**Schmutzler, *(Bick),*** Albert, Hahne, Lebeau, Madjar, Meindl, Rhiem, Schreer
Chapter 4 Locoregionally limited primary disease		
4.1	General diagnostic and therapeutic concepts	Steering Committee
4.2	Pre-therapeutic diagnostics for patients with conspicuous or suspicious findings of the mamma	**Kühn, *(Albert),*** Bick, Degenhardt, Kreienberg, Kreipe, Lebeau, Madjar, Schreer
4.3	Preinvasive neoplasia	**Kreipe/Beckmann, *(Lebeau/Dietel),*** Albert, Harbeck, Kühn, Marx, Schlake, Schreer, Souchon
4.4	Operative therapy of invasive carcinoma	**Blohmer, *(Kühn),*** Angele, Budach, Dietel, Engel, Kreienberg, Lebeau, Marx, Scharl, Souchon, Wagner
4.5	Pathomorphological examination	**Lebeau, *(Kreipe/Dietel),*** Harbeck, Janni, Schlake, Thomssen
4.6	Adjuvant radiotherapy of breast cancer	**Souchon/Dunst, *(Thomssen),*** Blohmer, Budach, Hölzel, Kühn, Untch
4.7	Systemic adjuvant therapy (endocrine, chemo-, antibody therapy)	
4.7.1	Selection of adjuvant therapy and risk assessment	**Kreienberg,** Gerber, Harbeck, Possinger, Thomssen
4.7.2	Endocrine therapy	**Possinger, *(Maass),*** Emons, Scharl

Chapter/topic complex		Speaker, (Reviewer), Working Group
4.7.3	Chemotherapy	**Harbeck,** ***(Möbus),*** Janni, Possinger
4.7.4	Neoadjuvant (primarily systemic) therapy (NACT or PST)	**Gerber, (*v. Minckwitz*)**, Marschner, Untch
4.7.5	Antibody Therapy	**Thomssen,** ***(Snow White),*** Jackisch
4.7.6	Bisphosphonates	**Thomssen,** ***(Snow White),*** Jackisch
4.8	Management of primarily local/local/regional advanced tumours	Steering Committee
Chapter 5 Recurrent or metastatic breast cancer		
5.1	Definition and forecast	Steering Committee
5.2	Diagnosis of local/local recurrence	**Bick,** ***(Sharl),*** Blohmer, Buck, Degenhardt, Madjar
5.3	Therapy of local/local recurrence	**Dunst,** ***(Kühn),*** Angele, Blohmer, Dietel, Heitmann, Marx, Gerber
5.4	Remote Metastases	**Marschner,** ***(Emons),*** Angele, Dunst, Harbeck, Possinger, Thomssen
Chapter 6 Treatment, care, support		
6.1	General concept	Steering Committee
6.2	Psychosocial aspects and psycho-oncology	**Weis/Beckmann,** ***(Scharl),*** Albert, Bartsch, Ernst, Faller, King, Naß-Griegoleit, Schulte
6.3	Supportive therapy	**Link,** ***(Follmann),*** tree, Emons, Henscher, Rup-pert, Skoetz
6.4	Rehabilitation	**Bartsch,** ***(Schulte),*** Baum, Henscher, Knauth, Ruppert
6.5	Aftercare with recurrence and metastasis diagnostics and therapy support	**Janni,** ***(Beckmann),*** Hölzel, King, Wet-Griegoleit, Paradise, Schulte, Souchon, Thomssen, Weis
6.6	Palliative Care	**Gardener,** ***(Schulte),*** Beckmann, Gerlach, Naß-Griegoleit

Chapter/topic complex		Speaker, (Reviewer), Working Group
6.7	Complementary therapy	**Hübner,** Wet Grigoleit, Schulte, Albert, Wöckel
6.8	Documentation	**Angel,** wood, Clinker Hammer Scarf, Pot Fighter
Chapter 7 Supply coordination and quality management		**Wagner, *(Kopp),*** Albert, Beckmann, Bungard, Engel, Ernst, Follmann, Geraedts, Hölzel, Klinkhammer-Schalke, Lebeau, Souchon, Thomssen, Pottkaemper, Feller, Wesselmann, Wöckel

12. Evidence Tables

13. List of Figures

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