

Interdisciplinary Screening, Diagnosis, Therapy and Follow-up of Breast Cancer. Guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/0450L, December 2017) – Part 2 with Recommendations for the Therapy of Primary, Recurrent and Advanced Breast Cancer

Interdisziplinäre Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Leitlinie der DGGG und DKG (S3-Level, AWMF-Registernummer 032/0450L, Dezember 2017) – Teil 2 mit Empfehlungen zur Therapie des primären, rezidivierten und fortgeschrittenen Mammakarzinoms



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Key words

breast cancer, guideline, therapy, primary breast cancer, metastatic breast cancer

Schlüsselwörter

Brustkrebs, Leitlinie, Therapie, primäres Mammakarzinom, metastasiertes Mammakarzinom

received 19.6.2018


accepted 20.6.2018

Bibliography

DOI <https://doi.org/10.1055/a-0646-4630>
 Geburtsh Frauenheilk 2018; 78: 1056–1088 © Georg Thieme
 Verlag KG Stuttgart · New York | ISSN 0016-5751

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 Deutsche Version unter:
<https://doi.org/10.1055/a-0646-4630>

ABSTRACT

Purpose The aim of this official guideline coordinated and published by the German Society for Gynecology and Obstetrics (DGGG) and the German Cancer Society (DKG) was to optimize the screening, diagnosis, therapy and follow-up care of breast cancer.

Method The process of updating the S3 guideline published in 2012 was based on the adaptation of identified source

guidelines. They were combined with reviews of evidence compiled using PICO (Patients/Interventions/Control/Outcome) questions and with the results of a systematic search of literature databases followed by the selection and evaluation of the identified literature. The interdisciplinary working groups took the identified materials as their starting point and used them to develop suggestions for recommendations and statements, which were then modified and graded in a structured consensus process procedure.

Recommendations Part 2 of this short version of the guideline presents recommendations for the therapy of primary, recurrent and metastatic breast cancer. Loco-regional therapies are de-escalated in the current guideline. In addition to reducing the safety margins for surgical procedures, the guideline also recommends reducing the radicality of axillary surgery. The choice and extent of systemic therapy depends on the respective tumor biology. New substances are becoming available, particularly to treat metastatic breast cancer.

ZUSAMMENFASSUNG

Ziele Das Ziel dieser offiziellen Leitlinie, die von der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) und der Deutschen Krebsgesellschaft (DKG) publiziert und koordiniert wurde, ist es, die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms zu optimieren.

Method Der Aktualisierungsprozess der S3-Leitlinie aus 2012 basierte zum einen auf der Adaptation identifizierter Quellleitlinien und zum anderen auf Evidenzübersichten, die nach Entwicklung von PICO-Fragen (PICO: Patients/Interventions/Control/Outcome), systematischer Recherche in Literaturdatenbanken sowie Selektion und Bewertung der gefundenen Literatur angefertigt wurden. In den interdisziplinären Arbeitsgruppen wurden auf dieser Grundlage Vorschläge für Empfehlungen – und Statements erarbeitet, die im Rahmen von strukturierten Konsensusverfahren modifiziert und graduiert wurden.

Empfehlungen Teil 2 dieser Kurzversion der Leitlinie zeigt Empfehlungen zur Therapie des primären, rezidivierten und metastasierten Mammakarzinoms: Die lokoregionären Therapien erfahren in der aktuellen Leitlinie eine Deeskalation. Neben einer Verringerung des Sicherheitsabstandes bei den operativen Verfahren gibt die Leitlinie auch Empfehlungen zu einer reduzierten Radikalität bei axillären Interventionen. Die Systemtherapie richtet sich nach den tumorbiologischen Eigenschaften, neue Substanzen stehen insbesondere beim metastatierten Mammakarzinom zur Verfügung.

I Guideline Information

Guidelines program of the DGGG, OEGGG and SGGG

Information on the guidelines program is available at the end of the guideline.

Citation format

Interdisciplinary Screening, Diagnosis, Therapy and Follow-up of Breast Cancer. Guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/045OL, December 2017) – Part 2 with Recommendations for the Therapy of Primary, Recurrent and Advanced Breast Cancer. Geburtsh Frauenheilk 2018; 78: 1056–1088

Guideline documents

The complete long version together with a summary of the conflicts of interest of all the authors and a short version of the guideline are available in German on the AWMF homepage under: <http://www.awmf.org/leitlinien/detail/II/032-045OL.html> or www.leitlinienprogramm-onkologie.de

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The German Society for Gynecology and Obstetrics (DGGG), working together with the German Cancer Society (DKG), was the lead professional organization behind this guideline. The updated guideline presented here was supported by German Cancer Aid in the context of their oncology guidelines program (OL program). The working groups for this guideline consisted of members of the guideline steering group (► **Table 1**), specialists nominated by participating professional societies and organizations (► **Table 2**), and experts invited to participate by the steering committee (► **Table 3**), and they are the authors of this guideline. Only mandate holders nominated by participating professional societies and organizations were eligible to vote on a chapter-by-chapter basis during the voting process (consensus process) after they had disclosed and excluded any conflicts of interest. The guideline was compiled with the direct participation of four patient representatives.

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Abbreviations of the S3 Breast Cancer Guideline

ADH	atypical (intra) ductal hyperplasia
AI	aromatase inhibitor
AML	acute myeloid leukemia
APBI	accelerated partial breast irradiation
ASCO	American Society of Clinical Oncology
ADL	activities of daily living
AUC	area under the curve
BÄK	German Medical Association (Bundesärztekammer)
BCT	breast-conserving therapy
BI-RADS	breast imaging reporting and data system
BMI	body mass index
BPM	bilateral prophylactic mastectomy
BPSO	bilateral prophylactic salpingo-oophorectomy
BRCA1/2	breast cancer-associated gene 1/2
CAM	complementary and alternative methods
CAP	College of American Pathologists
CD	cognitive dysfunction
CDLT	complex/complete decongestive lymphatic therapy
CGA	comprehensive geriatric assessment
CHF	chronic heart failure
CIPN	chemotherapy-induced peripheral neuropathy
CISH	chromogenic in situ hybridization
CM	contrast media
CNB	core needle biopsy
CNS	central nervous system
CT	computed tomography
DCIS	ductal carcinoma in situ
DBT	digital breast tomosynthesis
DFS	disease-free survival
DGS	German Society for Senology (Deutsche Gesellschaft für Senologie)
DKG	German Cancer Society
DMP	disease management program
EC	expert consensus
ECE	extracapsular tumor extension
EIC	extensive intraductal component
ER	estrogen receptor
ESA	erythropoiesis-stimulating agents
ESAS	Edmonton Symptom Assessment Scale
ET	estrogen therapy
FEA	flat epithelial atypia
FISH	fluorescent in situ hybridization
FN	febrile neutropenia
FNA	fine needle aspiration
FNB	fine needle biopsy
G-CSF	granulocyte colony-stimulating factor
GnRH _a	gonadotropin-releasing hormone agonist
HADS	Hospital Anxiety and Depression Scale
HER2	human epidermal growth factor receptor 2
HT	hormone therapy
IARC	International Agency for Research on Cancer
IBC	inflammatory breast cancer
IHC	immunohistochemistry
IMRT	intensity-modulated radiotherapy
IORT	intraoperative radiation therapy

IQWiG	Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
ISH	in situ hybridization
ITC	intrathecal chemotherapy
LABC	locally advanced breast cancer
LCIS	lobular carcinoma in situ
LN	lymph node
LoE	level of evidence
L-spine	lumbar spine
LVEF	left ventricular ejection fraction
LVI	lymphatic vessel invasion
MDS	myelodysplastic syndrome
MG	mammography
MRI	magnetic resonance imaging
MSP	mammography screening program
NAC	nipple-areolar complex
NACT	neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
NZGG	New Zealand Guidelines Group
OP	operation
OS	overall survival
PBI	partial breast irradiation
pCR	pathological complete remission
PET	positron emission tomography
PFS	progression-free survival
PI	proliferation index
PMRT	postoperative radiotherapy
PNP	polyneuropathy
POS	Palliative Outcome Scale
PR	progesterone receptor
PST	primary systemic therapy
QoL	quality of life
RCT	randomized controlled trial
RFA	radiofrequency ablation
ROR	risk of recurrence
RR	relative risk
RS	recurrence score
SABCS	San Antonio Breast Cancer Symposium
SBRT	stereotactic radiotherapy
SGB	German Social Security Code (Sozialgesetzbuch)
SIB	simultaneous integrated boost
SIGN	Scottish Intercollegiate Guidelines Network
SISH	silver-enhanced in situ hybridization
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
SLNE	sentinel lymph node excision
s/p	status post
SSM	skin-sparing mastectomy
TACE	transarterial chemoembolization
TILs	tumor-infiltrating lymphocytes
TNBC	triple-negative breast cancer
TNM classification	tumor–node–metastasis classification
T-spine	thoracic spine

UICC	Union for International Cancer Control
US	ultrasound
VMAT	volumetric arc therapy
WHO	World Health Organization

II Guideline Application

Purpose and objectives

The most important reason to update this interdisciplinary guideline was the epidemiological impact of breast cancer and its associated burden of disease, both of which are still high. This is the context in which the impact of new management concepts and their implementation needed to be evaluated.

Targeted areas of patient care

The guideline covers outpatient, inpatient and rehabilitative care.

Target patient groups

The recommendations of the guideline are aimed at all women and men who develop breast cancer as well as their relatives.

Target user groups/Target audience

The recommendations of the guideline are addressed to all physicians and professionals who provide screening services for women or care for patients with breast cancer (gynecologists, general practitioners, human geneticists, radiologists, pathologists, radio-oncologists, hemato-oncologists, psycho-oncologists, physiotherapists, nursing staff, etc.).

Adoption of the guideline and period of validity

This guideline is valid from December 1, 2017 through to November 30, 2022. Because of the contents of this guideline, this period of validity is only an estimate. It may become necessary to update the guideline because of new scientific evidence and knowledge as well as new developments affecting the methodology used for these guidelines. It is also necessary to edit and revise the guideline's contents and re-evaluate and revise the key statements and recommendations of the guidelines at regular intervals.

III Methodology

Basic principles

The method used to prepare this guideline was determined by the class to which this guideline was assigned. The AWMF Guidance Manual (version 1.0) has set out the respective rules and regulations for the different classes of guidelines. Guidelines are differentiated into lowest (S1), intermediate (S2) and highest class (S3). The lowest class is defined as a set of recommendations for action compiled by a non-representative group of experts. In 2004, the S2 class was subdivided into two subclasses: a systematic evidence-based subclass (S2e) and a structural consensus-based subclass (S2k). The highest class (S3) combines both approaches. This guideline is classified as: S3.

Grading of evidence

This guideline used the 2009 version of the system of the Oxford Centre for Evidence-based Medicine (levels 1–5) to classify the risk of bias in identified studies. This system classifies studies according to various clinical questions (benefit of therapy, prognostic value, diagnostic validity). For more detailed information, abbreviations and notes, see: <https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>

Grading of recommendations

While the classification of the quality of the evidence (strength of evidence) serves as an indication of the robustness of the published data and therefore expresses the extent of certainty/uncertainty regarding the data, the classification of the level of recommendation reflects the results of weighing up the desirable and adverse consequences of alternative approaches. This guideline shows the level of evidence for the underlying studies as well as the strength of the recommendation (level of recommendation) for all evidence-based Statements and Recommendations. This guideline differentiates between three levels of recommendation (► **Table 4**). The levels reflect the strength of the respective recommendation and are also mirrored in the terms used to formulate the recommendation.

► **Table 4** Grading of recommendations.

Level of recommendation	Description	Syntax
A	strong recommendation, highly binding	must/ must not
B	recommendation, moderately binding	should/ should not
0	open recommendation, not binding	may/ may not

Statements

Statements are expositions or explanations of specific facts, circumstances or problems with no direct recommendations for action. Statements are adopted after a formal consensus process using the same approach as that used when formulating recommendations and can be based either on trial results or expert opinions.

Expert consensus

As the expression implies, this term refers to consensus decisions taken specifically with regard to Recommendations/Statements

without a previous systematic search of the literature (S2k) or when evidence is lacking (S2e/S3). The term “Expert Consensus” (EC) used here is synonymous with terms such as “Good Clinical Practice” (GCP) or “Clinical Consensus Point” used in other guidelines. The level of recommendation is graded as previously described in the Chapter “Grading of recommendations”, but the grading is only presented semantically (“must”/“must not” or “should”/“should not” or “may”/“may not”) without the use of symbols.

Guideline report

To edit and update the various topic areas, an adaptation of existing guidelines was planned for around 80% of Statements and Recommendations in accordance with the AWMF Guidance Manual. To do this, a systematic search was carried out for source guidelines developed specifically for women with breast cancer and published after 2013. Findings were compared with the IQWiG guideline report No. 224 (Systematische Leitlinienrecherche und -bewertung sowie Extraktion relevanter Recommendations für das DMP Brustkrebs [Systematic guideline search and appraisal as well as extraction of relevant recommendations for a breast cancer DMP]). A further inclusion criterion was compliance with methodological standards. Guidelines were included if they complied with at least 50% of Domain 3 (Rigour of Development) of the AGREE II instrument. A corresponding search and evidence assessment was specified in accordance with AWMF guidelines (systematic search, selection, compilation of evidence tables) for those recommendations which could not be adapted or had to be newly created. For newly developed Recommendations and Statements, appropriate key questions were formulated and a systematic search was carried out using aggregated sources of evidence (meta-analyses, systematic reviews, etc.) as well as individual publications in specific cases. A suitable list of titles and abstracts up to and including the identification of the full text were selected by two independent raters. After the search and selection processes were completed, the necessary evidence tables which formed the basis for the consensus conferences were compiled by the Methods group (financial support was provided and allowed a researcher to be specifically hired for this purpose). The classification system of the Oxford Centre for Evidence-based Medicine (version 2009) was used to grade the evidence. To update this guideline, Recommendations and Statements were adopted and levels of recommendation (► **Table 4**) were determined during two structured consensus conferences which were preceded by a preliminary online ballot.

The guideline report provides an overview of the search strategies and selection processes used to select the literature and to formulate and grade the recommendations.

IV Guideline

1 Treatment of primary breast cancer

1.1 Surgical treatment for invasive carcinoma

1.1.1 General recommendations

No.	Recommendations/ Statements	EG	LoE	Sources
4.19.	a) The basic therapy for all non-advanced breast cancers is complete resection of the tumor (R0 status).	A	1a	[1, 2]
	b) The resection margin status has a prognostic effect on invasive breast cancer. There is a significant association between resection margin status (positive vs. negative) and local rate of recurrence.	A	1a	[3]

1.1.2 Breast-conserving therapy

Randomized clinical studies have shown that if certain clinical and histological parameters are taken into account, breast-conserving therapy achieves identical survival rates to those of mastectomy.

No.	Recommendations/ Statements	EG	LoE	Sources
4.20.	a) The goal of surgical therapy is complete removal of the tumor. Breast-conserving therapy (BCT) followed by full breast radiotherapy is equivalent to mastectomy alone in terms of survival rates.		1a	[4–10]
	b) All appropriate patients, whether or not they have previously had primary systemic therapy, must be informed about the possibility of breast-conserving therapy (BCT) and about mastectomy with the options of primary or secondary reconstruction.	EC		

1.1.3 Mastectomy

No.	Recommendations/ Statements	EG	LoE	Sources
4.21.	a) Mastectomy must be performed if any of the following indications are present: <ul style="list-style-type: none"> ▪ Incomplete removal of the tumor (incl. any intraductal component), even after secondary resection ▪ Inflammatory breast cancer (generally even in cases with pathological complete remission) ▪ When follow-up radiation of the breast after breast-conserving therapy is contraindicated but radiation is absolutely indicated ▪ at the request of the patient who has been fully informed about her range of options 	A	2b	[11–13]
	b) If the resection margins are tumor-free, mastectomy may also be performed as a skin-sparing procedure with or without preservation of the NAC.	0	2a	[14–17]
	c) Depending on the tumor location and tumor size, mastectomy may be necessary in individual cases, even if multiple cancers are present.	0	2a	[18–25]
	d) Contralateral prophylactic mastectomy to reduce the risk of contralateral breast cancer should not be carried out in non-mutation carriers or patients with no evidence of high familial risk.	B	2b	[26–28]

1.1.4 Reconstructive plastic surgery procedures

No.	Recommendations/ Statements	EG	LoE	Sources
4.22.	Every patient scheduled for mastectomy must be informed about the options of having immediate or subsequent breast reconstruction or the option of foregoing reconstructive procedures; these patients should be offered the opportunity to contact other similarly affected people and self-help groups or organizations.	A	2b	[16, 29, 30]

1.1.5 Axillary surgery

No.	Recommendations/Statements	EG	LoE	Sources
4.23.	a) Axillary staging is an essential part of the surgical therapy of invasive breast cancer.	EC		
	b) Staging must include sentinel lymph node biopsy (SLNB) even if the lymph node status is unremarkable on palpation and ultrasound.	A	1a	[30–32]
	c) Clinically significant lymph nodes that are negative on biopsy should also be resected during SLNB.	B	2b	[30, 33]
	d) Patients with pT1–pT2/cN0 tumors who undergo breast-conserving surgery followed by percutaneous radiation by tangential opposing fields (tangential radiation therapy) and who have one or two positive sentinel lymph nodes should not undergo axillary dissection.	B	1b	[31]
	e) Patients who have mastectomy or to whom the above-listed criteria do not apply should undergo axillary dissection or receive axillary radiotherapy.	B	1b	[31, 34]
	f) Targeted therapy of the lymph drainage areas (surgery, radiotherapy) must not be carried out if the patient only has micro-metastasis.	B	1b	[35, 36]
	g) Patients treated with primary systemic therapy (PST) and whose lymph node status on palpation and ultrasound is negative prior to treatment should have SLN after PST.	B	2b	[37, 38]
	h) Patients treated with primary systemic therapy (PST) whose nodal status on punch biopsy is positive (cN1) prior to treatment but whose nodal status after PST is clinically negative (ycN0) should undergo axillary dissection.	B	2b	[38, 39]
	i) Patients treated with primary systemic therapy (PST) who have a positive nodal status before and after PST must undergo axillary dissection.	EC		
	j) Patients must not undergo axillary staging if there is evidence of distant metastasis.	EC		

1.2 Adjuvant radiation therapy for breast cancer

No.	Recommendations/Statements	EG	LoE	Sources
4.36.	After breast-conserving surgery for invasive carcinoma the affected breast must be treated with radiotherapy. Provided the resection margins were tumor-free, patients with a clearly limited life expectancy (< 10 years) and a small (pT1), node-negative (pN0), hormone receptor-positive HER2-negative tumor and endocrine adjuvant therapy may avoid radiation therapy and accept the increased risk of local recurrence after receiving individual counselling. Note for all Recommendations: all single positions are OR conjunctions. AND conjunctions are represented by “and”.	A	1a	[40–47]
4.37.	Radiotherapy of the breast should be administered in hypofractionated doses (total dose: approx. 40 Gy in approx. 15–16 fractions over approx. 3 to 5 weeks) or may be administered as a standard fractionated regimen (total dose: approx. 50 Gy in approx. 25–28 fractions over approx. 5–6 weeks).	B/0	1a	[48–54]
4.38.	Local dose escalation (boost radiotherapy) of the tumor bed reduces the local rate of recurrence in the breast without achieving a significant survival benefit. Boost radiotherapy <ul style="list-style-type: none"> ▪ must therefore be carried out in all patients aged ≤ 50 years and ▪ should only be carried out in patients aged > 51 years if they have an increased risk of local recurrence (G3, HER2-positive, triple-negative, >T1). 	A/B	1a	[55–58]
4.39.	Partial breast irradiation alone (as an alternative to secondary whole breast irradiation) may be carried out in patients with a low risk of recurrence.	0	1a	[59–64]
4.40.	Postoperative radiotherapy of the thoracic wall after mastectomy reduces the risk of loco-regional recurrence and improves the survival of patients with locally advanced, node-positive breast cancer.	A	1a	[65]
4.41.	Radiation of the thoracic wall after mastectomy is indicated in the following situations: <ul style="list-style-type: none"> ▪ pT4 ▪ pT3 pN0 R0 when additional risk factors are present (lymph node invasion (L1), G3 grading, premenopausal, age < 50 years) ▪ R1/R2 resection and no possibility of a second curative resection <p>a) Post-mastectomy radiation must be carried out as a standard procedure if more than 3 axillary lymph nodes are affected.</p> <p>b) If 1–3 axillary lymph nodes show tumor involvement, post-mastectomy radiation must be carried out if the patient has an increased risk of recurrence (e.g. HER2-positive, triple-negative, G3, L1, Ki-67 > 30%, > 25% of excised lymph nodes show tumor involvement; age ≤ 45 years with additional risk factors such as medial tumor location or tumor size > 2 cm, or ER-negative).</p> <p>c) PMRT should not be carried out if 1–3 axillary lymph nodes show tumor involvement and the tumor has a low risk of local recurrence (pT1, G1, ER-positive, HER2-negative, at least 3 characteristics must apply).</p> <p>d) For all other patients with 1–3 axillary lymph nodes with tumor involvement, the individual indication for treatment must be decided on by an interdisciplinary board.</p>	A	1a	[65–79]

No.	Recommendations/Statements	EG	LoE	Sources
4.42.	After primary (neoadjuvant) systemic therapy, the indication for post-mastectomy radiotherapy must be based on the clinical staging prior to treatment; for pCR (ypT0 and ypN0) the indication for treatment must be decided on by an interdisciplinary tumor board and depends on the patient's individual risk profile.	A	1a	[80–83]

Pretreatment	Post-treatment	RT-BCT ¹	PMRT ²	RT-LAW ³
locally advanced	pCR/no pCR	yes	Yes	yes
cT1/2 cN1+	ypT1+ o. ypN1+ (no pCR)	yes	yes	yes
cT1/2 cN1+	ypT0/is ypN0 (SLNE ≥ 3 LN)	yes	cases with high risk ⁴	
cT1/2 cN0 (US obligatory)	ypT0/is ypN0 (SLNE ≥ 3 LN)	yes	no	no

¹ with standard tangential treatment

² if the patient underwent a mastectomy

³ together with PMRT or RT because of BCT

⁴ Criteria for a high risk of recurrence:

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

pN1 a high risk: central or medial location and (G2–3 or ER/PgR-negative) or premenopausal, lateral location and (G2–3 or ER/PgR-negative)

No.	Recommendations/Statements	EG	LoE	Sources
4.43.	Adjuvant irradiation of regional lymph drainage areas improves disease-free survival and overall survival rates in a subgroup of patients.		1a	[84–88]
4.44.	a) Irradiation of the supra-/infraclavicular lymph nodes may be an option for patients with pN0 or pN1mi stage disease under the following circumstances if all of the following conditions are met: <ul style="list-style-type: none"> premenopausal and central or medial tumor location and G2–3 and ER/PgR-negative. 	0	2a/2b	[84–90]
	b) Irradiation of the supra-/infraclavicular lymph nodes should be carried out in patients with 1–3 affected lymph nodes in the following circumstances: <ul style="list-style-type: none"> central or medial location and (G2–3 or ER/PgR-negative) premenopausal, lateral location and (G2–3 or ER/PgR-negative) 	B	2a	[84–90]
	c) Irradiation of the supra-/infraclavicular lymph nodes must be generally carried out in all patients with > 3 affected axillary lymph nodes.	A	2a	[84–90]
4.45.	a) Irradiation of the internal thoracic artery lymph nodes may be carried out in patients without or with minimal axillary involvement (pN0 or pN1mi) in the following circumstances: <ul style="list-style-type: none"> premenopausal and central or medial location and G2–3 and ER/PgR-negative 	0	2b	[84–88]
	b) Irradiation of the internal thoracic artery lymph nodes should be carried out in patients with 1–3 affected lymph nodes in the following circumstances: <ul style="list-style-type: none"> central or medial location and (G2–3 or ER/PgR-negative) premenopausal, lateral location and (G2–3 or ER/PgR-negative) 	B	2b	[84–88]
	c) Irradiation of the internal thoracic artery lymph nodes should be carried out in patients with > 3 affected axillary lymph nodes in the following circumstances: <ul style="list-style-type: none"> G2–3 or ER/PgR-negative 	B	2b	[84–88]
	d) If tumor involvement of the internal thoracic artery lymph nodes is confirmed, they should be treated with radiotherapy.	B	2b	[84–90]
	e) If patients have an increased cardiac risk or are receiving treatment with trastuzumab, the decision whether or not to irradiate the internal thoracic artery lymph nodes must be made on an individual basis by an interdisciplinary tumor board.	A	4	[91, 92]
4.46.	Expanded axillary radiation may be used to treat patients with 1–2 affected axillary sentinel lymph nodes if no axillary dissection is carried out or if the interdisciplinary tumor board agrees that no further local axillary therapy should be carried out (analogous to ACOSOG Z0011). The decision about the appropriate approach must be taken by an interdisciplinary tumor board.	0/A	2b	[35, 93–95]
4.47.	Radiotherapy of lymph drainage areas should be administered in standard fractions (5 × week 1.8 to 2.0 Gy, total dose: approx. 50 Gy over a period of approx. 5–6 weeks) or in hypofractionated doses (total dose: approx. 40 Gy in approx. 15–16 fractions over a period of approx. 3 to 5 weeks).	EC		
4.48.	Treatment of patients with primary inoperable or inflammatory cancer must consist of primary systemic therapy followed by surgery and postoperative radiotherapy or, if the cancer continues to be inoperable, radiotherapy alone or preoperative radiotherapy.	A	1b	[96, 97]

No.	Recommendations/Statements	EG	LoE	Sources
4.49.	a) Postoperative chemotherapy and radiotherapy must be administered sequentially. Note: No specific sequence (chemotherapy first or radiotherapy first) has been confirmed as superior. The sequence of chemotherapy followed by radiotherapy is the established sequence in clinical practice.	A	1b	[98–101]
	b) If only RT is administered, treatment with RT should commence within a period of 8 weeks postoperatively.			[102, 103]
	c) Adjuvant endocrine therapy can be started independently of any radiotherapy. (1a) Therapy with trastuzumab may be continued during radiotherapy. If the patient is receiving simultaneous irradiation of the internal thoracic artery lymph nodes, the appropriate approach must be decided on by an interdisciplinary tumor board. (4)			[91, 92, 104, 105]

1.3 Systemic adjuvant therapy (endocrine therapy, chemotherapy, antibody therapy)

1.3.1 Choice of adjuvant therapy and classification of risk

The 2009 St. Gallen Recommendations have pointed out the significance of endocrine sensitivity and the 2011 Recommendations have highlighted the importance of molecular subtypes as the decisive criteria whether adjuvant chemotherapy is indicated or not [106]. The markers ER, PgR, HER2 and Ki-67, which are identified by immunohistochemistry, are considered surrogate parameters for different molecular subtypes [106]. ER-positive and/or PgR-positive, HER2-negative tumors with low proliferation rates are classified as luminal A; if the proliferation rates are high, they are classified as luminal B. It should be noted that there is currently no validated threshold value for Ki-67 (e.g. for classifying a tumor as luminal A vs. luminal B or to confirm the decision for/against adjuvant chemotherapy).

Indications for adjuvant chemotherapy:

- simultaneous anti-HER2 therapy with trastuzumab over a period of 1 year combined with (neo-) adjuvant chemotherapy is the standard approach for HER2-positive tumors
- non-endocrine-sensitive tumors (ER- and PgR-negative)
- tumors which may not be endocrine-sensitive
- node-positive tumors (studies are currently being carried out to evaluate whether patients with low numbers of affected lymph nodes [1–3 affected LN] and favorable tumor biology [luminal A] may not need adjuvant chemotherapy)
- G III
- young age at onset (< 35 years)

Chemotherapy is always indicated if the individual expected benefit is higher than potential side effects and long-term negative effects. This requires careful, in-depth counselling and discussions with the patient, particularly if the expected benefit is minimal.

1.3.2 Endocrine therapy

No.	Recommendations/Statements	EG	LoE	Sources
4.50.	a) Patients with estrogen and/or progesterone receptor-positive* invasive tumors must receive endocrine therapy.	A	1a	[30, 107–110]
	b) Endocrine therapy must only be started after chemotherapy has been completed but it can be administered in parallel to radiotherapy.	A	1a	[30, 45, 107–110]
4.51.	After 5 years of tamoxifen the decision whether or not to continue endocrine therapy must be re-evaluated in every patient with ER+ breast cancer. When considering whether or not to continue endocrine therapy, the risk of recurrence and the therapy-related side effects (toxicity, decreased adherence) should be weighed up. The patient's current menopausal status must be taken into account when selecting the appropriate endocrine therapy.	A/B	Adapt. from guideline	[111]
4.52.	Premenopausal patients must receive tamoxifen therapy for at least 5 years. Antiestrogen therapy with tamoxifen 20 mg per day must be administered for a period of 5–10 years depending on the risk of recurrence or until recurrence occurs. Whether or not expanded therapy is indicated depends on the risk of recurrence and the patient's wishes.	A	1a	[107, 108, 112–114]
4.53.	a) High-risk patients with ER+ breast cancer who are still premenopausal after completing chemotherapy may be treated with an aromatase inhibitor after suppressing ovarian function.	EC		
	b) Suppression of ovarian function alone can be considered in premenopausal women with ER+ breast cancer who cannot receive tamoxifen or do not want to be treated with tamoxifen; suppression can be achieved either by administering a GnRHa or by oophorectomy.	EC		
	c) Suppression of ovarian function (by GnRHa or bilateral oophorectomy) in addition to tamoxifen or an aromatase inhibitor must only be considered in patients with a high risk of recurrence who are premenopausal after receiving adjuvant chemotherapy. Suppression of ovarian function is mandatory when treatment consists of administering aromatase inhibitor.	A	Adapt. from guideline	[115]
4.54.	Adjuvant endocrine therapy for postmenopausal patients with ER+ breast cancer should include an aromatase inhibitor.	B	1b	[115]

* ≥ 10% progesterone-receptor-positive tumor cell nuclei

1.3.3 Adjuvant chemotherapy

No.	Recommendations/Statements	EG	LoE	Sources
4.55.	a) Adjuvant chemotherapy is indicated for: <ul style="list-style-type: none"> ▪ HER2-positive tumors (from pT1b, N0; pT1a, N0 if additional risks are present: e.g., G3, ER/PR-negative, high Ki67 levels) ▪ Triple-negative tumors (ER- and PgR-negative, HER2-negative) Luminal-B tumors with a high risk of recurrence (high Ki-67 levels, G3, high-risk multigene assay, young age at onset, lymph nodes show tumor involvement)	B	1a	[4, 11, 116–119]
	b) Chemotherapy must be administered in the recommended doses. Under-dosing or reducing the number of cycles risks reducing the efficacy of chemotherapy.	A	1a	[118, 120–124]
4.56.	Cytostatic agents may be administered simultaneously or sequentially (according to the evidence-based protocols). Dose-dense therapies should be used to treated suitable patients with a high tumor-related risk of mortality.	B	1b.	[125–130]
4.57.	Adjuvant chemotherapy should include a taxane and an anthracycline.	B	1a	[116, 126, 131–139]
	6 cycles of TC (docetaxel/cyclophosphamide) may be an alternative in patients with moderate clinical risk (≤ 3 affected lymph nodes).	0	1a	
	Standard adjuvant chemotherapy must take 18–24 weeks.	A	1a	

1.3.4 Neoadjuvant therapy

No.	Recommendations/Statements	EG	LoE	Sources
4.58.	a) Neoadjuvant (primary, preoperative) systemic therapy is considered the standard treatment for patients with locally advanced, primary inoperable or inflammatory breast cancer in the context of a multimodal therapy concept.	EC		
	b) Neoadjuvant systemic therapy should be preferred if the same postoperative adjuvant chemotherapy is indicated.	EC		
4.59.	a) If chemotherapy is indicated, it can be administered prior to surgery (neoadjuvant) or after surgery (adjuvant). Both approaches are equivalent with regard to overall survival. Neoadjuvant therapy may lead to a higher rate of breast-conserving therapies.		1a	[140–142]
	b) The effect (pathohistological remission) is greatest for hormone receptor-negative cancers.		1a	[140, 141, 143, 144]
	c) Resection within the new tumor margins is possible if R0 resection can be achieved.	EC		
4.60.	a) Postmenopausal patients with endocrine-sensitive breast cancer, for whom surgery or chemotherapy is not possible or who do not want surgery or chemotherapy, may be treated with primary endocrine therapy.	EC		
	b) Neoadjuvant endocrine therapy is not a standard therapy; neoadjuvant endocrine therapy may be considered in special situations (inoperable cancer, multiple morbidities).	EC		
4.61.	a) If a neoadjuvant chemotherapy combination is used, it should include an anthracycline and a taxane. Preoperative therapy should take 18–24 weeks. HER2-positive tumors for which neoadjuvant chemotherapy is indicated should be treated with trastuzumab. High-risk (clinical/sonographic findings or N+ on punch biopsy, tumor size > 2 cm) HER2-positive patients should additionally receive pertuzumab.	EC		
	b) Platinum salts increase the complete remission rate (pCR rate) in patients with triple-negative breast cancer (TNBC) irrespective of their BRCA status. The benefit for progression-free survival (PFS) and overall survival has not yet been conclusively confirmed. The toxicity is higher.	EC		
4.62.	If anthracycline-taxane-based neoadjuvant chemotherapy is adequate, no additional adjuvant chemotherapy is recommended for tumor residues in the breast and/or lymph nodes. Post-neoadjuvant chemotherapy treatment should only be carried out in the context of clinical trials.	EC		

1.3.5 Antibody therapy

No.	Recommendations/Statements	EG	LoE	Sources
4.63.	a) Patients with HER2-overexpressing tumors with a diameter ≥ 1 cm (immunohistochemical score 3+ and/or ISH-positive) must receive (neo) adjuvant treatment with an anthracycline followed by a taxane in combination with trastuzumab. Trastuzumab must be administered over a total period of one year.	A	1b	[16, 29, 30]
	b) Adjuvant treatment with trastuzumab should preferably be started at the same time as the taxane phase of adjuvant chemotherapy.	B	2a	[145]
	c) If chemotherapy is indicated to treat HER2+ tumors ≤ 5 mm, trastuzumab should be additionally administered. Six cycles of TCH (docetaxel, carboplatin, trastuzumab) every 3 weeks may also be recommended as an adjuvant treatment. The cardiotoxicity of this approach is lower than after treatment with anthracyclines	EC		

1.3.6 Bone-targeted therapy

1.3.6.1 Therapy and prevention of cancer treatment-induced bone loss

The risk of bone density loss with destruction of bone structure and the risk of therapy-related osteoporosis followed by an increased risk of fractures is significantly higher in patients with malignant disease [146]. Apart from such commonly reported changes as immobilization and changes in lifestyle (e.g. discontinuation of estrogen therapy), it is primarily drug therapies that are responsible for osseous changes. Supportive therapies (e.g. cortisone preparations) are as likely to damage bones as cytotoxic or endocrine drugs. This issue is becoming increasingly important following the high curative rates for many solid tumors, particularly for breast cancer.

In premenopausal women with hormone receptor-positive breast cancer, ovarian function suppression (e.g. using GnRH analogs) alone or in combination with tamoxifen or an aromatase inhibitor and treatment with tamoxifen alone leads to a loss of bone density and an increased incidence of osteoporosis compared to

healthy control populations [147–149]. The combination of ovarian function suppression with an aromatase inhibitor led to the greatest decrease in bone density [147].

In postmenopausal women, treatment with aromatase inhibitors also leads to a loss of bone density and an increased incidence of fractures compared to women treated with tamoxifen [150–153].

Chemotherapies can also result in a significant loss of bone density [154, 155].

The indication for preventive treatment depends on the patient's gender, age and bone density and should take the patient's history and lifestyle into account. Primary prevention of cancer therapy-induced bone loss should be considered if patients present with a special combination of risks [156, 157]. These include advanced age, low body mass index, nicotine abuse, therapy with aromatase inhibitors, familial disposition, long-term cortisone therapy, immobility, endocrine disease, medication (Confederation of German-speaking Scientific Osteology Society, <http://www.dv-osteologie.org>) [158].

No.	Recommendations/Statements	EG	LoE	Sources
4.64.	In patients with an increased familial or cancer therapy-related risk of bone loss, bone density measurements should be carried out prior to starting treatment. Bone density measurements should be repeated at regular intervals depending on the results and the presence of additional risk factors.	EC		
4.65.	Depending on the patient's individual combination of risk factors for developing osteoporosis, preventive treatment should be considered to prevent cancer therapy-induced osteoporosis (http://www.dv-osteologie.org ; ESMO bone health guidance).	EC		
4.66.	Osteoprotective therapy should be considered for premenopausal patients receiving GnRH and/or TAM and postmenopausal patients receiving treatment with AI.	B	1b	[147, 150, 152, 158]
4.67.	Hormone therapy with estrogens should not be used to prevent cancer therapy-related osteoporosis in breast cancer patients as an increased rate of recurrence cannot be excluded, particularly in patients with hormone receptor-positive disease.	B	1a	[159]
4.68.	In addition to these general recommendations, bisphosphonates or denosumab may be used for primary prevention of cancer therapy-induced bone loss.	EC		
4.69.	A reduced risk of fractures associated with endocrine therapy has only been clearly confirmed for denosumab but has not yet been confirmed for bisphosphonates.	A	1	[150]
4.70.	Bone-targeted therapy to prevent therapy-related osteoporosis should be carried out for the duration of endocrine therapy.	EC		

1.3.6.1.1 Therapy for cancer therapy-induced osteoporosis

No.	Recommendations/ Statements	EG	LoE	Sources
4.71.	It is important to exclude bone metastasis if a bone fracture occurs which was not caused by sufficiently powerful trauma.	EC		

1.3.6.2 Adjuvant therapy to improve bone metastasis-free survival and overall survival

According to the “seed and soil” hypothesis, luminal breast cancer cells are particularly prone to metastasize in bone where they are then detected in the form of disseminated tumor cells [160–162]. Bisphosphonates and probably also denosumab appear to have a therapeutic effect with regard to the persistence of these cells and thus on the incidence of secondary bone metastasis [163].

Two meta-analyses evaluated studies on the adjuvant use of different bisphosphonates. Ben-Aharon and colleagues found a positive effect on survival in postmenopausal patients with breast cancer (HR 0.81 [0.69–0.95]) [164]. In their meta-analysis, Coleman and colleagues reported a significant positive effect on bone metastasis-free survival of 34% and on overall survival of 17% for postmenopausal patients (including premenopausal patients with ovarian function suppression from GnRH analogs; ABCSG-12) [165].

The meta-analyses found no significant benefit for premenopausal patients (without ovarian function suppression from GnRH analogs) with regard to disease-free survival, bone metastasis-free survival and overall survival. No effect on prognosis was detected in an evaluation of a secondary endpoint carried out in a subpopulation of premenopausal patients (the majority of whom did not have suppression of ovarian function), despite the high therapy density at the start of treatment (AZURE trial [158]).

To date, no bisphosphonate has been approved for use in adjuvant therapy in the European Union, meaning that treatment can currently only be carried out as an off-label use.

No.	Recommendations/ Statements	EG	LoE	Sources
4.72.	Adjuvant bisphosphonate therapy prolongs bone metastasis-free survival and overall survival in postmenopausal patients with breast cancer and in premenopausal patients with ovarian function suppression (off-label use).	A	1	[164, 165]
4.73.	It is currently not possible to recommend the adjuvant use of bisphosphonates or denosumab for premenopausal patients with suppression of ovarian function.	0	1b	[158, 164, 165]

1.3.6.3 Bone-targeted therapy for patients with bone metastasis

The most common metastases of breast cancer occur in bone marrow. Luminal tumors have a particular affinity to the skeleton. The most common complications of bone metastases are pain, pathological fractures, vertebral compression syndrome, and hypercalcemia [166]. If the aforementioned symptoms (with the exception of pain) occur, then morbidity is significantly increased. A number of different measures can be initiated to prevent these serious complications.

The interdisciplinary AWMF S3 guideline 032-054OL “Supportive Therapy for Oncology Patients” provides a detailed discussion of the diagnosis and therapy of bone metastases [167]).

No.	Recommendations/ Statements	EG	LoE	Sources
4.74.	Patients must go to the dentist before starting adjuvant osteoprotective therapy. The Recommendations of the S3 guideline on “Antiresorptive drug-related necrosis of the jaw” apply.	EC		

1.3.7 Lifestyle factors which can be influenced

No.	Recommendations/Statements	EG	LoE	Sources
4.75.	Patients must be motivated to carry out physical exercise and to normalize their body weight (if their BMI is high). Patients should receive support and assistance. It is particularly recommended that patients: a) avoid physical inactivity and return to normal daily activities as early as possible after diagnosis (LoE 2a) b) work towards achieving the goal of 150 minutes of moderate or 75 minutes of strenuous physical activity per week (LoE 1a)	A	2a/1a	[168–171]
4.76.	Patients should be offered weight training programs, particularly when they are undergoing chemotherapy and hormone therapy.	B	1b	[172–175]
4.77.	Patients should be advised and taught to do regular sports activities and physical exercise to treat breast cancer-associated fatigue.	B	1a	[176–179]

No.	Recommendations/Statements	EG	LoE	Sources
4.78.	If manifest chemotherapy-induced polyneuropathy is present, patients should have exercise therapy to improve functionality. This may include: <ul style="list-style-type: none"> balance exercises sensorimotor training coordination training vibration training fine motor skills training 	B	1a/2a	[173, 174, 180, 181]
4.79.	Patients with lymphedema after surgery for breast cancer must be started on monitored, gradually progressive weight training to treat lymphedema.	B	1b	[182–187]
4.80.	Patients should be counselled (a) about achieving and maintaining a healthy body weight, and (b) if they are overweight or obese, about how to limit their consumption of highly-calorific food and drinks and how to increase their physical activity to promote moderate weight loss and maintain it over the long-term.	A	Adapt. From guideline	[188]
4.81.	Patients should be counselled on how to achieve and adhere to a nutritional program rich in vegetables, fruit, wholegrain and pulses which contains few saturated fats and only limited alcohol consumption.	A	Adapt. from guideline	[188]
4.82.	Patients must receive counselling not to smoke; if necessary, smokers must be recommended smoking cessation programs.	A	2a	[188]
4.83.	To prevent late recurrence (> 5 years after primary diagnosis), patients with receptor-positive disease should avoid a daily alcohol consumption of > 12 g pure alcohol.	B	2a	[189]

1.4 Breast cancer during pregnancy and lactation, pregnancy after breast cancer, fertility preservation

1.4.1 Pregnancy after breast cancer

No.	Recommendations/Statements	EG	LoE	Sources
7.1.	Patients who have had breast cancer must not be counselled against becoming pregnant. This applies irrespective of their hormone status.	A	3a	[190, 191]
7.2.	a) The interval until becoming pregnant after breast cancer is not correlated with a poorer prognosis. b) The risk of recurrence depends on the tumor biology and the stage of disease. This must be discussed during counselling for any subsequent pregnancy.	A EC	3a	[190]
7.3.	The longer the endocrine therapy, the better the chances for a cure (see Chapter 4.7.2 Endocrine therapy). If the patient wished to become pregnant before completing endocrine therapy, then endocrine therapy should be continued after the patient has given birth and stopped breastfeeding.	EC		
7.4.	a) Patients can try to become pregnant after breast cancer with the help of reproductive medical procedures. b) The chances of success (i.e. an intact pregnancy or baby) are lower for breast cancer patients when autologous eggs are used compared to women without breast cancer.	0	4 2c	[192–194] [195]

1.4.2 Breast cancer during pregnancy

No.	Recommendations/Statements	EG	LoE	Sources
7.5.	a) Treatment (systemic therapy, surgery, RT) for breast cancer (in pregnant patients) during pregnancy must be as similar as possible to treatment administered to younger, non-pregnant patients with breast cancer.	EC		
	b) Standard chemotherapy with anthracyclines and taxanes may be administered in the 2nd and 3rd trimester of pregnancy.	0	2b	[196–200]
	c) Anti-HER2 therapy must not be administered during pregnancy.	A	3a	[196, 197, 199]
	d) Endocrine therapy must not be administered during pregnancy.	EC		
	e) Surgery may be carried out in the same way as in non-pregnant patients.	EC		

1.4.3 Fertility preservation

No.	Recommendations/Statements	EG	LoE	Sources
7.6.	a) Patients of childbearing age with breast cancer must receive counselling about fertility and preserving fertility before starting cancer treatment.	EC		
	b) The administration of a GnRH analog before starting chemotherapy may be considered in all women who wish to preserve their ovarian function/fertility.	0	1b	[200–206]

1.5 Breast cancer in older patients

1.5.1 General comments

No.	Recommendations/Statements	EG	LoE	Sources
8.1.	Therapeutic decisions for older patients should be based on current standard recommendations but also take account of the patient's biological age, life-expectancy and preferences; the benefits and risks of such therapy must be weighed up.	EC		

1.5.2 Geriatric patients

No.	Recommendations/Statements	EG	LoE	Sources
8.2.	Patients who are older than 75 years should have a geriatric assessment or screening using a geriatric assessment algorithm, particularly if chemotherapy or surgery requiring a general anesthetic is planned, with the aim of improving therapy adherence, tolerance of chemotherapy and possibly survival.	B	2a	[207–210]
8.3.	Geriatric assessment and management should cover therapy-relevant geriatric domains (particularly functionality-related parameters such as activities of daily living, mobility, cognition, falls, and morbidity-related parameters such as multiple medication, nutrition, fatigue, and number of comorbidities) in order to adapt the choice of therapy accordingly and start supportive measures.	B	2a	[30, 211–214]

1.5.3 Local therapy

No.	Recommendations/Statements	EG	LoE	Sources
8.4.	a) Surgical therapy to treat older patients is basically no different from the surgical therapy used to treat younger patients.	EC		
	b) Patients with ER/PR-positive breast cancer: primary endocrine therapy should be started if surgery is not carried out because of the patient's frailty (e.g., comorbidities and higher anesthetic risk) or because the patient rejects surgery. When deciding on the appropriate therapy, any drug-related specific side effects, particularly the risk of thrombosis/embolism (tamoxifen) and the risk of bone fractures (aromatase inhibitors), must be taken into consideration.	B	1b	[215]
	c) Patients with ER- and PR-negative breast cancer: if surgery under general anesthesia is not carried out because of the patient's frailty (e.g. comorbidities and increased surgical risk) or because the patient rejects surgery, surgery under local anesthesia, primary radiotherapy or purely palliative medical treatment may be considered.	EC		

1.5.4 Adjuvant endocrine therapy

No.	Recommendations/Statements	EG	LoE	Sources
8.5.	Endocrine therapy is recommended for patients with hormone receptor-positive disease. Endocrine therapy may be dispensed with in individual cases (i.e., when treating patients with very low-grade tumors or very favorable tumor biology or if the patient is very frail).	0	2b	[213, 216]

1.5.5 Adjuvant chemotherapy

No.	Recommendations/Statements	EG	LoE	Sources
8.6.	As patients become frailer with increasing age, their reduced physical reserves and changes in their pharmacokinetics may lower the tolerability of chemotherapy and increase the rate of side effects requiring treatment.	EC		
8.7.	Chemotherapy may be associated with a significant reduction in cognitive performance in older women aged >70 years.		2b	[217, 218]
8.8.	Preference should be given to anthracycline and/or taxane-based combinations or sequential regimens. The increased risk of cardiotoxicity and of MDS/AML associated with anthracyclines must be taken into consideration.	B	2a	[219–227]

1.5.6 Anti-HER2 therapy

No.	Recommendations/Statements	EG	LoE	Sources
8.10.	Treatment is analogous to the treatment administered to younger patients and consists of trastuzumab combined sequential anthracycline-taxane-based chemotherapy. It is important to be aware of the increased risk of cardiotoxicity associated with this approach. (EC) An anthracycline-free combination consisting of carboplatin-docetaxel or docetaxel-cyclophosphamide may be used. (1b)		EC/1b	[214, 228–230]
8.11.	Paclitaxel administered weekly (over 12 weeks) with trastuzumab may be used to treat T1–2 (up to 3 cm) pN0 tumors.	0	2b	[231, 232]

1.6 Breast cancer in men

Breast cancer in men should be diagnosed and treated by an interdisciplinary group of specialists. Because of the type of tumor biology and the similarities to breast cancer in women, specialists for gynecologic oncology must also be involved when treating breast cancer in men. An interdisciplinary cooperation between

breast centers, gynecologists, urologists and andrologists is particularly advisable when treating sexual disorders caused by therapy with tamoxifen, men with BRCA mutations [233] who have an increased associated risk of prostate cancer, and men with breast cancer who must be treated for benign prostate syndrome [234].

No.	Recommendations/Statements	EG	LoE	Sources
9.1.	a) Patients must be encouraged to ask for medical counselling early on and provided with information about disease, particularly about symptoms and changes in the breast; they must be encouraged to monitor themselves. b) If there is a suspicion of malignancy, the initial investigation must include taking the patient's history, clinical examination, mammography, and ultrasound examination of the breast and of the lymphatic drainage areas. There are no data on the diagnostic use of CM-MRI. c) If there are malignant findings in the breast and axilla, further examinations with staging/investigation into the extent and spread of disease must be carried out in accordance with the recommendations made for women in the same situation, although there are no data on the diagnostic use of CM-MRI.	EC		
9.2.	a) The aim of surgery is complete resection of the tumor. Surgery should consist of a mastectomy. Breast-conserving surgery should be considered if the tumor is small enough. b) If the axilla are clinically unremarkable (cN0), sentinel lymph node resection must be carried out, with the same rules applying as for women.	EC		
9.3.	Irrespective of surgery, adjuvant radiotherapy of the thoracic wall and, if necessary, of the lymphatic drainage areas (the indications for this are the same as for women) must be carried out to treat large tumors (≥ 2 cm) and axillary lymph node involvement if the hormone receptor status is negative.	EC		
9.4.	When deciding whether adjuvant chemotherapy and antibody therapy (anti-HER2) are indicated, the same rules apply as for women and the same therapy must be carried out.	EC		
9.5.	Patients with hormone receptor-positive breast cancer must receive adjuvant endocrine therapy with tamoxifen, usually over a period of 5 years. There are no data available about treatment for more than 5 years. It may be considered in individual cases in the same way it would be considered when treating women.	EC		
9.6.	a) Metastatic disease should be treated according to the same rules as those used to treat women. b) It is not clear whether aromatase inhibitors are sufficiently effective in men without suppression of testicular function. Aromatase inhibitors should therefore be administered together with suppression of testicular function.	EC		

No.	Recommendations/Statements	EG	LoE	Sources
9.7.	Men with breast cancer should be offered the opportunity to participate in trials/be included in tumor registers.	EC		
9.8.	Genetic testing must be recommended to all men with breast cancer.	EC		
9.9.	The follow-up regimen including imaging evaluations must be analogous to the approach used for women.	EC		
9.10.	The patient should be provided with qualified and relevant gender-specific information (in print and online) by the professionals who treat them, and the patient should be helped to access the targeted support and information available from self-help groups.	EC		

► **Table 5** Risk factors for men to develop breast cancer.

Age	Unimodal age distribution; the highest incidence is in the 71st year of life
Ethnicity	Increased risk for men of African or Caribbean descent, who usually also have an advanced stage of disease when they are first diagnosed
Germline mutations	If the patient's family has a positive history of germline mutations for both sexes, they have a 2.5-fold higher risk of disease; BRCA-2 mutations were confirmed in 4–40% of all cases; RAD51B gene modifications increase the risk by 50%
Endocrine causes	Exposure to exogenous estrogen, e.g. hormone therapy for transsexuals, treatment of prostate cancer, professional exposure
	Increased endogenous estrogen synthesis: Klinefelter syndrome, obesity
	Decreased levels of androgen: orchiectomy, undescended testicle, mumps orchitis, cirrhosis of the liver
Environment	Lifestyle: obesity, lack of exercise, excessive consumption of alcohol
	Exposure to radiation: nuclear weapons, radiotherapy, diagnostic radiology
	Professional exposure: high temperatures, petroleum, exhaust gases

2 Therapy (Recurrence/Metastasis)

2.1 Therapy for local/loco-regional recurrence

2.1.1 Local (intramammary) recurrence

No.	Recommendations/Statements	EG	LoE	Sources
5.7.	a) If there is a suspicion of loco-regional recurrence, the first step must be histological verification including repeat determination of ER, PR and HER2/neu status and complete re-staging to exclude metastasis and make it possible to plan an interdisciplinary therapy strategy.	EC		
	b) The highest level of local tumor control in patients with intramammary recurrence (DCIS/invasive carcinoma) is achieved by secondary mastectomy.	EC		
	c) If the initial situation is favorable (e.g. DCIS or invasive carcinoma with a lengthy recurrence-free interval and no skin involvement), then breast-conserving surgery can be carried out again after careful counselling of the patient.	0	4a	[235 – 238]
	d) Prior to carrying out another breast-conserving surgery, the possibility of carrying out repeat radiotherapy (partial breast irradiation) should be investigated and discussed by an interdisciplinary tumor conference; if necessary, the patient should have an appointment with a radiotherapist.	EC		
	e) After breast-conserving surgery, the patient must be informed about the increased risk of repeat intramammary recurrence.	EC		

2.1.2 Local recurrence after mastectomy

No.	Recommendations/Statements	EG	LoE	Sources
5.8.	Any isolated recurrence in the thoracic wall must be completely resected (R0) where possible. If the main site of recurrence is the ribs/intercostal muscles, the decision for therapy should be taken after interdisciplinary consultation with a specialist for thoracic surgery.	EC		
5.9.	Local therapy (surgical intervention, radiotherapy) may be considered for symptomatic local recurrence (e.g. ulceration, pain) to reduce symptoms, even if the patient has distant metastasis.	EC		

2.1.3 Axillary lymph node recurrence

No.	Recommendations/Statements	EG	LoE	Sources
5.10.	In the event of axillary lymph node recurrence, local recurrence of disease should be controlled by repeat surgical axillary intervention, if need be with radiotherapy. Thoracic CT should be done preoperatively to identify the extent of LN metastasis.	EC		

2.1.4 Drug therapy

No.	Recommendations/Statements	EG	LoE	Sources
5.11.	Systemic therapy after R0 resection of loco-regional recurrence must be considered to prolong the disease-free interval and overall survival.	EC		

2.1.5 Radiotherapy

No.	Recommendations/Statements	EG	LoE	Sources
5.12.	a) The question whether radiation is indicated after surgery for recurrence must be discussed and decided by an interdisciplinary tumor board. Postoperative radiotherapy should be carried out if no radiotherapy was carried out previously or if the local recurrence was not radically resected (R1–2).	EC		
	b) Palliative radiotherapy, if necessary in combination with chemotherapy, may be used to treat inoperable local recurrence and control symptoms.	EC		
	c) If there is intramammary recurrence or recurrence in the thoracic wall after breast-conserving surgery (R0) or mastectomy (R0) which was not followed by radiotherapy, the decision whether adjuvant radiotherapy is indicated must follow the recommendations for primary disease.	EC		
	d) If intramammary recurrence occurs after breast-conserving surgery (R0) followed by radiotherapy, the question whether adjuvant radiotherapy is indicated must be discussed by an interdisciplinary tumor board. Radiotherapy may be indicated for patients who did not experience serious late sequelae after the 1st radiotherapy.	EC		
	e) In the event of recurrence in the thoracic wall after mastectomy (R0) followed by radiotherapy, the question whether repeat radiotherapy is indicated for local control should be discussed by an interdisciplinary tumor board.	EC		
	f) In the event of recurrence in the thoracic wall after primary mastectomy without subsequent radiotherapy, adjuvant radiotherapy should be carried out after resection of the recurrence (R0) if additional risk factors are present (very small resection margins, rpN+, G3, lymph node invasion).	EC		
	g) In the event of recurrence in the thoracic wall after primary mastectomy without subsequent radiotherapy, the question whether repeat adjuvant radiotherapy is indicated after resection of the recurrence (R0) when additional risk factors are present (very small resection margins, rpN+, G3, lymph node invasion) should be discussed by an interdisciplinary tumor board. Radiotherapy may be indicated for patients who did not experience serious late sequelae after the 1st radiotherapy.	EC		
	h) Additional radiotherapy must be recommended if recurrence occurs in an area which was not previously irradiated, the recurrence was not completely resected (R1/R2), and the risk associated with complete surgical resection (R0) cannot be justified.	EC		
	i) An interdisciplinary tumor board must decide whether repeat radiotherapy is indicated when recurrence occurs after prior radiotherapy, the recurrence was not completely resected (R1/R2), and the risk associated with complete surgical resection (R0) cannot be justified. Radiotherapy may be indicated in patients who did not experience serious late sequelae after the 1st radiotherapy.	EC		

2.2 Distant metastases

2.2.1 Systemic therapy for metastatic breast cancer

No.	Recommendations/Statements	EG	LoE	Sources
5.13.	Endocrine therapy ± targeted therapy is the therapy of choice for patients with hormone receptor-positive and HER2-negative cancer. Endocrine therapy is not indicated in patients for whom rapid remission is important to avoid pronounced symptoms in the affected organ.	A	1b	[30, 239–243]

No.	Recommendations/Statements	EG	LoE	Sources
5.14.	Combined chemo-endocrine therapy is not recommended. Although this approach can increase the rate of remission, it also leads to increased toxicity without prolonging the progression-free interval or improving overall survival.	A	1a	[244]
5.15.	In premenopausal patients, suppression of ovarian function (with GnRH analogs, oophorectomy) combined with tamoxifen is the first-choice therapy if treatment with tamoxifen was not concluded less than 12 months previously. An alternative approach consisting of suppression of ovarian function followed by the same treatment as that recommended for postmenopausal women may be chosen, and endocrine therapy may be combined with CDK 4/6 inhibitors.	A	1b	[30, 242, 245, 246]
5.16.	Subsequently, ovarian suppression combined with an aromatase inhibitor or fulvestrant, if necessary in combination with palbociclib, can be used to treat premenopausal patients. As long as ovarian suppression is maintained, treatment may be administered in the same way as therapy for postmenopausal patients.	0	2c/EC	[247, 248]
5.17.	In postmenopausal patients, the first step of endocrine treatment for metastasis should consist of an aromatase inhibitor if adjuvant therapy consisted exclusively of tamoxifen or the patient did not receive adjuvant therapy. It is not possible to give a clear recommendation whether primary endocrine treatment should consist of a steroidal or a non-steroidal aromatase inhibitor. Letrozole may be combined with a CDK 4/6 inhibitor.	A	1a	[30, 239, 242, 249–252]
5.18.	Treatment with fulvestrant should be carried out after pretreatment with an aromatase inhibitor, although fulvestrant may also be used as a first-line therapy, particularly for patients who have not previously received endocrine therapy.	EC		
5.19.	No specific therapy sequence is recommended. A combination treatment consisting of letrozole or fulvestrant with a CDK 4/6 inhibitor represents an alternative to monotherapy. Follow-up therapy with exemestane and the mTOR inhibitor everolimus may be administered after anti-hormonal pretreatment with a non-steroidal aromatase inhibitor. Studies have shown that combination therapies prolonged progression-free survival but it has not yet been proven that they improve overall survival.	EC		
5.20.	Depending on the patient's previous treatment, the next steps in the endocrine treatment sequence for postmenopausal patients consist of administration of antiestrogens, estrogen receptor antagonists, switching from a steroidal to a non-steroidal aromatase inhibitor or vice versa, or the use of high-dose progestogens. If disease progression continues during treatment with a non-steroidal aromatase inhibitor, patients may be treated with a combination of letrozole or fulvestrant with palbociclib or a combination of exemestane and everolimus.	EC		

2.2.2 Chemotherapy for metastatic breast cancer

No.	Recommendations/Statements	EG	LoE	Sources
5.21.	Before starting chemotherapy, the patient's general condition, co-morbidities and previous therapies must be evaluated and her probable compliance with treatment must be assessed.	EC		
5.22.	Regular evaluations of toxicity (subjective and objective) must be carried out during therapy. Treatment doses and scheduled treatment intervals must follow generally accepted standard regimens or recently published therapy regimens. After determining suitable representative parameters (symptoms, tumor markers, imaging) prior to starting therapy, the effect of treatment must be evaluated at least every 6–12 weeks according to clinical requirements. Over time, the intervals between imaging procedures can be extended for patients with sustained remission and a good clinical and laboratory assessment of disease status.	EC		
5.23.	Therapy should be discontinued if the patient has clinically relevant progression or toxicity is intolerable. Patients should not change to a different chemotherapy regimen unless the patient has documented progression or toxicity is intolerable.	EC		
5.24.	a) If chemotherapy is indicated, patients not in need of rapid remission should receive sequential chemotherapy.	B	1a	[253, 254]
	b) A combination therapy consisting of chemotherapy and bevacizumab may improve progression-free survival as a first-line therapy, but this approach is associated with a higher rate of side effects and has no impact on overall survival.	0	1a	[255–260]
	c) Polychemotherapy or chemotherapy + bevacizumab may be administered to patients with severe symptoms and rapid tumor growth or aggressive tumor behavior, i.e. to patients who urgently require remission.	0	1a	[253, 261]

2.2.2.1 Bevacizumab for metastatic breast cancer (1st line)

In summary, higher rates of remission and an improved PFS (but no survival benefit) has been reported for additional therapy with bevacizumab, which seems to indicate that combination therapy is the appropriate treatment for patients in urgent need of remis-

sion and no combination of risk factors predisposing them to side effects (no previous history of uncontrolled arterial hypertension, cerebrovascular ischemia and deep vein thrombosis). See the long version for more details.

2.2.2.2 Regimens

Specific information on the regimens are available in the long version of this guideline (in German).

No.	Recommendations/ Statements	EG	LoE	Sources
5.25.	Possible monotherapies can consist of the following substances: alkylating agents, anthraquinones, anthracyclines (also in liposomal form), eribulin, fluoropyrimidine, platinum complexes, taxanes, and vinorelbine. These substances can be combined with each another or with further substances for polychemotherapy. However, patients should only be treated with combinations that have previously been investigated in trials.	EC		

2.2.3 Metastatic HER2-positive breast cancer

No.	Recommendations/ Statements	EG	LoE	Sources
5.26.	Systemic therapy after R0 resection of loco-regional recurrence must be considered to prolong the disease-free interval and overall survival.	B	1a	[262, 263]
5.27.	First-line therapy for metastasized HER2-positive breast cancer should consist of a dual blockade with trastuzumab/pertuzumab and a taxane.	B	1b	[262]
5.28.	Second-line therapy for metastasized HER2-positive breast cancer should consist of therapy with T-DM1.	B	1b	[262]

2.2.4 Specific locations of metastases

2.2.4.1 Basic approach for distant metastasis

No.	Recommendations/ Statements	EG	LoE	Sources
5.29.	The decision whether distant metastases should be treated with surgery or local ablation should be made on an individual basis by an interdisciplinary tumor board.	EC		

2.2.4.2 Special treatment for skeletal metastases

For the diagnosis and therapy of skeletal metastasis, please refer to the S3 guideline on Supportive Therapy for Oncology Patients (<http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html>).

2.2.4.2.1 Indications for radiotherapy

No.	Recommendations/ Statements	EG	LoE	Sources
5.30.	Indications for local percutaneous radiotherapy for bone metastasis are: <ul style="list-style-type: none"> local pain, limited mobility, reduced stability (danger of fractures), s/p surgical stabilization, impending or existing neurological symptoms (e.g. compression of the spinal cord). 	EC		

2.2.4.2.2 Indications for surgical therapy

No.	Recommendations/ Statements	EG	LoE	Sources
5.31.	Indications for the surgical therapy of osseous manifestations may be: <ul style="list-style-type: none"> myeloid compression with neurological symptoms, pathological fracture, impending fracture (risk of fracture, e.g. based on Mirels' scoring system, the Spinal Instability Neoplastic Scale [SINS]), solitary late metastasis, osteolysis which does not respond to radiotherapy, pain which does not respond to treatment. 	EC		

2.2.4.2.3 Osteoprotective therapy

No.	Recommendations/ Statements	EG	LoE	Sources
5.32.	Osteoprotective therapy with bisphosphonates/denosumab should be carried out to prevent complications from osseous manifestations.	EC		

2.2.4.3 Treatment for brain metastasis

No.	Recommendations/Statements	EG	LoE	Sources
5.26.	<ul style="list-style-type: none"> Single or solitary brain metastases should be resected if the patient has an otherwise favorable prognosis and the metastasis is in a location which permits its resection, and the risk of postoperative neurological deficits resulting from resection is low. Local fractionated radiotherapy or radiosurgery of the tumor bed should be subsequently carried out. Radiosurgery represents an alternative to resection for patients with single metastases if the metastases are not larger than 3 cm and there is no midline shift with symptoms of intracranial compression. Primary treatment of infratentorial metastasis consists of resection, which should be carried out to prevent imminent occlusive hydrocephalus. If the patient only has a limited number of brain metastases (between 2–4) and their total volume can be treated with targeted radiation, initial radiosurgery is preferable to whole brain radiation therapy because of the lower negative impact on neurocognition, the shorter treatment time, and the better control rates. If surgery or radiosurgery cannot be carried out because of other negative prognostic criteria, the patient must receive whole brain radiation therapy alone. Whole brain radiation therapy alone must be used to treat patients with multiple brain metastases. A combination of resection or radiosurgery with whole brain radiation therapy improves the brain-specific progression-free survival compared to surgery or radiosurgery alone but does not improve overall survival. However, this approach can be considered in individual cases. It is not necessary to combine whole brain radiation therapy with radiosensitizing drugs. 		1b/EC	[264 – 273]

No.	Recommendations/Statements	EG	LoE	Sources
5.34.	If cerebral metastasis is present, the patient should also receive systemic therapy (chemotherapy/endocrine therapy/anti-HER2 therapy) in addition to local therapy (surgery/radiotherapy).	EC		

2.2.4.4 Treatment for liver metastases

No.	Recommendations/Statements	EG	LoE	Sources
5.35.	<p>If the patient has liver metastases, resection or another form of local therapy (RFA, TACE, SBRT, SIRT) may be indicated in individual cases; the preconditions for this are:</p> <ul style="list-style-type: none"> no disseminated metastases controlled extrahepatic metastasis 	0	3b	[274 – 285]

2.2.4.5 Treatment for lung metastases

No.	Recommendations/Statements	EG	LoE	Sources
5.36.	<p>Resection or another local therapy (RFA, stereotactic radiotherapy) may be indicated to treat individual patients with lung metastases; the preconditions for this are:</p> <ul style="list-style-type: none"> no disseminated metastases controlled extrapulmonary metastasis 	0	4	[286 – 290]

2.2.4.5.1 Malignant pleural effusion

No.	Recommendations/Statements	EG	LoE	Sources
5.37.	Patients with pleural carcinosis and symptomatic pleural effusions must be offered pleurodesis.	A	1a	[291]

2.2.4.6 Skin and soft tissue metastasis

No.	Recommendations/Statements	EG	LoE	Sources
5.34.	Surgical excision or another form of local therapy (e.g. radiotherapy) can be considered to treat skin and soft tissue metastasis.	EC		

Conflict of Interest

See <https://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/>

References

- [1] Moran MS, Schnitt SJ, Giuliano AE et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *J Clin Oncol* 2014; 32: 1507–1515
- [2] Department of Health. Diagnosis, staging and treatment of patients with breast cancer. National Clinical Guideline No. 7. June 2015. ISSN 2009-6259. Online: <https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/breast/>; last access: May 2016
- [3] Houssami N, Macaskill P, Marinovich ML et al. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol* 2014; 21: 717–730
- [4] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 365: 1687–1717
- [5] Fisher B, Anderson S, Tan-Chiu E et al. Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-23. *J Clin Oncol* 2001; 19: 931–942
- [6] Veronesi U, Cascinelli N, Mariani L et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002; 347: 1227–1232
- [7] Fisher B, Anderson S, Bryant J et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; 347: 1233–1241
- [8] Wald NJ, Murphy P, Major P et al. UKCCCR multicentre randomised controlled trial of one and two view mammography in breast cancer screening. *BMJ* 1995; 311: 1189–1193
- [9] Weaver DL, Krag DN, Ashikaga T et al. Pathologic analysis of sentinel and nonsentinel lymph nodes in breast carcinoma: a multicenter study. *Cancer* 2000; 88: 1099–1107
- [10] McCahill LE, Single RM, Aiello Bowles EJ et al. Variability in reexcision following breast conservation surgery. *JAMA* 2012; 307: 467–475
- [11] New Zealand Guidelines Group (NZGG). Management of Early Breast Cancer – Evidence-based Best Practice Guideline. New Zealand Guidelines Group (2009). Online: <https://www.health.govt.nz/system/files/documents/publications/mgmt-of-early-breast-cancer-aug09.pdf>; last access: 01.09.2016
- [12] Fisher B, Anderson S. Conservative surgery for the management of invasive and noninvasive carcinoma of the breast: NSABP trials. National Surgical Adjuvant Breast and Bowel Project. *World J Surg* 1994; 18: 63–69
- [13] Voogd AC, Nielsen M, Peterse JL et al. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *J Clin Oncol* 2001; 19: 1688–1697
- [14] De La Cruz L, Moody AM, Tappy EE et al. Overall Survival, Disease-Free Survival, Local Recurrence, and Nipple-Areolar Recurrence in the Setting of Nipple-Sparing Mastectomy: A Meta-Analysis and Systematic Review. *Ann Surg Oncol* 2015; 22: 3241–3249
- [15] Endara M, Chen D, Verma K et al. Breast reconstruction following nipple-sparing mastectomy: a systematic review of the literature with pooled analysis. *Plast Reconstr Surg* 2013; 132: 1043–1054
- [16] Lanitis S, Tekkis PP, Sgourakis G et al. Comparison of skin-sparing mastectomy versus non-skin-sparing mastectomy for breast cancer: a meta-analysis of observational studies. *Ann Surg* 2010; 251: 632–639
- [17] Piper M, Peled AW, Foster RD et al. Total skin-sparing mastectomy: a systematic review of oncologic outcomes and postoperative complications. *Ann Plast Surg* 2013; 70: 435–437
- [18] Gentilini O, Botteri E, Rotmensz N et al. Conservative surgery in patients with multifocal/multicentric breast cancer. *Breast Cancer Res Treat* 2009; 113: 577–583
- [19] Lynch SP, Lei X, Hsu L et al. Breast cancer multifocality and multicentricity and locoregional recurrence. *Oncologist* 2013; 18: 1167–1173
- [20] Neri A, Marrelli D, Megha T et al. Clinical significance of multifocal and multicentric breast cancers and choice of surgical treatment: a retrospective study on a series of 1158 cases. *BMC Surg* 2015; 15: 1
- [21] Patani N, Carpenter R. Oncological and aesthetic considerations of conservative surgery for multifocal/multicentric breast cancer. *Breast J* 2010; 16: 222–232
- [22] Shaikh T, Tam TY, Li T et al. Multifocal and multicentric breast cancer is associated with increased local recurrence regardless of surgery type. *Breast J* 2015; 21: 121–126
- [23] Tan MP, Sitoh NY, Sim AS. Breast conservation treatment for multifocal and multicentric breast cancers in women with small-volume breast tissue. *ANZ J Surg* 2017; 87: E5–E10. doi:10.1111/ans.12942
- [24] Wolters R, Wöckel A, Janni W et al. Comparing the outcome between multicentric and multifocal breast cancer: what is the impact on survival, and is there a role for guideline-adherent adjuvant therapy? A retrospective multicenter cohort study of 8,935 patients. *Breast Cancer Res Treat* 2013; 142: 579–590
- [25] Yerushalmi R, Tyldesley S, Woods R et al. Is breast-conserving therapy a safe option for patients with tumor multicentricity and multifocality? *Ann Oncol* 2012; 23: 876–881
- [26] Rhiem K, Engel C, Graeser M et al. The risk of contralateral breast cancer in patients from BRCA1/2 negative high risk families as compared to patients from BRCA1 or BRCA2 positive families: a retrospective cohort study. *Breast Cancer Res* 2012; 14: R156
- [27] Fayanju OM, Stoll CR, Fowler S et al. Contralateral prophylactic mastectomy after unilateral breast cancer: a systematic review and meta-analysis. *Ann Surg* 2014; 260: 1000–1010
- [28] Kurian AW, Lichtensztajn DY, Keegan TH et al. Use of and mortality after bilateral mastectomy compared with other surgical treatments for breast cancer in California, 1998–2011. *JAMA* 2014; 312: 902–914
- [29] Potter S, Brigid A, Whiting PF et al. Reporting clinical outcomes of breast reconstruction: a systematic review. *J Natl Cancer Inst* 2011; 103: 31–46
- [30] The National Institute for Health and Care Excellence (NICE). Advanced breast cancer: diagnosis and treatment. 2009 [addendum 2014]. Online: <https://www.nice.org.uk/guidance/cg81/evidence/addendum-242246990>
- [31] Lyman GH, Temin S, Edge SB et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2014; 32: 1365–1383
- [32] Krag DN, Anderson SJ, Julian TB et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol* 2010; 11: 927–933
- [33] Houssami N, Ciatto S, Turner RM et al. Preoperative ultrasound-guided needle biopsy of axillary nodes in invasive breast cancer: meta-analysis of its accuracy and utility in staging the axilla. *Ann Surg* 2011; 254: 243–251
- [34] Straver ME, Meijnen P, van Tienhoven G et al. Role of axillary clearance after a tumor-positive sentinel node in the administration of adjuvant therapy in early breast cancer. *J Clin Oncol* 2010; 28: 731–737
- [35] Giuliano AE, Hunt KK, Ballman KV et al. Axillary dissection vs. no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011; 305: 569–575
- [36] Galimberti V, Cole BF, Zurrada S et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol* 2013; 14: 297–305

- [37] Classe JM, Bordes V, Campion L et al. Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: results of Ganglion Sentinelle et Chimiothérapie Neoadjuvante, a French prospective multicentric study. *J Clin Oncol* 2009; 27: 726–732
- [38] Boughey JC, Suman VJ, Mittendorf EA et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA* 2013; 310: 1455–1461
- [39] Kuehn T, Bauerfeind I, Fehm T et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol* 2013; 14: 609–618
- [40] Clarke M, Collins R, Darby S et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 366: 2087–2106
- [41] Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Darby S, McGale P, Correa C et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011; 378: 1707–1716
- [42] Pötter R, Gnant M, Kwasny W et al. Lumpectomy plus tamoxifen or anastrozole with or without whole breast irradiation in women with favorable early breast cancer. *Int J Radiat Oncol Biol Phys* 2007; 68: 334–340
- [43] Hughes KS, Schnaper LA, Bellon JR et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol* 2013; 31: 2382–2387
- [44] Kunkler IH, Williams LJ, Jack WJ et al. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol* 2015; 16: 266–273
- [45] Blamey RW, Bates T, Chetty U et al. Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial. *Eur J Cancer* 2013; 49: 2294–2302
- [46] Fyles AW, McCreedy DR, Manchul LA et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med* 2004; 351: 963–970
- [47] Kauer-Dorner D, Pötter R, Resch A et al. Partial breast irradiation for locally recurrent breast cancer within a second breast conserving treatment: alternative to mastectomy? Results from a prospective trial. *Radiother Oncol* 2012; 102: 96–101
- [48] Owen JR, Ashton A, Bliss JM et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *Lancet Oncol* 2006; 7: 467–471
- [49] Haviland JS, Owen JR, Dewar JA et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013; 14: 1086–1094
- [50] Whelan TJ, Pignol JP, Levine MN et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; 362: 513–520
- [51] Yarnold J, Ashton A, Bliss J et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. *Radiother Oncol* 2005; 75: 9–17
- [52] START Trialists' Group; Bentzen SM, Agrawal RK, Aird EG et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008; 9: 331–341
- [53] START Trialists' Group, Bentzen SM, Agrawal RK, Aird EG et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008; 371: 1098–1107
- [54] Shaitelman SF, Schlembach PJ, Arzu I et al. Acute and Short-term Toxic Effects of Conventionally Fractionated vs. Hypofractionated Whole-Breast Irradiation: A Randomized Clinical Trial. *JAMA Oncol* 2015; 1: 931–941
- [55] Antonini N, Jones H, Horiot JC et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. *Radiother Oncol* 2007; 82: 265–271
- [56] Bartelink H, Maingon P, Poortmans P et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol* 2015; 16: 47–56
- [57] Vrieling C, van Werkhoven E, Maingon P et al. Prognostic Factors for Local Control in Breast Cancer After Long-term Follow-up in the EORTC Boost vs. No Boost Trial: A Randomized Clinical Trial. *JAMA Oncol* 2017; 3: 42–48
- [58] Romestaing P, Lehingue Y, Carrie C et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 1997; 15: 963–968
- [59] Polgár C, Van Limbergen E, Pötter R et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). *Radiother Oncol* 2010; 94: 264–273
- [60] Polgár C, Fodor J, Major T et al. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. *Radiother Oncol* 2013; 108: 197–202
- [61] Veronesi U, Orecchia R, Maisonneuve P et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* 2013; 14: 1269–1277
- [62] Vaidya JS, Wenz F, Bulsara M et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014; 383: 603–613
- [63] Strnad V, Ott OJ, Hildebrandt G et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet* 2016; 387: 229–238
- [64] Polgár C, Ott OJ, Hildebrandt G et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2017; 18: 259–268
- [65] EBCTCG (Early Breast Cancer Trialists' Collaborative Group); McGale P, Taylor C, Correa C et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; 383: 2127–2135
- [66] Gradishar WJ, Anderson BO, Balassanian R et al. Invasive breast cancer version 1.2016, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2016; 14: 324–354
- [67] Wang H, Kong L, Zhang C et al. Should all breast cancer patients with four or more positive lymph nodes who underwent modified radical mastectomy be treated with postoperative radiotherapy? A population-based study. *Oncotarget* 2016; 7: 75492–75502
- [68] Elmore L, Deshpande A, Daly M et al. Postmastectomy radiation therapy in T3 node-negative breast cancer. *J Surg Res* 2015; 199: 90–96

- [69] Francis SR, Frandsen J, Kokeny KE et al. Outcomes and utilization of post-mastectomy radiotherapy for T3N0 breast cancers. *Breast* 2017; 32: 156–161
- [70] Karlsson P, Cole BF, Chua BH et al. Patterns and risk factors for locoregional failures after mastectomy for breast cancer: an International Breast Cancer Study Group report. *Ann Oncol* 2012; 23: 2852–2858
- [71] Kyndi M, Overgaard M, Nielsen HM et al. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. *Radiother Oncol* 2009; 90: 74–79
- [72] Nagao T, Kinoshita T, Tamura N et al. Locoregional recurrence risk factors in breast cancer patients with positive axillary lymph nodes and the impact of postmastectomy radiotherapy. *Int J Clin Oncol* 2013; 18: 54–61
- [73] Danish Breast Cancer Cooperative Group; Nielsen HM, Overgaard M, Grau C et al. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. *J Clin Oncol* 2006; 24: 2268–2275
- [74] Recht A, Comen EA, Fine RE et al. Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update. *J Clin Oncol* 2016; 34: 4431–4442
- [75] Wang H, Zhang C, Kong L et al. Better survival in PMRT of female breast cancer patients with >5 negative lymph nodes: A population-based study. *Medicine (Baltimore)* 2017; 96: e5998
- [76] Heaton H, Kasem A, Almkubel R et al. Improvement of survival with postmastectomy radiotherapy in patients with 1–3 positive axillary lymph nodes: A systematic review and meta-analysis of the current literature. *Mol Clin Oncol* 2016; 5: 429–436
- [77] Valli MC. Controversies in loco-regional treatment: post-mastectomy radiation for pT2–pT3N0 breast cancer arguments in favour. *Crit Rev Oncol Hematol* 2012; 84 (Suppl. 1): e70–e74
- [78] Overgaard M, Hansen PS, Overgaard J et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997; 337: 949–955
- [79] Overgaard M, Jensen MB, Overgaard J et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomized trial. *Lancet* 1999; 353: 1641–1648
- [80] Rusthoven CG, Rabinovitch RA, Jones BL et al. The impact of postmastectomy and regional nodal radiation after neoadjuvant chemotherapy for clinically lymph node-positive breast cancer: a National Cancer Database (NCDB) analysis. *Ann Oncol* 2016; 27: 818–827
- [81] Mamounas EP, Anderson SJ, Dignam JJ et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. *J Clin Oncol* 2012; 30: 3960–3966
- [82] Kishan AU, McCloskey SA. Postmastectomy radiation therapy after neoadjuvant chemotherapy: review and interpretation of available data. *Ther Adv Med Oncol* 2016; 8: 85–97
- [83] Kantor O, Pesce C, Singh P et al. Post-mastectomy radiation therapy and overall survival after neoadjuvant chemotherapy. *J Surg Oncol* 2017; 115: 668–676. doi:10.1002/jso.24551
- [84] Poortmans PM, Collette S, Kirkove C et al. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med* 2015; 373: 317–327
- [85] Thorsen LB, Offersen BV, Danø H et al. DBCG-IMN: A Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer. *J Clin Oncol* 2016; 34: 314–320
- [86] Whelan TJ, Olivetto IA, Parulekar WR et al. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015; 373: 307–316
- [87] Hennequin C, Bossard N, Servagi-Vernat S et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. *Int J Radiat Oncol Biol Phys* 2013; 86: 860–866
- [88] Budach W, Bölke E, Kammers K et al. Adjuvant radiation therapy of regional lymph nodes in breast cancer – a meta-analysis of randomized trials- an update. *Radiat Oncol* 2015; 10: 258
- [89] Recht A, Edge SB, Solin LJ et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; 19: 1539–1569
- [90] Yates L, Kirby A, Crichton S et al. Risk factors for regional nodal relapse in breast cancer patients with one to three positive axillary nodes. *Int J Radiat Oncol Biol Phys* 2012; 82: 2093–2103
- [91] Causa L, Kirova YM, Gault N et al. The acute skin and heart toxicity of a concurrent association of trastuzumab and locoregional breast radiotherapy including internal mammary chain: a single-institution study. *Eur J Cancer* 2011; 47: 65–73
- [92] Shaffer R, Tyldesley S, Rolles M et al. Acute cardiotoxicity with concurrent trastuzumab and radiotherapy including internal mammary chain nodes: a retrospective single-institution study. *Radiother Oncol* 2009; 90: 122–126
- [93] Donker M, van Tienhoven G, Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC10981–22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014; 15: 1303–1310
- [94] Gruber G, Cole BF, Castiglione-Gertsch M et al. Extracapsular tumor spread and the risk of local, axillary and supraclavicular recurrence in node-positive, premenopausal patients with breast cancer. *Ann Oncol* 2008; 19: 1393–1401
- [95] Jaggi S, Chadha M, Moni J et al. Radiation field design in the ACOSOG Z0011 (Alliance) Trial. *J Clin Oncol* 2014; 32: 3600–3606
- [96] Bartelink H, Rubens RD, van der Schueren E et al. Hormonal therapy prolongs survival in irradiated locally advanced breast cancer: a European Organization for Research and Treatment of Cancer Randomized Phase III Trial. *J Clin Oncol* 1997; 15: 207–215
- [97] Scotti V, Desideri I, Meattini I et al. Management of inflammatory breast cancer: focus on radiotherapy with an evidence-based approach. *Cancer Treat Rev* 2013; 39: 119–124
- [98] Bellon JR, Come SE, Gelman RS et al. Sequencing of chemotherapy and radiation therapy in early-stage breast cancer: updated results of a prospective randomized trial. *J Clin Oncol* 2005; 23: 1934–1940
- [99] Hickey BE, Francis D, Lehman MH. Sequencing of chemotherapy and radiation therapy for early breast cancer. *Cochrane Database Syst Rev* 2006; (4): CD005212
- [100] Hickey BE, Francis DP, Lehman M. Sequencing of chemotherapy and radiotherapy for early breast cancer. *Cochrane Database Syst Rev* 2013; (4): CD005212
- [101] Pinnarò P, Rambone R, Giordano C et al. Long-term results of a randomized trial on the sequencing of radiotherapy and chemotherapy in breast cancer. *Am J Clin Oncol* 2011; 34: 238–244
- [102] Chen Z, King W, Pearcey R et al. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. *Radiother Oncol* 2008; 87: 3–16
- [103] Huang J, Barbera L, Brouwers M et al. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. *J Clin Oncol* 2003; 21: 555–563
- [104] Halyard MY, Pisansky TM, Dueck AC et al. Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCTG Phase III Trial N9831. *J Clin Oncol* 2009; 27: 2638–2644

- [105] Li YF, Chang L, Li WH et al. Radiotherapy concurrent versus sequential with endocrine therapy in breast cancer: A meta-analysis. *Breast* 2016; 27: 93–98
- [106] Goldhirsch A, Wood WC, Coates AS et al. Strategies for subtypes – dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol* 2011; 22: 1736–1747
- [107] Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1998; 352: 930–942
- [108] Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Davies C, Godwin J, Gray R et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011; 378: 771–784
- [109] Fisher B, Dignam J, Wolmark N et al. Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. *J Natl Cancer Inst* 1997; 89: 1673–1682
- [110] The International Breast Cancer Study Group; Thürlimann B, Price KN, Castiglione M et al. Randomized controlled trial of ovarian function suppression plus tamoxifen versus the same endocrine therapy plus chemotherapy: Is chemotherapy necessary for premenopausal women with node-positive, endocrine-responsive breast cancer? First results of International Breast Cancer Study Group Trial 11-93. *The Breast* 2001; 10: 130–138
- [111] Burstein HJ, Temin S, Anderson H et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *J Clin Oncol* 2014; 32: 2255–2269
- [112] Davies C, Pan H, Godwin J et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013; 381: 805–816
- [113] Gray RG, Rea D, Handley K. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. *J Clin Oncol* 2013; 31: 18_suppl, 5-5
- [114] Rea DW, Gray RG, Bowden SJ. Overall and subgroup findings of the aTTom trial: A randomised comparison of continuing adjuvant tamoxifen to 10 years compared to stopping after 5 years in 6953 women with ER positive or ER untested early breast cancer. *Eur J Cancer* 2013; 49: S402
- [115] Eisen A, Fletcher GG, Gandhi S et al. Optimal Systemic Therapy for Early Female Breast Cancer. Toronto (ON): Cancer Care Ontario; 2014 Sep 30. Program in Evidence-Based Care Evidence-Based Series No.: 1–21
- [116] Ferguson T, Wilcken N, Vagg R et al. Taxanes for adjuvant treatment of early breast cancer. *Cochrane Database Syst Rev* 2007; (4): CD004421
- [117] Sparano JA, Zhao F, Martino S et al. Long-Term Follow-Up of the E1199 Phase III Trial Evaluating the Role of Taxane and Schedule in Operable Breast Cancer. *J Clin Oncol* 2015; 33: 2353–2360
- [118] Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Peto R, Davies C, Godwin J et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet* 2012; 379: 432–444
- [119] EBM Reviews. Multi-agent chemotherapy for early breast cancer. *Cochrane Database Syst Rev* 2003
- [120] Budman DR, Berry DA, Cirincione CT et al. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. *J Natl Cancer Inst* 1998; 90: 1205–1211
- [121] Fisher B, Anderson S, Wickerham DL et al. Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-22. *J Clin Oncol* 1997; 15: 1858–1869
- [122] French Adjuvant Study Group. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 randomized trial. *J Clin Oncol* 2001; 19: 602–611
- [123] Fumoleau P, Kerbrat P, Romestaing P et al. Randomized trial comparing six versus three cycles of epirubicin-based adjuvant chemotherapy in premenopausal, node-positive breast cancer patients: 10-year follow-up results of the French Adjuvant Study Group 01 trial. *J Clin Oncol* 2003; 21: 298–305
- [124] Swain SM, Jeong JH, Geyer CE jr. et al. Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. *N Engl J Med* 2010; 362: 2053–2065
- [125] Bonadonna G, Zambetti M, Valagussa P. Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes. Ten-year results. *JAMA* 1995; 273: 542–547
- [126] Citron ML, Berry DA, Cirincione C et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003; 21: 1431–1439
- [127] Eiermann W, Pienkowski T, Crown J et al. Phase III study of doxorubicin/cyclophosphamide with concomitant versus sequential docetaxel as adjuvant treatment in patients with human epidermal growth factor receptor 2-normal, node-positive breast cancer: BCIRG-005 trial. *J Clin Oncol* 2011; 29: 3877–3884
- [128] Francis P, Crown J, Di Leo A et al. Adjuvant chemotherapy with sequential or concurrent anthracycline and docetaxel: Breast International Group 02-98 randomized trial. *J Natl Cancer Inst* 2008; 100: 121–133
- [129] Moebus V, Jackisch C, Lueck HJ et al. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. *J Clin Oncol* 2010; 28: 2874–2880
- [130] Del Mastro L, De Placido S, Bruzzi P et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial. *Lancet* 2015; 385: 1863–1872
- [131] Bria E, Nistico C, Cuppone F et al. Benefit of taxanes as adjuvant chemotherapy for early breast cancer: pooled analysis of 15,500 patients. *Cancer* 2006; 106: 2337–2344
- [132] Clavarezza M, Del Mastro L, Venturini M. Taxane-containing chemotherapy in the treatment of early breast cancer patients. *Ann Oncol* 2006; 17 (Suppl. 7): vii22–vii26
- [133] Estévez LG, Muñoz M, Alvarez I et al. Evidence-based use of taxanes in the adjuvant setting of breast cancer. A review of randomized phase III trials. *Cancer Treat Rev* 2007; 33: 474–483
- [134] Henderson IC, Berry DA, Demetri GD et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol* 2003; 21: 976–983
- [135] Mamounas EP, Bryant J, Lembersky B et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. *J Clin Oncol* 2005; 23: 3686–3696
- [136] Roché H, Fumoleau P, Spielmann M et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS01 Trial. *J Clin Oncol* 2006; 24: 5664–5671
- [137] Blum JL, Flynn PJ, Yothers G et al. Anthracyclines in Early Breast Cancer: The ABC Trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). *J Clin Oncol* 2017; 35: 2647–2655

- [138] Ejlertsen B, Tuxen MK, Jakobsen EH et al. Adjuvant Cyclophosphamide and Docetaxel With or Without Epirubicin for Early TOP2A-Normal Breast Cancer: DBCG 07-READ, an Open-Label, Phase III, Randomized Trial. *J Clin Oncol* 2017; 35: 2639–2646. doi:10.1200/JCO.2017.72.3494
- [139] Harbeck N, Gluz O, Clemens MR et al. Prospective WSG phase III PlanB trial: Final analysis of adjuvant 4xEC→4x doc vs. 6x docetaxel/cyclophosphamide in patients with high clinical risk and intermediate-to-high genomic risk HER2-negative, early breast cancer. *J Clin Oncol* 2017; 35:15_suppl, 504-504
- [140] von Minckwitz G, Untch M, Nüesch E et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. *Breast Cancer Res Treat* 2011; 125: 145–156
- [141] Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014; 384: 164–172
- [142] Kaufmann M, Hortobagyi GN, Goldhirsch A et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. *J Clin Oncol* 2006; 24: 1940–1949
- [143] Bear HD, Anderson S, Smith RE et al. Sequential preoperative or post-operative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 2006; 24: 2019–2027
- [144] von Minckwitz G, Blohmer JU, Raab G et al. In vivo chemosensitivity-adapted preoperative chemotherapy in patients with early-stage breast cancer: the GEPARTRIO pilot study. *Ann Oncol* 2005; 16: 56–63
- [145] Petrelli F, Barni S. Meta-analysis of concomitant compared to sequential adjuvant trastuzumab in breast cancer: the sooner the better. *Med Oncol* 2012; 29: 503–510
- [146] Pfeilschifter J, Diel IJ. Osteoporosis due to cancer treatment: pathogenesis and management. *J Clin Oncol* 2000; 18: 1570–1593
- [147] Gnant M, Mlineritsch B, Schippinger W et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009; 360: 679–691
- [148] Gnant M, Mlineritsch B, Stoeger H et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. *Lancet Oncol* 2011; 12: 631–641
- [149] Hadji P, Kauka A, Ziller M et al. Effects of zoledronic acid on bone mineral density in premenopausal women receiving neoadjuvant or adjuvant therapies for HR+ breast cancer: the ProBONE II study. *Osteoporos Int* 2014; 25: 1369–1378
- [150] Gnant M, Pfeiler G, Dubsy PC et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015; 386: 433–443
- [151] Kalder M, Hans D, Kyvernitakis I et al. Effects of Exemestane and Tamoxifen treatment on bone texture analysis assessed by TBS in comparison with bone mineral density assessed by DXA in women with breast cancer. *J Clin Densitom* 2014; 17: 66–71
- [152] Hadji P, Asmar L, van Nes JG et al. The effect of exemestane and tamoxifen on bone health within the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial: a meta-analysis of the US, German, Netherlands, and Belgium sub-studies. *J Cancer Res Clin Oncol* 2011; 137: 1015–1025
- [153] Rabaglio M, Sun Z, Price KN et al. Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial. *Ann Oncol* 2009; 20: 1489–1498
- [154] Greep NC, Giuliano AE, Hansen NM et al. The effects of adjuvant chemotherapy on bone density in postmenopausal women with early breast cancer. *Am J Med* 2003; 114: 653–659
- [155] Hadji P, Ziller M, Maskow C et al. The influence of chemotherapy on bone mineral density, quantitative ultrasonometry and bone turnover in pre-menopausal women with breast cancer. *Eur J Cancer* 2009; 45: 3205–3212
- [156] Kanis JA, Oden A, Johnell O et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 2007; 18: 1033–1046
- [157] Frost SA, Nguyen ND, Center JR et al. Timing of repeat BMD measurements: development of an absolute risk-based prognostic model. *J Bone Miner Res* 2009; 24: 1800–1807
- [158] Coleman R, Cameron D, Dodwell D et al. Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial. *Lancet Oncol* 2014; 15: 997–1006
- [159] Col NF, Hirota LK, Orr RK et al. Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. *J Clin Oncol* 2001; 19: 2357–2363
- [160] Pantel K, Alix-Panabieres C, Riethdorf S. Cancer micrometastases. *Nat Rev Clin Oncol* 2009; 6: 339–351
- [161] Wilson C, Holen I, Coleman RE. Seed, soil and secreted hormones: potential interactions of breast cancer cells with their endocrine/paracrine microenvironment and implications for treatment with bisphosphonates. *Cancer Treat Rev* 2012; 38: 877–889
- [162] Domschke C, Diel IJ, Englert S et al. Prognostic value of disseminated tumor cells in the bone marrow of patients with operable primary breast cancer: a long-term follow-up study. *Ann Surg Oncol* 2013; 20: 1865–1871
- [163] Banys M, Solomayer EF, Gebauer G et al. Influence of zoledronic acid on disseminated tumor cells in bone marrow and survival: results of a prospective clinical trial. *BMC Cancer* 2013; 13: 480
- [164] Ben-Aharon I, Vidal L, Rizel S et al. Bisphosphonates in the adjuvant setting of breast cancer therapy – effect on survival: a systematic review and meta-analysis. *PLoS One* 2013; 8: e70044
- [165] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet* 2015; 386: 1353–1361
- [166] Coleman R, Body JJ, Aapro M et al. Bone health in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol* 2014; 25 (Suppl. 3): iii124–iii137
- [167] Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). Supportive Therapie bei onkologischen PatientInnen-Konsultationsfassung, Langversion, 2016, AWMF Registernummer: 032-054OL, 2016. Online: <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html>; last access: 13.10.2016
- [168] Grunfeld E, Dhesy-Third S, Levine M. Clinical practice guidelines for the care and treatment of breast cancer: follow-up after treatment for breast cancer (summary of the 2005 update). *CMAJ* 2005; 172: 1319–1320
- [169] Hauner D, Janni W, Rack B et al. The effect of overweight and nutrition on prognosis in breast cancer. *Dtsch Arztebl Int* 2011; 108: 795–801
- [170] Voskuil DW, van Nes JG, Junggeburst JM et al. Maintenance of physical activity and body weight in relation to subsequent quality of life in postmenopausal breast cancer patients. *Ann Oncol* 2010; 21: 2094–2101
- [171] Rock CL, Doyle C, Demark-Wahnefried W et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin* 2012; 62: 243–274
- [172] Cheema BS, Kilbreath SL, Fahey PP et al. Safety and efficacy of progressive resistance training in breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2014; 148: 249–268

- [173] Courneya KS, McKenzie DC, Mackey JR et al. Subgroup effects in a randomised trial of different types and doses of exercise during breast cancer chemotherapy. *Br J Cancer* 2014; 111: 1718–1725
- [174] Irwin ML, Cartmel B, Gross CP et al. Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. *J Clin Oncol* 2015; 33: 1104–1111
- [175] Steindorf K, Schmidt ME, Klassen O et al. Randomized, controlled trial of resistance training in breast cancer patients receiving adjuvant radiotherapy: results on cancer-related fatigue and quality of life. *Ann Oncol* 2014; 25: 2237–2243
- [176] Furmaniak AC, Menig M, Markes MH. Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database Syst Rev* 2016; (9): CD005001
- [177] Meneses-Echavez JF, Gonzalez-Jimenez E, Ramirez-Velez R. Effects of supervised exercise on cancer-related fatigue in breast cancer survivors: a systematic review and meta-analysis. *BMC Cancer* 2015; 15: 77
- [178] Bower JE, Bak K, Berger A et al. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. *J Clin Oncol* 2014; 32: 1840–1850
- [179] Carayol M, Bernard P, Boiché J et al. Psychological effect of exercise in women with breast cancer receiving adjuvant therapy: what is the optimal dose needed? *Ann Oncol* 2013; 24: 291–300
- [180] Mishra SI, Scherer RW, Geigle PM et al. Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev* 2012; (8): CD007566
- [181] Streckmann F, Kneis S, Leifert JA et al. Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. *Ann Oncol* 2014; 25: 493–499
- [182] Keilani M, Hasenoehrl T, Neubauer M et al. Resistance exercise and secondary lymphedema in breast cancer survivors – a systematic review. *Support Care Cancer* 2016; 24: 1907–1916
- [183] Nelson NL. Breast Cancer-Related Lymphedema and Resistance Exercise: A Systematic Review. *J Strength Cond Res* 2016; 30: 2656–2665
- [184] Bok SK, Jeon Y, Hwang PS. Ultrasonographic Evaluation of the Effects of Progressive Resistive Exercise in Breast Cancer-Related Lymphedema. *Lymphat Res Biol* 2016; 14: 18–24
- [185] Letellier ME, Towers A, Shimony A et al. Breast cancer-related lymphedema: a randomized controlled pilot and feasibility study. *Am J Phys Med Rehabil* 2014; 93: 751–759; quiz 760–761
- [186] Cormie P, Galvão DA, Spry N et al. Neither heavy nor light load resistance exercise acutely exacerbates lymphedema in breast cancer survivor. *Integr Cancer Ther* 2013; 12: 423–432
- [187] Cormie P, Pumpa K, Galvão DA et al. Is it safe and efficacious for women with lymphedema secondary to breast cancer to lift heavy weights during exercise: a randomised controlled trial. *J Cancer Surviv* 2013; 7: 413–424
- [188] Runowicz CD, Leach CR, Henry NL et al. American Cancer society/ American society of clinical oncology breast Cancer survivorship care guideline. *CA Cancer J Clin* 2016; 66: 43–73
- [189] Nechuta S, Chen WY, Cai H et al. A pooled analysis of post-diagnosis lifestyle factors in association with late estrogen-receptor-positive breast cancer prognosis. *Int J Cancer* 2016; 138: 2088–2097
- [190] Azim HA jr., Kroman N, Paesmans M et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. *J Clin Oncol* 2013; 31: 73–79
- [191] Azim HA jr., Santoro L, Pavlidis N et al. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. *Eur J Cancer* 2011; 47: 74–83
- [192] Goldrat O, Kroman N, Peccatori FA et al. Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome. *Eur J Cancer* 2015; 51: 1490–1496
- [193] Lambertini M, Del Mastro L, Pescio MC et al. Cancer and fertility preservation: international recommendations from an expert meeting. *BMC Med* 2016; 14: 1
- [194] Gennari A, Costa M, Puntoni M et al. Breast cancer incidence after hormonal treatments for infertility: systematic review and meta-analysis of population-based studies. *Breast Cancer Res Treat* 2015; 150: 405–413
- [195] Luke B, Brown MB, Missmer SA et al. Assisted reproductive technology use and outcomes among women with a history of cancer. *Hum Reprod* 2016; 31: 183–189
- [196] Loibl S, Han SN, von Minckwitz G et al. Treatment of breast cancer during pregnancy: an observational study. *Lancet Oncol* 2012; 13: 887–896
- [197] Loibl S, Schmidt A, Gentilini O et al. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. *JAMA Oncol* 2015; 1: 1145–1153
- [198] National Toxicology Program. NTP Monograph: Developmental Effects and Pregnancy Outcomes Associated With Cancer Chemotherapy Use During Pregnancy. *NTP Monogr* 2013; (2): i–214
- [199] Zagouri F, Sergentanis TN, Chrysikos D et al. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2013; 137: 349–357
- [200] Del Mastro L, Rossi G, Lambertini M et al. New insights on the role of luteinizing hormone releasing hormone agonists in premenopausal early breast cancer patients. *Cancer Treat Rev* 2016; 42: 18–23
- [201] Vitek WS, Shayne M, Hoeger K et al. Gonadotropin-releasing hormone agonists for the preservation of ovarian function among women with breast cancer who did not use tamoxifen after chemotherapy: a systematic review and meta-analysis. *Fertil Steril* 2014; 102: 808–815.e1
- [202] Moore HC, Unger JM, Phillips KA et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med* 2015; 372: 923–932
- [203] Del Mastro L, Boni L, Michelotti A et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. *JAMA* 2011; 306: 269–276
- [204] Lambertini M, Boni L, Michelotti A et al. Ovarian Suppression With Triptorelin During Adjuvant Breast Cancer Chemotherapy and Long-term Ovarian Function, Pregnancies, and Disease-Free Survival: A Randomized Clinical Trial. *JAMA* 2015; 314: 2632–2640
- [205] Gerber B, von Minckwitz G, Stehle H et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. *J Clin Oncol* 2011; 29: 2334–2341
- [206] Munster PN, Moore AP, Ismail-Khan R et al. Randomized trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo)adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2012; 30: 533–538
- [207] Kalsi T, Babic-Illman G, Ross PJ et al. The impact of comprehensive geriatric assessment interventions on tolerance to chemotherapy in older people. *Br J Cancer* 2015; 112: 1435–1444
- [208] Hall DE, Arya S, Schmid KK et al. Association of a Frailty Screening Initiative With Postoperative Survival at 30, 180, and 365 Days. *JAMA Surg* 2017; 152: 233–240
- [209] Le Saux O, Ripamonti B, Bruyas A et al. Optimal management of breast cancer in the elderly patient: current perspectives. *Clin Interv Aging* 2015; 10: 157–174
- [210] Decoster L, Van Puyvelde K, Mohile S et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†. *Ann Oncol* 2015; 26: 288–300

- [211] Clough-Gorr KM, Stuck AE, Thwin SS et al. Older breast cancer survivors: geriatric assessment domains are associated with poor tolerance of treatment adverse effects and predict mortality over 7 years of follow-up. *J Clin Oncol* 2010; 28: 380–386
- [212] Mislang AR, Biganzoli L. Adjuvant Systemic Therapy in Older Breast Cancer Women: Can We Optimize the Level of Care? *Cancers (Basel)* 2015; 7: 1191–1214
- [213] Biganzoli L, Wildiers H, Oakman C et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012; 13: e148–e160
- [214] Thavarajah N, Menjak I, Trudeau M et al. Towards an optimal multidisciplinary approach to breast cancer treatment for older women. *Can Oncol Nurs J* 2015; 25: 384–408
- [215] Morgan J, Wyld L, Collins KA et al. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). *Cochrane Database Syst Rev* 2014; (5): CD004272. doi:10.1002/14651858.CD004272.pub3
- [216] Christiansen P, Bjerre K, Ejlersen B et al. Mortality rates among early-stage hormone receptor-positive breast cancer patients: a population-based cohort study in Denmark. *J Natl Cancer Inst* 2011; 103: 1363–1372
- [217] Lange M, Heutte N, Rigal O et al. Decline in Cognitive Function in Older Adults With Early-Stage Breast Cancer After Adjuvant Treatment. *Oncologist* 2016; 21: 1337–1348. doi:10.1634/theoncologist.2016-0014
- [218] Ono M, Ogilvie JM, Wilson JS et al. A meta-analysis of cognitive impairment and decline associated with adjuvant chemotherapy in women with breast cancer. *Front Oncol* 2015; 5: 59
- [219] Jones S, Holmes FA, O'Shaughnessy J et al. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. *J Clin Oncol* 2009; 27: 1177–1183
- [220] Perrone F, Nuzzo F, Di Rella F et al. Weekly docetaxel versus CMF as adjuvant chemotherapy for older women with early breast cancer: final results of the randomized phase III ELDA trial. *Ann Oncol* 2015; 26: 675–682
- [221] Biganzoli L, Aapro M, Loibl S et al. Taxanes in the treatment of breast cancer: Have we better defined their role in older patients? A position paper from a SIOG Task Force. *Cancer Treat Rev* 2016; 43: 19–26
- [222] Muss HB, Berry DA, Cirrincione CT et al. Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med* 2009; 360: 2055–2065
- [223] Freyer G, Campone M, Peron J et al. Adjuvant docetaxel/cyclophosphamide in breast cancer patients over the age of 70: results of an observational study. *Crit Rev Oncol Hematol* 2011; 80: 466–473
- [224] Loibl S, von Minckwitz G, Harbeck N et al. Clinical feasibility of (neo)-adjuvant taxane-based chemotherapy in older patients: analysis of >4,500 patients from four German randomized breast cancer trials. *Breast Cancer Res* 2008; 10: R77
- [225] Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer* 2003; 97: 2869–2879
- [226] Freedman RA, Seisler DK, Foster JC et al. Risk of acute myeloid leukemia and myelodysplastic syndrome among older women receiving anthracycline-based adjuvant chemotherapy for breast cancer on Modern Cooperative Group Trials (Alliance A151511). *Breast Cancer Res Treat* 2017; 161: 363–373
- [227] Pinder MC, Duan Z, Goodwin JS et al. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol* 2007; 25: 3808–3815
- [228] Dall P, Lenzen G, Göhler T et al. Trastuzumab in the treatment of elderly patients with early breast cancer: Results from an observational study in Germany. *J Geriatr Oncol* 2015; 6: 462–469
- [229] Brollo J, Curigliano G, Disalvatore D et al. Adjuvant trastuzumab in elderly with HER-2 positive breast cancer: a systematic review of randomized controlled trials. *Cancer Treat Rev* 2013; 39: 44–50
- [230] Jones SE, Savin MA, Holmes FA et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol* 2006; 24: 5381–5387
- [231] Dang C, Guo H, Najita J et al. Cardiac Outcomes of Patients Receiving Adjuvant Weekly Paclitaxel and Trastuzumab for Node-Negative, ERBB2-Positive Breast Cancer. *JAMA Oncol* 2016; 2: 29–36
- [232] Tolaney SM, Barry WT, Dang CT et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med* 2015; 372: 134–141
- [233] Castro E, Goh C, Olmos D et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol* 2013; 31: 1748–1757
- [234] Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM, Bonn); Paul-Ehrlich-Institut (PEI, Langen). BfArM Bulletin zur Arzneimittelsicherheit. 2010. Online: https://www.bfarm.de/DE/Arzneimittel/Pharmakovigilanz/Bulletin/_node.html
- [235] Deutsch M. Repeat high-dose external beam irradiation for in-breast tumor recurrence after previous lumpectomy and whole breast irradiation. *Int J Radiat Oncol Biol Phys* 2002; 53: 687–691
- [236] Haffty BG, Reiss M, Beinfield M et al. Ipsilateral breast tumor recurrence as a predictor of distant disease: implications for systemic therapy at the time of local relapse. *J Clin Oncol* 1996; 14: 52–57
- [237] Kurtz JM, Jacquemier J, Amalric R et al. Is breast conservation after local recurrence feasible? *Eur J Cancer* 1991; 27: 240–244
- [238] Whelan T, Clark R, Roberts R et al. Ipsilateral breast tumor recurrence postlumpectomy is predictive of subsequent mortality: results from a randomized trial. Investigators of the Ontario Clinical Oncology Group. *Int J Radiat Oncol Biol Phys* 1994; 30: 11–16
- [239] Fossati R, Confalonieri C, Torri V et al. Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. *J Clin Oncol* 1998; 16: 3439–3460
- [240] Stockler M, Wilcken N, Ghersi D, Simes RJ. The management of advanced breast cancer: systemic reviews of randomised controlled trials regarding the use of cytotoxic chemotherapy and endocrine therapy. Woolloomooloo: NHMRC National Breast Cancer Centre; 1997
- [241] Stockler M, Wilcken NR, Ghersi D et al. Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer. *Cancer Treat Rev* 2000; 26: 151–168
- [242] Rugo HS, Rumble RB, Macrae E et al. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. *J Clin Oncol* 2016; 34: 3069–3103
- [243] Partridge AH, Rumble RB, Carey LA et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2014; 32: 3307–3329
- [244] Sledge GW jr., Hu P, Falkson G et al. Comparison of chemotherapy with chemohormonal therapy as first-line therapy for metastatic, hormone-sensitive breast cancer: An Eastern Cooperative Oncology Group study. *J Clin Oncol* 2000; 18: 262–266
- [245] Klijn JG, Blamey RW, Boccardo F et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001; 19: 343–353

- [246] National Breast and Ovarian Cancer Centre. Recommendations for follow-up of women with early breast cancer. SurryHills, NSW: National Breast and Ovarian Cancer Centre; 2010. Online: https://guidelines.cancer australia.gov.au/guidelines/early_breast_cancer/
- [247] Taylor CW, Green S, Dalton WS et al. Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. *J Clin Oncol* 1998; 16: 994–999
- [248] Loibl S, Turner NC, Ro J et al. Palbociclib (PAL) in combination with fulvestrant (F) in pre-/peri-menopausal (PreM) women with metastatic breast cancer (MBC) and prior progression on endocrine therapy – results from Paloma-3. *J Clin Oncol* 2016; 34 (Suppl.): Abstr. 524
- [249] Ellis M, Hayes D, Lippman M. Treatment of metastatic breast cancer. *Cancer* 2000; 2000: 749–797
- [250] Hayes DF, Henderson IC, Shapiro CL. Treatment of metastatic breast cancer: present and future prospects. *Semin Oncol* 1995; 22 (2 Suppl. 5): 5–19; discussion 19–21
- [251] Mouridsen H, Gershanovich M, Sun Y et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 2001; 19: 2596–2606
- [252] Mouridsen H, Sun Y, Gershanovich M et al. First-line therapy with letrozole (femara®) for advanced breast cancer prolongs time to worsening of Karnofsky Performance Status compared with tamoxifen. *Breast Cancer Res Treat* 2001; 69: 185. doi:10.1023/A:1017475415273
- [253] Dear RF, McGeechan K, Jenkins MC et al. Combination versus sequential single agent chemotherapy for metastatic breast cancer. *Cochrane Database Syst Rev* 2013; (12): CD008792
- [254] Sledge GW, Neuberg D, Bernardo P et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol* 2003; 21: 588–592
- [255] Miller K, Wang M, Gralow J et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007; 357: 2666–2676
- [256] Gray R, Bhattacharya S, Bowden C et al. Independent review of E2100: a phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. *J Clin Oncol* 2009; 27: 4966–4972
- [257] Robert NJ, Diéras V, Glaspy J et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2–negative, locally recurrent or metastatic breast cancer. *J Clin Oncol* 2011; 29: 1252–1260
- [258] Welt A, Marschner N, Lerchenmueller C et al. Capecitabine and bevacizumab with or without vinorelbine in first-line treatment of HER2/neu-negative metastatic or locally advanced breast cancer: final efficacy and safety data of the randomised, open-label superiority phase 3 CARIN trial. *Breast Cancer Res Treat* 2016; 156: 97–107
- [259] Lang I, Brodowicz T, Ryvo L et al. Bevacizumab plus paclitaxel versus bevacizumab plus capecitabine as first-line treatment for HER2-negative metastatic breast cancer: interim efficacy results of the randomised, open-label, non-inferiority, phase 3 TURANDOT trial. *Lancet Oncol* 2013; 14: 125–133
- [260] Zielinski C, Láng I, Inbar M et al. Bevacizumab plus paclitaxel versus bevacizumab plus capecitabine as first-line treatment for HER2-negative metastatic breast cancer (TURANDOT): primary endpoint results of a randomised, open-label, non-inferiority, phase 3 trial. *Lancet Oncol* 2016; 17: 1230–1239
- [261] Carrick S, Parker S, Wilcken N et al. Single agent versus combination chemotherapy for metastatic breast cancer. *Cochrane Database Syst Rev* 2005; (2): CD003372
- [262] Giordano SH, Temin S, Kirshner JJ et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2014; 32: 2078–2099
- [263] Balduzzi S, Mantarro S, Guarneri V et al. Trastuzumab-containing regimens for metastatic breast cancer. *Cochrane Database Syst Rev* 2014; (6): CD006242
- [264] Kalkanis SN, Kondziolka D, Gaspar LE et al. The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neuro-oncol* 2010; 96: 33–43
- [265] Patchell RA, Tibbs PA, Walsh JW et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990; 322: 494–500
- [266] Vecht CJ, Haaxma-Reiche H, Noordijk EM et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol* 1993; 33: 583–590
- [267] Patchell RA, Tibbs PA, Regine WF et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 1998; 280: 1485–1489
- [268] Kondziolka D, Patel A, Lunsford LD et al. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys* 1999; 45: 427–434
- [269] Andrews DW, Scott CB, Sperduto PW et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004; 363: 1665–1672
- [270] Aoyama H, Shirato H, Tago M et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs. stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* 2006; 295: 2483–2491
- [271] Chang EL, Wefel JS, Hess KR et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 2009; 10: 1037–1044
- [272] Kocher M, Soffietti R, Abacioglu U et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* 2011; 29: 134–141
- [273] Brown PD, Jaeckle K, Ballman KV et al. Effect of Radiosurgery Alone vs. Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. *JAMA* 2016; 316: 401–409
- [274] Li XP, Meng ZQ, Guo WJ et al. Treatment for liver metastases from breast cancer: results and prognostic factors. *World J Gastroenterol* 2005; 11: 3782–3787
- [275] Mariani P, Servois V, De Rycke Y et al. Liver metastases from breast cancer: Surgical resection or not? A case-matched control study in highly selected patients. *Eur J Surg Oncol* 2013; 39: 1377–1383
- [276] Taşçı Y, Aksoy E, Taşkın HE et al. A comparison of laparoscopic radio-frequency ablation versus systemic therapy alone in the treatment of breast cancer metastasis to the liver. *HPB (Oxford)* 2013; 15: 789–793
- [277] Fairhurst K, Leopardi L, Satyadas T et al. The safety and effectiveness of liver resection for breast cancer liver metastases: A systematic review. *Breast* 2016; 30: 175–184
- [278] Sadot E, Lee SY, Sofocleous CT et al. Hepatic Resection or Ablation for Isolated Breast Cancer Liver Metastasis: A Case-control Study With Comparison to Medically Treated Patients. *Ann Surg* 2016; 264: 147–154
- [279] Ruiz A, Wicherts DA, Sebahg M et al. Predictive Profile-Nomogram for Liver Resection for Breast Cancer Metastases: An Aggressive Approach with Promising Results. *Ann Surg Oncol* 2017; 24: 535–545

- [280] Ruiz A, Castro-Benitez C, Sebahg M et al. Repeat Hepatectomy for Breast Cancer Liver Metastases. *Ann Surg Oncol* 2015; 22 (Suppl. 3): S1057–S1066
- [281] Zhou JH, Rosen D, Andreou A et al. Residual tumor thickness at the tumor-normal tissue interface predicts the recurrence-free survival in patients with liver metastasis of breast cancer. *Ann Diagn Pathol* 2014; 18: 266–270
- [282] Polistina F, Costantin G, Febbraro A et al. Aggressive treatment for hepatic metastases from breast cancer: results from a single center. *World J Surg* 2013; 37: 1322–1332
- [283] van Walsum GA, de Ridder JA, Verhoef C et al. Resection of liver metastases in patients with breast cancer: survival and prognostic factors. *Eur J Surg Oncol* 2012; 38: 910–917
- [284] Abbott DE, Brouquet A, Mittendorf EA et al. Resection of liver metastases from breast cancer: estrogen receptor status and response to chemotherapy before metastasectomy define outcome. *Surgery* 2012; 151: 710–716
- [285] Spolverato G, Vitale A, Bagante F et al. Liver Resection for Breast Cancer Liver Metastases: A Cost-utility Analysis. *Ann Surg* 2017; 265: 792–799. doi:10.1097/SLA.0000000000001715
- [286] Fan J, Chen D, Du H et al. Prognostic factors for resection of isolated pulmonary metastases in breast cancer patients: a systematic review and meta-analysis. *J Thorac Dis* 2015; 7: 1441–1451
- [287] Meimarakis G, Rüttinger D, Stemmler J et al. Prolonged overall survival after pulmonary metastasectomy in patients with breast cancer. *Ann Thorac Surg* 2013; 95: 1170–1180
- [288] Kycler W, Laski P. Surgical approach to pulmonary metastases from breast cancer. *Breast J* 2012; 18: 52–57
- [289] García-Yuste M, Cassivi S, Paleru C. Pulmonary metastasectomy in breast cancer. *J Thorac Oncol* 2010; 5: S170–S171
- [290] Yhim HY, Han SW, Oh DY et al. Prognostic factors for recurrent breast cancer patients with an isolated, limited number of lung metastases and implications for pulmonary metastasectomy. *Cancer* 2010; 116: 2890–2901
- [291] Clive AO, Jones HE, Bhatnagar R et al. Interventions for the management of malignant pleural effusions: a network meta-analysis. *Cochrane Database Syst Rev* 2016; (5): CD010529

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