Leitlinienprogramm Onkologie

Evidenztabellen der S3-Leitlinie Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms

Version 5.0 – Dezember 2025

Evidenztabellen

DKG Krebsgesellschaft · Deutsche Krebshilfe Helfen. Forschen. Informieren. · AWMF

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1 Informationen zu dieser Leitlinie

1.1 Herausgeber

Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (AWMF), Deutschen Krebsgesellschaft e. V. (DKG) und der Stiftung Deutsche Krebshilfe (DKH).

1.2 Federführende Fachgesellschaft(en)

DGS
Deutsche Gesellschaft für Senologie (DGS)

AGO
Arbeitsgemeinschaft Gynäkologische Onkologie der DGGG und DKG (AGO)

DGGG
Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)

1.3 Finanzierung der Leitlinie

Diese Leitlinie wurde von der Deutschen Krebshilfe im Rahmen des Leitlinienprogramms Onkologie gefördert.

1.4 Kontakt

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1.5 Zitierweise

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Langversion 5.0, 2025, AWMF-Registernummer: 032-045OL https://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/; Zugriff am [tt.mm.jjj]

1.6 Abkürzungsverzeichnis

Tabelle 1: Abkürzungsverzeichnis

Abkürzung	Erläuterung
ADH	(intra-)duktale atypische Hyperplasie
AI	Aromatase inhibitor
AML	Akute myeloische Leukämie
APBI	Accelerated partial breast irradiation
ASCO	American Society of Clinical Oncology
ATL	Aktivitäten des täglichen Lebens
AUC	Area under the curve
BÄK	Bundesärztekammer
bds	beiderseits
BET	brusterhaltende Therapie
CGA	Comprehensive geriatric assessment
CHF	chronische Herzinsuffizienz
CIPN	Chemotherapie-induzierte periphere Neuropathie
CISH	Chromogene-in-situ-Hybridisierung
CNB	Core Needle Biopsy
CT	Computertomographie
DBT	digitale Brust-Tomosynthese
DCIS	Duktales Carcinoma in situ

Abkürzung	Erläuterung
DFS	Krankheitsfreies Überleben (engl. disease-free survival)
DGS	Deutsche Gesellschaft für Senologie e.V.
DKG	Deutsche Krebsgesellschaft e.V.
ECE	extrakapsulären Tumorwachstum an den Lymphknoten
EIC	extensive intraduktale Komponente
EK	Expertenkonsens (siehe zur Erläuterung Kapitel "Expertenkonsens" unter "Grundlagen der Methodik")
ER	Estrogenrezeptor
ESA	Erythropoese-stimulierende Agenzien
ESAS	Edmonton Symptom Assessment System
ET	Östrogen-Therapie
FEA	flache Epithelatypie
FISH	Fluoreszenz-in-situ Hybridisierung
FN	febrile Neutropenie
FNA	Feinnadelaspiration
FNB	Feinnadelbiopsie
G-CSF	Granulozyten-Kolonie-stimulierender Faktor
GnRHa	Gonadotropin-releasing hormone agonist
HADS	Hospital Anxiety and Depression Scale
HER2	Human Epidermal Growth Factor Receptor Typ 2
HT	Hormontherapie
IARC	International Agency for Research on Cancer, internationales Institut für Krebsforschung
IBC	inflammatorisches Mammakarzinom

Abkürzung	Erläuterung
iFE	intensivierte Früherkennung
IHC	Immunhistochemie
IMRT	intensitätsmodulierte Radiotherapie
IORT	intraoperative Strahlentherapie
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISH	In-situ-Hybridisierung
ITC	intrathekale Chemotherapie
KD	kognitive Dysfunktion
KM-MRT	Kontrastmittel-Magnetresonanztomographie
KPE	komplexe Physikalische Erstauungstherapie
LABC	Locally advanced breast cancer
LCIS	lobuläres Carcinoma in situ
LK	Lymphknoten
LL	Leitlinie
LN	lobuläre Neoplasie
LoE	Level of Evidence
LVEF	linksventrikuläre Ejektionsfraktion
LVI	(Lymph-)Gefäßinvasion
LWS	Lendenwirbelsäule
MAK	Mamillen-Areola-Komplex
MDS	Myelodysplastisches Syndrom
MG	Mammographie
MRT	Magnetresonanztomographie

Abkürzung	Erläuterung
MSP	Mammographie-Screening-Programm
NACT	neoadjuvante Chemotherapie
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
NZGG	New Zealand Guidelines Group
OP	Operation
OS	Gesamtüberleben / overall survival
PBI	Partial breast irradiation
pCR	pathological complete remission (dt.: pathologische Komplettremission)
PET	Positronen-Emissions-Tomographie
PFS	progressionsfreies Überleben (engl.: progression-free survival)
PI	Proliferationsindex
PMRT	postoperative Strahlentherapie
PNP	Polyneuropathie
POS	Palliative Care Outcome Scale
PST	primär systemische Therapie
QoL	Lebensqualität / Quality of Life
RCT	Randomized Controlled Trial
RFA	Radiofrequenzablation
ROR	Risk of recurrence
RR	Relatives Risiko
RS	Recurrence Score

Abkürzung	Erläuterung
SABCS	San Antonio Breast Cancer Symposium
SBRT	stereotaktische Bestrahlung
SGB	Sozialgesetzbuch
SIB	simultan-integrierter Boost
SIGN	Scottish Intercollegiate Guidelines Network
SISH	Silber verstärkte In-situ-Hybridisierung
AC	Anthrazyklin/Cyclophosphamid
ACR	American College of Radiology
ADC	Antikörper-Wirkstoff-Konzentrate (engl.: antibody-drug conjugate)
ADC	Antibody-drug conjugate
ADT	Working Group of German Tumor Centers
AG	Arbeitsgruppe
AGO	Arbeitsgemeinschaft für Gynäkologie in der DKG
AGREE	Appraisal of Guidelines for Research & Evaluation
AHB	Anschlussheilbehandlung
AK	Antikörper
AMNOG	Arzneimittelmarktneuordnungsgesetz
AOP	Arbeitsgemeinschaft Onkologische Pathologie (DKG)
AS	Aktive Überwachung (engl.: Active Surveillance)
ASTRO	American Society for Radiation Oncology
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.
AWMF	Association of the Scientific Medical Societies
AWMF-IMWi	AWMF-Institut für Medizinisches Wissensmanagement

Abkürzung	Erläuterung
AWMF-IMWi	AWMF Institute for Medical Knowledge Management
OSF	Supression der Ovarialfunktion

2 Evidenztabellen

Kapitel 3: Allgemeines

Kapitel 3.1: Informations- und Gesundheitskompetenz

Kapitel 3.1.1: E-Health und digitale Gesundheitsanwendungen (DiGA)

Verknüpfte Empfehlungen:

Empfehlung 3.6:

Der Einsatz von E-Health kann zur verbesserten Versorgung von Patientinnen und Patienten beitragen.

Literaturreferenzen: [1], [2]

Source: AC, Singleton, Raeside R, Hyun KK, Partridge SR, Di Tanna GL, Hafiz N, Tu Q, et al. "Electronic Health Interventions for Patients with Breast Cancer: Systematic Review and Meta-Analyses." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 40, no. 20 (2022-7-10 2022): 2257-70. https: //doi.org/doi: 10.1200/JCO.21.01171. https: //pubmed.ncbi.nlm.nih.gov/35500200/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Effectiveness of eHealth interventions to improve Patient-reported outcomes (PROs: Quality of Live [QoL], self-	**Design**: Systematic review and Meta-Analyses **Search date**: until October 21, 2019, and	**Intervention** Patient-directed eHealth interventions	**Primary Outcomes** 1. Health-related QOL 2. Self-efficacy	**Primary Outcome**: **1. Health-related QOL:** SMD 0.20, 95% CI 0.03 to 0.36	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review:

Source: AC, Singleton, Raeside R, Hyun KK, Partridge SR, Di Tanna GL, Hafiz N, Tu Q, et al. "Electronic Health Interventions for Patients with Breast Cancer: Systematic Review and Meta-Analyses." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 40, no. 20 (2022-7-10 2022): 2257-70. https: //doi.org/doi: 10.1200/JCO.21.01171. https: //pubmed.ncbi.nlm.nih.gov/35500200/.

efficacy, and mental [anxiety, depression, and distress] and physical [physical activity, nutrition, and fatigue] health) during and after breast cancer treatment and patient-reported experience measures (acceptability and engagement)	updated on June 27, 2021 **Searches databases**: PreMEDLINE, MEDLINE via OvidSP, Cochrane Central Registry of Controlled Trials, Embase via OvidSP, PsycINFO via OvidSP, Allied and Complementary Medicine, Scopus, Web of Science, and Cumulative Index to Nursing and Allied Health Literature via EBSCO **Included study designs**: RCTs **Number of included studies**: 32 **Number of included patients**: 4790 **Mean/median age**: pooled mean age [pooled SD] 51.7 [8.9] years	(including but not limited to e-mail, videoconference, videos, activity trackers, website, podcast, chatroom, mobile applications, or text messages/SMS) **Control** Standard care or control intervention (ie, internet access)	3. Mental health 4. Physical health outcomes **Secondary outcomes:** 1. Patients reported acceptability 2. Patients engagement (logins, completed modules and usage tracking)	Patient type was a significant moderator for QOL, where studies that only included patients were more likely to result in higher QOL than studies including patients/ survivors or only survivors; age, intervention period, and post intervention follow-up were not significant moderators **2. Self-efficacy**: SMD 0.45, 95% CI 0.24 to 0.65 **3. Mentalhealth**: 3.1.Anxiety: SMD -0.09, 95% CI -0.22 to 0.04 3.2. Depressive symptoms:	critically low; 2 critical flaws (items: 4, 7) **Quality of the included studies:** *Evaluated with Cochrane Risk of Bias (RoB) tool:* 10 out of 32 studies had high RoB, 19 studies unclear RoB, 3 studies low RoB **Additional concerns about quality / limitations**: all studies conducted in high-income countries, with younger, highly educated women, and this may mean those with lower eHealth literacy were not included; all participants were female - most studies excluded men; RoB: most studies did not clearly report

Source: AC, Singleton, Raeside R, Hyun KK, Partridge SR, Di Tanna GL, Hafiz N, Tu Q, et al. "Electronic Health Interventions for Patients with Breast Cancer: Systematic Review and Meta-Analyses." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 40, no. 20 (2022-7-10 2022): 2257-70. https: //doi.org/doi: 10.1200/JCO.21.01171. https: //pubmed.ncbi.nlm.nih.gov/35500200/.					
	Inclusion criteria: *Population:* Adults (≥18 years, female or male) with a breast cancer diagnosis who are undergoing or completed active breast cancer treatment (surgery and/or chemotherapy and/or radiotherapy **Exclusion***:* NR			SMD -0.11, 95% CI -0.41 to 0.20 3.3. Psychologic distress: SMD -0.41, 95% CI -0.63 to -0.20 **4. Physical health** 4.1. Fatigue: SMD -0.37, 95%CI -0.61 to -0.13 4.2. Physical activity: * web-based exercise program and website plus smartwatch and mobile app found significant improvements in physical activity, but the interactive website with smartwatch and text message reminders did not 4.3.BMI and nutritional:	blinding procedures or protocols; but: studies with high RoB were excluded from metaanalyses, to improve precision of treatment effect and reliability of pooled effects **Sources of funding**: No specific funding

Source: AC, Singleton, Raeside R, Hyun KK, Partridge SR, Di Tanna GL, Hafiz N, Tu Q, et al. "Electronic Health Interventions for Patients with Breast Cancer: Systematic Review and Meta-Analyses." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 40, no. 20 (2022-7-10 2022): 2257-70. https: //doi.org/doi: 10.1200/JCO.21.01171. https: //pubmed.ncbi.nlm.nih.gov/35500200/.					
				no difference between groups at follow-up (only 1 study) **Secondary Outcomes**: **1. Patients reported acceptability:** 9 studies, most participants found psychoeducational websites acceptable (satisfaction: 71%-100%), useful (71%-95%), easy to use (73%-92%), and easy to understand (98%-100%). One study reported that participants found written and video content more useful than psychoeducational activities (76%, 69%, and 49%, respectively), and participants of a web-based exercise program found videos valuable (mean rating: 3.8/4; 95%)	

Source: AC, Singleton, Raeside R, Hyun KK, Partridge SR, Di Tanna GL, Hafiz N, Tu Q, et al. "Electronic Health Interventions for Patients with Breast Cancer: Systematic Review and Meta-Analyses." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 40, no. 20 (2022-7-10 2022): 2257-70. https: //doi.org/doi: 10.1200/JCO.21.01171. https: //pubmed.ncbi.nlm.nih.gov/35500200/.					
				2. Patients engagement: Participants' engagement was broad, completing 0%-100% modules; most participants (61%-100%) engaged with the intervention at least 1 time (login and opened module) 9 studies reported engagement dropping over time; 5 out of 9 studies had repeated contact; Websites: participants engaged most with content about living with side effects, coping strategies healthy living, advice, blogs, and discussion boards; 1 study found participant engagement with e-mails was consistently high;	

Source: AC, Singleton, Raeside R, Hyun KK, Partridge SR, Di Tanna GL, Hafiz N, Tu Q, et al. "Electronic Health Interventions for Patients with Breast Cancer: Systematic Review and Meta-Analyses." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 40, no. 20 (2022-7-10 2022): 2257-70. https: //doi.org/doi: 10.1200/JCO.21.01171. https: //pubmed.ncbi.nlm.nih.gov/35500200/.

				35/37 participants (94.6%) engaged from baseline to 3 months; an avatar-based app game found quests, level-ups, and rewards most engaging	

Abbreviations and comment:

SMD: Standard mean difference

*due to low number of study meta-analysis didn't conducted for this outcome

Verknüpfte Empfehlungen:

Empfehlung 3.6:

Der Einsatz von E-Health kann zur verbesserten Versorgung von Patientinnen und Patienten beitragen.

Literaturreferenzen: [1], [2]

Source: A, Wanchai, Anderson EA, and Armer JM. "A Systematic Review of M-Health Apps on Managing Side Effects of Breast Cancer Treatment." [In eng]. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer 31, no. 1 (2022-12-27 2022): 86. https: //doi.org/doi: 10.1007/s00520-022-07464-x. https: //pubmed.ncbi.nlm.nih.gov/36574048/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Effectiveness of mobile and web apps in helping breast cancer survivors manage the side effects of breast cancer treatments	**Design**: Systematic Review **Search date**: January 2011 to December 2021 **Searches databases**: CINAHL, ScienceDirect, Scopus, PubMed, Cochrane library **Included study designs**: RCTs or non-RCT **Number of included studies**: 11 (8 RCT, 3 non-RCT)	**Intervention**: 1. Mobile application 2. Web application 3. Combination (Mobile + Web) **Control** the study was required to have a control group or at least two comparative group; heterogeneous controls: e.g. usual care;	**Primary Outcome**: side effects of breast cancer treatment including Physical or psychological side effects **Secondary Outcome**: n.a.	**Primary Outcome**: **1) Psychological effects of mobile apps:** mobile apps helped patients experience more self-efficacy and symptom interference and enhanced their quality of life and upper limb functionality, decreased anxiety scores and reduce distress **2) Physical effects of mobile apps:** mobile apps motivate breast cancer survivors to	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 4 critical flaws (items 2, 4, 7, 13) **Overall quality of evidence**: critically low **Additional concerns about quality**: only studies published in the English language were included; only available published materials were used to assess the risk of bias, no contact with

Source: A, Wanchai, Anderson EA, and Armer JM. "A Systematic Review of M-Health Apps on Managing Side Effects of Breast Cancer Treatment." [In eng]. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer 31, no. 1 (2022-12-27 2022): 86. https: //doi.org/doi: 10.1007/s00520-022-07464-x. https: //pubmed.ncbi.nlm.nih.gov/36574048/.					
	Number of included patients: 1063 (sample size range: 48 to 149) **Participants age range:** 34 to 77 years **Inclusion criteria:** (1) participants were women or men with breast cancer; (2) mobile or web application as the intervention; (3) at least two comparative groups; (4) the primary outcomes were physical or psychological effects from breast cancer treatments; (5) randomized controlled trials (RCTs) or non-RCT. **Exclusion:** qualitative, cross-sectional,	conventional education / information (brochure); received app later on; received same information but via a self-guided kit; care from healthcare team when needed; access to app but without reminder		improve physical activity and dietary patterns, resulting in controlling their body weight. Apps could help improve drug adherence, reduce chemotherapy-related side effects rates, and improve these patients' quality of life **3. health effect of combination of mobile apps and web apps:** It is likely that using the web and mobile apps in combination could be more beneficial for breast cancer survivors in managing their physical symptoms from the side effects of cancer treatments; Patients in the interactive web and mobile apps: lower levels of nausea and vomiting, appetite loss, and	authors; different outcomes in the included studies (meta-analysis not possible) **Quality of the included studies** Assessed with Cochrane risk of bias tool 8 RCTs: 7 studies had low and 1 study high risk of bias *Non-RCTs did not evaluate using an appropriate tool (were evaluated using the same tool applied for RCTs)* **Sources of funding**: Boromarajonani College of Nursing Buddhachinaraj, Faculty of Nursing, Praboromarajchanok Institute, Ministry of Public Health, Thailand

Source: A, Wanchai, Anderson EA, and Armer JM. "A Systematic Review of M-Health Apps on Managing Side Effects of Breast Cancer Treatment." [In eng]. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer 31, no. 1 (2022-12-27 2022): 86. https: //doi.org/doi: 10.1007/s00520-022-07464-x. https: //pubmed.ncbi.nlm.nih.gov/36574048/.

	longitudinal, or case studies			constipation, than the control group; reported lower distress and higher emotional functioning than the control group; web and mobile apps could help breast cancer survivors manage chronic pain, soreness, general bodily pain, arm/hand swelling, heaviness, and impaired limb mobility **4. Web apps alone:** only one paper reporting that if the patients received a web app plus a reminder, they would adhere more to the medications. It cannot be concluded whether applying a web app alone or a web app with a reminder from the health	

Source: A, Wanchai, Anderson EA, and Armer JM. "A Systematic Review of M-Health Apps on Managing Side Effects of Breast Cancer Treatment." [In eng]. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer 31, no. 1 (2022-12-27 2022): 86. https: //doi.org/doi: 10.1007/s00520-022-07464-x. https: //pubmed.ncbi.nlm.nih.gov/36574048/.

				care team might yield better outcomes **Secondary Outcome**: n.a.	

Abbreviations:

RCT = Randomised Controlled Trial

n.a. = not Available, not Applicable

Kapitel 3.2: Brustkrebsfrüherkennung

Kapitel 3.2.1: Mammographiescreening

Verknüpfte Empfehlungen:

Empfehlung 3.20:

Die digitale Tomosynthese (3D-Mammographie oder digitale Brust-Tomosynthese) mit synthetischem 2D-Bild ist bezüglich Sensitivität und Spezifität der digitalen Mammographie (DM) überlegen.

Literaturreferenzen: [3], [4], [5], [6], [7], [8]

Source: SH, Heywang-Köbrunner, Jänsch A, Hacker A, Weinand S, and Vogelmann T. "Digital Breast Tomosynthesis (Dbt) Plus Synthesised Two-Dimensional Mammography (S2d) in Breast Cancer Screening Is Associated with Higher Cancer Detection and Lower Recalls Compared to Digital Mammography (Dm) Alone: Results of a Systematic Review and Meta-Analysis." European radiology 32, no. 4 (2022-4 2022): 2301-12. https: //dx.doi.org/doi: .

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: screening performance outcomes in women screened with Digital breast tomosynthesis (DBT) plus synthesized two-dimensional mammography (s2D) compared to digital mammography (DM) alone	**Design**: Systematic Review and Meta-Analysis **Search date**: January 1, 2010 – September 2, 2020 **Searched databases**: PubMed **Included study designs**:	**Index test** DBT plus s2D **Comparator** DM alone	Cancer detection rate (CDR), Recall rates, Interval cancer rate (ICR), Biopsy rates, Positive predictive value(PPV) for: Recalls (PPV-1)	**Cancer detection rate (CDR)** *Favor DBT plus s2D* RR 1.35, 95% CI 1.20-1.52; p<0.01; I^2=58% (10 studies) **Recall rates** *Favor DBT plus s2D*	**ROBIS** **Risk of bias in the review: low** **Domain** Concerns regarding specification of study eligibility criteria: low risk Concerns regarding methods used to identify

Source: SH, Heywang-Köbrunner, Jänsch A, Hacker A, Weinand S, and Vogelmann T. "Digital Breast Tomosynthesis (Dbt) Plus Synthesised Two-Dimensional Mammography (S2d) in Breast Cancer Screening Is Associated with Higher Cancer Detection and Lower Recalls Compared to Digital Mammography (Dm) Alone: Results of a Systematic Review and Meta-Analysis." European radiology 32, no. 4 (2022-4 2022): 2301-12. https: //dx.doi.org/doi: .					
	Prospective and retrospective studies with a comparative design **Number of included studies**: Twelve studies representing the results of 10 populations **Number of included patients**: 414,281 women **Mean/median age**: n.a. **Inclusion criteria**: asymptomatic women with an average risk of breast cancer presenting for screening were considered, including women with symptoms at a regular screening **Exclusion**:		biopsies recommended (PPV-2) biopsies performed (PPV-3)	RR 0.79, 95% CI 0.64-0.98; p=0.03; I²=97% (8 studies) **Interval cancer rate (ICR)** *Favor DM alone* RR 1.03, 95% CI 0.66-1.63; p=0.88, I²=70% (2 studies) **Biopsy rates** *Favor DBT plus s2D* RR 0.87, 95% CI 0.70-1.09; p=0.22; I²=91% (5 studies) **Positive predictive value (PPV) for:** **recalls (PPV-1)** *Favor DBT plus s2D* RR 1.69, 95% CI 1.45-1.96; p<0.01; I²=73%	and/or select studies: high risk Concerns regarding methods used to collect data and appraise studies: low risk Concerns regarding the synthesis and findings: low risk **Additional concerns about quality**: only English paper, only PubMed **Limitations by authors:** 9 of 10 trials: women were not randomly assigned to screening modalities; heterogeneity among studies **Quality of included studies**: *Risk of bias assesd using the QUADAS-2 tool*

Source: SH, Heywang-Köbrunner, Jänsch A, Hacker A, Weinand S, and Vogelmann T. "Digital Breast Tomosynthesis (Dbt) Plus Synthesised Two-Dimensional Mammography (S2d) in Breast Cancer Screening Is Associated with Higher Cancer Detection and Lower Recalls Compared to Digital Mammography (Dm) Alone: Results of a Systematic Review and Meta-Analysis." European radiology 32, no. 4 (2022-4 2022): 2301-12. https: //dx.doi.org/doi: .					
	Studies without human subjects, studies evaluating solely women with symptoms, findings suspicious of breast cancer, or screened for diagnostic work-up only			(8 studies) **biopsies recommended (PPV-2)** *Favor DBT plus s2D* RR 1.57, 95% CI 1.08-2.28; p=0.02; I²=82% (2 studies) **biopsies performed (PPV-3)** *Favor DBT plus s2D* RR 1.36, 95% CI 1.17-1.58; p<0.01; I²=67% (5 studies)	All studies: High risk of bias in domain: flow and timing (not every woman received the same reference test after screening); 1 study (Aujero 2017) high risk of bias in domain patient selection All other domains in all studies: low risk of bias **Level of evidence:** Oxford 2011: Level 3 (downgrade due to included study designs) **Sources of funding:** Hologic
Abbreviations: DBT = Digital Breast Tomosynthesis s2D = Synthesized Two-Dimensional Mammography					

Source: SH, Heywang-Köbrunner, Jänsch A, Hacker A, Weinand S, and Vogelmann T. "Digital Breast Tomosynthesis (Dbt) Plus Synthesised Two-Dimensional Mammography (S2d) in Breast Cancer Screening Is Associated with Higher Cancer Detection and Lower Recalls Compared to Digital Mammography (Dm) Alone: Results of a Systematic Review and Meta-Analysis." European radiology 32, no. 4 (2022-4 2022): 2301-12. https: //dx.doi.org/doi: .

DM = Digital Mammography

CDR = Cancer Detection Rate

ICR = Interval Cancer Rates

PPV = Positive Predictive Value

PPV-1 = Positive Predictive Values for Recalls

PPV-2 = Positive Predictive Values for Biopsies Recommended

PPV-3 = Positive Predictive Values for Biopsies Performed

RR = Risk Ratio or Relative Risk

95% CI = 95 Confidence Interval

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 3.20:

Die digitale Tomosynthese (3D-Mammographie oder digitale Brust-Tomosynthese) mit synthetischem 2D-Bild ist bezüglich Sensitivität und Spezifität der digitalen Mammographie (DM) überlegen.

Literaturreferenzen: [3], [4], [5], [6], [7], [8]

Source Lin H, Zhang Y, Wu L, Li C. Diagnostic accuracy of digital breast tomosynthesis and digital mammography in women with dense or non-dense breast tissue: A systematic review and meta-analysis. AdvClinExp Med. 2025 Mar;34(3): 315-326. doi: 10.17219/acem/185522. PMID: 39087824

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To systematically evaluate and meta-analyze selected studies comparing the diagnostic accuracy and reliability of DBT and DM for BC screening in women with dense or non-dense breast tissue.	**Design**: Systematic review and meta-analysis **Search date**: 2015 until March 2023 **Searched databases**: PubMed, Embase, Web of Science, Scopus, Cochrane Library **Included study designs**: Prospective and retrospective **Number of included studies**: 11	**Intervention** Digital Breast Tomosynthesis (DBT) **Control** Digital Mammography (DM)	**Primary Outcome**: Cancer Detection Rate (CDR) Overall Recall Rate **Secondary Outcome**: Sensitivity Specificity	**Primary Outcome**: DBT resulted in a greater cancer detection rate (OR = 2.29, 95% CI: 1.49–3.51; I^2=69%) DBT group higher accuracy in detecting cancer: (RR = 1.27, 95% CI: 1.14-1.41, I^2=95%) DM group greater recall rate than DBT group: (RR = 0.88, 95% CI: 0.78-0.99; I^2=85%)	**ROBIS** Low risk of bias **Additional concerns about quality**: Moderate to high levels of heterogeneity; number of patients varied substantially among studies; significant portion of the data presented pertains to the screening of prevalent cases of DBT at the first stage; studies included in the analysis solely focused on the

Source Lin H, Zhang Y, Wu L, Li C. Diagnostic accuracy of digital breast tomosynthesis and digital mammography in women with dense or non-dense breast tissue: A systematic review and meta-analysis. AdvClinExp Med. 2025 Mar;34(3): 315-326. doi: 10.17219/acem/185522. PMID: 39087824					
	Number of included patients: 2,124,018 (range: 98 to 452,320) **Inclusion criteria**: Women with dense or non-dense breast tissue; screening of BC using DBT or DM; >18 years; English language **Exclusion**: n.a.			**Secondary outomes:** DBT had higher sensitivity (pooled sensitivity of 0.91 (95% CI: 0.59-0.99)) and specificity (pooled specificity of 0.90 (95% CI: 0.42-1.0)) than DM (pooled sensitivity of 0.86 (95% CI: 0.52-1.0) and pooled specificity of 0.81 (95% CI: 0.12-1.0)) **Secondary Outcome**: **Subgroup analysis:**	assessment of initial detection measures – no long-term health outcomes **Quality of included studies**: Cochrane Risk of Bias Assessment Tool; Included studies had low to moderate risk of bias **Level of evidence:** Oxford 2011: **Sources of funding**: No funding
Abbreviations and comment: DBT: Digital Breast Tomosynthesis DM: Digital Mammography RR: Risk Ratio DBT is a more effective screening and diagnostic assessment tool for women with dense or non-dense breasts than DM.					

Verknüpfte Empfehlungen:

- In dichtem Gewebe ist die Tomosynthese in Sensitivität und Spezifität der digitalen Mammographie (DM) klar überlegen.
- Der Einsatz der Tomosynthese im hohen Dichtebereich sollte wegen der wesentlich besseren Sensitivität bei mindestens gleicher Spezifität der Tomosynthese möglichst zeitnah (beginnend mit Dichtetyp D und schrittweise C) im Rahmen des Mammographie-Screening-programms unter strenger Qualitätssicherung und Ergebnis-Evaluation ermöglicht werden.

Literaturreferenzen: [5], [9], [10], [11], [12]

Source: Heywang-Köbrunner et al. 2022: Tomosynthesis with synthesized two-dimensional mammography yields higher cancer detection compared to digital mammography alone, also in dense breasts and in younger women: A systematic review and meta-analysis, https: //doi.org/10.1016/j.ejrad.2022.110324

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Comparison of digital breast tomosynthesis (DBT) plus synthesised two-dimensional digital mammography (s2D) to digital mammography (DM) alone in screening for the outcomes CDR, recall rates, interval cancer rates (ICR), and positive predictive values for recalls (PPV-1), for biopsies recommended (PPV-2), and for biopsies	**Design**: Systematic Review and Meta-Analysis **Search date**: 01/01/2010-01/07/2021 **Searched databases**: PubMed, Cochrane library **Included study designs**: Prospective and retrospective studies **Number of included studies**: 13 (10 study populations) **Number of included patients**: 414.281	**Intervention** digital breast tomosynthesis plus synthesised two-dimensional digital mammography **Control** digital mammography alone	Cancer detection rate (CDR) recall rates interval cancer rates (ICR) positive predictive values for recalls (PPV-1) for biopsies recommended (PPV-2) and for biopsies performed (PPV-3)	**Cancer detection rate (CDR)** 3 studies *DBT plus s2D to DM alone* Women with high breast density REM (Random-Effect Model) RR=1.70, 95% CI 0.98-2.96, p=0.06, I^2= 65% *DBT plus s2D to DM alone* Women with low breast density	**ROBIS** **Risk of bias in the review: unclear** **Domain** Concerns regarding specification of study eligibility criteria: unclear risk Concerns regarding methods used to identify and/or select studies: high risk Concerns regarding methods used to collect

Source: Heywang-Köbrunner et al. 2022: Tomosynthesis with synthesized two-dimensional mammography yields higher cancer detection compared to digital mammography alone, also in dense breasts and in younger women: A systematic review and meta-analysis, https: //doi.org/10.1016/j.ejrad.2022.110324					
performed (PPV-3)	**Mean/median age**: n.a. **Inclusion criteria**: Prospective and retrospective studies considering asymptomatic women presenting for regular breast cancer screening, in which DBT plus s2D was compared to DM alone with at least data of CDR, recall rates, ICR, biopsy rates or PPV-1, PPV-2, or PPV-3 were included **Exclusion**: n.a.			REM RR=1.32, 95% CI 1.08-1.61, p<0.01; I²=0% <u>Total</u> REM RR=1.39, 95% CI 1.07-1.81, p=0.01, I²=58% <u>Age Groups</u> 2 studies Women <60 years *DBT plus s2D to DM alone* REM RR=1.64, 95% CI 1.18-2.29, p<0.01, I²=0% 2 studies Women >=60 *DBT plus s2D to DM alone* REM RR=1.51, 95% CI 0.87-2.60,	data and appraise studies: unclear risk Concerns regarding the synthesis and findings: low risk **Additional concerns about quality**: Search terms not provided **Limitations by authors** Data for DBT plus s2D compared to DM are limited No a priori power analyses conducted No identified reported interval cancer rates (ICR), biopsy rates or PPV-2 in women screened with DBT plus s2D compared to DM alone separately given for breast densityand age à lack of

Source: Heywang-Köbrunner et al. 2022: Tomosynthesis with synthesized two-dimensional mammography yields higher cancer detection compared to digital mammography alone, also in dense breasts and in younger women: A systematic review and meta-analysis, https: //doi.org/10.1016/j.ejrad.2022.110324

				P=0.14, I²=75% <u>Total</u> REM RR=1.58, 95% CI 1.28-1.95, p<0.01, I²=0% **Recall rates** 2 studies *Favours DBT plus s2D* <u>Women with high breast density</u> REM (Random-Effect Model) RR=0.86, 95% CI 0.72-1.03, p=0.10) <u>Women with low breast density</u> *Favours DBT plus s2D* REM RR 0.65, 95% CI 0.57-0.75, <0.01, I²=44% Total	data, therefor not involved in meta-analyses calculation Outcomes influenced by reading procedure and other factors **Quality of included studies**: QUADAS-2 <u>Risk of Bias</u> Patient selection: 1 high/12 low Index Test: 13 low Reference Standard: 13 low Flow and Timing: 13 high <u>Applicability</u> Patient Selection: 13 low Index Test: 13 low Reference standard: 13 low

Source: Heywang-Köbrunner et al. 2022: Tomosynthesis with synthesized two-dimensional mammography yields higher cancer detection compared to digital mammography alone, also in dense breasts and in younger women: A systematic review and meta-analysis, https: //doi.org/10.1016/j.ejrad.2022.110324					
				REM RR=0.72, 95% CI 0.62-0.83, p<0.01, I²=75% **<u>Positive predictive values</u> for recalls (PPV-1)** *DBT plus s2D to DM alone* Stratified per reading procedure (double reading vs. non-double reading) REM RR=1.69, 95% CI 1.45-1.96, p<0.01, I²=73% **For biopsies performed (PPV-3)** *DBT plus s2D to DM alone* Stratified per reading procedure (double reading vs. non-double reading) REM	**Level of evidence:** Oxford 2011: Level 3 (downgrade due to included study designs) **Sources of funding:** n.a.

Source: Heywang-Köbrunner et al. 2022: Tomosynthesis with synthesized two-dimensional mammography yields higher cancer detection compared to digital mammography alone, also in dense breasts and in younger women: A systematic review and meta-analysis, https: //doi.org/10.1016/j.ejrad.2022.110324

				RR=1.36, 95% CI 1.17-1.58, p<0.01; I^2=80%	

Abbreviations:

DBT = Digital Breast Tomosynthesis

s2D = Synthesised Two-Dimensional Digital Mammography

DM = Digital Mammography

CDR = Cancer Detection Rate

ICR = Interval Cancer Rates

PPV-1 = Positive Predictive Values for Recalls

PPV-2 = Positive Predictive Values for Biopsies Recommended

PPV-3 = Positive Predictive Values for Biopsies Performed

RR = Risk Ratio

95% CI = 95% Confidence Interval

REM = Random Effect Model

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

- In dichtem Gewebe ist die Tomosynthese in Sensitivität und Spezifität der digitalen Mammographie (DM) klar überlegen.
- Der Einsatz der Tomosynthese im hohen Dichtebereich sollte wegen der wesentlich besseren Sensitivität bei mindestens gleicher Spezifität der Tomosynthese möglichst zeitnah (beginnend mit Dichtetyp D und schrittweise C) im Rahmen des Mammographie-Screening-programms unter strenger Qualitätssicherung und Ergebnis-Evaluation ermöglicht werden.

Literaturreferenzen: [5], [9], [10], [11], [12]

Source: Li T, Houssami N, Noguchi N, Zeng A, Marinovich ML. Differential detection by breast density for digital breast tomosynthesis versus digital mammography population screening: a systematic review and meta-analysis. Br J Cancer. 2022 Jul;127(1): 116-125. doi: 10.1038/s41416-022-01790-x. Epub 2022 Mar 28. PMID: 35352019; PMCID: PMC9276736.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To examine whether digital breast tomosynthesis (DBT) detects differentially in high or low-density screens.	**Design**: Systematic review and meta-analysis **Search date**: **Searched databases**: **Included study designs**: Prospective and retrospective **Number of included studies**: 13 **Number of included patients**: 1,238,735	**Intervention** Digital Breast Tomosynthesis (DBT) **Control** Digital Mammography (DM)	**Primary Outcome**: Cancer Detection Rate (CDR) Recall Rate	**Primary Outcome**: Pooled within-study difference in incremental CDR for high- versus low-density was 1.0/1000 screens (95% CI: 0.3 - 1.6; p=0.003) CDR: European studies: the pooled incremental CDR low density was 1.6 per 1000 screens (95% CI: 0.8, 2.5; p < 0.001; I2 =	**ROBIS** **Additional concerns about quality**: No long-term health outcomes; most of the data reported on prevalent (initial) DBT screening, even though repeat breast screening represents the majority of screens in screening programmes **Quality of included studies**:

Source: Li T, Houssami N, Noguchi N, Zeng A, Marinovich ML. Differential detection by breast density for digital breast tomosynthesis versus digital mammography population screening: a systematic review and meta-analysis. Br J Cancer. 2022 Jul;127(1): 116-125. doi: 10.1038/s41416-022-01790-x. Epub 2022 Mar 28. PMID: 35352019; PMCID: PMC9276736.					
	participants/examinations (522,846 with DBT and 715,889 with DM) **Median age**: DBT: 57 (range: 54 - 59) DM: 57.6 (range: 53.8 – 58.6) **Inclusion criteria**: Asymptomatic women attending population-based breast cancer screening programs; English language **Exclusion**:			71%) and the pooled incremental CDR high density was 3.5 per 1000 screens (95% CI: 1.9, 5.1; p < 0.001; I2 = 53%). Recall rate: European studies: the pooled incremental recall rate was 0.2% (95% CI: −0.6%, 1.1%; p=0.60; I2 =93%) in low density and 1.0% (95% CI: −0.1%, 2.1%; p=0.07; I2 =84%) in high density DBT has differential incremental cancer detection and recall by breast density	QUADAS-2 criteria adapted - 5 of the 13 studies were rated as low risk of bias and low concerns of applicability **Level of evidence:** Oxford 2011: **Sources of funding**: Open Access funding enabled and organized by CAUL and its Member Institutions.
Abbreviations and comment: DBT: Digital Breast Tomosynthesis					

Source: Li T, Houssami N, Noguchi N, Zeng A, Marinovich ML. Differential detection by breast density for digital breast tomosynthesis versus digital mammography population screening: a systematic review and meta-analysis. Br J Cancer. 2022 Jul;127(1): 116-125. doi: 10.1038/s41416-022-01790-x. Epub 2022 Mar 28. PMID: 35352019; PMCID: PMC9276736.

DM: Digital Mammography

Kapitel 3.3: Familiäres Mammakarzinom

Verknüpfte Empfehlungen:

Empfehlung 3.27:

Eine genetische Untersuchung zum Nachweis einer erblichen Belastung sollte angeboten werden, wenn eine familiäre bzw. individuelle Belastung vorliegt, die mit einer mindestens 10 %-igen Nachweiswahrscheinlichkeit für eine wahrscheinlich pathogene / pathogene konstitutionelle Variante (PV) einhergeht.
Dies trifft zu, wenn in einer Linie der Familie

- mindestens 3 Frauen an Brustkrebs erkrankt sind, unabhängig vom Alter
- mindestens 2 Frauen an Brustkrebs erkrankt sind, davon 1 vor dem 50. Geburtstag
- mindestens 1 Frau an Brustkrebs und 1 weitere Frau an Eierstockkrebs erkrankt sind
- mindestens 2 Frauen an Eierstockkrebs erkrankt sind
- mindestens 1 Frau an Brust- und Eierstockkrebs erkrankt ist
- mindestens 1 Frau vor dem 36. Geburtstag an Brustkrebs erkrankt ist
- mindestens 1 Frau vor dem 50. Geburtstag an bilateralem Brustkrebs erkrankt ist
- mindestens 1 Mann an Brustkrebs und eine Frau an Brust- oder Eierstockkrebs erkrankt sind

Es ist eine angemessene Bedenkzeit vor Durchführung der Diagnostik zu beachten.

Literaturreferenzen: [13], [14]

Source: Nelson HD, Pappas M, Cantor A, Haney E, Holmes R. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2019 Aug 20;322(7): 666-685. doi: 10.1001/jama.2019.8430. PMID: 31429902.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To update the 2013 US Preventive Services Task Force review on benefits and harms of risk	**Design**: Systematic review	**Intervention** Risk assessment, genetic counseling, and genetic	Cancer incidence and mortality; Discriminatory accuracy of risk assessment tools for	No studies evaluated the effectiveness of risk assessment, genetic counseling, and genetic	**ROBIS** Low risk of bias

Source: Nelson HD, Pappas M, Cantor A, Haney E, Holmes R. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2019 Aug 20;322(7): 666-685. doi: 10.1001/jama.2019.8430. PMID: 31429902.					
assessment, genetic counseling, and genetic testing for *BRCA1/2*-related cancer in women.	**Search date**: January 1, 2013, to March 6, 2019, for updates; January 1, 1994, to March 6, 2019 **Searched databases**: Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, Ovid EMBASE, and MEDLINE **Included study designs**: accuracy studies, RCTs, and observational studies **Number of included studies**: 103 **Number of included patients**: 92,712 **Mean/median age**: **Inclusion criteria**: Women without recently diagnosed *BRCA1/2*-	testing for *BRCA1/2*-related cancer **Control** No intervention or standard care (depending on the study)	*BRCA1/2* mutations Benefits and harms of risk assessment, genetic counseling, genetic testing, and risk-reducing interventions	testing in reducing incidence and mortality of BRCA1/2-related cancer. 14 studies of risk assessment tools showed moderate to high accuracy (AUC = 0.68-0.96); 28 studies indicated that genetic counseling was associated with reduced breast cancer worry, anxiety, and depression; increased understanding of risk; and decreased intention for testing; 20 studies showed that breast cancer worry and anxiety were higher after testing for women with positive results and lower for others; understanding of risk was higher after testing In 8 RCTs, tamoxifen, raloxifene, and aromatase inhibitors	**Additional concerns about quality**: number, quality, and applicability of studies evaluated varied widely; most studies included highly selected samples of women, some with preexisting breast or ovarian cancer or from high-risk groups that were defined in various ways, or from previously identified cancer kindreds **Quality of included studies**: **Level of evidence:** Oxford 2011: **Sources of funding**: funded under

Source: Nelson HD, Pappas M, Cantor A, Haney E, Holmes R. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2019 Aug 20;322(7): 666-685. doi: 10.1001/jama.2019.8430. PMID: 31429902.

	related cancer; English language articles **Exclusion**: women with a history of breast or ovarian cancer, unless the cancer was diagnosed at least 5 years before enrollment and treatment was completed			were associated with lower risks of invasive breast cancer compared with placebo; results were not specific to mutation carriers;Mastectomy was associated with 90% to 100% reduction in breast cancer incidence and 81% to 100% reduction in breast cancer mortality; Oophorectomy was associated with 69% to 100% reduction in ovarian cancer; complications were common with mastectomy	contract HHSA290201500009I, Task Order 7, from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, under a contract to support the US Preventive Services Task Force (USPSTF)

Abbreviations and comment: Benefits and harms of risk assessment, genetic counseling, and genetic testing to reduce cancer incidence and mortality have not been directly evaluated by current research

Verknüpfte Empfehlungen:

Empfehlung 3.35:

Bei Patientinnen mit einer konstitutionellen wahrscheinlich pathogenen / pathogenen Variante (PV) im *BRCA1*- oder *BRCA2-Gen* sollte und bei Patientinnen mit PV in anderen Risikogenen für das Mammakarzinom kann eine intensivierte Brustkrebs-Früherkennung unter Hinzunahme des MRT und der Sonographie nur im Rahmen einer wissengenerierenden Versorgung und entsprechender Ergebnisevaluation erfolgen.

Unter diesen Voraussetzungen kann diese Früherkennung nicht informativ getesteter Frauen zwischen 30 und 50 Jahren mit einem Mammakarzinomrisiko von 5 % in 10 Jahren erfolgen.
Eine zusätzliche, alle zwei Jahre erfolgende Mammographie ab dem 40. Lebensjahr sollte ebenso im Rahmen einer wissengenerierenden Versorgung und entsprechender Ergebnisevaluation erfolgen.

Literaturreferenzen: [15], [16], [17], [18], [19], [20], [21]

Source: Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. Breast Cancer Res Treat. 2019;175(1): 217-228. doi: 10.1007/s10549-019-05152-9

Aim and Country	Design and participants	Comparison groups & surveillance program	Outcomes	Results	Quality and comment
Country: Germany **Aim**: 10 years of high-risk service screening with annual MRI in the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) -> report on the	**Design**: registry-based, prospective cohort study **Setting**: 12 University Centers across Germany **Enrollment**: 2006-2015 **Number of included patients**: 4,573	**3 risk groups** BRCA1 carriers BRCA2 carriers BRCA1/2 non-carriers with high risk **Surveillance program** Annual MRI supplemented by clinical	Primary breast cancer (PBC) Screening performance	**PBC during active surveillance:** 221 PBC (185 invasive cancers and 36 DCIS) 38.5% (85/221) detected at first screening round	**Quality of study** Assessed with SIGN checklist for cohort studies: Overall assessment: acceptable **Limitations by authors:**

Source: Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. Breast Cancer Res Treat. 2019;175(1): 217-228. doi: 10.1007/s10549-019-05152-9					
outcome of the program 10 years of operation	BRCA1 carriers: 954 (20.9%) BRCA2 carriers: 598 (13.1%) BRCA1/2 non-carriers with high risk: 3,021 (66.1%) **Mean age**: Mean (SD): Total: 38.8 (8.7) BRCA1: 37.4 (9.8) BRCA2: 39.4 (9.8) BRCA1/2 non-carriers with high risk: 39.2 (8.0) **Inclusion criteria**: No history of BC and/or another malignancy; 3 risk groups: carrying a pathogenic (1) BRCA 1 or (2) BRCA 2 mutation or (3) high-risk women from BRCA1/2-negative families;	exam and ultrasound every 6 months		51.1% (113/221) at a subsequent screening round 10.4% (23/221) during the 12-month interval following a negative annual screening round with MRI Stage distribution: 84.5% (174/206) of all PBC stage 0 or I Interval cancers: more frequently observed in BRCA1 carriers (14.5%, 12/83) than in BRCA2 carriers (11.3%, 6/53) and other high-risk patients (5.9%, 5/85) **Overall program sensitivity** for all 14,142 regular screening rounds with MRI was 89.6% (95% CI 84.9-93.0)	Stratification by risk group based on BRCA1/2 testing only as broader multi-gene panel testing – introduced in the GC-HBOC only towards end of recruitment period; interpreting physician had access to all imaging studies performed during a particular screening round to maximize screening performance à overestimation of detection performance of individual surveillance modalities possible **Additional concerns about quality**: No information about blinding of imaging interpreting physician to risk group of patient No information about the number of patients asked to participate (only

Source: Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. Breast Cancer Res Treat. 2019;175(1): 217-228. doi: 10.1007/s10549-019-05152-9					
	at least one documented screening round with MRI in one of the 12 participating centers between 01/01/2006 and 31/12/2015 **Exclusion**: women with prior risk reducing mastectomy			(no significant differences in sensitivity between the 3 risk groups or by age) **Detection performance of individual imaging modalities** Overall: 82% (183/221) of all cancers were positive on MRI 53.3% (98/184) for mammography (performed in addition to MRI) and 50.9% (111/218) for ultrasound Cancer detection rates per 1000 screening rounds varied strongly with type of screening round, risk group and patient age: **Detection performance** **BRCA1** First rounds	number provided of participating patients) No information about patients lost to follow-up **Sources of funding:** Grant (110837) from the German Cancer Aid (Deutsche Krebshilfe)

Source: Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. Breast Cancer Res Treat. 2019;175(1): 217-228. doi: 10.1007/s10549-019-05152-9					
				Detection rate: 19.9‰ PPV: 12.9% <u>Subsequent rounds</u> Detection rate: 28.4‰ PPV: 27.4% <u>30-39 years</u> Detection rate: 43.2‰ PPV: 29.4% <u>40-49 years</u> Detection rate: 21.8‰ PPV: 25.5% <u>≥50 years</u> Detection rate: 30.5‰ PPV: 33.3% **BRCA 2** <u>First rounds</u> Detection rate: 43.5‰ PPV: 23.4% <u>Subsequent rounds</u>	

Source: Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. Breast Cancer Res Treat. 2019;175(1): 217-228. doi: 10.1007/s10549-019-05152-9					
				Detection rate: 19.5‰ PPV: 22.0% <u>30-39 years</u> Detection rate: 22.7‰ PPV: 23.3% <u>40-49 years</u> Detection rate: 24.3‰ PPV: 27.5% <u>≥50 years</u> Detection rate: 16.3‰ PPV: 23.5% **BRCA1/2 non-carriers with high risk** <u>First rounds</u> Detection rate: 13.6‰ PPV: 7.9% <u>Subsequent rounds</u> Detection rate: 5.9‰ PPV: 5.9%	

Source: Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. Breast Cancer Res Treat. 2019;175(1): 217-228. doi: 10.1007/s10549-019-05152-9					
				30-39 years Detection rate: 2.9‰ PPV: 2.8% 40-49 years Detection rate: 7.4‰ PPV: 6.8% ≥50 years Detection rate: 10.9‰ PPV: 13.8% **Patient follow-up** 5 deaths (of 4,573 patients) recorded up to Dec. 31, 2016 only 1 related to BC à BRCA2-pos. patient, detected in first screening round 2 BRCA1 pos. patients died of ovarian cancer 1 BRCA2 pos. patient died of pancreatic cancer	

Source: Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. Breast Cancer Res Treat. 2019;175(1): 217-228. doi: 10.1007/s10549-019-05152-9

				1 BRCA1/2 neg. patient died unrelated to an oncologic diagnosis *Conclusion:* BRCA1 carriers: surveillance with MRI is less effective in preventing advanced stage BC; CDRs and with this PPVs for subsequent screening rounds in young premenopausal high-risk women without a *BRCA1/2* mutation were lower than expected, shifting the balance towards negative side effects	

Abbreviations:

GC-HBOC = German Consortium for Hereditary Breast and Ovarian Cancer

PBC = Primary Breast Cancer

Source: Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. Breast Cancer Res Treat. 2019;175(1): 217-228. doi: 10.1007/s10549-019-05152-9

MRI = Magnetic Resonance Imaging

PPV = Positive Predictive Value

Verknüpfte Empfehlungen:

Empfehlung 3.36:

Die operative Therapie des *BRCA1*- bzw. *BRCA2*-assoziierten Mammakarzinoms richtet sich nach den Leitlinienempfehlungen für das sporadische Mammakarzinom.

Die Mastektomie hat keinen Überlebensvorteil im Vergleich zur brusterhaltenden Therapie.

Die medikamentöse Therapie des *BRCA*-assoziierten Mammakarzinoms richtet sich nach den Leitlinienempfehlungen für das sporadische Mammakarzinom.

Ausnahme ist die zielgerichtete Therapie des frühen bzw. fortgeschrittenen/metastasierten Her2-negativen Mammakarzinoms und Nachweis einer wahrscheinlich pathogenen / pathogenen konstitutionellen Variante (PV) in den Genen *BRCA1* und *BRCA2* mit PARP-Inhibitoren (s. Kapitel medikamentöse Therapie).

Empfehlung 3.37: Risiko-reduzierende Operation bei gesunden Trägerinnen wahrscheinlich pathogener / pathogener konstitutioneller Varianten (PV) in den Genen *BRCA1* oder *BRCA2* (Klasse 4/5): prophylaktische bilaterale Mastektomie.

Gesunde Frauen mit einer PV in den Genen *BRCA1* oder *BRCA2* haben ein lebenszeitlich erhöhtes Risiko für die Entwicklung eines Mammakarzinoms.

Bei gesunden Frauen mit einer PV in den Genen *BRCA1*- oder *BRCA2* führt die beidseitige prophylaktische Mastektomie zu einer Reduktion der Brustkrebsinzidenz. Eine Reduktion der Brustkrebs-spezifischen Mortalität bzw. der Gesamtmortalität durch die beidseitige prophylaktische Mastektomie ist nicht ausreichend gesichert.

Daher setzt eine Einzelfallentscheidung für oder gegen eine bilaterale risiko-reduzierend Mastektomie stets fallbezogen eine umfassende Aufklärung und ausführliche multidisziplinäre Beratung über potentielle Vor- und Nachteile eines solchen Eingriffs mit Berücksichtigung der möglichen Alternativen voraus.

Empfehlung 3.39: Risikoreduzierende Operation bei bereits unilateral an Brustkrebs erkrankten Trägerinnen wahrscheinlich pathogener / pathogener konstitutioneller Varianten (PV) in den Genen *BRCA1* oder *BRCA2* (Klasse 4/5): kontralaterale prophylaktische Mastektomie und prophylaktische bilaterale Adnexektomie

Bereits an Brustkrebs erkrankte Frauen mit einer PV in den Genen *BRCA1* oder *BRCA2* haben ein erhöhtes Risiko für die Entstehung eines kontralateralen Mammakarzinoms. Dieses Risiko hängt u. a. ab vom betroffenen Gen und dem Ersterkrankungsalter und ist bei der Beratung zu berücksichtigen.

Bei Frauen mit einer PV in den Genen *BRCA1* oder *BRCA2* führt die kontralaterale, prophylaktische Mastektomie zu einer Reduktion des kontralateralen Karzinomrisikos. Bei der Indikationsstellung zur kontralateralen prophylaktischen Mastektomie soll die Prognose des Erstkarzinoms berücksichtigt werden.

Bei Patientinnen mit einer PV in den Genen *BRCA1* oder *BRCA2* führt die prophylaktische Adnexektomie zu einer Reduktion der Brustkrebs-spezifischen Mortalität und zu einer Verbesserung des Gesamtüberlebens.

Empfehlung 3.40: Risiko-reduzierende Operation bei Risikopersonen ohne nachgewiesene wahrscheinlich pathogene / pathogene Variante (PV) (Klasse 4/5) in den Genen *BRCA1* oder *BRCA2*

Bei Frauen ohne nachgewiesene einer PV in den Genen *BRCA1* oder *BRCA2* ist der Nutzen einer risiko-reduzierend bilateralen Mastektomie oder einer risiko-reduzierend kontralateralen Mastektomie nicht nachgewiesen.

Literaturreferenzen: [22], [23], [24], [25], [26], [27], [28], [29], [30], [31]

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: (i)To determine whether risk-reducing mastectomy reduces death rates from any cause in women who have never had breast cancer and in women who have a history of breast cancer in one breast, and (ii) to examine the effect of risk-reducing mastectomy on other	**Design**: Systematic review **Search date**: 9 July 2016 **Searched databases**: Cochrane Breast Cancer Specialized Register, Cochrane Central Register of Controlled Trials, MEDLINE, Embase	**Intervention** Risk-reducing mastectomy (including subcutaneous mastectomy, total or simple mastectomy, modified radical mastectomy, and radical mastectomy) **Control**	**Primary Outcome**: All-cause mortality **Secondary Outcome**: 1. Beast cancer mortality 2. Disease-free survival (e.g. disease-specific (breast cancer), any disease-free, all-cause survival, overall survival)	**BILATERAL RISK-REDUCING MASTECTOMY** **Primary Outcome:** **All-cause mortality** (2 of 21 studies) *Heemskerk-Gerritsen 2013* (FU BRRM group: 8.5 y and 4.1 y control group)	**ROBIS** **Risk of bias in the review:** low **Domain** Concerns regarding specification of study eligibility criteria: unclear risk Concerns regarding methods used to identify

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.

endpoints, including breast cancer incidence, breast cancer mortality, disease-free survival, physical morbidity, and psychosocial outcomes.	and the WHO International Clinical Trials Registry Platform **Included study designs**: Observational studies **Number of included studies**: 61 **Number of included patients**: 15077 **Mean/median age**: n.a. **Inclusion criteria**: women with a positive family history of breast cancer, BRCA1/2 mutation carriers, previous cancer in one breast, previous multiple breast biopsies, and previous diagnosis of	No risk-reducing mastectomy	3. Breast cancer incidence 4. Physical morbidity (e.g. postoperative complications, surgical complications, infections, necrosis, hematoma) 5. Quality of life (including satisfaction with the decision to have RRM, satisfaction with cosmetic outcome, satisfaction with the medical process, psychological well-being, impact on body image, and impact on primary relationships and sexuality) [not covered in evidence table]	for bilateral risk-reducing mastectomy (BRRM) group HR 0.20 (95% confidence interval (CI) 0.02 to 1.68). Ten-year overall survival for the BRRM participants was 99%, while that for the controls was 96%. *Klijn 2004* (FU RRM group: 4.8 y and 3.5 y surveillance group) no deaths among the 113 BRRM women, but two of the 173 women in the surveillance group had died **Secondary Outcome**: **1. Breast cancer (disease-specific) mortality** (5 studies)	and/or select studies: low risk Concerns regarding methods used to collect data and appraise studies: low risk Concerns regarding the synthesis and findings: low risk Concerns: **Additional concerns about quality**: only English language papers included **Risk of Bias in included studies:** varied among studies; Most common source of potential bias: selection bias (30/61 studies); unclear performance bias because of data sources or age of collected data;

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
	lobular carcinoma in situ, atypical hyperplasia, or proliferating breast disease. **Exclusion**: non-English studies			BRCA1 and BRCA2 mutations (2 studies) *Heemskerk-Gerritsen 2013* 212 women underwent BRRM [1 death] and 358 controls surveillance only [6 deaths] *Meijers-Heijboer 2001* 3y FU: 76 women underwent BRRM [no deaths] 63 women surveillance [1 death] *Ingham 2013 (retrospective)* N=58 BRCA1/2 carriers with BRRM: no improved survival HR 0.25, 95% CI 0.03 to 1.81, p=0.14 10-y survival: 98.1% (95% CI 87.1% to 99.7%)	Detection bias varied among 61 studies **Sources of funding:** n.a.

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				Ingham 2013 (retrospective) N=68 BRCA1/2 carriers with BRRM and BRRSO Survival advantage: HR 0.14, 95% CI 0.02 to 1.02, p=0.02 Analysis matched: each individual with BRRM matched by date of birth, gene and undergone BRRSO – to individuals without BRRM: HR 0.28, 95% CI 0.06 to 1.35 Women undergoing just BRRM compared with no risk-reducing surgery: HR 0.12, 95% CI 0.02 to 1.01 Only BRRSO (n=108) was significantly associated with improved survival:	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				HR 0.22, 95% CI 0.08 to 0.61, p=0.002 <u>High risk (strong family history, but not necessarily BRCA1/2 mutation carriers)</u> *Hartmann 1999a* N=639 women (at high and moderate risk) of developing BC; median FU-length: 14y 214 patients (high risk) 2 developed and died of BC; compared to 90 deaths in control group (participants`sisters) 81%-94% risk reduction dying from BC following BRRM (depending on statistical model) <u>Moderate risk</u> *Hartmann 1999a* No deaths in moderate risk group (n=425	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				participants), compared to an expected 10.4 deaths using the Gail model (risk reduction of 100%) *Geiger 2005* 10y of FU 276 women who had BRRM (of those 65% multiple BC risk factors): no deaths Matched controls (12% multiple BC risk factors): 0.2% death rate (1600/666,800) *Heemskerk-Gerritsen 2013* BRRR: 1 death of 212 Control: 6 death of 358 HR for BRRM group=0.29, 95% CI: 0.03 to 2.61 **2. Disease-free survival**	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				Heemskerk-Gerritsen 2013 BRCA1/2 women; 10y BC-free-survival BRRM group: 100% (212 participants) Control group: 74% (358 participants) **3. Breast cancer incidence** 16 studies: effects of BRRM on incidence of BC (of those: 7 studies BRCA1/2 mutations, 6 high risk women, 3 risk unknown) BRCA1 / BRCA2 mutations *Arver 2011 (retrospective case series)* BRRM: 0 of 223 in high risk women vs expected 12 cases after a mean FU of 6.6y	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.

				Hartmann 2001 BRRM: 0 of 26 vs expected incidence of 6 to 9 cancers in 26 women with BRCA1/2 mutations *Heemskerk-Gerritsen 2013* (prospective case series) BRRM (n=212); surveillance only (n=358) BRRM: Incidence rate per 1000 women was zero Surveillance: Incidence rate per 1000 women was 28 *Kass 2010* (retrospective series) 147 asymptomatic BRCA1/2 mutation carriers who had BRRM BC incidence: 0 out of 147 (median FU time 6.1y for BRCA1 and 3.7y in BRCA 2 carriers)	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				Confounding factor: 54% had BRRSO *Meijers-Heijboer 2001* (prospective cohort) BRCA1/2 with BRRM vs surveillance Significant risk reduction in BRRM group: 0 of 76 vs 8 of 63, p=0.003 (3y FU) *Klijn 2004* 1 of 73 with BRRM developed distant metastasis 24 of 173 in surveillance group developed BC Significant difference (p=0.01) in 5-y incidence rate *Rebbeck 2004* (retrospective) 5y FU: significant difference (p<0.0001)	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				BRRM (2/102); without BRRM (184/378) Women with BRRSO excluded: 2/59 vs 149/305, p<0.001 *Skytte 2011* (prospective cohort) Annual incidence BC rate: BRRM: 0.8% (3/96) Non-BRRM: 1.7% (16/211) Protective effect, but not statistically significant <u>High risk (strong family history, but not necessarily BRCA1/2 mutation carriers)</u> *Contant 2002* BRRM: no incidence of BC within 2.8y FU (79 women who were BRCA1/2 mutations	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				carriers or had a 50% risk for BC) *Hartmann 1999* (retrospective cohort) High risk group (strong family history of BC; BRCA1/2 not excluded) vs sisters as control group 90-94% reduction in incidence for surgery group <u>Moderate risk</u> *Geiger 2005* BRRM compared to control group HR 0.005, 95% CI 0.001 to 0.044 *Hartmann 1999a* (case series) Significantly reduced incidence of BC following BRRM	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.

				CONTRALATERAL RISK-REDUCING MASTECTOMY (CRRM) 26 studies involved only participants with a previous diagnosis of BC in one breast who chose to undergo CCRM; 4 studies included both: BRRM & CRRM **Primary Outcome:** **All-cause mortality** 15 studies reported all-cause mortality *Boughey 2010* 10-year overall survival: CRRM (128 of 385 died non-CRRM group (162 of 385 died) with a HR of 0.68 (95% CI 0.54 to 0.86, P= 0.001) resulted in a 10-year survival after a multivariate analysis of	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				HR 0.77 (95% CI 0.60 to 0.98, P = 0.03) *Goldflam 2004* All-cause mortality following CRRM: 5.8 (14/239); mean FU: 7.8y Herrington 2005: Improved survival: CRRM vs no CRRM group: HR 0.60, 95% CI 0.50 to 0.72 (women with BC in one breast) *Zeichner 2014* 237 participants <40 years with breast cancer, 42 having CRRM and 195 with No CRRM. Overall survival at 10 years for the CRRM versus no CRRM was HR 2.35, 95% CI 1.02 to 5.41, P = 0.046, with five deaths (11.9%) in the CRRM group versus 51	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				(26.2%) in the no-CRRM group (P = 0.05) *Brewster 2012* CRRM: n=532; no CRRM: 335 Adjusted model favored CRRM (overall survival) HR 0.74, 95% 0.56 to 0.99 Matched model (497 CRRM vs 497 no CRRM) HR 0.77, 95% CI 0.53 to 1.13 Hormone receptor positive adjusted and matched models were not statistically significant; the hormone receptor-negative adjusted model favored CRRM, with HR 0.58, 95% CI 0.36 to 0.96	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				Chung 2012 CRRM: no significant predictor for overall survival *Kiely 2010* 1018 women with a family history of breast Cancer, median follow-up of 11.1 years (8 years for 154 in the CRRM group and 11.7 years for the non-CRRM group). At last follow-up, there was no apparent difference in survival as 144 of 154 women in the CRRM group (93.5%) and 800 of 864 women (92.6%)in the non-CRRM group were alive *Jatoi 2014* CRRM was associated with lower all-cause	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				mortality (HR 0.83, 95% CI 0.80, 0.88) (retrospective case-control study) *Kruper 2014* comparing CRRM to no CRRM, there was greater overall survival (HR 0.76, 95% CI 0.71 to 0.81) for CRRM women CRRM decreased the risk of overall death by 24%; 3-, 5-, and 10-year overall survival was greater for CRRM women versus no CRRM. (SEER database) *Peralta 2000* 246 participants with at least one first- or second-degree relative with BC; overall survival at 15y: CRRM was 64% (41 of 64) versus 48% (87 of 182)	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				for those in the comparison group after controlling for multiple prognostic factors (P = 0.26) *Pesce 2014* 10,289 women who had unilateral treatment mastectomy (UM) and 4338 who had CRRM CRRM: better survival than UM without adjustments (P < 0.001); the unadjusted Kaplan-Meier survival curve showed CRRM was statistically significantly better than UM (P = 0.0002) overall survival (adjusted for various factors): HR 0.93, 95% CI 0.79 to 1.09, P = 0.38 (USA National Cancer Database)	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				<u>BRCA1 and BRCA2 mutations</u> *Evans 2013* 105 women had CRRM, 473 had No CRRM, and 120 BRRSO only All deaths were: CRRM = 9/105, controls = 180/473 (median follow-up of 9.7 y) in the CRRM group and 8.6 in the non-CRRM group with a HR 0.37 (95% CI 0.17 to 0.80, P = 0.008.) 10-year survival figures were: CRRM and BRRSO = 92% (HR 0.16, 95% CI 0.06 to 0.44); CRRM no BRRSO = 83% (HR 0.48, 95% CI 0.19 to 1.14); BRRSO no CRRM = 81% (HR 0.46, 95% CI 0.27 to 0.78); no CRRM = 65% (no HR). In the adjusted analysis, after adjusting for	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				potential confounders, only CRRM (HR 0.28, 95% CI 0.14 to 0.55) and BRRSO (HR 0.34, 95% CI 0.21 to 0.55) were independently predictive of improved survival. *Heemskerk-Gerritsen 2015* all-cause mortality was lower in the CRRM group (242 women) than the control (surveillance; 341 women) group, with 19 in CRRM versus 65 in controls, 21.6 versus 9.6 per person-years of observation 10-year survival, fewer women died in the CRRM group (8% versus 19%, P < 0.001); the 15-year survival was also better in the CRRM group (86%) than in the control group (74%).	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				Survival curves (Kaplan-Meier), death by all causes favoredCRRM (P logrank < 0.119) but was not statistically significant *Metcalfe 2014* 390 women with stage 1 or 2 BC; BRCA 1/2 carrier or untested with family history of BC and/or BRCA 1/2 mutations Overall survival of BRCA1/2 or high-risk women at 20y FU CRRM: 88% (95% CI 83% to 93%) and No CRRM: 66% (95% CI 59 to 73%) propensity score adjusted analysis of 79 matched pairs (CRRM versus no CRRM), the association was not significant (0.60, 0.34 to	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				1.06, P = 0.08). The adjusted HR for CRRM compared with no CRRM was 0.58 (95% CI 0.34 to 0.97, P = 0.04) for the entire study period and 0.36 (95% CI 0.13 to 0.96, P = 0.04) for the second period of 10 to 20 years of follow-up *Van Sprundel 2005* Improved survival for CRRM participants (94% vs 77%, p=0.03) After adjusting for BRRSO, the CRRM effect of all-cause mortality was not significant **Secondary Outcome:** **1. Breast cancer (disease-specific) mortality**	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				9 studies: data on BC mortality (inconsistent results) *Bedrosian 2010* CRRM: associated with improved disease-specific survival in specific patient populations: Women with stages I-III BC: HR of death 0.63, 95% CI 0.57 to 0.69, p<0.001 Adjusted analysis: Women under 50 years: HR 0.84, 95% CI, 0.72 to 0.97, p=0.02 Women >60 years: HR 0.88, 95% CI 0.75 to 1.03, p=0.13 Women <50y with stage I/II ER neg BC	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				HR 0.68, 95% CI 0.53 to 0.88, p=0.004 Women with stage I/II ER pos BC and CRRM: HR 0.88, 95% CI 0.66 to 1.17, p=0.38 *Goldflam 2004* BC mortality rate 2.5% (8/239) in women with stage 0 to II BC (mean FU 7.8y) *Herrington 2005* CRRM vs no-CRRM (after approx. 5y) BC mortality: HR 0.57, 95% CI 0.45 to 0.72 *Jatoi 2014* CRRM vs no-CRRM BC specific mortality: HR 0.84, 95% CI 0.79 to 0.89 Non-cancer mortality:	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				HR 0.71, 95% 0.64 to 0.80 (5y hazard of death) *King 2011a* Alive without disease: Multivariate Cox regression (adjusting for age and treatment factors): no difference in BC event rates p=0.23 *Lee 1995* Significant survival advantage for thosewho had CRRM or biopsy in the contralateral breast at 15y FU **Peralta 2000** Disease specific survival: Subgroup with initial diagnoses of stage 0, I or II BC 71% (95% CI 52% to 84%) vs 53% (95% CI 42% to 62%)	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				<u>BRCA1 and BRCA2 mutations</u> *Evans 2013* CRRM group (105 participants) of BRCA1/2 mutation carriers, all deaths = 9 of 105 participants, deaths from breast cancer = 8/105; deaths from other cause = 1 The 10-year survival was 89%. In the control group (473 participants), all deaths = 26, deaths from breast cancer = 24, and other deaths = 2. The 10-year survival was 71%. *Metcalfe 2014* BRCA1/2 mutations or high risk: CRRM vs no-CRRM HR 0.52, 95% 0.29-0.93	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				10y FU: no significant differences 20y FU: BC-specific mortality for no CRRM: 31% CRRM: 48% reduction in risk of mortality (vs no CRRM) **2. Disease-free survival** 11 studies (varying results on data for disease-free survival) *Brewster 2012* All-patients adjusted model favored CRRM: HR 0.75, 95% CI 0.59 to 0.97 All-patients matched model: HR 0.77, 95% CI 0.53 to 1.13 Hormone-receptor negative adjusted model:	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				HR 0.60, 95% CI 0.38 to 0.95 Matched model: HR 0.48, 95% CI 0.22 to 1.01 *Boughey 2010* CRRM vs no-CRRM HR 0.66, 95% CI 0.53 to 0.82 Multivariate analysis: HR 0.67, 95% CI 0.54 to 0.84 *Chung 2012* 177 women with CRRM and 178 controls; median FU 61 months; Both the local recurrence free survival curve difference (P = 0.225) and the distant metastasis free	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.

				survival curve difference (P = 0.417) were not statistically significant between the groups *Kiely 2010* systemic recurrence rate of 6.2 per 1000 women-years for CRRM women and 10.4 per 1000 women-years for non-CRRM women (P = 0.04) confounding factor: CRRM group, 86 of 154 women (59%) had also had BRRSO and only 240 of 864 women in the non-CRRM (24%) had also had BRRSO *King 2011a* at last follow-up for women with CRRM, 91% were alive without disease as opposed to	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				those without CRRM (84% alive, P = 0.02) *Kruper 2014* CRRM associated with improved disease-specific survival HR 0.86, 95% CI 0.79 to 0.93 *Peralta 2000* At 15y: disease-free-survival CRRM: 55%, 95% CI 38% to 69% Control: 28%, 95% CI 19% to 36% (p=0.01) *Zeichner 2014* CRRM: 42 participants Overall 5y-survival: 81.3% Overall 10y survival: 73.3% Compared to the no CRRM: 195 participants,	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				the CRRM participants had significantly smaller tumors <u>BRCA1 and BRCA2 mutations</u> *Van Sprundel 2005* No improved survival in CRRM group without BRSSO CRRM + BRRSO: significantly better disease-free survival: HR 0.16, 95% CI 0.04 to 0.61 (than those who did not have BRRSO *Heemskerk-Gerritsen 2015* 242 women with CRRM and 341 without (controls), with a median follow-up for CRRM of 11.4 years and for controls of	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				11.3 years. Time to onset of breast cancer statistically significantly favored CRRM (P logrank < 0.001). Cox analysis adjusted for BRRSO for mortality yielded a HR 0.49 (95% CI 0.29 to 0.82) which favors CRRM. **3. Breast cancer incidence** 17 studies reported data for contralateral BC incidence after CRRM, with 11 having controls showing significantly lower breast cancer incidence in those who had CRRM *Bedrosian 2010 (SEER data)* Early-stage ER-neg cancer and CRRM Cumulative incidence of CBC was 0.16%;	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				No-CRRM 0.90% (p=0.05) Early stage ER+ and CRRM: 0.13% No-CRRM 0.46% (p=0.07) *Boughey 2010* Incidence of CBC: CRRM 2/385 No-CRRM 31/385 HR 0.05, 95%CI 0.01 to 0.22, p=0.0001 Multivar. Analysis: HR 0.05, 95% CI 0.01 to 0.19, p=0.0001 *Brewster 2012* CRRM: 1/532 Control: 67/335 Chung 2012 Development of CBC: CRRM: 0/177 Control: 3/178	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				Herrinton 2005 and Metcalfe 2014 HR 0.03 in CRRM treatment groups *Kiely 2010* CRRM: 1 chest wall event in 154 participants No-CRRM: 177/864 invasive or in situ event (p<0.0001) *King 2011* CRRM: 0/407 incidence of CBC No-CRRM: 14/2572 (p=0.02) Adjusted analysis for age, treatment (chemotherapy, radiotherapy, MRI): p=0.23 *Kruper 2014* CBC in 1.6% of cohort McDonnell 2001 (case series of 745 women	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				(388 premenopausal, 357 postmenopausal) who underwent CRRM; median FU 10 y 8 CBC (6/8 premenopausal) 2/357 postmenopausal women developed CBC following CRRM *Metcalfe 2004* BRRSO: HR 0.41, 95% CI 0.18 to 0.90 *Peralta 2000* CRRM: 0/64 Control: 36/182 (19.8%) P=0.02 *Zeichner 2014* CRRM: 6/42 (14.3%) No-CRRM: 60/195 (30.8%) **COMBINED BILATERAL AND COLATERAL RISK-**	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				REDUCING MASTECTOMY 12 studies included participants receiving BRRM as well as participants receiving CRRM. 4 studies separated BRRM and CRRM participants when reporting data and those results are reported above. Collectively, the other 10 studies involved 2157 participants; 1809 of them (83.7%) received BRRM, 348 (16.3%) received CRRM, and 36 were unclear. **Primary Outcome:** **All-cause mortality** 1 study *Pennisi 1989*	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				70% of 1500 participants who were followed for 9 years, 0.3% died of "other causes". These are the only data provided concerning mortality from causes other than breast cancer; no data for all-cause mortality **2. Breast cancer (disease specific survival)** *Mutter 2015* 13 of 1065 women with BRRM and 12 of 1643 with CRRM developed breast cancer in the risk-reducing mastectomy breast with a median follow-up of 22 years Kaplan-Meier curve for disease-free-survival (5y):	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				69% overall (95% CI 52% to 94%) **3. Breast cancer incidence** 5 studies reported data on BC incidence – all 5 reported fewer cases following risk-reducing surgery *Evans 1999* 178 participants: 141 received BRRM and 37 received CRRM No BC in participants with risk-reducing mastectomy; FU < 5y *Horton 1978* 104 women: 93 received BRRM and 11 received CRRM No BC developed in any participants *Mutter 2015*	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.					
				BRRM: 13/1065 Median time to develop BC: 6y CRRM: 12/1643 Median time to develop BC: 8y *Pennisi 1989* 1500 participants: BRRM: 1361 CRRM: 139 6/1500 (0.4%) developed BC 30% were lost-to FU <u>BRCA1 and BRCA2 mutations</u> *Koskenuvo 2014* (retrospective cohort) 136 BRCA1/2 mutation carriers; median FU 52 months (range 1-133 months)	

Source: NE, Carbine, Lostumbo L, Wallace J, and Ko H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer." [In eng]. The Cochrane database of systematic reviews 4, no. 4 (2018-4-5 2018): CD002748. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29620792/.

				52 had RRM; 33/52 also had RRSO 45 months postsurgery: 1/52 metastatic axillary lymph nodes	

Abbreviations:

BRRM = Bilateral Risk-Reducing Mastectomy

RRM = Risk-Reducing Mastectomy

BC = Breast Cancer

CRRM = Contralateral Risk-Reducing Mastectomy

CBC = Contralateral Breast Cancer

BRRSO = Bilateral Risk-Reducing Salpingo-Oophorectomy

n.a. = not Available, not Applicable

FU = Follow-Up

HR = Hazard Ratio

95% CI = 95% Confidence Interval

y = Years

Grey Text: Further Outcomes not related to recommendation

Verknüpfte Empfehlungen:

Empfehlung 3.37: Risiko-reduzierende Operation bei gesunden Trägerinnen wahrscheinlich pathogener / pathogener konstitutioneller Varianten (PV) in den Genen *BRCA1* oder *BRCA2* (Klasse 4/5): prophylaktische bilaterale Mastektomie.

Gesunde Frauen mit einer PV in den Genen *BRCA1* oder *BRCA2* haben ein lebenszeitlich erhöhtes Risiko für die Entwicklung eines Mammakarzinoms.

Bei gesunden Frauen mit einer PV in den Genen *BRCA1*- oder *BRCA2* führt die beidseitige prophylaktische Mastektomie zu einer Reduktion der Brustkrebsinzidenz. Eine Reduktion der Brustkrebs-spezifischen Mortalität bzw. der Gesamtmortalität durch die beidseitige prophylaktische Mastektomie ist nicht ausreichend gesichert.

Daher setzt eine Einzelfallentscheidung für oder gegen eine bilaterale risiko-reduzierend Mastektomie stets fallbezogen eine umfassende Aufklärung und ausführliche multidisziplinäre Beratung über potentielle Vor- und Nachteile eines solchen Eingriffs mit Berücksichtigung der möglichen Alternativen voraus.

Literaturreferenzen: [32], [33], [34], [35], [36], [37], [38], [39], [40], [31], [20], [41]

Source: Bernadette A. M. Heemskerk-Gerritsen, Agnes Jager: Survival after bilateral risk-reducing mastectomy in healthy BRCA1and BRCA2 mutation carriers. Breast Cancer Research and Treatment (2019) 177: 723–733, https: //doi.org/10.1007/s10549-019-05345-2

Aim	Design and participants	Surveillance program; groups	Outcomes	Results	Quality and comment
Does bilateral risk-reducing mastectomy lead to survival benefit?	**Design**: Prospective nationwide cohort study (surveillance) **Setting**: Hereditary Breast and Ovarian Cancer Netherlands (HEBON) study members of breast and/ or ovarian cancer families were identified	BC surveillance for BRCA1/2 mutation carriers: Annual imaging by MRI between 25 and 60 years (since 1998)	Breast cancer occurrence, Overall mortality, Breast cancer specific mortality	1,712 BRCA1 mutation carriers: 722 opted for BRRM; 1,145 BRCA2 mutation carriers: 406 opted for BRRM	**Quality of study** Assessed with SIGN checklist for cohort studies: Acceptable **Limitations by authors:** Self-reported data regarding BC screening modality and frequency

Source: Bernadette A. M. Heemskerk-Gerritsen, Agnes Jager: Survival after bilateral risk-reducing mastectomy in healthy BRCA1and BRCA2 mutation carriers. Breast Cancer Research and Treatment (2019) 177: 723–733, https: //doi.org/10.1007/s10549-019-05345-2					
	through the departments of Clinical Genetics/Family Cancer Clinics at 8 Dutch academic centers and the Netherlands Cancer Institute **Enrollment**: started Jan 1999 **Number of included patients**: 2,857 healthy BRCA1/2 mutation carriers (1,712 BRCA1 and 1,145 BRCA2); had both breasts and both ovaries in situ at the date of DNA test result **Mean age**: n.r. **Inclusion criteria**: Women without history of cancer **Exclusion**: n.r.	Annual imaging by mammography from 30-60y Biennial (annual since 2012) mammography from age 60 - 75 Annual clinical breast examination from 25y onward BRRM groups vs non-BRRM group (surveillance group)		Women opting for BRRM underwent DNA testing at a younger age (than women that stayed under surveillance until end of FU) Women in the BRRM group opted more often for risk-reducing salpingo-oophorectomy at a younger age Mean follow-up: 10.3y Observation period, median y (IQR) BRCA1 mutation carriers: BRRM: 10.6 (7.9-15.4) Surveillance: 9.3 (6.7-13.3) BRCA2 mutation carriers: BRRM: 9.9 (7.1-12.5) Surveillance: 8.6 (6.5-11.7)	(unknown in ~50% in surveillance group; family history not available for all participants; possible bias toward BRRM being offered more often to healthier women (in BRCA2 mutation carriers women in surveillance group showed more other cancers – but not in BRCA1 group); median age at diagnosis of cancer other than BC/ovarian cancer was higher in the surveillance group; no data about health-related issues available (weight, smoking) **Sources of funding:** Grant from the Dutch Pink Ribbon foundation (Grant No. 2016-209)

Source: Bernadette A. M. Heemskerk-Gerritsen, Agnes Jager: Survival after bilateral risk-reducing mastectomy in healthy BRCA1and BRCA2 mutation carriers. Breast Cancer Research and Treatment (2019) 177: 723–733, https: //doi.org/10.1007/s10549-019-05345-2					
				Observation period after BRRM, median years (IQR) BRCA1: 8.5 (5.5-12.9) BRCA2: 7.2 (4.8-10.8) **Breast cancer occurrence** Lower in the BRRM group than in the surveillance group BRCA1: 1% [n=8] vs 27% [n=268] BRCA 2: 0% [n=0] vs 19% [n=144] BRCA2-associated BCs were diagnosed with more favorable characteristics than BRCA2 mutation carriers Consequently, BRCA2 less often treated with chemotherapy and more often with endocrine therapy	

Source: Bernadette A. M. Heemskerk-Gerritsen, Agnes Jager: Survival after bilateral risk-reducing mastectomy in healthy BRCA1and BRCA2 mutation carriers. Breast Cancer Research and Treatment (2019) 177: 723–733, https: //doi.org/10.1007/s10549-019-05345-2					
				Overall mortality Lower for women opting for BRRM than women under surveillance: BRCA1: HR 0.40, 95% CI 0.20-0.80 (multivar. Cox model) Unadjusted survival curves: Probability of being alive at 65y: BRRM: 93% Surveillance group: 83% BRCA2: HR 0.45, 95% CI 0.15-1.36 (multivar. Cox model) Probability of being alive at 65y: BRRM: 93% Surveillance group: 90% **Breast cancer-specific mortality**	

Source: Bernadette A. M. Heemskerk-Gerritsen, Agnes Jager: Survival after bilateral risk-reducing mastectomy in healthy BRCA1and BRCA2 mutation carriers. Breast Cancer Research and Treatment (2019) 177: 723–733, https: //doi.org/10.1007/s10549-019-05345-2					
				Lower for women opting for BRRM than women under surveillance: BRRM: 1 BRCA1 and no BRCA2 mutation carrier died due to BC Surveillance group: 20 BRCA1 (2.0%) and 7 BRCA2 (0.9%) mutation carriers died due to BC BRCA1: HR 0.06, 95% CI 0.01-0.46 (in favor for BRRM) Probability not having died due to BC at 65y: BRRM: 99.7% Surveillance group: 93% BRCA2: no HR could be estimated (no BRCA2 mutation carrier died due to BC)	
Abbreviations: HEBON = Hereditary Breast and Ovarian Cancer Netherlands					

Source: Bernadette A. M. Heemskerk-Gerritsen, Agnes Jager: Survival after bilateral risk-reducing mastectomy in healthy BRCA1and BRCA2 mutation carriers. Breast Cancer Research and Treatment (2019) 177: 723–733, https: //doi.org/10.1007/s10549-019-05345-2

BRRM = Bilateral Risk-Reducing Mastectomy

BC = Breast Cancer

FU = Follow-Up

y = years

IQR = Interquartile Range

HR = Hazard Ratio

95 % CI = 95% Confidence Interval

n.r. = not reported

Verknüpfte Empfehlungen:

Empfehlung 3.38: Risikoreduzierende Operation bei gesunden Trägerinnen wahrscheinlich pathogener / pathogener konstitutioneller Varianten in den Genen *BRCA1* oder *BRCA2* (Klasse 4/5): prophylaktische bilaterale Adnexektomie.

Frauen mit einer PV in den Genen *BRCA1* oder *BRCA2* haben ein lebenszeitlich erhöhtes Risiko für ein Ovarialkarzinom, Tubenkarzinom und/oder ein primäres Peritonealkarzinom.

Bei gesunden Frauen mit einer PV in den Genen *BRCA1*- oder *BRCA2* führt die prophylaktische Adnexektomie zu einer Reduktion der Ovarialkarzinominzidenz und der Gesamtmortalität.

Daher soll die prophylaktische beidseitige Salpingo-Oophorektomie fallbezogen im Rahmen einer umfassenden, multidisziplinären Beratung über potentielle Vor- und Nachteile eines solchen Eingriffs und unter Berücksichtigung fehlender effektiver Früherkennungsmöglichkeiten diskutiert und empfohlen werden.

Literaturreferenzen: [42], [32], [34], [36], [43], [44], [45], [46], [47], [48]

Source: GU, Eleje, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, and Okonkwo OO. "Risk-Reducing Bilateral Salpingo-Oophorectomy in Women with Brca1 or Brca2 Mutations." [In eng]. The Cochrane database of systematic reviews 8, no. 8 (2018-8-24 2018): CD012464. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30141832/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: To assess the benefits and harms of RRSO in women with BRCA1 or BRCA2 mutations.	**Design**: Systematic Review and Meta-Analysis **Search date**: up to July 2017 **Searched databases**: Cochrane Central Register of Controlled Trials, MEDLINE Ovid, Embase Ovid	**Intervention** Risk-reducing bilateral salpingo-ooporectomy (RRSO) **Control** No RRSO	**Primary Outcome**: Overall survival, HGSC (fallopian tube, ovarian and primary peritoneal cancer) mortality, breast cancer mortality **Secondary Outcome**: High-grade serous cancer incidence	**1. Risk-reducing salpingo-oophorectomy (RRSO) versus no** **RRSO in BRCA1 or BRCA2 mutation carriers** **Primary Outcomes**: **Overall survival: survival until death from all causes**	**ROBIS** **Risk of bias in the review:** low **Domain** Concerns regarding specification of study eligibility criteria: low risk Concerns regarding methods used to identify

Source: GU, Eleje, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, and Okonkwo OO. "Risk-Reducing Bilateral Salpingo-Oophorectomy in Women with Brca1 or Brca2 Mutations." [In eng]. The Cochrane database of systematic reviews 8, no. 8 (2018-8-24 2018): CD012464. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30141832/.					
	+ Trial registers for ongoing trials + Handsearch **Included study designs**: Non-randomised studies (NRS), prospective and retrospective cohort studies, and case series (all with concurrent comparison groups) **Number of included studies**: 10 studies in narrative synthesis; 9 studies in meta-analysis **Number of included patients**: 8087 (10 cohort studies) 7927 (9 studies in meta-analysis) **Mean/median age**: **Inclusion criteria**:		BC incidence Bone fracture incidence DSF Morbidity Recovery and readmission Quality of life Severe adverse events	BRCA1 or BRCA2 mutation carriers who had RRSO compared to women with no RRSO (after adjustment for important prognostic factors including age and BRCA mutation status): HR 0.32, 95% CI: 0.19 to 0.54; P < 0.001; I^2 0% (3 studies, 2548 patients) **High-grade serous cancer mortality** Favour of RRSO versus no RRSO in HGSC (fallopian tube, ovarian and primary peritoneal cancer) mortality, after adjustment for important prognostic factors including age and BRCA mutation	and/or select studies: low risk Concerns regarding methods used to collect data and appraise studies: low risk Concerns regarding the synthesis and findings: low risk **Additional concerns about quality**: none **Certainty of Evidence (GRADE)**: very low for all outcomes **Sources of funding:** National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group, UK.

Source: GU, Eleje, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, and Okonkwo OO. "Risk-Reducing Bilateral Salpingo-Oophorectomy in Women with Brca1 or Brca2 Mutations." [In eng]. The Cochrane database of systematic reviews 8, no. 8 (2018-8-24 2018): CD012464. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30141832/.

	women without a previous or coexisting breast, ovarian or fallopian tube malignancy, and women with or without concomitant hysterectomy **Exclusion**: women with a previous or coexisting breast malignancy and women with unilateral oophorectomy or salpingectomy or salpingo-oophorectomy (both). In addition, we excluded women with prophylactic salpingectomy with delayed oophorectomy or ovarian conservation			status (HR 0.06, 95% CI 0.02 to 0.17; P < 0.0001; I^2 69% (3 studies, 2534 participants) **Breast cancer mortality** favour of RRSO versus no RRSO in breast cancer mortality, aJer adjustment for important prognostic factors including age and BRCA mutation status (HR 0.58, 95% CI 0.39 to 0.88; P = 0.009; I^2 65%) (7 studies, 7198 participants) **Secondary Outcome**: **High-grade serous cancer incidence** total of 14/1269 (1%) participants with RRSO versus 194/2059 (9%)	

Source: GU, Eleje, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, and Okonkwo OO. "Risk-Reducing Bilateral Salpingo-Oophorectomy in Women with Brca1 or Brca2 Mutations." [In eng]. The Cochrane database of systematic reviews 8, no. 8 (2018-8-24 2018): CD012464. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30141832/.					
				participants with no RRSO developed HGSC (RR 0.17, 95% CI 0.04 to 0.75; P = 0.02; I^2 84%) (4 studies, 1269 participants RRSO groups and 2059 participants control group) **Breast cancer incidence** A total of 230/2285 (10%) participants who had had RRSO versus 429/3310 (13%) participants with no RRSO developed breast cancer. (RR 0.64, 95% CI 0.43 to 0.96; P = 0.03; I^2 75%) (7 studies, 2285 participants RRSO groups and 3310 participants control group) **Bone fracture incidence**	

Source: GU, Eleje, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, and Okonkwo OO. "Risk-Reducing Bilateral Salpingo-Oophorectomy in Women with Brca1 or Brca2 Mutations." [In eng]. The Cochrane database of systematic reviews 8, no. 8 (2018-8-24 2018): CD012464. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30141832/.

				None of the studies reported this outcome **Disease-free survival** None of the studies reported this outcome **Morbidity: direct surgical morbidity and surgically related systemic** **morbidity** None of the studies reported this outcome **Recovery and readmission** None of the studies reported this outcome **2. Risk-reducing salpingo-oophorectomy (RRSO) versus no** **RRSO according to BRCA mutation status: subgroup analyses** **Primary outcomes**	

Source: GU, Eleje, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, and Okonkwo OO. "Risk-Reducing Bilateral Salpingo-Oophorectomy in Women with Brca1 or Brca2 Mutations." [In eng]. The Cochrane database of systematic reviews 8, no. 8 (2018-8-24 2018): CD012464. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30141832/.

				Overall survival: survival until death from all causes lower risk of death among women with BRCA1 mutations who had had RRSO than in women who had not had RRSO (HR 0.30, 95% CI 0.17 to 0.52; P < 0001; I^2 23% (3 studies) lower risk of death among women who were BRCA2 mutation carriers who received RRSO than in women with no RRSO (HR 0.44, 95% CI 0.23 to 0.85; P = 0.01; I^2 0% (2 studies) subgroup differences showed no significant difference in effect between studies assessing RRSO versus no RRSO on overall survival	

Source: GU, Eleje, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, and Okonkwo OO. "Risk-Reducing Bilateral Salpingo-Oophorectomy in Women with Brca1 or Brca2 Mutations." [In eng]. The Cochrane database of systematic reviews 8, no. 8 (2018-8-24 2018): CD012464. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30141832/.

				according to the mutation status: BRCA1 and BRCA2 (P = 0.38) **High-grade serous cancer mortality** difference in favour of RRSO than no RRSO for HGSC deaths among women who were BRCA1 mutation carriers (HR 0.10, 95% CI 0.02 to 0.41; P = 0.001; I^2 54% (2 studies) **Breast cancer mortality** difference in favour of RRSO compared with no RRSO for breast cancer mortality among women who were BRCA1 only mutation carriers (HR 0.45, 95% CI 0.30 to 0.67; P < 0.0001; I^2 0% (4 studies)	

Source: GU, Eleje, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, and Okonkwo OO. "Risk-Reducing Bilateral Salpingo-Oophorectomy in Women with Brca1 or Brca2 Mutations." [In eng]. The Cochrane database of systematic reviews 8, no. 8 (2018-8-24 2018): CD012464. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30141832/.

				no difference in favour of RRSO compared with no RRSO for breast cancer mortality among women who were BRCA2 mutation carriers (HR 0.88, 95% CI 0.42 to 1.87; P = 0.75; I^2 63% (3 studies) no difference in eHect between studies assessing RRSO versus no RRSO on breast cancer mortality according to the mutation status: BRCA1 and BRCA2 (P = 0.12) **3. BRCA1 or BRCA2 mutation carriers according to type of risk-reducing surgery: subgroup analyses** **Primary Outcomes** **Overall survival: survival until death from all causes**	

Source: GU, Eleje, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, and Okonkwo OO. "Risk-Reducing Bilateral Salpingo-Oophorectomy in Women with Brca1 or Brca2 Mutations." [In eng]. The Cochrane database of systematic reviews 8, no. 8 (2018-8-24 2018): CD012464. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30141832/.

				RRSO alone versus RRSO and risk-reducing mastectomy (RRM) None of the studies reported overall survival among participants who were BRCA1 or BRCA2 mutation carriers who received RRSO alone versus RRSO and RRM. **RRSO and RRM versus no RRSO** increase in overall survival among women who were BRCA1 or BRCA2 mutation carriers who received RRSO and RRM compared to women with no RRSO (HR 0.14, 95% CI 0.02 to 0.98; P = 0.0001) (1 study) **Breast cancer mortality** No difference between bilateral salpingo-	

Source: GU, Eleje, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, and Okonkwo OO. "Risk-Reducing Bilateral Salpingo-Oophorectomy in Women with Brca1 or Brca2 Mutations." [In eng]. The Cochrane database of systematic reviews 8, no. 8 (2018-8-24 2018): CD012464. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30141832/.

				oophorectomy plus bilateral mastectomy and no RRSO for breast cancer mortality among women who received bilateral salpingo-oophorectomy plus bilateral mastectomy (HR 0.78, 95% CI 0.51 to 1.19; P = 0.25) (1 study) **No data for secondary outcomes** **4. Risk-reducing salpingo-oophorectomy (RRSO) versus no** **RRSO for BRCA1 mutation carriers according to age at time of RRSO: subgroup analyses** **Primary outcomes** **Breast cancer mortality** No difference between RRSO and no RRSO for breast cancer mortality	

Source: GU, Eleje, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, and Okonkwo OO. "Risk-Reducing Bilateral Salpingo-Oophorectomy in Women with Brca1 or Brca2 Mutations." [In eng]. The Cochrane database of systematic reviews 8, no. 8 (2018-8-24 2018): CD012464. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30141832/.

				among women who were BRCA1 mutation carriers who received RRSO at 50 years of age or less (HR 0.78, 95% CI 0.55 to 1.09; P = 0.15 I^2 42%) (3 studies) no difference between RRSO and no RRSO for breast cancer mortality among women who were BRCA1 mutation carriers who received RRSO at more than 50 years of age (HR 1.27, 95% CI 0.67 to 2.38; P = 0.46; I^2 0% (3 studies) no difference in studies that reported breast cancer mortality according to age at surgery: 50	

Source: GU, Eleje, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, and Okonkwo OO. "Risk-Reducing Bilateral Salpingo-Oophorectomy in Women with Brca1 or Brca2 Mutations." [In eng]. The Cochrane database of systematic reviews 8, no. 8 (2018-8-24 2018): CD012464. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30141832/.

				years of age or less and more than 50 years of age (P = 0.18; I^2 = 43.8%) **No data for secondary outcomes** **5. Risk-reducing salpingo-oophorectomy (RRSO) versus no** **RRSO for BRCA2 mutation carriers according to age at time of RRSO: subgroup analyses** **Primary outcomes** **Overall survival: survival until death from all causes** **Breast cancer mortality** no difference between RRSO and no RRSO for breast cancer mortality among women who were BRCA2 mutation carriers who	

Source: GU, Eleje, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, and Okonkwo OO. "Risk-Reducing Bilateral Salpingo-Oophorectomy in Women with Brca1 or Brca2 Mutations." [In eng]. The Cochrane database of systematic reviews 8, no. 8 (2018-8-24 2018): CD012464. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30141832/.					
				received RRSO at 50 years of age or less (HR 0.49, 95% CI 0.08 to 2.90; P = 0.43; I^2 85% (2 studies) no difference between RRSO and no RRSO for breast cancer mortality among women who were BRCA2 mutation carriers who received RRSO at more than 50 years of age (HR 1.36, 95% CI 0.68 to 2.75; P = 0.39; I^2 0% (2 studies) no difference in studies that reported breast cancer mortality among participants who were BRCA2 mutation carriers according to age at surgery: 50 years of age or less and more than 50	

Source: GU, Eleje, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, and Okonkwo OO. "Risk-Reducing Bilateral Salpingo-Oophorectomy in Women with Brca1 or Brca2 Mutations." [In eng]. The Cochrane database of systematic reviews 8, no. 8 (2018-8-24 2018): CD012464. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30141832/.

				years of age (P = 0.29; I^2 = 8.9%). **No data for secondary outcomes**	

Abbreviations:

RRSO = Risk-reducing bilateral salpingo-ooporectomy

NRS = Non-randomised studies

HGSC = High-grade serous cancer

BC = Breast Cancer

DSF = Disease-Free Survival

RR = Risk Ratio

HR = Hazard Ratio

95% CI = 95% Confidence Interval

UK = United Kingdom

Verknüpfte Empfehlungen:

Empfehlung 3.38: Risikoreduzierende Operation bei gesunden Trägerinnen wahrscheinlich pathogener / pathogener konstitutioneller Varianten in den Genen *BRCA1* oder *BRCA2* (Klasse 4/5): prophylaktische bilaterale Adnexektomie.

Frauen mit einer PV in den Genen *BRCA1* oder *BRCA2* haben ein lebenszeitlich erhöhtes Risiko für ein Ovarialkarzinom, Tubenkarzinom und/oder ein primäres Peritonealkarzinom.

Bei gesunden Frauen mit einer PV in den Genen *BRCA1*- oder *BRCA2* führt die prophylaktische Adnexektomie zu einer Reduktion der Ovarialkarzinominzidenz und der Gesamtmortalität.

Daher soll die prophylaktische beidseitige Salpingo-Oophorektomie fallbezogen im Rahmen einer umfassenden, multidisziplinären Beratung über potentielle Vor- und Nachteile eines solchen Eingriffs und unter Berücksichtigung fehlender effektiver Früherkennungsmöglichkeiten diskutiert und empfohlen werden.

Empfehlung 3.39: Risikoreduzierende Operation bei bereits unilateral an Brustkrebs erkrankten Trägerinnen wahrscheinlich pathogener / pathogener konstitutioneller Varianten (PV) in den Genen *BRCA1* oder *BRCA2* (Klasse 4/5): kontralaterale prophylaktische Mastektomie und prophylaktische bilaterale Adnexektomie

Bereits an Brustkrebs erkrankte Frauen mit einer PV in den Genen *BRCA1* oder *BRCA2* haben ein erhöhtes Risiko für die Entstehung eines kontralateralen Mammakarzinoms. Dieses Risiko hängt u. a. ab vom betroffenen Gen und dem Ersterkrankungsalter und ist bei der Beratung zu berücksichtigen.

Bei Frauen mit einer PV in den Genen *BRCA1* oder *BRCA2* führt die kontralaterale, prophylaktische Mastektomie zu einer Reduktion des kontralateralen Karzinomrisikos. Bei der Indikationsstellung zur kontralateralen prophylaktischen Mastektomie soll die Prognose des Erstkarzinoms berücksichtigt werden.

Bei Patientinnen mit einer PV in den Genen *BRCA1* oder *BRCA2* führt die prophylaktische Adnexektomie zu einer Reduktion der Brustkrebs-spezifischen Mortalität und zu einer Verbesserung des Gesamtüberlebens.

Literaturreferenzen: [42], [32], [34], [36], [43], [44], [45], [46], [47], [48]

Source: YL, Xiao, Wang K, Liu Q, Li J, Zhang X, and Li HY. "Risk Reduction and Survival Benefit of Risk-Reducing Salpingo-Oophorectomy in Hereditary Breast Cancer: Meta-Analysis and Systematic Review." [In eng]. Clinical breast cancer 19, no. 1 (2019-2 2019): e48-e65. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30470623/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: explore the relationships between a history of BC and type of mutation with, respectively, the incidence and mortality of BC	**Design**: Systematic review and meta-analysis **Search date**: until 26.11.2017 **Searched databases**: Medline, Embase **Included study designs**: Prospective cohort studies (9), retrospective studies (9), case-control study (1) **Number of included studies**: 19 **Number of included patients**: n.a. Sample size ranged from 36 to 3722 **Mean/median age**: n.a. **Inclusion criteria**:	**Intervention** RRSO **Control** No RRSO	**Primary Outcome**: Breast cancer risk; all-cause mortality	**Breast cancer risk** No history of BC HR=0.58; 95% CI: 0.37-0.78; I² 69.2% (8 studies) **Subgroup-Analysis** **Breast cancer risk in patients with previous BC before RRSO** BRCA1/2 HR=0.50; 95% CI: 0.31-0.69; I² 4.4% (5 studies, 2200 patients) BRCA1 HR=0.51; 95% CI: 0.20-0.83; I² 44.8% (4 studies, 1215 patients) BRCA2	**ROBIS** **Risk of bias in the review:** unclear **Domain** Concerns regarding specification of study eligibility criteria: unclear risk Concerns regarding methods used to identify and/or select studies: low risk Concerns regarding methods used to collect data and appraise studies: low risk Concerns regarding the synthesis and findings: unclear risk **Additional concerns about quality**: no protocol for conducting

Source: YL, Xiao, Wang K, Liu Q, Li J, Zhang X, and Li HY. "Risk Reduction and Survival Benefit of Risk-Reducing Salpingo-Oophorectomy in Hereditary Breast Cancer: Meta-Analysis and Systematic Review." [In eng]. Clinical breast cancer 19, no. 1 (2019-2 2019): e48-e65. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30470623/.					
	(1) Both the case and control subjects were women who had BRCA1 or BRCA2 mutations, regardless of history of BC before surgery. (2) The case subjects were treated with prophylactic surgeries, including oophorectomy and salpingooophorectomy. (3) The control subjects were women who did not undergo these surgeries. (4) BC risk or mortality due to prophylactic surgeries for women with and without a history of BC, and hazard ratio (HR) values were provided. (5) Study type was a			HR=0.24; 95% CI -0.05-0.52; I² 0.0% (4 studies, 808 patients) **All-Cause mortality in patients with previous BC** BRCA1/2 HR 0.33; 95% CI: 0.28-0.38; I² 0.0% (6 studies, 5481 patients) BRCA1 HR 0.31; 95% CI: 0.24-0.38; I² 0% (3 studies, n.a. patients) BRCA2 HR 0.36; 95% CI: 0.22-0.50; I² 0% (3 studies, n.a. patients)	the systematic review, search restricted to English, no information about assessment of risk of bias **Sources of funding:** n.a.

Source: YL, Xiao, Wang K, Liu Q, Li J, Zhang X, and Li HY. "Risk Reduction and Survival Benefit of Risk-Reducing Salpingo-Oophorectomy in Hereditary Breast Cancer: Meta-Analysis and Systematic Review." [In eng]. Clinical breast cancer 19, no. 1 (2019-2 2019): e48-e65. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30470623/.

	cohort study or a case-control study. ***Exclusion**:*				

Abbreviations:

BC = Breast Cancer

RRSO = Risk-reducing bilateral salpingo-ooporectomy

n.a. = not Available, not Applicable

HR = Hazard Ratio

Verknüpfte Empfehlungen:

Empfehlung 3.38: Risikoreduzierende Operation bei gesunden Trägerinnen wahrscheinlich pathogener / pathogener konstitutioneller Varianten in den Genen *BRCA1* oder *BRCA2* (Klasse 4/5): prophylaktische bilaterale Adnexektomie.

Frauen mit einer PV in den Genen *BRCA1* oder *BRCA2* haben ein lebenszeitlich erhöhtes Risiko für ein Ovarialkarzinom, Tubenkarzinom und/oder ein primäres Peritonealkarzinom.

Bei gesunden Frauen mit einer PV in den Genen *BRCA1*- oder *BRCA2* führt die prophylaktische Adnexektomie zu einer Reduktion der Ovarialkarzinominzidenz und der Gesamtmortalität.

Daher soll die prophylaktische beidseitige Salpingo-Oophorektomie fallbezogen im Rahmen einer umfassenden, multidisziplinären Beratung über potentielle Vor- und Nachteile eines solchen Eingriffs und unter Berücksichtigung fehlender effektiver Früherkennungsmöglichkeiten diskutiert und empfohlen werden.

Empfehlung 3.39: Risikoreduzierende Operation bei bereits unilateral an Brustkrebs erkrankten Trägerinnen wahrscheinlich pathogener / pathogener konstitutioneller Varianten (PV) in den Genen *BRCA1* oder *BRCA2* (Klasse 4/5): kontralaterale prophylaktische Mastektomie und prophylaktische bilaterale Adnexektomie

Bereits an Brustkrebs erkrankte Frauen mit einer PV in den Genen *BRCA1* oder *BRCA2* haben ein erhöhtes Risiko für die Entstehung eines kontralateralen Mammakarzinoms. Dieses Risiko hängt u. a. ab vom betroffenen Gen und dem Ersterkrankungsalter und ist bei der Beratung zu berücksichtigen.

Bei Frauen mit einer PV in den Genen *BRCA1* oder *BRCA2* führt die kontralaterale, prophylaktische Mastektomie zu einer Reduktion des kontralateralen Karzinomrisikos. Bei der Indikationsstellung zur kontralateralen prophylaktischen Mastektomie soll die Prognose des Erstkarzinoms berücksichtigt werden.

Bei Patientinnen mit einer PV in den Genen *BRCA1* oder *BRCA2* führt die prophylaktische Adnexektomie zu einer Reduktion der Brustkrebs-spezifischen Mortalität und zu einer Verbesserung des Gesamtüberlebens.

Literaturreferenzen: [42], [32], [34], [36], [43], [44], [45], [46], [47], [48]

Source: Gaba F, Blyuss O, Tan A, et al. Breast Cancer Risk and Breast-Cancer-Specific Mortality following Risk-Reducing Salpingo-Oophorectomy in BRCA Carriers: A Systematic Review and Meta-Analysis. Cancers (Basel). 2023;15(5): 1625. Published 2023 Mar 6. doi: 10.3390/cancers15051625					
Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Breast cancer risk and mortality in BRCA1/2 carriers after Risk-Reducing Salpingo-Oophorectomy (RRSO)	**Design**: Systematic Review and Meta-Analysis **Search date**: time of inception of database to 14 June 2022 **Searched databases**: Pubmed, Medline, Embase, CINAHL, PsycINFO, PROSEPRO and Cochrane **Included study designs**: Observational studies (23 cohort, 5 case control, 1 cross-sectional) **Number of included studies**: 29 **Number of included patients**: n.a.	**Intervention** Risk-Reducing Salpingo-Oophorectomy **Control** No Risk-Reducing Salpingo-Oophorectomy	**Outcomes** (1) primary breast cancer (PBC), defined as the risk of invasive BC occurring in a previously unaffected individual; (2) contralateral breast cancer (CBC), defined as the risk of a second case of primary invasive BC occurring in a previously unaffected contralateral breast; and (3) BC-specific mortality (BCSM), defined as cause of death due to BC	**Primary breast cancer** N=16 studies RRSO was not associated with a significant reduction in the overall PBC risk in the analyses incorporating both BRCA1 and BRCA2 carriers combined RRSO was associated with a significant reduction in PBC risk in BRCA2 carriers alone, although there did not appear to be a reduction in PBC risk in BRCA1 carriers alone *Details: Relative Risks and 95% CI* PBC risk in BRCA1 and BRCA2 combined N=4 studies	**ROBIS** **Risk of bias in the review:** low **Domain** Concerns regarding specification of study eligibility criteria: low risk Concerns regarding methods used to identify and/or select studies: low risk Concerns regarding methods used to collect data and appraise studies: low risk Concerns regarding the synthesis and findings: unclear risk **Additional concerns about quality**: Deviations between study protocol (PROSPERO

Source: Gaba F, Blyuss O, Tan A, et al. Breast Cancer Risk and Breast-Cancer-Specific Mortality following Risk-Reducing Salpingo-Oophorectomy in BRCA Carriers: A Systematic Review and Meta-Analysis. Cancers (Basel). 2023;15(5): 1625. Published 2023 Mar 6. doi: 10.3390/cancers15051625					
	Size of studies varied from 98 to 8977 participants **Mean/median age**: n.a. **Inclusion criteria**: female BRCA1 and BRCA2 mutation carriers undergoing RRSO **Exclusion**: participants who had a personal history of ovarian cancer (OC) or had undergone prophylactic Risk-Reducing Mastectomy (RRM) prior to RRSO			RR 0.84, 95% CI 0.59 to 1.21, I^2=86% (4 studies) PBC risk in BRCA1 carriers RR 0.89, 95% CI 0.68 to 1.17, I^2=61% (5 studies) PBC risk in BRCA2 carriers RR 0.63, 95% CI 0.41 to 0.97, I^2=55% (4 studies) Min NNT: 57.05, 95% CI 35.88 to 607.28 Mean NNT: 20.55, 95% CI 12.93 to 218.75 Max NNT: 11.47, 95% CI 7.22 to 122.1 PBC risk in pre-menopausal BRCA1 and BRCA2 carriers combined RR 0.84, 95% CI 0.62 to 1.12, I^2=0%	CRD42018077613) and publication regarding outcomes assessed; no sensitivity analysis performed **Quality of included studies**: Assessed by review authors with Newcastle-Ottawa-Scale **Certainty of Evidence:** **GRADE** Outcomes: Primary BC: Low Contralateral BC: Low BC-specific mortality: moderate **Sources of funding:** Rosetrees Trust, grant number CF1n100001, and Barts Charity, grant number ECMG1C3R

Source: Gaba F, Blyuss O, Tan A, et al. Breast Cancer Risk and Breast-Cancer-Specific Mortality following Risk-Reducing Salpingo-Oophorectomy in BRCA Carriers: A Systematic Review and Meta-Analysis. Cancers (Basel). 2023;15(5): 1625. Published 2023 Mar 6. doi: 10.3390/cancers15051625					
				(2 studies) <u>PBC risk in post-menopausal BRCA1 and BRCA2 carriers combined</u> RR 0.65, 95% CI 0.18 to 2.42, I^2=79% (2 studies) **Contralateral breast cancer** N=6 studies RRSO was not associated with a significant reduction in CBC risk in the analyses incorporating both BRCA1 and BRCA2 carriers combined, nor is CBC risk significantly reduced when analysed separately by the type of BRCA mutation *Details:*	

Source: Gaba F, Blyuss O, Tan A, et al. Breast Cancer Risk and Breast-Cancer-Specific Mortality following Risk-Reducing Salpingo-Oophorectomy in BRCA Carriers: A Systematic Review and Meta-Analysis. Cancers (Basel). 2023;15(5): 1625. Published 2023 Mar 6. doi: 10.3390/cancers15051625					
				CBC risk in BRCA1 and BRCA2 carriers combined RR 0.95, 95% CI 0.65 to 1.39, I^2=77% (4 studies) CBC risk in BRCA1 carriers RR 0.85, 95% CI 0.59 to 1.24, I^2=0% (2 studies) CBC risk in BRCA2 carriers RR 0.35, 95% CI 0.07 to 1.74, I^2=69% (2 studies) **Breast cancer specific mortality** N=7 studies Mortality in BC-affected BRCA1	

Source: Gaba F, Blyuss O, Tan A, et al. Breast Cancer Risk and Breast-Cancer-Specific Mortality following Risk-Reducing Salpingo-Oophorectomy in BRCA Carriers: A Systematic Review and Meta-Analysis. Cancers (Basel). 2023;15(5): 1625. Published 2023 Mar 6. doi: 10.3390/cancers15051625

				and BRCA2 carriers combined RR 0.26, 95% CI 0.18 to 0.39, I²=41% (3 studies) Min NNT: 11.79, 95% CI 10.58 to 14.18 Mean NNT: 5.58, 95% CI 5 to 6.71 Max NNT: 4.2, 95% CI 3.77 to 5.05 Mortality in BC affected BRCA1 carriers RR 0.46, 95% CI 0.30 to 0.70, I²=4% (2 studies) Min NNT: 30.29, 95% CI 23.44 to 54.81 Mean NNT: 14.51, 95% CI 11.23 to 26.26 Max NNT: 9.54, 95% CI 7.38 to 17.27	

Source: Gaba F, Blyuss O, Tan A, et al. Breast Cancer Risk and Breast-Cancer-Specific Mortality following Risk-Reducing Salpingo-Oophorectomy in BRCA Carriers: A Systematic Review and Meta-Analysis. Cancers (Basel). 2023;15(5): 1625. Published 2023 Mar 6. doi: 10.3390/cancers15051625

Abbreviations:

RRSO = Risk-Reducing Salpingo-Oophorectomy

OC = Ovarian Cancer

RRM = Risk-Reducing Mastectomy

BC = Breast Cancer

PBC = Primary Breast Cancer

CBC = Contralateral Breast Cancer

BCSM = Breast Cancer Specific Mortality

RR = Relative Risk

95% CI = 95% Confidence Interval

NNT = Number Needed to Treat

Verknüpfte Empfehlungen:

Empfehlung 4.53:

Eine kontralaterale risiko-reduzierend Mastektomie sollte bei Nicht-Mutationsträgerinnen bzw. bei Patientinnen ohne Nachweis einer familiären Hochrisikosituation zur Reduktion des kontralateralen Mammakarzinomrisikos nicht durchgeführt werden.

Empfehlung 3.39: Risikoreduzierende Operation bei bereits unilateral an Brustkrebs erkrankten Trägerinnen wahrscheinlich pathogener / pathogener konstitutioneller Varianten (PV) in den Genen *BRCA1* oder *BRCA2* (Klasse 4/5): kontralaterale prophylaktische Mastektomie und prophylaktische bilaterale Adnexektomie

Bereits an Brustkrebs erkrankte Frauen mit einer PV in den Genen *BRCA1* oder *BRCA2* haben ein erhöhtes Risiko für die Entstehung eines kontralateralen Mammakarzinoms. Dieses Risiko hängt u. a. ab vom betroffenen Gen und dem Ersterkrankungsalter und ist bei der Beratung zu berücksichtigen.

Bei Frauen mit einer PV in den Genen *BRCA1* oder *BRCA2* führt die kontralaterale, prophylaktische Mastektomie zu einer Reduktion des kontralateralen Karzinomrisikos. Bei der Indikationsstellung zur kontralateralen prophylaktischen Mastektomie soll die Prognose des Erstkarzinoms berücksichtigt werden.

Bei Patientinnen mit einer PV in den Genen *BRCA1* oder *BRCA2* führt die prophylaktische Adnexektomie zu einer Reduktion der Brustkrebs-spezifischen Mortalität und zu einer Verbesserung des Gesamtüberlebens.

Literaturreferenzen: [49], [50], [51], [52], [53], [54], [55], [56], [57], [46], [48], [31], [58]

Source: D, Akdeniz, Schmidt MK, Seynaeve CM, McCool D, Giardiello D, van den Broek AJ, Hauptmann M, Steyerberg EW, and Hooning MJ. "Risk Factors for Metachronous Contralateral Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Breast (Edinburgh, Scotland) 44 (2019-4 2019): 1-14. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30580169/.

Aim	Design and participants	Exposure / Comparator	Outcomes	Results	Quality and comment
Aim: quantify the association of various patient, pathological, and	**Design**: Systematic Review & Meta-Analysis	**Exposure / Comparator** patient, pathological and treatement-related	**Primary Outcome**: Risk factors for CBC **Secondary Outcome**: n.a.	**Primary Outcome**: *Results cohort studies* **Patient characteristics:**	**ROBIS** **Risk of bias in the review:** unclear

Source: D, Akdeniz, Schmidt MK, Seynaeve CM, McCool D, Giardiello D, van den Broek AJ, Hauptmann M, Steyerberg EW, and Hooning MJ. "Risk Factors for Metachronous Contralateral Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Breast (Edinburgh, Scotland) 44 (2019-4 2019): 1-14. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30580169/.					
treatment-related characteristics with metachronous contralateral breast cancer (CBC) risk	**Search date**: between 01/1990 and 04/07/2016 **Searched databases**: PubMed **Included study designs**: cohort studies, case-control studies, RCT **Number of included studies**: 68 **Number of included patients**: n.a. Between 247 and 205316 primary BC patients (PBC) and 21 and 6924 second BCs per study **Mean/median age**: n.a. **Inclusion criteria**: experimental and observational studies published in English, CBC risk in women with no	characteristics and their influence on CBC risk		*30 papers included* <u>Positive family history of BC</u> RR= 1.72; 95% CI: 1.15-2.57; I^2 93.1% Additional analysis without outlier study Hemminki 2007: RR=1.43; 95% CI: 1.22-1.68; $I^2$41.6% <u>Risk in first degree relatives</u> RR=1.54; 95% CI: 1.25-1.90; I^2 60.1% <u>Second degree relatives</u> RR=1.17; 95% CI: 0.90-1.52; I^2 0% <u>Age at PBC diagnosis</u> 7% decrease in CBC risk per decade	**Domain** Concerns regarding specification of study eligibility criteria: unclear risk Concerns regarding methods used to identify and/or select studies: high risk Concerns regarding methods used to collect data and appraise studies: low risk Concerns regarding the synthesis and findings: low risk Concerns: limited number of searched databases (only PubMed) **Additional concerns about quality**:

Source: D, Akdeniz, Schmidt MK, Seynaeve CM, McCool D, Giardiello D, van den Broek AJ, Hauptmann M, Steyerberg EW, and Hooning MJ. "Risk Factors for Metachronous Contralateral Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Breast (Edinburgh, Scotland) 44 (2019-4 2019): 1-14. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30580169/.					
	history of other invasive malignancies **Exclusion**: Number of second BC events < 20; not providing HR, RR, or OR for CBC risk; only consults for BRCA1 and BRCA2 mutation carriers			RR=0.93; 95% CI: 0.88-0.98,I^2 86.9% <u>BMI ≥ 25kg/m² compared to normal weight (BMI <25kg/m²)</u> RR=1.26; 95% CI: 1.10-1.44; I^2 44.4% <u>BMI ≥ 30kg/m² compared to normal weight (BMI <25kg/m²)</u> RR=1.54; 95% CI: 1.26-1.87; I^2 0% No association for: Mammographic breast density and menopausal status **Pathological characteristics** *15 papers included* <u>PBC tumor size >2cm vs ≤ 2cm</u>	No information about screening process of included studies **Quality of included studies**: 46 out of 68 papers high quality (used for sensitivity analysis) **Sources of funding:** Dutch Cancer Society/Alpe d'HuZes [A6C/6253]

Source: D, Akdeniz, Schmidt MK, Seynaeve CM, McCool D, Giardiello D, van den Broek AJ, Hauptmann M, Steyerberg EW, and Hooning MJ. "Risk Factors for Metachronous Contralateral Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Breast (Edinburgh, Scotland) 44 (2019-4 2019): 1-14. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30580169/.					
				RR=1.17; 95% CI: 1.03-1.34; I^2 21.6% <u>Negative ER hormone receptor status</u> RR=1.53; 95% CI: 1.04-2.26; I^2 67.3% Additional analysis excluding Filleron 2012 RR=1.32; 95% CI: 0.99-1.76; I^2 38.5% <u>PR hormone receptor status</u> RR: 1.23; 95% CI: 1.02-1.48; I^2 0% <u>Lobular morphology vs. ductal/non-lobular morphology</u> RR=1.43; 95% CI: 1.13-1.82; I^2 42.5% No association for: nodal status, tumor grade	

Source: D, Akdeniz, Schmidt MK, Seynaeve CM, McCool D, Giardiello D, van den Broek AJ, Hauptmann M, Steyerberg EW, and Hooning MJ. "Risk Factors for Metachronous Contralateral Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Breast (Edinburgh, Scotland) 44 (2019-4 2019): 1-14. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30580169/.

				Treatment-related characteristics <u>Adjuvant chemotherapy</u> *9 papers included* RR=0.70; 95% CI: 0.62-0.79; I^2 21.3% <u>Adjuvant endocrine therapy</u> *15 papers included* RR=0.61; 95% CI: 0.53-0.72 (I2 73.6%) Analysis only patients with ER+ RR=0.57; 95% CI: 0.49-0.66; I^2 19.4% <u>Radiotherapy (vs non radiotherapy)</u> *8 papers included* Diagnosed at least 5 years after PBC	

Source: D, Akdeniz, Schmidt MK, Seynaeve CM, McCool D, Giardiello D, van den Broek AJ, Hauptmann M, Steyerberg EW, and Hooning MJ. "Risk Factors for Metachronous Contralateral Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Breast (Edinburgh, Scotland) 44 (2019-4 2019): 1-14. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30580169/.

				RR=1.10; 95% CI: 1.05-1.15; I^2 0% Patients aged below 40 years at PBC diagnosis CBCs occurring any time after PBC RR=1.37; 95% CI: 1.13-1.66; I^2 0% CBC occurring >5 years after PBC RR=1.34; 95% CI: 1.07-1.67; I^2 0% Mutation carriers vs. patients from mutation-negative BC families *Analysed in 5 papers* Carriership of a BRCA1, BRCA2 or CHEK2c.1100delC mutation vs. non-carriership BRCA1:	

Source: D, Akdeniz, Schmidt MK, Seynaeve CM, McCool D, Giardiello D, van den Broek AJ, Hauptmann M, Steyerberg EW, and Hooning MJ. "Risk Factors for Metachronous Contralateral Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Breast (Edinburgh, Scotland) 44 (2019-4 2019): 1-14. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30580169/.					
				RR=3.68; 95% CI: 2.76-4.89; I^2 12.4% BRCA2 RR=2.75; 95% CI: 1.77-4.27; I^2 20.8% CHEK2c.1100delC RR=2.68, 95% CI: 1.96-3.65; I^2 0% Risk-reducing salpingo-oophorectomy in BRCA1 mutation carriers *2 studies* Crude RR=0.56; 95% CI: 0.32-0.99; I^2 46.8%	
Abbreviations: BC = Breast Cancer CBC = Contralateral Breast Cancer PCB = Primary Breast Cancer RCT = Randomised Controlled Trial HR = Hazard Ratio					

Source: D, Akdeniz, Schmidt MK, Seynaeve CM, McCool D, Giardiello D, van den Broek AJ, Hauptmann M, Steyerberg EW, and Hooning MJ. "Risk Factors for Metachronous Contralateral Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Breast (Edinburgh, Scotland) 44 (2019-4 2019): 1-14. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30580169/.

RR = Relative Risk

OR = Odds Ratio

n.a. = not Available, not Applicable

Kapitel 4: Lokoregional begrenzte Primärerkrankung

Kapitel 4.1: Diagnostik bei der Abklärung auffälliger Befunde sowie prätherapeutische Ausbreitungsdiagnostik bei gesichertem Mammakarzinom

Kapitel 4.1.1: Bildgebende Verfahren

Verknüpfte Empfehlungen:

Empfehlung 4.7:

Bei aktuell nachgewiesenem Malignom soll prätherapeutisch eine Mammographie oder Tomosynthese bds. in guter Qualität vorliegen oder durchgeführt werden.

Literaturreferenzen: [59], [60]

Source: Ko, M. J., D. A. Park, S. H. Kim, E. S. Ko, K. H. Shin, W. Lim, B. S. Kwak, and J. M. Chang. "Accuracy of Digital Breast Tomosynthesis for Detecting Breast Cancer in the Diagnostic Setting: A Systematic Review and Meta-Analysis." [In eng]. Korean J Radiol 22, no. 8 (Aug 2021): 1240-52. https: //doi.org/10.3348/kjr.2020.1227.

Aim	Design and participants	Index and Reference standard	Outcomes	Results	Quality and comment
To compare the accuracy for detecting breast cancer in the diagnostic setting between the use of digital breast tomosynthesis (DBT), defined as DBT alone or	**Design**: Systematic Review and meta-analysis. **Search date**: articles published until March 25, 2020	**Intervention** DBT alone or combined DBT and DM **Comparison** DM alone	Diagnostic accuracy: Sensitivity Specificity Area under the ROC curve	**Sensitivity** DBT alone or combined DBT and DM: 0.90 (95% CI 0.86–0.93) **vs.** DM alone: 0.76 (95% CI 0.68–0.83); p<0.001	**ROBIS** **Risk of bias in the review:** unclear **Domain** Concerns regarding specification of study

Source: Ko, M. J., D. A. Park, S. H. Kim, E. S. Ko, K. H. Shin, W. Lim, B. S. Kwak, and J. M. Chang. "Accuracy of Digital Breast Tomosynthesis for Detecting Breast Cancer in the Diagnostic Setting: A Systematic Review and Meta-Analysis." [In eng]. Korean J Radiol 22, no. 8 (Aug 2021): 1240-52. https: //doi.org/10.3348/kjr.2020.1227.

combined DBT and digital mammography (DM), and the use of DM alone Hypothesis: DBT might offer superior diagnostic accuracy compared to DM alone	**Searched databases**: Ovid-MEDLINE, Ovid-Embase, Cochrane Library and five Korean local databases **Included study designs**: Prospective and retrospective studies **Number of included studies**: 20 **Number of included patients**: 44513 patients and 58388 lesions **Mean/median age**: Mean: 52 years (range, 45–62 years) **Inclusion criteria**: The selection criteria were as follows: 1) breast imaging using both DM and DBT for breast symptoms, abnormal findings on screening examinations,	**Reference standards** biopsy and/or imaging follow-up		DBT alone: 0.93 (95% CI 0.89–0.96) **vs.** DM alone: 0.80 (95% CI 0.69–0.91); p=0.03 DBT combined with DM: 0.86(95% CI 0.81–0.92) **vs.** DM alone: 0.74 (95% CI 0.68–0.80); p<0.001 **Specificity** DBT alone or combined DBT and DM: 0.90 (95% CI 0.86–0.93) **vs.** DM alone: 0.76 (95% CI 0.68–0.83); p<0.001 DBT alone: 0.90 (95% CI 0.84–0.97) **vs.** DM alone: 0.75 (95% CI 0.81–0.98); p=0.02 DBT combined with DM: 0.89 (95% CI 0.82–0.97) **vs.**	eligibility criteria: unclear risk Concerns regarding methods used to identify and/or select studies: low risk Concerns regarding methods used to collect data and appraise studies: low risk Concerns regarding the synthesis and findings: high risk **Additional concerns about quality**: No information about protocol for systematic review; no sensitivity or subgroup analysis based on risk of bias **Quality of included studies**: Most studies had low or unclear risk of bias

Source: Ko, M. J., D. A. Park, S. H. Kim, E. S. Ko, K. H. Shin, W. Lim, B. S. Kwak, and J. M. Chang. "Accuracy of Digital Breast Tomosynthesis for Detecting Breast Cancer in the Diagnostic Setting: A Systematic Review and Meta-Analysis." [In eng]. Korean J Radiol 22, no. 8 (Aug 2021): 1240-52. https: //doi.org/10.3348/kjr.2020.1227.					
	or a need for follow-up imaging; 2) DBT (DBT alone or combined DBT and DM) compared to DM alone; 3) sufficient information to discriminate among true-positive, false-positive, false-negative, and true-negative results for breast cancer to determine the sensitivity and specificity; 4) Reference standards of biopsy and/or imaging follow-up. **Exclusion**: Non-original articles; screening setting or participants solely composed of patients with breast cancer; single arm; non-comparative study; or fewer than 50 participants.			DM alone: 0.89 (95% CI 0.68–0.80); p=0.99 **The area under the summary receiver operating characteristics curve** DBT alone or combined DBT and DM: 0.95 (95% CI 0.93–0.97) **vs.** DM alone: 0.86 (95% CI 0.82–0.88) **Subgroup analysis** Comparison of the diagnostic accuracy between DBT and DM alone using meta-regression and subgroup analyses by: modality of intervention, country, existence of calcifications, breast density, Breast Imaging Reporting and Data System category threshold, study design, protocol for participant	**Sources of funding:** Not stated

Source: Ko, M. J., D. A. Park, S. H. Kim, E. S. Ko, K. H. Shin, W. Lim, B. S. Kwak, and J. M. Chang. "Accuracy of Digital Breast Tomosynthesis for Detecting Breast Cancer in the Diagnostic Setting: A Systematic Review and Meta-Analysis." [In eng]. Korean J Radiol 22, no. 8 (Aug 2021): 1240-52. https: //doi.org/10.3348/kjr.2020.1227.

				sampling, sample size, reason for diagnostic examination, and number of readers who interpreted the studies **Sensitivity** The higher sensitivities of DBT compared with those of DM alone were preserved in most analyses, except those for non-Asian, BI-RADS category threshold ≥ 3, breast density ≥ 2 or b, no calcification, diagnostic exam for symptomatic reason, and number of readers who interpreted the studies ≥ 5. **Specificity** Higher specificity of DBT in the subgroups DBT alone, Asian, and non-consecutive sampling ($p < 0.05$).	

Source: Ko, M. J., D. A. Park, S. H. Kim, E. S. Ko, K. H. Shin, W. Lim, B. S. Kwak, and J. M. Chang. "Accuracy of Digital Breast Tomosynthesis for Detecting Breast Cancer in the Diagnostic Setting: A Systematic Review and Meta-Analysis." [In eng]. Korean J Radiol 22, no. 8 (Aug 2021): 1240-52. https: //doi.org/10.3348/kjr.2020.1227.

Abbreviations:

DBT = Digital Breast Tomosynthesis

DM = Digital Mammography

Verknüpfte Empfehlungen:

Empfehlung 4.11:

Bei der Abklärung auffälliger Befunde sollte die Kontrastmittel-MRT auf diejenigen Fälle eingegrenzt werden, die mit konventioneller Diagnostik (MG, US) sowie perkutaner Biopsie nicht ausreichend sicher gelöst werden können.

Literaturreferenzen: [61]

Source Bennani-Baiti B, Bennani-Baiti N, Baltzer PA. Diagnostic Performance of Breast Magnetic Resonance Imaging in Non-Calcified Equivocal Breast Findings: Results from a Systematic Review and Meta-Analysis. PLoS One. 2016 Aug 2;11(8): e0160346. doi: 10.1371/journal.pone.0160346. PMID: 27482715; PMCID: PMC4970763.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To evaluate the performance of breast MRI for diagnosis of breast cancer in non-calcified equivocal breast findings.	**Design**: Systematic review and meta-analysis **Search date**: **:** 01/01/1986 to 06/15/2015 **Searched databases**: PubMed **Included study designs**: retrospective and prospective studies **Number of included studies**: 14 **Number of included patients**: 2,316	**Intervention** Dynamic contrast-enhanced breast MRI **Control** Conventional imaging (mammography, ultrasound)	Diagnostic parameters of breast MRI, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)	The pooled diagnostic parameters were: Sensitivity: 99% (95% CI: 93-100%) Specificity: 89% (95% CI: 85-92%) Positive Predictive Value (PPV): 56% (95% CI: 42-70%) Negative Predictive Value (NPV): 100% (95% CI: 99-100%) There was significant heterogeneity among the studies for all the	**ROBIS** Unclear risk of bias **Additional concerns about quality**: No protocol for systematic review; search only in Pubmed **Quality of included studies**: patient selection bias was identified in some studies; unclear applicability bias was assigned to some

Source Bennani-Baiti B, Bennani-Baiti N, Baltzer PA. Diagnostic Performance of Breast Magnetic Resonance Imaging in Non-Calcified Equivocal Breast Findings: Results from a Systematic Review and Meta-Analysis. PLoS One. 2016 Aug 2;11(8): e0160346. doi: 10.1371/journal.pone.0160346. PMID: 27482715; PMCID: PMC4970763.					
	Age (range): 47 to 57.3 years across studies **Inclusion criteria:** Studies applying dynamic contrast-enhanced breast MRI as an adjunct to conventional imaging (mammography, ultrasound) to clarify equivocal findings without microcalcifications Reference standard for MRI findings was histopathological sampling or imaging follow-up of at least 12 months **Exclusion**: Small sample size (n<20) Focus on exclusion of malignancy in biopsy-proven lesions with uncertain malignant potential (B3)			diagnostic parameters (p<0.001).	studies due to patients lost to follow-up or specific inclusion criteria; high between-study heterogeneity **Level of evidence:** Oxford 2011: 3 **Sources of funding**: supported by the Open Access Publishing Fund of the University of Vienna

Source Bennani-Baiti B, Bennani-Baiti N, Baltzer PA. Diagnostic Performance of Breast Magnetic Resonance Imaging in Non-Calcified Equivocal Breast Findings: Results from a Systematic Review and Meta-Analysis. PLoS One. 2016 Aug 2;11(8): e0160346. doi: 10.1371/journal.pone.0160346. PMID: 27482715; PMCID: PMC4970763.

	Aiming at diagnosing suspicious mammographic microcalcifications Limited to certain risk groups or specific clinical questions				

Abbreviations and comment:

PPV: positive predictive value

NPV: negative predictive value

Verknüpfte Empfehlungen:

Empfehlung 4.12:

Die ergänzende Kontrastmittel-MRT, alternativ Kontrastmittel-Mammographie, sollte bei gesichertem Malignom dort prätherapeutisch durchgeführt werden, wo mit konventioneller Bildgebung eine eingeschränkte Beurteilbarkeit der Befundausbreitung zu erwarten ist, z.B. invasiv-lobuläres Mammakarzinom, V.a. Multifokalität/-zentrizität, sehr dichtes Drüsengewebe etc.

Die Indikation hierzu sollte in einer multidisziplinären Konferenz gestellt werden.

Literaturreferenzen: [62], [63], [64], [65], [66], [67], [68], [69]

Source: Eisen A, Fletcher GG, Fienberg S, George R, Holloway C, Kulkarni S, Seely JM, Muradali D. Breast Magnetic Resonance Imaging for Preoperative Evaluation of Breast Cancer: A Systematic Review and Meta-Analysis. Can Assoc Radiol J. 2023 Aug 18: 8465371231184769. doi: 10.1177/08465371231184769. Epub ahead of print. PMID: 37593787.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: to summarize the evidence on whether additional information on disease extent obtained by use of preoperative breast MRI after mammography and/or ultrasound in patients with newly diagnosed breast cancer changes the relative use of breast conserving surgery (BCS) vs mastectomy or	**Design**: Systematic Review and Meta-Analysis **Search date**: until July 3, 2019 and updated until January 18, 2021. A targeted search was conducted in July 2022 to identify any additional publications related to the included RCTs and studies identified as ongoing.	**Intervention** Examination with breast MRI after diagnosis of breast cancer to give additional information on extent of disease prior to treatment. **Control** Breast mammography and/or ultrasound	1. Initial mastectomy rate 2. Final (overall) mastectomy rate 3. Positive margins rate 4. Re-operation 5. Re-excision 6. Conversion mastectomy	1. Initial mastectomy rate: OR 1.42 (95% CI 1.19 to 1.69) 2. Final (overall) mastectomy rate: OR 1.24 (95% CI 1.11 to 1.39) 3. Positive margins rate: OR 0.89 (95% CI 0.74 to 1.06)	**ROBIS** **Risk of bias in the review:** unclear **Domain** Concerns regarding specification of study eligibility criteria: low risk Concerns regarding methods used to identify and/or select studies: unclear risk

Source: Eisen A, Fletcher GG, Fienberg S, George R, Holloway C, Kulkarni S, Seely JM, Muradali D. Breast Magnetic Resonance Imaging for Preoperative Evaluation of Breast Cancer: A Systematic Review and Meta-Analysis. Can Assoc Radiol J. 2023 Aug 18: 8465371231184769. doi: 10.1177/08465371231184769. Epub ahead of print. PMID: 37593787.

improves rates of recurrence, survival, re-excision, and early detection of bilateral cancer	**Searched databases**: Embase, MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews **Included study designs**: 8 RCTs, 1 prospective cohort study, and 42 retrospective studies. **Number of included studies**: 60 publications of 51 trials **Number of included patients**: **Mean/median age**: **Inclusion criteria**: 1. Included patients with newly diagnosed breast cancer evaluating use of breast MRI prior to surgery, or patients		7. Synchronous Contralateral Breast Cancer 8. Metachronous Contralateral Breast Cancer 9. Recurrence: Locoregional + Distant (+ contralateral in some studies) 10. Locoregional Recurrence (ipsilateral breast or lymph nodes) 11. Distant Recurrence 12. Recurrence-Free Survival (Disease-Free Survival) 13. Overall Survival 14. Quality of life	4. Re-operation: OR 0.73 (95% CI 0.63 to 0.85) 5. Re-excision: OR 0.30 (95% CI 0.13 to 0.72) 6. Conversion mastectomy: OR 0.76 (95% CI 0.58 to 0.99) 7. Synchronous Contralateral Breast Cancer: HR 2.52 (95% CI 1.75 to 3.62) 8. Metachronous Contralateral Breast Cancer: HR 0.71 (95% CI 0.59 to 0.85) 9. Recurrence: Locoregional + Distant (+	Concerns regarding methods used to collect data and appraise studies: unclear risk Concerns regarding the synthesis and findings: unclear risk **Additional concerns about quality**: The outcome of mastectomy rates is commonly reported but of limited use in determining whether MRI should be used. There were serious limitations to the data for this outcome: several trials preselected only patients who were scheduled for BCS, patients may have received MRI for specific but non-recorded reasons related to tumour characteristics or patient factors, and mastectomy

Source: Eisen A, Fletcher GG, Fienberg S, George R, Holloway C, Kulkarni S, Seely JM, Muradali D. Breast Magnetic Resonance Imaging for Preoperative Evaluation of Breast Cancer: A Systematic Review and Meta-Analysis. Can Assoc Radiol J. 2023 Aug 18: 8465371231184769. doi: 10.1177/08465371231184769. Epub ahead of print. PMID: 37593787.

	referred for biopsy due to suspicion of breast cancer (but not yet diagnosed with cancer). 2. Were either (a) a randomized controlled trial (RCT) of MRI vs no MRI (≥30 patients per group) or (b) a comparative study with ≥100 patients comparing use of MRI vs no MRI in 2 or more groups with equivalent disease and patient characteristics or using methods such as multivariable analysis or propensity score matching to control potential confounders. As a minimum, studies should have considered stage and patient age and/or menopausal status. Cancer subtype/histology was considered important for			contralateral in some studies): HR 0.77 (95% CI 0.65 to 0.90) 10. Locoregional Recurrence (ipsilateral breast or lymph nodes): HR 0.85 (95% CI 0.69 to 1.04) 11. Distant Recurrence: HR 0.77 (95% CI 0.56 to 1.07) 12. Recurrence-Free Survival (Disease-Free Survival): HR 0.77 (95% CI 0.53 to 1.12) 13. Overall Survival: HR 0.89 (95% CI 0.74 to 1.07) **Subgroup analysis** **1.Outcome: Initial mastectomy rate**	decisions are often not due to medical necessity as exemplified by differences in mastectomy rates according to surgeon, institution, ethnic, and socioeconomic factors. Some of the trials that reported increased rates of mastectomy with MRI did not confirm whether the additional lesions were benign or cancerous; analysis of mastectomy specimens suggested that a change in some surgical plans (extent of surgery) was not indicated clinically. **Quality of included studies**: Out of 6 RCT included for mastectomy rate as outcome, 2 had high

Source: Eisen A, Fletcher GG, Fienberg S, George R, Holloway C, Kulkarni S, Seely JM, Muradali D. Breast Magnetic Resonance Imaging for Preoperative Evaluation of Breast Cancer: A Systematic Review and Meta-Analysis. Can Assoc Radiol J. 2023 Aug 18: 8465371231184769. doi: 10.1177/08465371231184769. Epub ahead of print. PMID: 37593787.					
	outcomes of margin status, reoperations, recurrence, and survival. Systemic therapy, radiotherapy, and HER2 and ER/PR status were also considered important for recurrence/ survival outcomes. 3. Primary or secondary outcomes included at least 1 of the following: recurrence; survival outcomes such as disease-free survival (DFS), event-free survival (EFS), distant metastasis-free survival (DMFS), or overall survival (OS); rates of mastectomy, re-excision, or re-operation; adverse effects/morbidity due to surgery; or quality of life. ***Exclusion**:*			1.1. among patients who were assigned to BCS prior to MRI: OR 5.18 (2.37 to 11.29) 1.2. among patients Surgery not specified prior to MRI: OR 1.29 (1.09 to 1.53) 1.3. among patients with In situ cancer: OR 1.90 (1.28 to 2.82) 1.4. among patients with invasive cancer: OR 1.48 (1.26 to 1.73) 1.5. among patients with invasive lobular carcinoma: OR 1.01 (0.80 to 1.27) **2. Outcome: Final (overall) mastectomy rate** 2.1. among patients BCS were assigned to them	ROB, 1 had some concerns, and 3 low ROB. The only RCT for positive resection margins had high ROB. Out of 7 RCT included for reoperations, re-excisions, and conversion mastectomy as outcome, 1 had high ROB, 3 had some concerns, and 3 low ROB. Most of non-RCT studies had moderate to high ROB. **Sources of funding:** This work was supported by the Ontario Health (Cancer Care Ontario ongoing operating funds, no specific grant/award). This work is editorially independant of the funder.

Source: Eisen A, Fletcher GG, Fienberg S, George R, Holloway C, Kulkarni S, Seely JM, Muradali D. Breast Magnetic Resonance Imaging for Preoperative Evaluation of Breast Cancer: A Systematic Review and Meta-Analysis. Can Assoc Radiol J. 2023 Aug 18: 8465371231184769. doi: 10.1177/08465371231184769. Epub ahead of print. PMID: 37593787.					
	1. MRI as the initial screening or diagnostic test, or when no index cancer was previously identified (occult cancer). 2. MRI as a tool to monitor response to neoadjuvant treatment. 3. Studies reporting on performance characteristics of MRI (eg, sensitivity, specificity) or detection rates of multicentric, multifocal, or contralateral breast cancer (CBC), but without outcomes listed in the inclusion criteria			prior to MRI: OR 1.87 (1.23 to 2.85) 2.2. among patients Surgery not specified prior to MRI: OR 1.19 (1.06 to 1.33) 2.3. among patients with In situ cancer: OR 1.68 (1.15 to 2.47) 2.4. among patients with invasive cancer: OR 1.31 (1.10 to 1.56) 2.5. among patients with invasive lobular carcinoma: OR 0.91 (0.75 to 1.11) **3. Outcome: Positive margins rate** 3.1. among studies with low or low-moderate RoB: OR 0.57 (0.36 to 0.89)	

Source: Eisen A, Fletcher GG, Fienberg S, George R, Holloway C, Kulkarni S, Seely JM, Muradali D. Breast Magnetic Resonance Imaging for Preoperative Evaluation of Breast Cancer: A Systematic Review and Meta-Analysis. Can Assoc Radiol J. 2023 Aug 18: 8465371231184769. doi: 10.1177/08465371231184769. Epub ahead of print. PMID: 37593787.					
				3.2. among patients with in situ cancer: OR 1.01 (0.77 to 1.32) 3.3. among patients with invasive cancer: OR 0.98 (0.84 to 1.13) 3.4. among patients with invasive lobular carcinoma: OR 0.63 (0.49 to 0.82) **4. Outcome: Re-operation** 4.1. RCT only: OR 0.78 (0.49 to 1.22) 4.2. non-RCT: OR 0.72 (0.61 to 0.85) 4.3. among patients with in situ cancer: OR 0.92 (0.68 to 1.26) 4.4. among patients with invasive cancer:	

Source: Eisen A, Fletcher GG, Fienberg S, George R, Holloway C, Kulkarni S, Seely JM, Muradali D. Breast Magnetic Resonance Imaging for Preoperative Evaluation of Breast Cancer: A Systematic Review and Meta-Analysis. Can Assoc Radiol J. 2023 Aug 18: 8465371231184769. doi: 10.1177/08465371231184769. Epub ahead of print. PMID: 37593787.					
				OR 0.96 (0.88 to 1.05) 4.5.among patients with invasive lobular carcinoma: OR 0.30 (0.13 to 0.72) **5. Outcome: Re-excision** 5.1. RCT only: OR 0.79 (0.45 to 1.37) 5.2. non-RCT: OR 0.54 (0.34 to 0.88) 5.3.among patients with in situ cancer: OR 0.92 (0.62 to 1.38) 5.4.among patients with invasive cancer: OR 1.21 (0.87 to 1.67) 5.5.among patients with invasive lobular carcinoma: OR 0.42 (0.13 to 1.35) **6. Conversion mastectomy**	

Source: Eisen A, Fletcher GG, Fienberg S, George R, Holloway C, Kulkarni S, Seely JM, Muradali D. Breast Magnetic Resonance Imaging for Preoperative Evaluation of Breast Cancer: A Systematic Review and Meta-Analysis. Can Assoc Radiol J. 2023 Aug 18: 8465371231184769. doi: 10.1177/08465371231184769. Epub ahead of print. PMID: 37593787.

				6.1. RCT only: OR 0.72 (0.53 to 0.96 6.2. non-RCT: OR 0.77 (0.54 to 1.11) 6.3. among patients with in situ cancer: OR 0.87 (0.43 to 1.76) 6.4. among patients with invasive cancer: OR 0.80 (0.43 to 1.49) 6.5. among patients with invasive lobular carcinoma: OR 0.38 (0.25 to 0.56)	

Abbreviations:

BCS = Breast Conserving Surgery

MRI = Magnetic Resonance Imaging

RCT = Randomised Controlled Trial

OR = Odds Ratio

HR = Hazard Ratio

Source: Eisen A, Fletcher GG, Fienberg S, George R, Holloway C, Kulkarni S, Seely JM, Muradali D. Breast Magnetic Resonance Imaging for Preoperative Evaluation of Breast Cancer: A Systematic Review and Meta-Analysis. Can Assoc Radiol J. 2023 Aug 18: 8465371231184769. doi: 10.1177/08465371231184769. Epub ahead of print. PMID: 37593787.

95% CI = 95% Confidence Interval

RoB = Cochrane Risk-of-Bias Tool

Verknüpfte Empfehlungen:

Empfehlung 4.12:

Die ergänzende Kontrastmittel-MRT, alternativ Kontrastmittel-Mammographie, sollte bei gesichertem Malignom dort prätherapeutisch durchgeführt werden, wo mit konventioneller Bildgebung eine eingeschränkte Beurteilbarkeit der Befundausbreitung zu erwarten ist, z.B. invasiv-lobuläres Mammakarzinom, V.a. Multifokalität/-zentrizität, sehr dichtes Drüsengewebe etc.

Die Indikation hierzu sollte in einer multidisziplinären Konferenz gestellt werden.

Empfehlung 4.48:

Unter Berücksichtigung der Tumorlokalisation und Tumorgröße kann bei multizentrischem Sitz auf eine Mastektomie verzichtet werden.

Literaturreferenzen: [62], [63], [64], [65], [66], [67], [68], [69]

Source: Boughey, JC, Rosenkranz, KM, Ballman, KV, McCall, L, Haffty, BG, Cuttino, LW, et.al. Local Recurrence After Breast-Conserving Therapy in Patients With Multiple Ipsilateral Breast Cancer: Results From ACOSOG Z11102 (Alliance). J Clin Oncol, 2023. 41(17): p. 3184-3193., https: //pubmed.ncbi.nlm.nih.gov/36977292/

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To evaluate whether the local recurrence (LR) rate with breast-conserving surgery followed by whole breast radiation with radiation boost to lumpectomy sites at 5 years is <8%.	**Design**: prospective single-arm phase II trial **Setting**: Clinical Trial **Enrollment**: 11/2012-08/2016 **Number of included patients**: 204 **Mean age:**	**Intervention** Patients underwent lumpectomies with negative margins followed by whole breast radiation with boost to all lumpectomy beds **Control**	**Primary Outcome:** cumulative incidence of local recurrence (LR) **Secondary Outcome:** Secondary end points have been previously reported of this trial, including	**Primary Outcome:** **Cumulative incidence of local recurrence** LR at 5 years: 3.1% (95% CI 1.3-6.4) Exploratory analysis5-year LR rate patients without preoperative magnetic	**Quality of study** assessed with SIGN checklist for Cohort Studies: Acceptable **Limitations by authors:** study was limited to female patients

Source: Boughey, JC, Rosenkranz, KM, Ballman, KV, McCall, L, Haffty, BG, Cuttino, LW, et.al. Local Recurrence After Breast-Conserving Therapy in Patients With Multiple Ipsilateral Breast Cancer: Results From ACOSOG Z11102 (Alliance). J Clin Oncol, 2023. 41(17): p. 3184-3193., https: //pubmed.ncbi.nlm.nih.gov/36977292/					
	Preamendment 5 (n=103) Mean (SD): 60.70 (10.3) Postamendment 5 (n=101) Mean (SD): 61.51 (10.2) Total (n=204) Mean (SD): 61.10 (10.2) **Inclusion criteria**: Women age 40 years and older diagnosed with two or three foci of biopsy-proven BC who were interested in pursuing breast-conserving surgery At least one of the sites of biopsy-proven disease had to be invasive BC, and the additional site(s) could be DCIS or invasive BC maximum single largest tumor dimension allowed	rate of clinical acceptability of <8% **Follow-up** median follow-up of 66.4 months	the conversion to mastectomy rate, cosmetic outcome, and radiation feasibility	resonance imaging (MRI; n 15): 22.6% Patients with a preoperative MRI (n=189): 1,7% p=0.002	patients requiring preoperative systemic therapy were excluded findings regarding patients who did not undergo a preoperative MRI are limited by small numbers hampering definitive recommendations in this regard although the 5-year follow-up is reassuring, longer-term follow up particularly for LR in ER1 disease is warranted. **Additional concerns about quality**: single-arm trial compared to standard therapy rate of clinical acceptability of <8% Confounding not mentioned

Source: Boughey, JC, Rosenkranz, KM, Ballman, KV, McCall, L, Haffty, BG, Cuttino, LW, et.al. Local Recurrence After Breast-Conserving Therapy in Patients With Multiple Ipsilateral Breast Cancer: Results From ACOSOG Z11102 (Alliance). J Clin Oncol, 2023. 41(17): p. 3184-3193., https: //pubmed.ncbi.nlm.nih.gov/36977292/					
	(by preoperative imaging) was 5 cm Patients with cN0 or cN1 disease were eligible Initially, enrollment was required before surgery, but in May 2015, postoperative enrollment of patients with MIBC treated with lumpectomy was allowed. **Exclusion**: Patients with prior or concurrent contralateral disease, known BRCA mutation, or current breast implants				Due to the single-arm trial design we propose to downgrade the **level of evidence** from 2b to **2c** **Source of Funding:** Lilly (Inst)
Abbreviations: LR = Local Recurrence BC = Breast Cancer DCIS = Ductal Carcinoma In Situ MRI = Magnetic Resonance Imaging					

Source: Boughey, JC, Rosenkranz, KM, Ballman, KV, McCall, L, Haffty, BG, Cuttino, LW, et.al. Local Recurrence After Breast-Conserving Therapy in Patients With Multiple Ipsilateral Breast Cancer: Results From ACOSOG Z11102 (Alliance). J Clin Oncol, 2023. 41(17): p. 3184-3193., https: //pubmed.ncbi.nlm.nih.gov/36977292/

95% CI = 95% Confidence Interval

Kapitel 4.1.2: Diagnostische Sicherung

Verknüpfte Empfehlungen:

Empfehlung 4.15:

Die histologische Abklärung von Befunden soll durch Stanzbiopsie, Vakuumbiopsie und in zu begründenden Ausnahmefällen durch offene Exzisionsbiopsie erfolgen.

Literaturreferenzen: [70], [71], [72], [73]

Source Knuttel FM, Menezes GL, van Diest PJ, Witkamp AJ, van den Bosch MA, Verkooijen HM. Meta-analysis of the concordance of histological grade of breast cancer between core needle biopsy and surgical excision specimen. Br J Surg. 2016 May;103(6): 644-655. doi: 10.1002/bjs.10128. Epub 2016 Mar 15. PMID: 26990850.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To derive a reliable estimate of the agreement in tumor grading between core needle biopsy (CNB) and the subsequent surgical excision specimen.	**Design**: Systematic review and meta-analysis **Search date**: Up to 16 July 2015 **Searched databases**: PubMed/MEDLINE, Embase, and the Cochrane Library **Included study designs**: Prospective and retrospective **Number of included studies**: 34	**Intervention** Core needle biopsy (CNB) **Control** Surgicalexcisionspecimen	**Primary Outcome**: Concordance of tumor grade between CNB and surgical excision in terms of percentage agreement and Cohen's kappa **Secondary Outcome**: Underestimation and overestimation of tumor grade by CNB, agreement per grade, and agreement per grade component	**Primary Outcome**: pooled agreement and Cohen's kappa were 71.1% (95% CI: 68.8 to 73.3) and 0.54 (95% CI: 0.50 to 0.58), respectively **Secondary Outcome**: underestimation and overestimation occurred in 19.1% (17.1 to 21.3) and 9.3% (7.7 to 11.4), respectively	**ROBIS** Low risk of bias **Additional concerns about quality**: **Quality of included studies**: Risk of bias (QUADAS-2) was most frequently high in patient selection. For all four domains, the risk of bias was unclear in at least 30% of studies; blinding of the

Source Knuttel FM, Menezes GL, van Diest PJ, Witkamp AJ, van den Bosch MA, Verkooijen HM. Meta-analysis of the concordance of histological grade of breast cancer between core needle biopsy and surgical excision specimen. Br J Surg. 2016 May;103(6): 644-655. doi: 10.1002/bjs.10128. Epub 2016 Mar 15. PMID: 26990850.					
	(19 retrospective, 7 prospective, 8 study design not reported) **Number of included patients**: 6029 in the systematic review and 4980 in the meta-analysis **Age (range)**: 44.2 – 65 years **Inclusion criteria**: Studies that reported the assessment of histological grade using the Nottingham grading system on both CNB and the surgical excision specimen from patients with breast cancer, and if the percentage agreement was provided or could be calculated from available data **Exclusion**: Conference abstracts, review articles, biopsy			Meta-regression showed associations between agreement of histological type (positive association) and proportion of patients with estrogen receptor-positive disease (negative association) and grade agreement	pathologist(s) participating in the studies was not reported in a number of articles; considerable heterogeneity between studies **Level of evidence:** Oxford 2011: 3 **Sources of funding**: n.r.

Source Knuttel FM, Menezes GL, van Diest PJ, Witkamp AJ, van den Bosch MA, Verkooijen HM. Meta-analysis of the concordance of histological grade of breast cancer between core needle biopsy and surgical excision specimen. Br J Surg. 2016 May;103(6): 644-655. doi: 10.1002/bjs.10128. Epub 2016 Mar 15. PMID: 26990850.

	techniques other than CNB, study size of ten patients or fewer, surgical excision not performed, CNB not performed, neoadjuvant chemotherapy in the entire study population, and only benign lesions in the study population				

Abbreviations and comment:

CNB: Core needle biopsy

n.r. not reported

Verknüpfte Empfehlungen:

Empfehlung 4.18:

Bei Vorliegen von Mikrokalk ohne begleitenden Herdbefund soll die röntgen gesteuerte Vakuumbiopsie eingesetzt werden.

Empfehlung 4.21:

Zur feingeweblichen Abklärung bildgebend suspekter Lymphknoten sollte primär die Stanzbiopsie eingesetzt werden.

Literaturreferenzen: [71], [74]

Source: XC, Huang, Hu XH, Wang XR, Zhou CX, Wang FF, Yang S, and Wang GY. A Comparison of Diagnostic Performance of Vacuum-Assisted Biopsy and Core Needle Biopsy for Breast Microcalcification: A Systematic Review and Meta-Analysis. Vol. 187, Ireland, 2018-11, 2018. https: //pubmed.ncbi.nlm.nih.gov/29549564/.

Aim	Design and participants	Diagnostic	Outcomes	Results	Quality and comment
To compare the diagnostic performance between core needle biopsy (CNB) and vacuum-assisted biopsy (VAB) for breast microcalcification (BM) regarding accuracy and safety	**Design**: Systematic Review and Meta-Analysis **Search date**: until June 10, 2016 **Searched databases**: PubMed, Embase, The Cochrane Library **Included study designs**: 6 retrospective and 1 prospective study **Number of included studies**: 7	**Index test** CNB and VAB **Reference standard** OSB	DCIS underestimation rate Microcalcification retrieval rate Complication rate	**DCIS underestimation rate** CNB: 94 (22.98%) underestimated lesions in 409 DCIS lesions VAB: 103 underestimated lesions in 932 DCIS lesions; Favours VAB vs CNB RR 1.83, 95% CI 1.40-2.40; I^2=0%	**ROBIS** **Risk of bias in the review:** unclear **Domain** Concerns regarding specification of study eligibility criteria: unclear risk Concerns regarding methods used to identify and/or select studies: low risk

Source: XC, Huang, Hu XH, Wang XR, Zhou CX, Wang FF, Yang S, and Wang GY. A Comparison of Diagnostic Performance of Vacuum-Assisted Biopsy and Core Needle Biopsy for Breast Microcalcification: A Systematic Review and Meta-Analysis. Vol. 187, Ireland, 2018-11, 2018. https: //pubmed.ncbi.nlm.nih.gov/29549564/.					
	Number of included patients: n.a. **Mean/median age**: n.a. **Inclusion criteria**: Diagnostic performance of both biopsy methods **Exclusion**: patients did not received subsequent open surgery biopsy (OSB) as reference standard to confirm their previous biopsy results; if none of clinic outcomes of interest was reported or derivable; if patients with microcalcification also presented with breast mass simultaneously; and if full text was not published in English			(5 studies, of those 1 RCT, 3 retrospective studies, 1 study without clear description) **Microcalcification retrieval rate** Calcification retrieved: CNB: 83.13% (399 in 480) lesions VAB: 98.31% (1691 in 1720) lesions; Favours VAB vs CNB RR 0.89, 95% CI 0.81-0.98; I^2=81% (4 studies, of those 1 prospective + 3 retrospective) **Complication rate** Lower complication rate in CNB (0.39%) vs VAB (2.9%) CNB vs VAB	Concerns regarding methods used to collect data and appraise studies: low risk Concerns regarding the synthesis and findings: high risk **Additional concerns about quality**: Only English studies included **Quality of included studies**: All studies: low concerns of risk of bias (RoB) in index test; Possible RoB in reference standard – whether they were performed without the knowledge of previously performed testes (lack of description in all included studies); 6 retrospective studies: high concerns of RoB in

Source: XC, Huang, Hu XH, Wang XR, Zhou CX, Wang FF, Yang S, and Wang GY. A Comparison of Diagnostic Performance of Vacuum-Assisted Biopsy and Core Needle Biopsy for Breast Microcalcification: A Systematic Review and Meta-Analysis. Vol. 187, Ireland, 2018-11, 2018. https: //pubmed.ncbi.nlm.nih.gov/29549564/.					
				RR 0.18, 95% CI 0.03-0.93; I^2=0% (3 studies)	flow and timing; low concerns of applicability in all studies **Sources of funding:** grants from the Health and Family Planning Commission of Hebei Province (No.20150362) and the Key Research Project of Medical Science of Hebei Province (No.20160194).

Abbreviations:

CNB = Core Needle Biopsy

VAB = Vacuum-Assisted Biopsy

BM = Breast Microcalcification

OSB = Open Surgery Biopsy

DCIS = Ductal Carcinoma in Situ

n.a. = not Available, not Applicable

RR = Risk Ratio

95% CI = 95% Confidence Interval

RoB = Risk of Bias

Verknüpfte Empfehlungen:

Empfehlung 4.21:

Zur feingeweblichen Abklärung bildgebend suspekter Lymphknoten sollte primär die Stanzbiopsie eingesetzt werden.

Literaturreferenzen: [75], [76], [77], [78], [79], [80]

Source Balasubramanian I, Fleming CA, Corrigan MA, Redmond HP, Kerin MJ, Lowery AJ. Meta-analysis of the diagnostic accuracy of ultrasound-guided fine-needle aspiration and core needle biopsy in diagnosing axillary lymph node metastasis. Br J Surg. 2018 Sep;105(10): 1244-1253. doi: 10.1002/bjs.10920. Epub 2018 Jul 4. PMID: 29972239.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To compare the diagnostic accuracy of ultrasound-guided fine-needle aspiration (US-FNA) and ultrasound-guided core needle biopsy (US-CNB) in axillary staging.	**Design**: Systematic review and meta-analysis **Search date**: Up to 31 August 2017 **Searched databases**: PubMed, Embase and Scopus, and the Cochrane Central Register of Controlled Trials **Included study designs**: **Number of included studies**: 6 (4 prospective and 2 retrospective; all single center studies)	**Intervention** Ultrasound-guided core needle biopsy (US-CNB) **Control** Ultrasound-guided fine-needle aspiration (US-FNA)	**Primary Outcome**: Sensitivity and specificity of US-FNA and US-CNB **Secondary Outcome**: Complications, incidence of repeat procedures and costs	**Primary Outcome**: US-CNB was superior to US-FNA in diagnosing axillary nodal metastases. Sensitivity: 88% for US-CNB vs 74% for US-FNA Specificity: 100% for both US-CNB and US-FNA **Secondary Outcome**: Complication rates were significantly higher for US-CNB (7.1%) compared with US-FNA (1.3%).	**ROBIS:** low risk of bias **Additional concerns about quality**: **Quality of included studies**: Assessed with QUADAS-2 tool: High risk of bias for patient selection in all six studies, and four studies had high risk for flow and timing;

Source Balasubramanian I, Fleming CA, Corrigan MA, Redmond HP, Kerin MJ, Lowery AJ. Meta-analysis of the diagnostic accuracy of ultrasound-guided fine-needle aspiration and core needle biopsy in diagnosing axillary lymph node metastasis. Br J Surg. 2018 Sep;105(10): 1244-1253. doi: 10.1002/bjs.10920. Epub 2018 Jul 4. PMID: 29972239.					
	Number of included patients: 1,353 (209 of these patients had bothUS-FNA and US-CNB performed as part of the study design) **Mean/median age**: n.r. **Inclusion criteria**: Studies that compared axillary lymph node assessment using preoperative US-FNA and US-CNB in patients with newly diagnosed invasive breast cancer; Studies that reported sensitivity and specificity, or provided raw data from which to calculate sensitivity and specificity compared with final histology;			The requirement for repeat diagnostic procedures was significantly greater for US-FNA (4.0%) vs US-CNB (0.5%).	low to moderate heterogeneity between studies **Level of evidence:** Oxford 2011: **Sources of funding**: n.r.

Source Balasubramanian I, Fleming CA, Corrigan MA, Redmond HP, Kerin MJ, Lowery AJ. Meta-analysis of the diagnostic accuracy of ultrasound-guided fine-needle aspiration and core needle biopsy in diagnosing axillary lymph node metastasis. Br J Surg. 2018 Sep;105(10): 1244-1253. doi: 10.1002/bjs.10920. Epub 2018 Jul 4. PMID: 29972239.					
	Final nodal histology was based on tissue sampling from axillary surgery. SNB or ALND was the reference standard for determining the presence of nodal metastasis **Exclusion**: Studies including pregnant women. Description of only one index test in a patient cohort (US-FNA or US-CNB). Results of axillary needle biopsy without data specific to US-FNA and US-CNB. Needle biopsy of breast tumors only.				
Abbreviations and comment: US-CNB: Ultrasound-guided core needle biopsy					

Source Balasubramanian I, Fleming CA, Corrigan MA, Redmond HP, Kerin MJ, Lowery AJ. Meta-analysis of the diagnostic accuracy of ultrasound-guided fine-needle aspiration and core needle biopsy in diagnosing axillary lymph node metastasis. Br J Surg. 2018 Sep;105(10): 1244-1253. doi: 10.1002/bjs.10920. Epub 2018 Jul 4. PMID: 29972239.

US-FNA: Ultrasound-guided fine-needle aspiration

n.r: not reported

Verknüpfte Empfehlungen:

Empfehlung 4.21:

Zur feingeweblichen Abklärung bildgebend suspekter Lymphknoten sollte primär die Stanzbiopsie eingesetzt werden.

Literaturreferenzen: [75], [76], [77], [78], [79], [80]

Source Huang Y, Zheng S, Lin Y. Accuracy and Utility of Preoperative Ultrasound-Guided Axillary Lymph Node Biopsy for Invasive Breast Cancer: A Systematic Review and Meta-Analysis. Comput Intell Neurosci. 2022 Sep 27;2022: 3307627. doi: 10.1155/2022/3307627. PMID: 36203726; PMCID: PMC9532070.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To obtain the accuracy and practicality of preoperative ultrasound-guided biopsy of invasive breast cancer.	**Design**: Systematic review and meta-analysis **Search date**: Up to July 2, 2022 **Searched databases**: PubMed, Embase, Cochrane Library, and Web of Science **Included study designs**: n.r. **Number of included studies**: 19 **Number of included patients**: 18,668 **Mean/median age**: n.r.	**Intervention** Preoperative ultrasound-guided axillary lymph node biopsy **Control** Intraoperative and postoperative pathological diagnosis	Accuracy and practicality of preoperative ultrasound-guided biopsy	Most studies in the SROC curve are at the upper left, indicating that the accuracy of ultrasound-guided axillary biopsy is very high (Figure 4 in Huang et al. 2022)	**ROBIS** Low risk of bias **Additional concerns about quality**: unclear included study designs **Quality of included studies**: degree of bias of the included literature is low; large distribution range of true positive, false positive, true negative, and false negative in the forest map, which may be

Source Huang Y, Zheng S, Lin Y. Accuracy and Utility of Preoperative Ultrasound-Guided Axillary Lymph Node Biopsy for Invasive Breast Cancer: A Systematic Review and Meta-Analysis. Comput Intell Neurosci. 2022 Sep 27;2022: 3307627. doi: 10.1155/2022/3307627. PMID: 36203726; PMCID: PMC9532070.					
	Inclusion criteria: studies on preoperative ultrasound-guided biopsy and intraoperative and postoperative pathological diagnosis of invasive breast cancer				related to the large difference in the number of patients in each study **Level of evidence:** Oxford 2011: **Sources of funding**: n.r.
Abbreviations and comment: n.r.: not reported					

Verknüpfte Empfehlungen:

Empfehlung 4.22:

Bei der interventionellen, vorzugsweise sonographisch gesteuerten Stanzbiopsie sollten ≥ 3 Proben bei ≤ 14 G bei nachweisbarer Zielerfassung der Stanznadel entnommen werden.

Literaturreferenzen: [81], [82], [83], [84]

Source: Gruber I, Oberlechner E, Heck K, Hoopmann U, Böer B, Fugunt R, Gall C, Hartkopf AD, Helms G, Hoffmann SM, Ott C, Röhm C, Stäbler A, Wallwiener D, Brucker SY,Hahn M. Percutaneous Ultrasound-Guided Core Needle Biopsy: Comparison of 16-Gauge versus 14-Gauge Needle and the Effect of Coaxial Guidance in 1065 Breast Biopsies - A Prospective Randomized Clinical Noninferiority TrialUltraschall Med. 2020 Oct;41(5): 534-543. doi: 10.1055/a-1014-2628.Epub 2019 Dec 2

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Diagnostic accuracy of 16-gauge versus (vs.) 14-gauge core needle biopsy (CNB), with and without coaxial guidance, and the minimum number of breast biopsy specimens necessary to achieve an accurate diagnosis **Country**: Germany	**Design**: monocentric RCT (noninferiority) **Setting:** Department of Gynecology and Obstetrics at the University of Tübingen **Enrollment:** 12/2011 – 02/2013 **Follow-up:** up to 5 years – until 06/2018 **Number of included patients**: 186	**Intervention** 4 study arms: 14-gauge CNB non-coaxial 14-gauge CNB coaxial 16-gauge CNB non-coaxial 16-gauge CNB coaxial Procedure: Eligible patients underwent a high-resolution ultrasound breast examination with a	**Primary Outcome**: Diagnostic accuracy (agreement between core needle biopsy and subsequent surgery of long-term follow-up) Specimens should reach an additive diagnostic accuracy for definitive histology in ≥99% of cases **Secondary Outcome**: Diagnostic quality of specimens (tissue	213 breast lesions in 186 patients; 5 core biopsies per breast lesion performed (n=1,056 [99.15%] core needle biopsies of 1,065 interventions were reached) **Primary Outcome**: **Diagnostic accuracy** The 16-gauge needle biopsy achieved an overall mean diagnostic accuracy for malignancy	**Quality of study** Assessed with SIGN checklist for RCT: low-quality **Limitations by authors** Not mentioned **Additional concern about quality** Monocentric Randomization method not explained

Source: Gruber I, Oberlechner E, Heck K, Hoopmann U, Böer B, Fugunt R, Gall C, Hartkopf AD, Helms G, Hoffmann SM, Ott C, Röhm C, Stäbler A, Wallwiener D, Brucker SY,Hahn M. Percutaneous Ultrasound-Guided Core Needle Biopsy: Comparison of 16-Gauge versus 14-Gauge Needle and the Effect of Coaxial Guidance in 1065 Breast Biopsies - A Prospective Randomized Clinical Noninferiority TrialUltraschall Med. 2020 Oct;41(5): 534-543. doi: 10.1055/a-1014-2628.Epub 2019 Dec 2					
	Number of breast lesions: 213 (5 core biopsies per breast lesion) **Number of breast biopsies:** 1,065 **Mean / median age:** 14-gauge CNB non-coaxial: 46.9y / 49 (34-58) 14-gauge CNB coaxial: 47.7y / 45 (34.5-63.5) 16-gauge CNB non-coaxial: 44.4y / 46 (31.8-52) 16-gauge CNB coaxial: 50.9y / 48 (41-67) **Inclusion criteria**: a) patients aged 18 to 85 years;	12-MHz linear array transducer; automated core biopsy needle; 5 consecutive passes performed for each patient; specimens reviewed by pathologists (determine if ultimate diagnosis could be made); each tissue sample categorized according to its diagnostic quality (class 1-5); diagnostic yield was reached in class 1 to 3 (pathological tissue evaluation of very good, good, moderate material quality) – class 4 to 5 (poor; inadequate material quality) unsuitable for an adequate histological diagnosis	specimen adequate to allow an appropriate and reliable histological diagnosis) In ≥99% if the cases sufficient diagnostic quality to define histological diagnosis Median pain level Mean duration of intervention Complications (minimal bleeding, hematomas, vasovagal reaction or patient discomfort)	of 87.59 %, which was inferior to the 14-gauge needle biopsy with a diagnostic accuracy for malignancy of 97.28 %. ITT and PP analysis: coaxial-guided CNB, which achieved an overall mean diagnostic accuracy for malignancy of 92.27 % and 93.01 %, respectively, was not noninferior (–0.59 % and 1.50 %, respectively) to on-coaxial-guided CNB, which achieved an overall mean diagnostic accuracy for malignancy of 92.86 % and 91.51 %, respectively to obtain a diagnostic accuracy of more than 99 %,	No information about concealment Duration of follow-up unclear: 2-5y mentioned, but no mean/median or percentage duration of FU provided Only 2 information (p.6): · in 4% of cases, FU was less than 2 years · In 43.6% of all cases image follow-up was acquired over at least 2-5 years But, 2 to 5 years is a wide time interval; exact percentage of patients with a e.g. with a 5 y of follow-up is not mentioned No information about drop-outs during follow-up

Source: Gruber I, Oberlechner E, Heck K, Hoopmann U, Böer B, Fugunt R, Gall C, Hartkopf AD, Helms G, Hoffmann SM, Ott C, Röhm C, Stäbler A, Wallwiener D, Brucker SY,Hahn M. Percutaneous Ultrasound-Guided Core Needle Biopsy: Comparison of 16-Gauge versus 14-Gauge Needle and the Effect of Coaxial Guidance in 1065 Breast Biopsies - A Prospective Randomized Clinical Noninferiority TrialUltraschall Med. 2020 Oct;41(5): 534-543. doi: 10.1055/a-1014-2628.Epub 2019 Dec 2					
	b) palpable or nonpalpable sonographically visible breast lesion; c) lesion size between 5 and 50mm; d) ultrasounddetected lesions classified by BIRADS-analogue DEGUM classification with category 3, 4 or 5; e) guideline-adherent diagnostic assessment **Exclusion**: nonguideline- adherent diagnostic assessment, pregnancy, or breastfeeding			two passes with 14-gauge CNB (with or without coaxial technique), three passes with 16-gauge non-coaxial-guided CNB, and five passes with 16-gauge coaxial-guided CNB were required. A diagnostic yield of 99 % to assess malignancy was achieved after one biopsy pass with the 14-gauge needle, independently of whether coaxial guidance was used in the ITT and PP analysis, 16-gauge CNB required three passes without coaxial guidance and five passes with coaxial guidance, to achieve a diagnostic	**Sources of funding:** n.a.

Source: Gruber I, Oberlechner E, Heck K, Hoopmann U, Böer B, Fugunt R, Gall C, Hartkopf AD, Helms G, Hoffmann SM, Ott C, Röhm C, Stäbler A, Wallwiener D, Brucker SY,Hahn M. Percutaneous Ultrasound-Guided Core Needle Biopsy: Comparison of 16-Gauge versus 14-Gauge Needle and the Effect of Coaxial Guidance in 1065 Breast Biopsies - A Prospective Randomized Clinical Noninferiority TrialUltraschall Med. 2020 Oct;41(5): 534-543. doi: 10.1055/a-1014-2628.Epub 2019 Dec 2

				accuracy of 99 % for malignancy (B5). **Secondary Outcome**: **Pain level** No significant difference between study groups (p=0.61) **Mean duration of intervention** 5 minutes, 95% CI 4.7-5.29; Coaxial-guided core needle biopsy was more time-consuming **Complication rates / Duration of intervention** No significant association between core needle size and those secondary endpoints 2 cases of complications registered	

Source: Gruber I, Oberlechner E, Heck K, Hoopmann U, Böer B, Fugunt R, Gall C, Hartkopf AD, Helms G, Hoffmann SM, Ott C, Röhm C, Stäbler A, Wallwiener D, Brucker SY,Hahn M. Percutaneous Ultrasound-Guided Core Needle Biopsy: Comparison of 16-Gauge versus 14-Gauge Needle and the Effect of Coaxial Guidance in 1065 Breast Biopsies - A Prospective Randomized Clinical Noninferiority TrialUltraschall Med. 2020 Oct;41(5): 534-543. doi: 10.1055/a-1014-2628.Epub 2019 Dec 2

Abbreviations:

CNB = Core Needle Biopsy

RCT = Randomised Controlled Trial

ITT = Intention-to-Treat

PP = Per-Protocol

95% CI = 95% Confidence Interval

n.a. = not Available, not Applicable

y = years

Kapitel 4.1.3: Vorgehen bei pathologischer Sekretion

Verknüpfte Empfehlungen:

Empfehlung 4.27:

Bei pathologischer Sekretion mit V.a. intramammäre Ursache soll eine Sonographie und altersabhängig eine Mammographie erfolgen. Ist eine weitere Bildgebung notwendig, soll eine MRT erfolgen, da die diagnostische Wertigkeit der MRT der Galaktographie überlegen ist. Eine histologische Klärung sollte bei bildgebendem Korrelat mittels minimalivasiver Intervention erfolgen.

Sollte trotz negativer Bildgebung der klinische Verdacht auf ein Malignom weiter bestehen, dann soll eine Duktektomie erfolgen.

Literaturreferenzen: [85], [86], [87]

Source Berger N, Luparia A, Di Leo G, Carbonaro LA, Trimboli RM, Ambrogi F, Sardanelli F. Diagnostic Performance of MRI Versus Galactography in Women With Pathologic Nipple Discharge: A Systematic Review and Meta-Analysis. AJR Am J Roentgenol. 2017 Aug;209(2): 465-471. doi: 10.2214/AJR.16.16682. Epub 2017 May 24. PMID: 28537847.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To perform a systematic review of the literature and to perform a meta-analysis to estimate the diagnostic accuracy of MRI compared with galactography in women with pathologic nipple discharge.	**Design**: Systematic review and meta-analysis **Search date**: December 2015 **Searched databases**: Medline, Embase, Web of Science **Included study designs**:	**Intervention** MRI **Control** Galactography	Diagnostic accuracy of MRI compared with galactography; sensitivity and specificity for the detection of any abnormality and cancer	The pooled sensitivity for any abnormality was significantly higher for MRI (92%; 95% CI, 85-96%) than for galactography (69%; 95% CI, 59-78%) (p < 0.001). The pooled specificity was 76% (95% CI, 49-92%) for MRI versus 39% (95% CI, 16-69%) for	**ROBIS** Low risk of bias **Additional concerns about quality**: High risk of publication bias for both sensitivity and specificity;

Source Berger N, Luparia A, Di Leo G, Carbonaro LA, Trimboli RM, Ambrogi F, Sardanelli F. Diagnostic Performance of MRI Versus Galactography in Women With Pathologic Nipple Discharge: A Systematic Review and Meta-Analysis. AJR Am J Roentgenol. 2017 Aug;209(2): 465-471. doi: 10.2214/AJR.16.16682. Epub 2017 May 24. PMID: 28537847.					
	retrospective and prospective **Number of included studies**: 10 (8 retrospective, 2 prospective) **Number of included patients**: 921 **Age (range)**: 42-56 **Inclusion criteria**: Estimation of the diagnostic performance of MRI in patients with pathologic nipple discharge; histologic verification after biopsy or clinical follow-up; and raw data provided or retrievable by back-calculating a 2x2 contingency table based on sensitivity and specificity **Exclusion**:			galactography ($p < 0.001$). The pooled sensitivity and specificity for cancer detection were calculated for MRI only and were 92% (95% CI, 74-98%) and 97% (95% CI, 80-100%), respectively.	Only 3 studies directly compared MRI and galactography **Quality of included studies**: Assessed with QUADAS-2 tool: except for the patient selection domain, where two studies were rated as having a high risk of bias, and the flow and timing domain, where the risk was rated unclear for one study, all other domains of the studies were rated as having a low risk of bias **Level of evidence:** Oxford 2011: **Sources of funding**: The Swiss Cancer Research Foundation and the Swiss Radiological Society.

Source Berger N, Luparia A, Di Leo G, Carbonaro LA, Trimboli RM, Ambrogi F, Sardanelli F. Diagnostic Performance of MRI Versus Galactography in Women With Pathologic Nipple Discharge: A Systematic Review and Meta-Analysis. AJR Am J Roentgenol. 2017 Aug;209(2): 465-471. doi: 10.2214/AJR.16.16682. Epub 2017 May 24. PMID: 28537847.

	Reviews, case reports, opinion articles, and other types of articles				

Abbreviations and comment:

MRI: Magnetic Resonance Imaging

Verknüpfte Empfehlungen:

Empfehlung 4.27:

Bei pathologischer Sekretion mit V.a. intramammäre Ursache soll eine Sonographie und altersabhängig eine Mammographie erfolgen. Ist eine weitere Bildgebung notwendig, soll eine MRT erfolgen, da die diagnostische Wertigkeit der MRT der Galaktographie überlegen ist. Eine histologische Klärung sollte bei bildgebendem Korrelat mittels minimalivasiver Intervention erfolgen.

Sollte trotz negativer Bildgebung der klinische Verdacht auf ein Malignom weiter bestehen, dann soll eine Duktektomie erfolgen.

Literaturreferenzen: [85], [86], [87]

Source Filipe MD, Patuleia SIS, de Jong VMT, Vriens MR, van Diest PJ, Witkamp AJ. Network Meta-analysis for the Diagnostic Approach to Pathologic Nipple Discharge. Clin Breast Cancer. 2020 Dec;20(6): e723-e748. doi: 10.1016/j.clbc.2020.05.015. Epub 2020 Jun 8. PMID: 32665191.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To compare the diagnostic efficacy of ultrasound, mammogram, cytology, magnetic resonance imaging (MRI), and ductoscopy in patients with pathologic nipple discharge (PND), and to determine the best diagnostic strategy to assess the risk of malignancy as a cause for PND.	**Design**: Systematic review and Network meta-analysis (NMA) **Search date**: up to January 27, 2020 **Searched databases**: Cochrane Library, PubMed, and Embase **Included study designs**: **Number of included studies**: 36	**Intervention** Ultrasound, mammogram, MRI, cytology, and ductoscopy **Control** Not explicitly defined as a separate group, but rather the comparison between the different diagnostic methods.	Diagnostic efficacy of different diagnostic tools to detect malignancy in patients with PND. sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy (DA) of each diagnostic method	MRI showed the highest sensitivity (83%), followed by ductoscopy (58%), ultrasound (50%), cytology (38%), and mammogram (22%) Specificity was highest for mammogram (93%), followed by ductoscopy (92%), cytology (90%), MRI (76%), and ultrasound (69%)	**ROBIS** Low risk of bias **Additional concerns about quality**: study could not provide enough direct comparisons between the 5 individual imaging methods as a result of limited evidence; heterogeneity

Source Filipe MD, Patuleia SIS, de Jong VMT, Vriens MR, van Diest PJ, Witkamp AJ. Network Meta-analysis for the Diagnostic Approach to Pathologic Nipple Discharge. Clin Breast Cancer. 2020 Dec;20(6): e723-e748. doi: 10.1016/j.clbc.2020.05.015. Epub 2020 Jun 8. PMID: 32665191.					
	Number of included patients: 3,764 **Mean/median age**: **Inclusion criteria**: Studies that evaluated ultrasound, mammogram, MRI, cytology, and/or ductoscopy, reported original data, and were written in English **Exclusion**: Studies where it was not possible to determine sensitivity and specificity from the studies by means of reported true-positive, true-negative, false-positive, and true-negative rates. Case reports, reviews, and conference abstracts.			Diagnostic accuracy was highest for ductoscopy (88%), followed by cytology (82%), MRI (77%), mammogram (76%), and ultrasound (65%)	was high within the groups and between different groups **Quality of included studies**: QUADAS-2 tool revealed that all included studies were of sufficient quality for both risk-of-bias and applicability domains **Level of evidence:** Oxford 2011: **Sources of funding**: n.r.
Abbreviations and comment:					

Source Filipe MD, Patuleia SIS, de Jong VMT, Vriens MR, van Diest PJ, Witkamp AJ. Network Meta-analysis for the Diagnostic Approach to Pathologic Nipple Discharge. Clin Breast Cancer. 2020 Dec;20(6): e723-e748. doi: 10.1016/j.clbc.2020.05.015. Epub 2020 Jun 8. PMID: 32665191.

n.r.: not reported

MRI: magnetic resonance imaging

NMA: Network meta-analysis

Kapitel 4.2: Duktales Carcinoma in situ (DCIS)

Kapitel 4.2.1: Operative Therapie des DCIS

Verknüpfte Empfehlungen:

Empfehlung 4.30:

Die vollständige Exzision ist die therapeutische Basis für die Behandlung des DCIS. Die Resektionsgrenzen sollten beim reinen DCIS mindestens 2 mm betragen, wenn eine adjuvante Radiotherapie angeschlossen wird.

Literaturreferenzen: [88], [89], [90], [91]

Source Marinovich ML, Azizi L, Macaskill P, Irwig L, Morrow M, Solin LJ, Houssami N. The Association of Surgical Margins and Local Recurrence in Women with Ductal Carcinoma In Situ Treated with Breast-Conserving Therapy: A Meta-Analysis. Ann Surg Oncol. 2016 Nov;23(12): 3811-3821. doi: 10.1245/s10434-016-5446-2. Epub 2016 Aug 15. PMID: 27527715; PMCID: PMC5160992.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To systematically review the evidence on margins in breast-conserving surgery (BCS) for ductal carcinoma in-situ (DCIS) and determine the optimal minimum negative margin width.	**Design**: Systematic review and meta-analysis **Search date**: **Searched databases**: Medline, Embase, Premedline, all EBM reviews **Included study designs**:	**Intervention** Breast-conserving surgery (BCS) **Control** Different margin distances in BCS	Local recurrence (LR)	Odds of LR were associated with margin status OR 0.53 (95% CI 0.45-0.62; P<0.001) for negative vs positive/close) margin status	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; X critical flaws (items 4, 7,9,13,15) **Additional concerns about quality**:

Source Marinovich ML, Azizi L, Macaskill P, Irwig L, Morrow M, Solin LJ, Houssami N. The Association of Surgical Margins and Local Recurrence in Women with Ductal Carcinoma In Situ Treated with Breast-Conserving Therapy: A Meta-Analysis. Ann Surg Oncol. 2016 Nov;23(12): 3811-3821. doi: 10.1245/s10434-016-5446-2. Epub 2016 Aug 15. PMID: 27527715; PMCID: PMC5160992.					
	Number of included studies: 20 (2 prospective, 18 retrospective) **Number of included patients**: 7,883 **Mean/median age**: **Median follow-up time:** 78.3 months (IQR 59.0-94.7) **Inclusion criteria**: Women with DCIS undergoing BCS **Exclusion**: studies that did not quantify negative margin distance, or used unclear margin definitions; if all patients had the same margin status: non-English studies			No evidence of a difference in LR between 2mm and 10mm margins Negative margins in BCS for DCIS reduce the odds of LR Minimum margin distances above 2mm are not significantly associated with further reduced odds of LR in women receiving radiation. Sensitivity analyses were conducted that included only study cohorts with adjuvant WBRT; the pattern of results was not altered	**Quality of included studies**: **Level of evidence:** Oxford 2011: **Sources of funding**: n.a.

Source Marinovich ML, Azizi L, Macaskill P, Irwig L, Morrow M, Solin LJ, Houssami N. The Association of Surgical Margins and Local Recurrence in Women with Ductal Carcinoma In Situ Treated with Breast-Conserving Therapy: A Meta-Analysis. Ann Surg Oncol. 2016 Nov;23(12): 3811-3821. doi: 10.1245/s10434-016-5446-2. Epub 2016 Aug 15. PMID: 27527715; PMCID: PMC5160992.

Abbreviations and comment:

Negative margins in BCS for DCIS reduce the odds of LR; however, minimum margins distances above 2mm are not significantly associated with further reduced odds of LR in women receiving radiation.

Verknüpfte Empfehlungen:

Empfehlung 4.31:

Eine Axilladissektion soll beim DCIS nicht durchgeführt werden. Eine Sentinel-Node-Biopsie soll nur durchgeführt werden, wenn eine sekundäre Sentinel-Node-Biopsie aus technischen Gründen nicht möglich ist, z. B. bei Mastektomie.

Literaturreferenzen: [92], [93], [94]

Source: MG, Davey, O'Flaherty C, Cleere EF, Nohilly A, Phelan J, Ronane E, Lowery AJ, and Kerin MJ. "Sentinel Lymph Node Biopsy in Patients with Ductal Carcinoma in Situ: Systematic Review and Meta-Analysis." [In eng]. BJS open 6, no. 2 (2022-3-8 2022). https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35380620/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Establish the likelihood of having lymph node metastases on sentinel lymph node biopsy (SLNB) positive SLNB (SLNB+) in patients being treated surgically for Ductal carcinoma in situ (DCIS), and to establish clinicopathological	**Design**: Systematic review and meta-analysis **Search date**: until 25 May 2021 **Searched databases**: PubMed, Embase, Scopus **Included study designs**: Prospective studies **Number of included studies**: 16 **Number of included patients**: 4.388	**Intervention** Any patient who underwent staging with SLNB and were subsequently found to have positive disease in the axilla at the time of their breast cancer surgery for DCIS **Control** Any patient in who underwent staging with SLNB and were	**Primary Outcome**: Included SLNB+ (including micro- and/or macrometastatic disease in the axillary lymph nodes) following an initial diagnosis of DCIS **Secondary Outcome**: Included any clinicopathological features predictive of those likely to have SLNB+ following an initial diagnosis of	**Primary Outcome**: Axillary lymph node positivity metastatic disease in axillary lymph nodes in patients with ductal carcinoma in situ OR=0.00, 95% CI 0.00-0.01, p<0.001; I^2=93% (16 studies) **Secondary Outcome**: Clinicopathological predictors of axillary lymph node positivity	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 6 critical flaws (items 2,4,7,11,13,15) **Additional concerns about quality**: Cautious interpretation of the results because of the absence of well-designed RCTs Observational studies of a non-randomized

Source: MG, Davey, O'Flaherty C, Cleere EF, Nohilly A, Phelan J, Ronane E, Lowery AJ, and Kerin MJ. "Sentinel Lymph Node Biopsy in Patients with Ductal Carcinoma in Situ: Systematic Review and Meta-Analysis." [In eng]. BJS open 6, no. 2 (2022-3-8 2022). https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35380620/.

parameters that may be useful in predicting those likely to be SLNB+ at the time of breast surgery for DCIS	**Mean age at diagnosis**: 54.8 (range: 24-92) **Inclusion criteria**: studies assessing patients with histologically confirmed DCIS breast cancer in the breast preoperatively with or without positive disease in the axilla (assessed using SLNB); and studies had to include data that were collected prospectively and included prospectively collected registry data **Exclusion**: Studies with patients with histologically confirmed invasive breast cancer (e.g. IDC	subsequently found not to have positive disease in the axilla at the time of their breast cancer surgery for DCIS	DCIS	<u>Palpable disease</u> OR=2.01, 95% CI 0.64-6.24, p=0.23; I²=0% (2 studies) <u>Tumour necrosis</u> OR=3.84, 95% CI 0.85-17.44), p=0.08; I²=83% (5 studies) <u>grade 3 ductal carcinoma in situ in predicting metastatic disease in axillary lymph nodes</u> OR=1.34, 95% CI 0.80-2.23, p=0.27; I²=0% (7 studies)	design, where retrospective analysis of prospectively collected data is performed, are subject to the inherent risk of selection and confounding biases. Detecting clinicopathological characteristics predictive of SLNB+ however, the paucity of such data may bring the validity of these results into question **Quality of included studies**: ROBINS-I 2: 9 studies 3: 7 studies **Level of evidence:**

Source: MG, Davey, O'Flaherty C, Cleere EF, Nohilly A, Phelan J, Ronane E, Lowery AJ, and Kerin MJ. "Sentinel Lymph Node Biopsy in Patients with Ductal Carcinoma in Situ: Systematic Review and Meta-Analysis." [In eng]. BJS open 6, no. 2 (2022-3-8 2022). https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35380620/.

	histological subtype); studies including data that were not collected prospectively; review articles; studies including fewer than five patients in their series or case reports; or editorial articles				Oxford 2011: **Sources of funding**: M.G.D., C.O'F., A.N., J.P., and E.R. received funding from the National Breast Cancer Research Institute, Ireland.

Abbreviations:

DCIS = carcinoma in situ

SLNB = sentinel lymph node biopsy

SLNB+ = positive SLNB

OR = Odds Ratio

95% CI = 95% Confidence intervall

Kapitel 4.2.2: Antihormonelle Therapie beim DCIS

Verknüpfte Empfehlungen:

Empfehlung 4.36:

Eine endokrine Therapie kann zur Prävention eines Zweitkarzinoms beim Östrogen-Rezeptor-positiven DCIS unter Berücksichtigung einer individuellen Risiko-Nutzen-Bewertung durchgeführt werden.

Literaturreferenzen: [95]

Source: Y, Yan, Zhang L, Tan L, Ma X, Zhang Y, Shao S, Liu J, et al. "Endocrine Therapy for Ductal Carcinoma in Situ (Dcis) of the Breast with Breast Conserving Surgery (Bcs) and Radiotherapy (Rt): A Meta-Analysis." [In eng]. Pathology oncology research: POR 26, no. 1 (2020-1 2020): 521-31. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30499075/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: to evaluate the effect of endocrine therapy of women with Ductal carcinoma in situ (DCIS) after breast conserving surgery (BCS) and radiotherapy (RT)	**Design**: Systematic Review and Meta-Analysis **Search date**: until June 30, 2017 **Searched databases**: PubMed, Cochrane Library, Web of Science **Included study designs**: RCTs **Number of included studies:** 4 studies (7 articles)	5 articles: **Intervention** BCS + RT + TAM **Control** BCS + RT 2 articles: **Intervention** BCS + RT + TAM **Control** BCS + RT + ANA	recurrence of ipsilateral breast cancer (IBCR), recurrence of ipsilateral invasive breast cancer (IBCR-INV), recurrence of ipsilateral DCIS (IBCR-DCIS), recurrence of contralateral breast cancer (CBCR),	***BCS+RT+TAM vs BCS+RT*** 2 studies: NSABP B-24 and UK/ANZ trial **IBCR** <10 years RR 0.75, 95% CI 0.57-0.98; I^2=0% >10 years RR 0.80, 95% CI 0.65-0.99; I^2=0% **IBCR-INV**	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review critically low; 4 critical flaws (items 2,7,13,15) **Additional concerns about quality**: study lacked the data of patients' characteristics,

Source: Y, Yan, Zhang L, Tan L, Ma X, Zhang Y, Shao S, Liu J, et al. "Endocrine Therapy for Ductal Carcinoma in Situ (Dcis) of the Breast with Breast Conserving Surgery (Bcs) and Radiotherapy (Rt): A Meta-Analysis." [In eng]. Pathology oncology research: POR 26, no. 1 (2020-1 2020): 521-31. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30499075/.					
	Number of included patients: BCS+RT vs BCS+RT+TAM 2322 BCS+RT+TAM: 1171 BCS+RT: 1151 5 articles reported 2 RCTs (NSABP B-24 and UK/ANZ trial) TAM vs ANA **Mean/median age**: n.a. **Inclusion criteria**: sufficient data for outcomes provided **Exclusion**: n.a.		recurrence of contralateral invasive breast cancer (CBCR-INV), recurrence of contralateral DCIS (CBCR-DCIS), distant metastases, event-free survival (EFS). mortality	<u><10 years</u> RR 0.63, 95% CI 0.41-0.95; I²=47% <u>>10 years</u> RR 0.76, 95% CI 0.56-1.03; I²=0% **IBCR-DCIS** <u><10 years</u> RR 0.86, 95% CI 0.60-1.23; I²=0% <u>>10 years</u> RR 0.85, 95% CI 0.63-1.16; I²=0% **CBCR** <u><10 years</u> RR 0.59, 95% CI 0.38-0.93; I²=0% <u>>10 years</u> RR 0.64, 95% CI 0.46-0.89; I²=0%	such as age, tumor size, pathology and immunohistochemistry status; small number of studies; certain publication bias possible **Quality of included studies**: Evaluated with CONSORT Statement **Level of evidence:** Oxford 2011: LoE 2 (downgraded due to low quality of systematic review) **Sources of funding:** supported by the National Natural Science Foundations of China

Source: Y, Yan, Zhang L, Tan L, Ma X, Zhang Y, Shao S, Liu J, et al. "Endocrine Therapy for Ductal Carcinoma in Situ (Dcis) of the Breast with Breast Conserving Surgery (Bcs) and Radiotherapy (Rt): A Meta-Analysis." [In eng]. Pathology oncology research: POR 26, no. 1 (2020-1 2020): 521-31. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30499075/.					
				CBCR-INV <u><10 years</u> RR 0.71, 95% CI 0.42-1.17; I²=0% <u>>10 years</u> RR 0.67, 95% CI 0.44-1.02; I²=0% **CBCR-DCIS** <u><10 years</u> RR 0.33, 95% CI 0.12-0.91; I² N.A. (only data from NSABP B-24 trial; no events in UK/ANZ trial) <u>>10 years</u> RR 0.59, 95% CI 0.32-1.09; I²=0% **EFS** <u><10 years</u> RR 1.07, 95% CI 1.02-1.12; I² n.a.	

Source: Y, Yan, Zhang L, Tan L, Ma X, Zhang Y, Shao S, Liu J, et al. "Endocrine Therapy for Ductal Carcinoma in Situ (Dcis) of the Breast with Breast Conserving Surgery (Bcs) and Radiotherapy (Rt): A Meta-Analysis." [In eng]. Pathology oncology research: POR 26, no. 1 (2020-1 2020): 521-31. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30499075/.					
				(only data from NSABP B-24 trial) <u>>10 years</u> RR 1.10, 95% CI 1.03-1.18; I² n.a. (only data from NSABP B-24 trial) **Mortality** RR 0.96, 95% CI 0.63-1.44; I² n.a. (only data from NSABP B-24 trial) **Non-BC death** RR 0.97, 95% CI 0.60-1.56; I² n.a. (only data from NSABP B-24 trial) **BC death** RR 0.50, 95% CI 0.17-1.46; I² n.a.	

Source: Y, Yan, Zhang L, Tan L, Ma X, Zhang Y, Shao S, Liu J, et al. "Endocrine Therapy for Ductal Carcinoma in Situ (Dcis) of the Breast with Breast Conserving Surgery (Bcs) and Radiotherapy (Rt): A Meta-Analysis." [In eng]. Pathology oncology research: POR 26, no. 1 (2020-1 2020): 521-31. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30499075/.					
				(only data from NSABP B-24 trial) **Local, regional and distant recurrence** <u><10 years</u> RR 0.38, 95% CI 0.10-1.41; I² n.a. (only data from NSABP B-24 trial) <u>>10 years</u> RR 0.70, 95% CI 0.27-1.83; I² n.a. (only data from NSABP B-24 trial) ***ANA vs TAM*** IBIS-II DCIS-Forbes and NSABP B35 trial **IBCR** OR 0.88, 95% CI 0.66-1.17; I²=0% **IBCR-DCIS**	

Source: Y, Yan, Zhang L, Tan L, Ma X, Zhang Y, Shao S, Liu J, et al. "Endocrine Therapy for Ductal Carcinoma in Situ (Dcis) of the Breast with Breast Conserving Surgery (Bcs) and Radiotherapy (Rt): A Meta-Analysis." [In eng]. Pathology oncology research: POR 26, no. 1 (2020-1 2020): 521-31. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30499075/.					
				OR 0.90, 95% CI 0.61-1.32; I²=0% **IBCR-INV** OR 0.85, 95% CI 0.55-1.32; I²=0% **CBCR** OR 0.70, 95% CI 0.51-0.97; I²=0% **CBCR-DCIS** OR 1.01, 95% CI 0.58-1.74; I²=0% **CBCR-INV** OR 0.59, 95% CI 0.39-0.88; I²=0% **Mortality** OR 1.07, 95% CI 0.83-1.37; I²=0% **BC death** OR 0.55, 95% CI 0.20-1.48; I²=0%	

Source: Y, Yan, Zhang L, Tan L, Ma X, Zhang Y, Shao S, Liu J, et al. "Endocrine Therapy for Ductal Carcinoma in Situ (Dcis) of the Breast with Breast Conserving Surgery (Bcs) and Radiotherapy (Rt): A Meta-Analysis." [In eng]. Pathology oncology research: POR 26, no. 1 (2020-1 2020): 521-31. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30499075/.

				Non-BC death OR 1.12, 95% CI 0.86-1.45; I^2=0% **Non-breast second primary cancer** OR 0.98, 95% CI 0.79-1.22; I^2=0% **Uterine cancer of non-breast second primary cancer** OR 0.31, 95% CI 0.15-0.66; I^2=59% **Non-gynecological of non-breast second primary cancer** OR 1.13, 95% CI 0.90-1.43; I^2=0% **Arthralgia** OR 1.49, 95% CI 1.34-1.66; I^2=31% **Osteoporosis**	

Source: Y, Yan, Zhang L, Tan L, Ma X, Zhang Y, Shao S, Liu J, et al. "Endocrine Therapy for Ductal Carcinoma in Situ (Dcis) of the Breast with Breast Conserving Surgery (Bcs) and Radiotherapy (Rt): A Meta-Analysis." [In eng]. Pathology oncology research: POR 26, no. 1 (2020-1 2020): 521-31. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30499075/.					
				OR 1.66, 95% CI 1.29-2.13; I²=32% **Deep-vein thrombosis** OR 0.15, 95% CI 0.05-0.51; I²=0% **Pulmonary embolism** OR 0.35, 95% CI 0.20-0.63; I²=28% *Following results only data from IBIS-II DCIS-Forbes* **Vasomotor or gynaecological** OR 0.69, 95% CI 0.59-0.80; I² n.a. **Hot flushes** OR 0.85, 95% CI 0.73-0.99; I² n.a. **Vaginal dryness** OR 1.25, 95% CI 1.00-1.57; I² n.a.	

Source: Y, Yan, Zhang L, Tan L, Ma X, Zhang Y, Shao S, Liu J, et al. "Endocrine Therapy for Ductal Carcinoma in Situ (Dcis) of the Breast with Breast Conserving Surgery (Bcs) and Radiotherapy (Rt): A Meta-Analysis." [In eng]. Pathology oncology research: POR 26, no. 1 (2020-1 2020): 521-31. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30499075/.					
				Vaginal haemorrhage OR 0.44, 95% CI 0.29-0.65; I² n.a. **Vaginal discharge** OR 0.21, 95% CI 0.14-0.31; I² n.a. **Vaginal candidiasis** OR 0.19, 95% CI 0.09-0.41; I² n.a. **Cardiovascular** OR 1.15, 95% CI 0.85-1.56; I² n.a. **Hypercholesteremia** OR 4.11, 95% CI 2.11-8.00; I² n.a. **Headache** OR 1.40, 95% CI 1.00-1.97; I² n.a. **Eye disease**	

Source: Y, Yan, Zhang L, Tan L, Ma X, Zhang Y, Shao S, Liu J, et al. "Endocrine Therapy for Ductal Carcinoma in Situ (Dcis) of the Breast with Breast Conserving Surgery (Bcs) and Radiotherapy (Rt): A Meta-Analysis." [In eng]. Pathology oncology research: POR 26, no. 1 (2020-1 2020): 521-31. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30499075/.

				OR 1.16, 95% CI 0.94-1.42; I² n.a.	

Abbreviations:

DCIS = Ductal carcinoma in situ

BCS = Breast Conserving Surgery

RT = Radiotherapy

IBCR = Recurrence of Ipsilateral Breast Cancer

IBCR-INV = Recurrence of Ipsilateral Invasive Breast Cancer

IBCR-DCIS = Recurrence of Ipsilateral DCIS

CBCR = Recurrence of Contralateral Breast Cancer

CBCR-DCIS = Recurrence of Contralateral DCIS

CBCR-INV = Recurrence of Contralateral Invasive Breast Cancer

EFS = Event-Free Survival

RCT = Randomised Controlled Trial

RR = Risk Ratio

OR = Odds Ratio

95% CI = 95% Confidence Interval

n.a. = not Available, not Applicable

Kapitel 4.3: Operative Therapie des invasiven Karzinoms

Kapitel 4.3.1: Brusterhaltende Operation

Verknüpfte Empfehlungen:

Empfehlung 4.50:

Die intraoperative Sonographie sollte zur Entfernung von palpablen und nicht-palpablen sonographisch sichtbaren Befunden als ergänzende oder alleinige Methode eingesetzt werden.

Literaturreferenzen: [96], [97], [98]

Source: Athanasiou, C, Mallidis, E, Tuffaha, H, Comparative effectiveness of different localization techniques for non-palpable breast cancer. A systematic review and network meta-analysis.. Eur J Surg Oncol, 2022. 48 (1)(1): p. 53-59., https: //pubmed.ncbi.nlm.nih.gov/34656392/

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: To compare effectiveness of different localization techniques that are in use for localization of non palpable breast using cancer network metaanalysis	**Design**: systematic review and network meta-analysis **Search date**: till December 2020 **Searched databases**: MEDLINE via Ovid, PubMed, Scopus, Cochrane Central	**Intervention** - Ultrasound guided surgery (UGS) - Cryo assisted localization(CAL) - Indocyanine green localization (ICG) - Radiocolloid and methylene blue localization (RCML),	**Primary Outcome**: Failure to localize lesion with the intended technique Positive margin defined as tumour at ink or within 1 mm for ductal carcinoma in situ (dcis) Re-operation rate, Operative time,	**Primary Outcome**: ***UGS VS.WGL*** 1. Positive margine Pairwise comparison OR 0.19 (0.11, 0.35) network meta-analysis OR0.19 (0.11,0.60) 2. Re-operation rate Pairwise comparison	**ROBIS** **Risk of bias in the review:** unclear **Domain** Concerns regarding specification of study eligibility criteria: low risk Concerns regarding methods used to identify

Source: Athanasiou, C, Mallidis, E, Tuffaha, H, Comparative effectiveness of different localization techniques for non-palpable breast cancer. A systematic review and network meta-analysis.. Eur J Surg Oncol, 2022. 48 (1)(1): p. 53-59., https: //pubmed.ncbi.nlm.nih.gov/34656392/					
	Register of Controlled Trials (CENTRAL) **Included study designs**: RCT **Number of included studies**: 20 **Number of included patients**: 3112 **Mean/median age**: No information **Inclusion criteria**: : females of any age with biopsy proven non palpable breast cancer ***Exclusion**:* palpable or benign lesions	- Magnetic resonance imaging guided surgery (MRIGS) - Radio-guided occult lesion localization (ROLL) - Radioactive seed localization (RSL) **Control** wire localization technique (WGL) or comparing the techniques with each other	Overall complications, Length of stay Tumour recurrence The probability of each technique being the best.	OR 0.19 (0.10, 0.36) network meta-analysis OR 0.37 (0.09, 1.45). 3.Operative time Pairwise comparison MD -4.24 (-7.85, -0.63) network meta-analysis MD -3.70 (-8.91, 1.51) 4. Specimen Volume Pairwise comparison MD -0.60 (-1.70, 0.50) network meta-analysis MD 9.16 (-21.16,39.48) ***ROLL VS.WGL*** 1.Positive margin Pairwise comparison OR 0.81(0.53, 1.24) network meta-analysis OR 0.19 (0.11, 0.60). 2. Re-operation rate	and/or select studies: unclear risk Concerns regarding methods used to collect data and appraise studies: low risk Concerns regarding the synthesis and findings: high risk **Quality of included studies**: The ROB in domains of blinding of participants and other biases was high, in other domains most of studies had low ROB or unclear ROB. **Certainty of Evidence:** **GRADE** Positive margins: very low Re-operation rate: very low Operative time: very low

Source: Athanasiou, C, Mallidis, E, Tuffaha, H, Comparative effectiveness of different localization techniques for non-palpable breast cancer. A systematic review and network meta-analysis.. Eur J Surg Oncol, 2022. 48 (1)(1): p. 53-59., https: //pubmed.ncbi.nlm.nih.gov/34656392/					
				Pairwise comparison OR 0.51 (0.21, 1.23) 3.Operative time Pairwise comparison MD -0.48 (-2.1, 1.13) 4. Localization complications Pairwise comparison OR 0.68(0.21,2.17) 5. Successful excision Pairwise comparison OR 1 (0.99,1.01) 6. Complications Pairwise comparison OR 0.79(0.33, 1.88) ***RSL VS.WGL*** 1. Positive margin Pairwise comparison OR 0.80 (0.55, 1.17) 2. Re-operation rate	Specimen volume: very low **Sources of funding:** No funding was received for this meta-analysis.

Source: Athanasiou, C, Mallidis, E, Tuffaha, H, Comparative effectiveness of different localization techniques for non-palpable breast cancer. A systematic review and network meta-analysis.. Eur J Surg Oncol, 2022. 48 (1)(1): p. 53-59., https: //pubmed.ncbi.nlm.nih.gov/34656392/					
				Pairwise comparison OR 0.76 (0.42, 1.39) 3. Operative time Pairwise comparison MD -0.06 (-0.28, 0.16) 4. Localization complications Pairwise comparison OR 1.37 (0.78, 2.41) 5. Successful excision Pairwise comparison OR 0.33 (0.01, 8.19) 6. Complications Pairwise comparison OR 1.37 [0.79, 2.39] 7. Specimen Volume Pairwise comparison MD 0.09(-0.10, 0.28) ***UGS VS.ROLL*** 1. Positive margin	

Source: Athanasiou, C, Mallidis, E, Tuffaha, H, Comparative effectiveness of different localization techniques for non-palpable breast cancer. A systematic review and network meta-analysis.. Eur J Surg Oncol, 2022. 48 (1)(1): p. 53-59., https: //pubmed.ncbi.nlm.nih.gov/34656392/					
				Network meta-analysis OR 0.19 (0.10, 0.35) 2. Re-operation rate Network meta-analysis OR 0.18(0.06, 0.53). 3. Specimen Volume Network meta-analysis MD -27.36(-71.81, 17.09). ***UGS VS.RSL*** 1. Positive margin Network meta-analysis OR 0.26(0.13, 0.52). 2. Specimen Volume Network meta-analysis MD -29.52(-70.35, 11.32). ***CAL VS.UGS*** 1. Positive margin Network meta-analysis OR 4.64(1.54, 10.71).	

Source: Athanasiou, C, Mallidis, E, Tuffaha, H, Comparative effectiveness of different localization techniques for non-palpable breast cancer. A systematic review and network meta-analysis.. Eur J Surg Oncol, 2022. 48 (1)(1): p. 53-59., https: //pubmed.ncbi.nlm.nih.gov/34656392/

				The probability of each technique being the best. UGS ranked first with a probability of 54.6% being the best technique for reduction of positive margin. All techniques were equivalent for successful excision, localization complications, operative time and overall complications.	

Abbreviations:

RCT = Randomised Controlled Trial

UGS = Ultrasound guided surgery

CAL = Cryo assisted localization

ICG = Indocyanine green localization

RCML = Radiocolloid and methylene blue localization

MRIGS = Magnetic resonance imaging guided surgery

ROLL = Radio-guided occult lesion localization

Source: Athanasiou, C, Mallidis, E, Tuffaha, H, Comparative effectiveness of different localization techniques for non-palpable breast cancer. A systematic review and network meta-analysis.. Eur J Surg Oncol, 2022. 48 (1)(1): p. 53-59., https: //pubmed.ncbi.nlm.nih.gov/34656392/

RSL = Radioactive seed localization

WGL = Wire Localization Technique

DCIS = Ductal Carcinoma in Situ

OR = Odds Ratio

Verknüpfte Empfehlungen:

Empfehlung 4.50:

Die intraoperative Sonographie sollte zur Entfernung von palpablen und nicht-palpablen sonographisch sichtbaren Befunden als ergänzende oder alleinige Methode eingesetzt werden.

Literaturreferenzen: [96], [97], [98]

Source: Banys-Paluchowski, M, Rubio, IT, Karadeniz Cakmak, G, Esgueva, A, Krawczyk, N, Paluchowski, P, et.al. Intraoperative Ultrasound-Guided Excision of Non-Palpable and Palpable Breast Cancer: Systematic Review and Meta-Analysis.. Ultraschall Med, 2022. 43 (4)(4): p. 367-379. https: //pubmed.ncbi.nlm.nih.gov/35760079/

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: use of intraoperative ultrasound for the localization of nonpalpable and palpable breast tumors to evaluate the current role of IOUS in surgical practice	**Design**: Systematic Review and Meta-Analysis **Search date**: until Dec 31, 2020 **Searched databases**: PubMed/Medline, ClinicalTrials.gov, the European Clinical Trials Database (EudraCT) and the Cochrane Database **Included study designs**: RCTs, cohort studies	**Intervention** Intraoperative ultrasound (IOUS) **Control** Wire-guided localization (WGL)	Negative and positive margins Reoperation rates	**Non-palpable invasive BC** *Results of 3 RCTs* Negative margins IOUS: 95.3% WGL: 79.7% *Results of 22 prospective and 19 retrospective cohort studies (3,291 patients)* Majority reported higher rates of negative margins and lower re-operation	**ROBIS** **Risk of bias in the review:** high **Domain** Concerns regarding specification of study eligibility criteria: high risk Concerns regarding methods used to identify and/or select studies: unclear risk Concerns regarding methods used to collect

Source: Banys-Paluchowski, M, Rubio, IT, Karadeniz Cakmak, G, Esgueva, A, Krawczyk, N, Paluchowski, P, et.al. Intraoperative Ultrasound-Guided Excision of Non-Palpable and Palpable Breast Cancer: Systematic Review and Meta-Analysis.. Ultraschall Med, 2022. 43 (4)(4): p. 367-379. https: //pubmed.ncbi.nlm.nih.gov/35760079/					
	(with and without control group) **Number of included studies**: 71 (6 RCTs, 33 cohort studies with a control group, 31 cohort studies without control group) **Number of included patients**: n.a. **Mean/median age**: n.a. **Inclusion criteria**: Articles published in English **Exclusion**: Case-reports, non-English language			rates in patients receiving IOUS compared to WGL Possible bias due to choice of technique was at the discretion of the treating physician <u>Positive surgical margins (favoring IOUS)</u> WGL vs. IOUS RR 4.34 (95% CI 2.52-7.45) 3 RCTs (616 patients, IOUS: 316; WGL: 300) **Palpable invasive BC** <u>Negative margins:</u> IOUS: 93.7% Palpation: 80.3% <u>Positive surgical margins (favoring IOUS)</u> Palpation-guided vs. IOUS RR 2.84 (95% CI 1.38-5.87)	data and appraise studies: high risk Concerns regarding the synthesis and findings: high risk **Quality of included studies**: No formal quality/bias assessment by review authors **Certainty of Evidence:** **GRADE** Positive margins WGL vs. IOUS: very low Positive margins Palpation-guided vs. IOUS: very low **Sources of funding:** n.a.

Source: Banys-Paluchowski, M, Rubio, IT, Karadeniz Cakmak, G, Esgueva, A, Krawczyk, N, Paluchowski, P, et.al. Intraoperative Ultrasound-Guided Excision of Non-Palpable and Palpable Breast Cancer: Systematic Review and Meta-Analysis.. Ultraschall Med, 2022. 43 (4)(4): p. 367-379. https: //pubmed.ncbi.nlm.nih.gov/35760079/					
				3 RCTs (254 patients, IOUS: 127 Palpation: 127) *Results of 9 prospective and 4 retrospective cohort studies (942 patients)* Negative margin rates were higher in patients receiving IOUS in most studies Re-operation rates higher in patients receiving palpation-guided surgery	

Abbreviations:

IOUS = Intraoperative ultrasound

WGL = Wire-guided localization

BC = Breast Cancer

RCT = Randomised Controlled Trial

RR = Risk Ratio

Verknüpfte Empfehlungen:

Empfehlung 4.50:

Die intraoperative Sonographie sollte zur Entfernung von palpablen und nicht-palpablen sonographisch sichtbaren Befunden als ergänzende oder alleinige Methode eingesetzt werden.

Literaturreferenzen: [96], [97], [98]

Source: Davey, MG, O'Donnell, JPM, Boland, MR, Ryan, ÉJ, Walsh, SR, Kerin, MJ, et.al. Optimal localization strategies for non-palpable breast cancers -A network meta-analysis of randomized controlled trials.. Breast, 2022. 62 (): p. 103-113., https: //pubmed.ncbi.nlm.nih.gov/35151049/

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Perform and updated systematic review and network meta-analysis (NMA) of RCTs which comprehensively evaluated all data comparing methods of localizing non-palpable breast cancers for BCS	**Design**: Systematic Review and network meta-analysis **Search date**: 22ndSeptember 2021 **Searched databases**: PubMed, Scopus and Cochrane Central Register of Controlled Trials **Included study designs**: RCTs	**Intervention** intraoperative ultrasound-guided localization (USGL) **Control** Any patient who was having their tumour localized using WG. **Population** Patients with a newly diagnosed non-palpable breast cancer aged 18 years or older who were	**Primary Outcome**: -Margin positivity rates -Margin widths **Secondary Outcome**: -Reoperation rate -Timing/duration of operation -Satisfaction rates among patients and surgeons -Cost of each localization technique -specimen volume	**Primary Outcome**: 1. margin positivity OR: 0.192, 95% CI: 0.079–0.450 **Secondary Outcome**: 1.reoperation rates OR: 0.182, 95% CI: 0.069–0.434 2. operation duration MD: -3.22, 95% CI: -13.4, 7.62 3. Specimen size	**ROBIS** **Risk of bias in the review:** unclear **Domain** Concerns regarding specification of study eligibility criteria: unclear risk Concerns regarding methods used to identify and/or select studies: low risk Concerns regarding methods used to collect

Source: Davey, MG, O'Donnell, JPM, Boland, MR, Ryan, ÉJ, Walsh, SR, Kerin, MJ, et.al. Optimal localization strategies for non-palpable breast cancers -A network meta-analysis of randomized controlled trials.. Breast, 2022. 62 (): p. 103-113., https: //pubmed.ncbi.nlm.nih.gov/35151049/					
	Number of included studies: 24 studies overall WGL and3 studies in USGL subgroup **Number of included patients**: 4225 patients overall 316 in USGL subgroup **Mean/median age**: 56.6 age range (25-81) **Inclusion criteria**: ll published RCTs with full-text manuscripts comparing the outcomes of at least two means of localizing non-palpable cancers in the breast were included. Studies included those evaluating localization techniques for suspected invasive or non-invasive breast cancers and were not limited based on patient demographics, tumour histopathological features	due to undergo tumour localization prior to BCS.	-specimen size -specimen weight Disease recurrence	MD: -0.996, 95% CI: -6. 83, 4.85 4. Specimen volume MD: -3.96, 95% CI: -16.3, 8.05	data and appraise studies: unclear risk Concerns regarding the synthesis and findings: high risk **Additional concerns about quality (limitations by review authors)**: The paucity of randomized patients reporting surgical outcomes in relation to USGL, IL, ML, AGL and SMRI is potentially too small to draw definitive (or significant) results, which may limit the conclusions in relation to these methods of tumour localization. This may inherently lead to the potential underestimation of their true value and/or risk profile in the clinical setting. Qualitative assessment of the definitions for margin

Source: Davey, MG, O'Donnell, JPM, Boland, MR, Ryan, ÉJ, Walsh, SR, Kerin, MJ, et.al. Optimal localization strategies for non-palpable breast cancers -A network meta-analysis of randomized controlled trials.. Breast, 2022. 62 (): p. 103-113., https: //pubmed.ncbi.nlm.nih.gov/35151049/

	or tumour molecular subtyping. Studies reporting outcomes following localization of invasive cancers which had associated non-invasive disease were included. Included studies were expected to report on the primary outcome of interest. ***Exclusion***: Studies comparing localization strategies for sentinel lymph node biopsy (SLNB), including data from patients with advanced breast cancer, and those not published in the English language were excluded.				positivity vary greatly in this systematic review; despite current best practice guidelines being in accordance to the SSO-ASTRO consensus, the heterogeneity of these results add inconsistencies to data pertaining to margin status; However, all 24 RCTs measured the margin status consistently for each localization modality versus WGL, providing some degree of congruency among their own results. Furthermore, analyses of secondary outcomes (i.e.: complication, haematoma, seroma, and SSI rates) were limited to just 4 localization strategies, with reported outcomes ranging from 24.4% to 28.7% of

Source: Davey, MG, O'Donnell, JPM, Boland, MR, Ryan, ÉJ, Walsh, SR, Kerin, MJ, et.al. Optimal localization strategies for non-palpable breast cancers -A network meta-analysis of randomized controlled trials.. Breast, 2022. 62 (): p. 103-113., https: //pubmed.ncbi.nlm.nih.gov/35151049/					
					patients in relation to seroma (1033/4236) and haematoma (1217/4236) respectively. This limits the robustness of these results. Moreover, 22.3% of the tumours included by Struik et al. were palpable (n = 15). Not able to decipher data for non-palpable or non-invasive cancers only, limiting the transferability of these findings to non-palpable cancers exclusively. As observed in the majority of RCTs in the field of surgery, none of the RCTs included in this analysis were 'blinded'. The inability to blind surgeons to interventions leads to these RCTs to be classed as 'open label', making them subject to unintentional bias; Potential confounders

Source: Davey, MG, O'Donnell, JPM, Boland, MR, Ryan, ÉJ, Walsh, SR, Kerin, MJ, et.al. Optimal localization strategies for non-palpable breast cancers -A network meta-analysis of randomized controlled trials.. Breast, 2022. 62 (): p. 103-113., https: //pubmed.ncbi.nlm.nih.gov/35151049/					
					(i.e.: patient age, body mass indices, smoking habits, surgeons experience, etc.) which may influence our primary and secondary outcomes of interest have not been considered in this study. **Quality of included studies**: most of 24 studies had moderate to low ROB; all three articles in USGL had low ROB **Certainty of Evidence:** **GRADE** Positive margine: very low Re-operation rate: low **Sources of funding:** MGD received funding from the National Breast Cancer Research Institute, Ireland.

Source: Davey, MG, O'Donnell, JPM, Boland, MR, Ryan, ÉJ, Walsh, SR, Kerin, MJ, et.al. Optimal localization strategies for non-palpable breast cancers -A network meta-analysis of randomized controlled trials.. Breast, 2022. 62 (): p. 103-113., https: //pubmed.ncbi.nlm.nih.gov/35151049/

Abbreviations:

BCS = Breast Conserving Surgery

SLNB = Sentinel Lymph Node Biopsy

USGL = Ultrasound-Guided Localization

WGL = Wire-Guided Localization

IL = Indocyanine green Fluorescence-Guided Lumpectomy

ML = Magneticmarker Localization

AGL = Anchor-Guided Localization

SMRI = Intraoperative Supine Magnetic Resonance Imaging

NMA = network meta-analysis

RCT = Randomised Controlled Trial

Kapitel 4.3.2: Mastektomie

Kapitel 4.3.3: Operative Therapie der Axilla

Kapitel 4.3.3.1: Primäre operative Therapie der Axilla

Verknüpfte Empfehlungen:

Empfehlung 4.57:

Bei postmenopausalen Patientinnen ≥ 50 Jahre mit cT1 cN0 HR+ HER2- G1-2-Tumoren, die eine brusterhaltende Operation mit anschließender perkutaner Ganzbrustbestrahlung und adäquater Systemtherapie erhalten, kann auf das operative axilläre Staging verzichtet werden.

Literaturreferenzen: [99], [100], [101]

Source: Gentilini, OD, Botteri, E, Sangalli, C, Galimberti, V, Porpiglia, M, Agresti, R, et.al. *Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial.*. JAMA Oncol, 2023. **9 (11)**(11): p. 1557-1564., https://pubmed.ncbi.nlm.nih.gov/37733364/

Aim and Country	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: To determine whether the omission of axillary surgery is noninferior to SLNB in patients with small BC and a negative result on preoperative axillary	**Design**: prospective multicenter noninferiority phase 3 randomized clinical trial **Setting**: hospitals **Enrollment**: 2008-2017	**Intervention** sentinel lymph node biopsy (SLNB) **Control** no axillary surgery (observation after axillary ultra-sound)	**Primary Outcome:** Distant disease-free survival (DDFS) **Secondary Outcome:** Cumulative incidence of distant metastases	**Primary Outcome:** **Distant disease-free survival (DDFS)** 5-year omission of axillary surgery was noninferior to SLNB	**Quality of study** assessed with SIGN checklist for RCT: High quality **Limitations by authors:** inclusion criteria of the study led to enrollment of patients who could be

Source: Gentilini, OD, Botteri, E, Sangalli, C, Galimberti, V, Porpiglia, M, Agresti, R, et.al. *Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial.*. JAMA Oncol, 2023. **9 (11)**(11): p. 1557-1564., https://pubmed.ncbi.nlm.nih.gov/37733364/					
lymph node ultrasonography. **Country**: Italy, Spain, Switzerland, chile	**Number of included patients**: 1,405 **Age group**: **SLNB Group (No. (%))** <40: 10 (1.4) 40-49: 114 (16.1) 50-64: 324 (45.8) ≥65: 260 (36.7) Median (IQR): 60 (52-68) **No axillary surgery group (No. (%))** <40: 10 (1.4) 40-49: 128 (18.4) 50-64: 298 (42.8) ≥65: 261 (37.4) Median (IQR): 60 (51-68) **Inclusion criteria**: women of any age with invasive BC up to 2 cm in diameter, lack of	**Study flow and follow-up** The median (IQR) follow-up for disease assessment was 5.7 (5.0-6.8) years in the SLNB group and 5.7 (5.0-6.6) years in the no axillary surgery group. The median (IQR) follow-up for vital status assessment was 5.8 (5.0-6.9) years in the SLNB group and 5.8 (5.0-6.8) years in the no axillary surgery group.	Cumulative incidence of axillary recurrences DFS Overall survival (OS) Adjuvant treatment recommendations	HR 0.84; 90% CI, 0.45-1.54; noninferiority *P* = .02) **Secondary Outcome:** **Cumulative incidence of distantmetastases** 5-year SLNB: 2.3% no axillary surgery group: 1.9% (Gray *P* = .69) **Cumulative incidence of axillary recurrences** 5-year SLNB: 0.4% no axillary surgery group: 0.4% (Gray *P* = .91) **DFS** 5-year SLNB: 94.7%	considered to be at low risk of recurrence in the short term analysis of adjuvant treatments was not the primary end point and that sample size calculations were not performed for this purpose all available options of radiotherapy were allowed, even partial breast radiotherapy unintentional late registration of the SOUND trial in ClinicalTrials.gov, but no data were examined and no interval analysis was conducted before the trial was registered **Additional concerns about quality**:

Source: Gentilini, OD, Botteri, E, Sangalli, C, Galimberti, V, Porpiglia, M, Agresti, R, et.al. *Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial.*. JAMA Oncol, 2023. **9 (11)**(11): p. 1557-1564., https://pubmed.ncbi.nlm.nih.gov/37733364/					
	involvement of axillary nodes at clinical evaluation, and a plan to undergo a breast-conserving surgery and radiotherapy. **Exclusion**: preoperative presence of multiple doubtful or suspicious lymph nodes, extensive multifocality or multicentricity, bilateral BC, diagnosis of Synchronous distant metastases, previous cancer, ongoing pregnancy or lactation, and obstacles to obtaining informed consent or undergoing regular follow-up			no axillary surgery group: 93.9% (log-rank *P* = .30) **Overall survival (OS)** 5-year SLNB: 98.2% no axillary surgery group: 98.4% (log-rank *P* = .72)	No concealment method reported **Sources of funding:** Obtained funding: n.a.
Abbreviations:					

Source: Gentilini, OD, Botteri, E, Sangalli, C, Galimberti, V, Porpiglia, M, Agresti, R, et.al. *Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial.*. JAMA Oncol, 2023. **9 (11)**(11): p. 1557-1564., https://pubmed.ncbi.nlm.nih.gov/37733364/

SLNB = Sentinel Lymph Node Biopsy

BC = Breast Cancer

IQR = Interquartile Range

DDFS = Distant Disease-Free Survival

OS = Overall survival

HR = Hazard Ratio

95% CI = 95% Confidence Interval

RCT = Randomised Controlled Trial

Verknüpfte Empfehlungen:

Empfehlung 4.57:

Bei postmenopausalen Patientinnen ≥ 50 Jahre mit cT1 cN0 HR+ HER2- G1-2-Tumoren, die eine brusterhaltende Operation mit anschließender perkutaner Ganzbrustbestrahlung und adäquater Systemtherapie erhalten, kann auf das operative axilläre Staging verzichtet werden.

Literaturreferenzen: [99], [100], [101]

Source Reimer T, Stachs A, Veselinovic K, Kühn T, Heil J, Polata S, Marmé F, Müller T, Hildebrandt G, Krug D, Ataseven B, Reitsamer R, Ruth S, Denkert C, Bekes I, Zahm DM, Thill M, Golatta M, Holtschmidt J, Knauer M, Nekljudova V, Loibl S, Gerber B. Axillary Surgery in Breast Cancer - Primary Results of the INSEMA Trial. N Engl J Med. 2024 Dec 12. doi: 10.1056/NEJMoa2412063. Epub ahead of print. PMID: 39665649.

Aim and Country	Design and participants	Intervention	Outcomes	Results	Quality and comment
To show that complete omission of axillary surgery in earlystage breast cancer treated with breast-conserving surgery is noninferior to sentinel-lymph-node biopsy with respect to invasive disease–free survival Acronym: INSEMA-trial **Country:** Germany and Austria	**Design**: prospective, multicenter, randomized, noninferiority trial [noninferiority was tested on the basis of the confidence interval of the hazard ratio from the Cox proportional- hazards model to exclude a hazard ratio of 1.271 or above for invasive disease or death] **Setting:** 142	**Intervention** omission of axillary surgery **Control** sentinel-lymph-node biopsy	**Primary Outcome**: Invasive disease-free survival (period between randomization and the first primary-outcome event (recurrence of local, axillary, or distant invasive disease; death from any cause; occurrence of contralateral invasive breast cancer; or occurrence of second primary invasive	**Primary Outcome**: Per-protocol analysis: **primary analysis of invasive disease–free survival** omission of axillary surgery was noninferior to sentinel-lymph-node biopsy HR 0.91; 95% CI 0.73 to 1.14 **5-year invasive disease–free survival rate**	Quality of study assessed with SIGN checklist for RCT: high quality (++) **Limitations provided by authors:** significance of reported results restricted to a low-risk population (patients≥50 yrs with G1 or G2 tumors) with HR-pos, HER2-neg invasive BC and a tumor size up to 3cm; only 20% of patients hat pT2 lesions; median pre-operative tumor size

Source Reimer T, Stachs A, Veselinovic K, Kühn T, Heil J, Polata S, Marmé F, Müller T, Hildebrandt G, Krug D, Ataseven B, Reitsamer R, Ruth S, Denkert C, Bekes I, Zahm DM, Thill M, Golatta M, Holtschmidt J, Knauer M, Nekljudova V, Loibl S, Gerber B. Axillary Surgery in Breast Cancer - Primary Results of the INSEMA Trial. N Engl J Med. 2024 Dec 12. doi: 10.1056/NEJMoa2412063. Epub ahead of print. PMID: 39665649.					
	sites in Germany, 9 sites in Austria **Enrollment**: 09/2015 – 04/2019 **Median follow-up:** 73.6 months (IQR: 61.3 to 86.4) **Number of included patients**: Intention-to-treat: 5,154 Per-protocol: 4,858 **Age (no. (%))**: No Sentinel-Lymph-Node Biopsy <35 yr = 4 (0.4) 35 to <50 yr = 110 (11.4) 50 to <60 yr = 295 (30.7) 60 to <70 yr = 355 (36.9) ≥70 yr = 198 (20.6) Sentinel-Lymph-Node		cancer of a type other than breast cancer)) **Secondary Outcome**: overall survival locoregional disease-free survival ipsilateral axillary recurrence distant disease-free survival quality-of-life measures dose distribution in ipsilateral axilla levels I through III during radiotherapy	surgery-omission group: 91.9%; 95% CI 89.9 to 93.5 surgery group: 91.7%; 95% CI 90.8 to 92.6 **Subgroup Analyses** **5-year invasive disease-free survival: 1) with respect to tumor size** patients with T1 cancer HR 0.95; 95% CI, 0.75 to 1.20 patients with T2 cancer HR 0.71; 95% CI, 0.39 to 1.32 **2) Age dichotomized at 50 years:** <50 years	(11mm) is far below the eligible tumor size; low percentage of G3 tumors (3.6%) **Level of evidence:** Oxford 2011: 2 **Sources of funding**: German Cancer Aid; INSEMA ClinicalTrials.gov number, NCT02466737

Source Reimer T, Stachs A, Veselinovic K, Kühn T, Heil J, Polata S, Marmé F, Müller T, Hildebrandt G, Krug D, Ataseven B, Reitsamer R, Ruth S, Denkert C, Bekes I, Zahm DM, Thill M, Golatta M, Holtschmidt J, Knauer M, Nekljudova V, Loibl S, Gerber B. Axillary Surgery in Breast Cancer - Primary Results of the INSEMA Trial. N Engl J Med. 2024 Dec 12. doi: 10.1056/NEJMoa2412063. Epub ahead of print. PMID: 39665649.

	Biopsy <35 yr = 6 (0.2) 35 to <50 yr = 407 (10.4) 50 to <60 yr = 1278 (32.8) 60 to <70 yr = 1454 (37.3) ≥70 yr = 751 (19.3) **Inclusion criteria**: Women with breast cancer who planned to undergo upfront breast-conserving surgery at least 18 years had a clinical tumor stage of T1 or T2 (tumor size, =5 cm) and node-negative status according to clinical assessment (cN0) and imaging			HR 0.99, 95% CI, 0.54-1.82 ≥50 years HR 0.90, 95% CI, 0.71-1.14 **Secondary Outcome**: **estimated 5-year overall survival rate** surgery-omission group 98.2%; 95% CI, 97.1 to 98.9 surgery group 96.9%; 95% CI 96.3 to 97.5 **long-term safety analysis** patients in the surgery-omission group as compared with those in the surgery group had reduced incidence of lymphedema (1.8% vs. 5.7%	

Source Reimer T, Stachs A, Veselinovic K, Kühn T, Heil J, Polata S, Marmé F, Müller T, Hildebrandt G, Krug D, Ataseven B, Reitsamer R, Ruth S, Denkert C, Bekes I, Zahm DM, Thill M, Golatta M, Holtschmidt J, Knauer M, Nekljudova V, Loibl S, Gerber B. Axillary Surgery in Breast Cancer - Primary Results of the INSEMA Trial. N Engl J Med. 2024 Dec 12. doi: 10.1056/NEJMoa2412063. Epub ahead of print. PMID: 39665649.

	(iN0) **Exclusion**: n.a.			restriction of arm or shoulder mobility (2.0% vs. 3.5%) pain with arm or shoulder movement (2.0% vs. 4.2%)	

Abbreviations:

RCT = Randomised Controlled Trial

HR = Hazard Ratio

95% CI = 95% Confidence Interval

BC = Breast Cancer

yr = Years

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.119:

Wenn bei Patientinnen mit befallenen axillären Wächterlymphknoten (> 2 mm) keine axilläre Dissektion erfolgt ist, sollte das klinische Zielvolumen der adjuvanten Strahlentherapie neben der Brust bzw. Thoraxwand die axillären Level I-IV mit erfassen.

Empfehlung 4.120:

Sind nur 1-2 axilläre Wächterlymphknoten befallen (> 2 mm) und besteht ansonsten keine Indikation zur Lymphabflussbestrahlung, kann in dieser Situation ein Verzicht auf die Bestrahlung von Level III-IV und des kranialen Anteils von Level I-II (obere Feldgrenze des PTV bis 5 mm unterhalb der V. axillaris) erwogen werden.

Empfehlung 4.60:

Bei Patientinnen mit pT1-pT3/cN0-Tumoren, die eine brusterhaltende Operation mit anschließender perkutaner Ganzbrustbestrahlung erhalten und einen oder zwei positive Sentinel-Lymphknoten aufweisen, sollte auf eine Axilladissektion verzichtet werden.

Empfehlung 4.61:

Bei Patientinnen mit pT1-pT3/cN0-Tumoren, die eine Mastektomie mit anschließender Bestrahlung erhalten und einen oder zwei positive Sentinel-Lymphknoten aufweisen, sollte auf eine Axilladissektion verzichtet werden.

Literaturreferenzen: [102], [103], [104]

Source: Tinterri C, Gentile D, Gatzemeier W, Sagona A, Barbieri E, Testori A, Errico V, Bottini A, Marrazzo E, Dani C, Dozin B, Boni L, Bruzzi P, Fernandes B, Franceschini D, Spoto R, Torrisi R, Scorsetti M, Santoro A, Canavese G; SINODAR-ONE Collaborative Group. Preservation of Axillary Lymph Nodes Compared with Complete Dissection in T1-2 Breast Cancer Patients Presenting One or Two Metastatic Sentinel Lymph Nodes: The SINODAR-ONE Multicenter Randomized Clinical Trial. Ann Surg Oncol. 2022 Sep;29(9): 5732-5744. doi: 10.1245/s10434-022-11866-w. Epub 2022 May 12. PMID: 35552930.

Aim and Country	Design and participants	Intervention	Outcomes	Results	Quality and comment

Source: Tinterri C, Gentile D, Gatzemeier W, Sagona A, Barbieri E, Testori A, Errico V, Bottini A, Marrazzo E, Dani C, Dozin B, Boni L, Bruzzi P, Fernandes B, Franceschini D, Spoto R, Torrisi R, Scorsetti M, Santoro A, Canavese G; SINODAR-ONE Collaborative Group. Preservation of Axillary Lymph Nodes Compared with Complete Dissection in T1-2 Breast Cancer Patients Presenting One or Two Metastatic Sentinel Lymph Nodes: The SINODAR-ONE Multicenter Randomized Clinical Trial. Ann Surg Oncol. 2022 Sep;29(9): 5732-5744. doi: 10.1245/s10434-022-11866-w. Epub 2022 May 12. PMID: 35552930.

Acronym of study: SINODAR-ONE **Aim**: assessing the role of axillary lymph node dissection (ALND) in patients undergoing either breast-conserving surgery or mastectomy for T1–2 breast cancer (BC) and presenting one or two macrometastatic sentinel lymph **Country**: Italy	**Design**: prospective noninferiority multicenter randomized study **Enrollment:** April 2015 until April 2020 from 52 Italian centers (closed early because of poor accrual rates and fewer than anticipated events) **Number of included patients**: randomized: n=889 879 (ITT Population) Standard treatment: n=439; Experimental treatment: n=440 **Median follow-up:** 34.0 months (IQR 20.5–46.5 months) **Mean Age (SD):**	**Intervention** SNLB (no further surgical intervention on the axilla but only adjuvant therapy) **Control** ALND (removal of ≥ 10 axillary level I/II nonsentinel nodes followed by adjuvant therapy)	**Primary Outcome**: Overall survival (OS) **Secondary Outcome**: lymph node recurrence recurrence-free survival (RFS; defined as regional disease/metastases-free survival)	**Primary Outcome**: Overall Survival (OS) 5-year rates ALND: 98.9% SNLB: 98.8% p=0.936 **Secondary Outcome**: lymph node recurrence 1 axillary lymph node recurrence in each group recurrence-free survival (RFS; defined as regional disease/ metastases-free survival) 5-year RFS rates ALND: 96.3% SNLB: 95.6% p= 0.511	**Quality of study** assessed with SIGN checklist for RCT: acceptable (+) **Limitations by authors** did not reach the pre specified sample size of 2000 participants or 535 events relatively short follow-up generalization of the long-term oncological results remains questionable (only 217 of 879 patients [24.8%] underwent mastectomy) **Additional concerns about quality**: **Level of Evidence:**

Source: Tinterri C, Gentile D, Gatzemeier W, Sagona A, Barbieri E, Testori A, Errico V, Bottini A, Marrazzo E, Dani C, Dozin B, Boni L, Bruzzi P, Fernandes B, Franceschini D, Spoto R, Torrisi R, Scorsetti M, Santoro A, Canavese G; SINODAR-ONE Collaborative Group. Preservation of Axillary Lymph Nodes Compared with Complete Dissection in T1-2 Breast Cancer Patients Presenting One or Two Metastatic Sentinel Lymph Nodes: The SINODAR-ONE Multicenter Randomized Clinical Trial. Ann Surg Oncol. 2022 Sep;29(9): 5732-5744. doi: 10.1245/s10434-022-11866-w. Epub 2022 May 12. PMID: 35552930.

	ALND: 56.1 (9.3) SNLB: 56.2 (9.6) **Inclusion criteria**: Age ≥ 40 and ≤ 75 years Invasive BC (cytology/core biopsy assessment) Unilateral lesion Tumor size B 5 cm (cT1–2) (ultrasound/mammography assessment) Clinically negative axillary nodes (N0) (ultrasound assessment) No more than two SLNs proven metastatic (histological assessment) Involved SLNs with macrometastasis (≥ 2 mm)				Oxford 2011 Level 3 (downgrade due to unreached sample size) **Sources of funding:** Fondazione Humanitas per la Ricerca – Rozzano (MI)

Source: Tinterri C, Gentile D, Gatzemeier W, Sagona A, Barbieri E, Testori A, Errico V, Bottini A, Marrazzo E, Dani C, Dozin B, Boni L, Bruzzi P, Fernandes B, Franceschini D, Spoto R, Torrisi R, Scorsetti M, Santoro A, Canavese G; SINODAR-ONE Collaborative Group. Preservation of Axillary Lymph Nodes Compared with Complete Dissection in T1-2 Breast Cancer Patients Presenting One or Two Metastatic Sentinel Lymph Nodes: The SINODAR-ONE Multicenter Randomized Clinical Trial. Ann Surg Oncol. 2022 Sep;29(9): 5732-5744. doi: 10.1245/s10434-022-11866-w. Epub 2022 May 12. PMID: 35552930.

	No distant metastasis (M0) No neoadjuvant therapy No previous invasive BC Signed and dated written informed consent **Exclusion**: Ongoing pregnancy or breast-feeding Inflammatory BC In situ BC Synchronous contralateral BC Comorbidity possibly preventing adjuvant therapy Disease, comorbidity, or psychological conditions preventing compliance to regular follow-up				

Source: Tinterri C, Gentile D, Gatzemeier W, Sagona A, Barbieri E, Testori A, Errico V, Bottini A, Marrazzo E, Dani C, Dozin B, Boni L, Bruzzi P, Fernandes B, Franceschini D, Spoto R, Torrisi R, Scorsetti M, Santoro A, Canavese G; SINODAR-ONE Collaborative Group. Preservation of Axillary Lymph Nodes Compared with Complete Dissection in T1-2 Breast Cancer Patients Presenting One or Two Metastatic Sentinel Lymph Nodes: The SINODAR-ONE Multicenter Randomized Clinical Trial. Ann Surg Oncol. 2022 Sep;29(9): 5732-5744. doi: 10.1245/s10434-022-11866-w. Epub 2022 May 12. PMID: 35552930.

	Previous neoplasm within the 3 years preceding randomization (with the exception of in situ carcinoma of the cervix, basalioma, and spinocellular carcinoma of the skin)				

Abbreviations:

ALND = Axillary Lymph Node Dissection

SLNB = Sentinel Lymph Node Biopsy

SLN = Sentinel Lymph Node

OS = Overall Survival

RFS = Recurrence-Free Survival

BC = Breast Cancer

IQR = Interquartile Range

ITT = Intention to Treat

Verknüpfte Empfehlungen:

Empfehlung 4.119:

Wenn bei Patientinnen mit befallenen axillären Wächterlymphknoten (> 2 mm) keine axilläre Dissektion erfolgt ist, sollte das klinische Zielvolumen der adjuvanten Strahlentherapie neben der Brust bzw. Thoraxwand die axillären Level I-IV mit erfassen.

Empfehlung 4.120:

Sind nur 1-2 axilläre Wächterlymphknoten befallen (> 2 mm) und besteht ansonsten keine Indikation zur Lymphabflussbestrahlung, kann in dieser Situation ein Verzicht auf die Bestrahlung von Level III-IV und des kranialen Anteils von Level I-II (obere Feldgrenze des PTV bis 5 mm unterhalb der V. axillaris) erwogen werden.

Empfehlung 4.60:

Bei Patientinnen mit pT1-pT3/cN0-Tumoren, die eine brusterhaltende Operation mit anschließender perkutaner Ganzbrustbestrahlung erhalten und einen oder zwei positive Sentinel-Lymphknoten aufweisen, sollte auf eine Axilladissektion verzichtet werden.

Empfehlung 4.61:

Bei Patientinnen mit pT1-pT3/cN0-Tumoren, die eine Mastektomie mit anschließender Bestrahlung erhalten und einen oder zwei positive Sentinel-Lymphknoten aufweisen, sollte auf eine Axilladissektion verzichtet werden.

Literaturreferenzen: [102], [103], [104]

Source: de Boniface J, Filtenborg Tvedskov T, Rydén L et al. Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases N Engl J Med. 2024 Apr 4;390(13): 1163-1175.

Aim and Country	Design and participants	Intervention	Outcomes	Results	Quality and comment
Acronym of study:	**Design**: RCT	**Intervention**	**Primary Outcome**:	**Primary Outcome**:	**Quality of study** assessed with SIGN

Source: de Boniface J, Filtenborg Tvedskov T, Rydén L et al. Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases N Engl J Med. 2024 Apr 4;390(13): 1163-1175.					
SENOMAC **Aim**: Validation of results from previous trials in a sufficiently large cohort focused only on patients with sentinel-node macrometastases and to extend eligibility criteria to include important underrepresented subgroups — namely, patients undergoing mastectomy, those with sentinel-node extracapsular extension or T3 tumors (tumor size, >50 mm in the largest dimension), and men **Country:** Sweden, Denmark, Germany, Greece, Italy	**Enrollment**: 67 hospitals: 31.01.2015 until 31.12.2021 **Number of included patients**: 2,766 **Mean Age (range):** Sentinel-Node Biopsy Only: 61 (20-94) Completion Axillary-Lymph-Node Dissection: 61 (34-90) Median follow-up (range): 46.8 months (1.5 to 94.5) **Inclusion criteria**: Female and male adult who had cN0 breast cancer with a tumor stage of T1, T2, or T3 (tumor size, T1, ≤20 mm; T2, 21 to 50 mm; and T3, >50 mm in the largest dimension) and	Sentinel-Node Biopsy only **Control** Completion Axillary-Lymph-Node Dissection	Overall survival **Secondary Outcome**: Recurrence-free survival Breast cancer specific survival Patient reported outcomes	Overall survival <u>5-year overall survival</u> sentinel-node biopsy–only: 92.9%; 95% CI 91.0 to 94.9 in the dissection group: 92.0%; 95% CI, 89.9 to 94.1 **Secondary Outcome**: Recurrence-free survival <u>5-year recurrence-free survival</u> sentinel-node biopsy–only group: 89.7%; 95% CI, 87.5 to 91.9 dissection group 88.7%; 95% CI, 86.3 to 91.1 Stratification factor of country: Hazard Ratio for recurrence or death sentinel-node biopsy–only group vs the dissection group was	checklist for RCT: acceptable (+) **Limitations by authors** The use of radiation therapy followed national guidelines, which is the standard care in Sweden and Denmark because of that the results are comparable with those of the AMAROS and OTOASOR trials rather than with those of the POSNOC, SINODAR-ONE, and ACOSOG Z0011 trials only 10 male patients could be enrolled over a 7-year period — that prevented subgroup analysis according to sex

Source: de Boniface J, Filtenborg Tvedskov T, Rydén L et al. Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases N Engl J Med. 2024 Apr 4;390(13): 1163-1175.					
	one or two sentinel-node macrometastases (metastasis size, >2 mm in the largest dimension) **Exclusion**: Extra-axillary regional or distant metastases history of invasive breast cancer breast cancer in both breasts if one of the breasts met exclusion criteria medical contraindications against radiation therapy or systemic treatment inability to understand the trial information			HR 0.89; 95% CI, 0.66 to 1.19; P<0.001 Result intention-to-treat population HR 0.89; 95% CI, 0.67 to 1.19 Breast cancer specific survival <u>5-year breast cancer–specific survival</u> sentinel-node biopsy–only group: 97.1%; 95% CI, 95.8 to 98.3 dissection group: 96.6%; 95% CI, 95.3 to 97.9 Patient reported outcomes n.a.	most of the patients had breast cancer of the luminal subtype, and also given the predilection of this subtype to recur late, the current follow-up is relatively short statistical power relies on the occurrence of events rather than on the target sample size, and given the high number of events, the narrow confidence intervals, and the large distance between the noninferiority margin and the observed upper boundary of the confidence interval, the presented results reflect a high precision of estimates

Source: de Boniface J, Filtenborg Tvedskov T, Rydén L et al. Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases N Engl J Med. 2024 Apr 4;390(13): 1163-1175.					
					the incidence of withdrawal was clearly higher in the dissection group than the sentinel-node biopsy–only group, a situation that reflects patients' awareness and desire to avoid completion axillary-lymph-node dissection **Additional concerns about quality**: Change of primary end point from cancer specific survival to overall survival in 2020 (on the basis of a recommendation from the independent data and safety monitoring board) **Level of Evidence:** Oxford 2011 Level 2 **Sources of funding:** The Swedish Research Council and others;

Source: de Boniface J, Filtenborg Tvedskov T, Rydén L et al. Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases N Engl J Med. 2024 Apr 4;390(13): 1163-1175.					
					SENOMAC ClinicalTrials.gov number, NCT02240472

Abbreviations:

RCT = Randomised Controlled Trial

95% CI = 95% Confidence Interval

HR = Hazard Ratio

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.62:

Bei Patientinnen, die eine primär systemische Therapie (PST) erhalten, und prätherapeutisch einen palpatorisch und sonographisch negativen Lymphknotenstatus (cN0) aufweisen, soll die SLNE nach der PST durchgeführt werden.

Literaturreferenzen: [105], [106]

Source Zarifmahmoudi L, Aghaee A, Treglia G, Sadeghi R. Sentinel lymph node mapping in breast cancer patients following neoadjuvant chemotherapy: systematic review and meta-analysis about head to head comparison of cN0 and cN + patients. Breast Cancer. 2022 Jan;29(1): 50-64. doi: 10.1007/s12282-021-01280-7. Epub 2021 Aug 2. PMID: 34341902.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
to compare the accuracy (in terms of detection rate and false negative rate) of sentinel lymph node (SLN) mapping and biopsy in lymph nodal staging of breast cancer (BCa) patients after NAC in patients with clinical node-negative status (cNO) and clinical node-positive status (cN+) status before neoadjuvant chemotherapy (NAC)	**Design**: Systematic review and meta-analysis **Search date**: until 2020 **Searched databases:** PubMed and Scopus **Included study designs**: Diagnostic studies **Number of included studies**: 27 (all of them: data for SLN detection rate evaluation and 17 for false negative assessment)	**Intervention** SLN mapping and biopsy following NAC **Control** Comparison between patients with initial cNO and patients with initial cN+	**Primary Outcome**: Pooled detection and false negative rates of SLN mapping and biopsy after NAC for CNO and cN+ BCa patients **Secondary Outcome**: Odds ratio and risk difference of SLN detection failure and false negative results in N+ patients compared to NO patients	The pooled detection rate of SLN mapping was 95% in the cNO group and 89% in the cN+ group. The odds ratio (OR) of detection failure in the cN+ group compared to the cN0 group was 2.22 (95% CI: 1.4-3.4, $p < 0.001$), and the risk difference (RD) was 4% (95% CI: 2-6%, $p < 0.001$). Significant heterogeneity was observed (Cochrane $Q = 51$, $p < 0.001$; $I^2 =$	**ROBIS:** unclear **Additional concerns about quality**: evidence of potential publication bias; study quality assessed but not its effect on the meta-analysis **Quality of included studies**: Evaluated with Newcastle-Ottawa Scale:

Source Zarifmahmoudi L, Aghaee A, Treglia G, Sadeghi R. Sentinel lymph node mapping in breast cancer patients following neoadjuvant chemotherapy: systematic review and meta-analysis about head to head comparison of cN0 and cN + patients. Breast Cancer. 2022 Jan;29(1): 50-64. doi: 10.1007/s12282-021-01280-7. Epub 2021 Aug 2. PMID: 34341902.					
	Study characteristics 18 studies used a dual tracer (radiocolloid and dye), 6 used radiotracer alone, and 3 used dye alone **Number of included patients**: 2623 BCa patients who were NO before NAC and 2114 BCa patients who were N+ before NAC (for detection rate) **Median age (range)**: n.r. **Inclusion criteria**: For detection rate: (1) compared BCa patients with initial cNO and cN+ status; (2) included patients who underwent SLN mapping and biopsy after NAC; and			49% for OR; Cochrane Q = 106, $p < 0.001$; $I^2 = 75\%$ for RD). Funnel plots suggested potential asymmetry, and Egger's test was significant for RD (p = 0.00) but not for OR (p = 0.2). The trim-and-fill method adjusted the pooled RD to 0.3% (95% CI: -2% to 2%), indicating a potential impact of publication bias on this measure. **Subgroup Analyses:** Subgroup analyses by tracer type and injection depth did not reveal significant differences in detection rates between the cN0 and cN+ groups Studies using radiotracer alone showed a higher OR (2.9, 95% CI: 1.8-4.7)	Representativeness of the study groups: not available in 16 studies **Level of evidence:** Oxford 2011: 2 **Sources of funding**: no funding

Source Zarifmahmoudi L, Aghaee A, Treglia G, Sadeghi R. Sentinel lymph node mapping in breast cancer patients following neoadjuvant chemotherapy: systematic review and meta-analysis about head to head comparison of cN0 and cN + patients. Breast Cancer. 2022 Jan;29(1): 50-64. doi: 10.1007/s12282-021-01280-7. Epub 2021 Aug 2. PMID: 34341902.

	(3) reported the total number of patients and number of detected SLN for each group. For false negative rate: Studies on SLN mapping and biopsy in BCa patients with (1) a history of NAC with initial cNO and CN+ status; (2) standard axillary lymph node dissection was performed for all patients; and (3) the number of cases with false negative SLN and positive axillary lymph nodes with at least one SLN detected was reported in each group. **Exclusion**: n.r.			and RD (7%) of detection failure compared to those using dual tracers (OR: 2.0, 95% CI: 1.0-3.9; RD: 5%). There was no significant difference in detection failure between superficial, deep, or combined injection methods. The pooled false negative rate of SLN mapping was 18% in BCa patients who were N+ before NAC and 12% in BCa patients who were NO before NAC. The OR of false negative results in the cN+ group compared to the cN0 group was 1.6 (95% CI: 1.0-2.6, p = 0.01), and the RD was 8% (95% CI: 1-14%, p = 0.02).	

Source Zarifmahmoudi L, Aghaee A, Treglia G, Sadeghi R. Sentinel lymph node mapping in breast cancer patients following neoadjuvant chemotherapy: systematic review and meta-analysis about head to head comparison of cN0 and cN + patients. Breast Cancer. 2022 Jan;29(1): 50-64. doi: 10.1007/s12282-021-01280-7. Epub 2021 Aug 2. PMID: 34341902.

				Heterogeneity was low for OR (Cochrane Q = 14, p = 0.5, I^2 = 0%) but moderate for RD (Cochrane Q = 25, p = 0.05, I^2 = 40%).	

Abbreviations and comment:

BCa: breast cancer

cN0: clinical node-negative status

cN+: clinical node-positive status

NAC: neoadjuvant chemotherapy

SLN: Sentinel lymph node

n.r.

Kapitel 4.4: Adjuvante Strahlentherapie des Mammakarzinoms

Verknüpfte Empfehlungen:

Empfehlung 4.95:

Die Radiotherapie der Brust soll in moderater Hypofraktionierung (Gesamtdosis ca. 40 Gy in ca. 15-16 Fraktionen in ca. 3 Wochen) erfolgen.

Empfehlung 4.96:

Eine ultra-hypofraktionierte Radiotherapie mit 26 Gy in 5 Fraktionen über eine Woche kann nach Aufklärung über die fehlenden Langzeitdaten und das möglicherweise erhöhte Spättoxizitätsrisiko zum Einsatz kommen.

Literaturreferenzen: [107], [108], [109], [110], [111], [112], [113], [114], [115], [116], [117], [118]

Source: GN, Marta, Riera R, Pacheco RL, Cabrera Martimbianco AL, Meattini I, Kaidar-Person O, and Poortmans P. "Moderately Hypofractionated Post-Operative Radiation Therapy for Breast Cancer: Systematic Review and Meta-Analysis of Randomized Clinical Trials." [In eng]. Breast (Edinburgh, Scotland) 62 (2022-4 2022): 84-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35131647/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: investigate the effectiveness and safety of moderately hypofractionated compared with conventional irradiation in the post-operative treatment of patients with breast cancer	**Design**: Systematic review and meta-analysis **Search date**: until 03/2021 **Searched databases**: CENTRAL, EMBASE, LILACS, MEDLINE **Included study designs**:	**Intervention** Use of moderately hypofractionated irradiation: fraction sizes up to 3 Gy, a reduced total dose given in 13–16 fractions, dose range 2.65 Gy–3.3	**Primary Outcome**: Local recurrence **Secondary Outcome**: 1) Loco-regional recurrence 2) Disease free survival 3) Overall survival	**Primary Outcome**: Local recurrence: HR 1.07, 95% CI 0.80 to 1.43; I^2=40.48%; p=0.65 **Secondary Outcome**: 1) Loco-regional recurrence	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 2 critical flaws (items 7, 15) **Overall quality of evidence**: critically low

Source: GN, Marta, Riera R, Pacheco RL, Cabrera Martimbianco AL, Meattini I, Kaidar-Person O, and Poortmans P. "Moderately Hypofractionated Post-Operative Radiation Therapy for Breast Cancer: Systematic Review and Meta-Analysis of Randomized Clinical Trials." [In eng]. Breast (Edinburgh, Scotland) 62 (2022-4 2022): 84-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35131647/.					
	RCTs with parallel design **Number of included studies**: n=8 **Number of included patients**: 12,139 BC patients N=10,809 (89.1%) underwent BCS N=3,491 (28.7%) received chemotherapy N=5,035 (41.4%) boost irradiation N=1,617 (13.3%) reginal nodal irradiation **Mean/median age**: n.a. **Inclusion criteria**: RCTs with parallel design, Patients with non-metastatic breast cancer that received post-operative RT, use of moderately hypofractionated	Gy over a course of 3 weeks **Control** Conventional radiation doses involving doses ranging from 45 to 50.4 Gy, fraction sizes up to 1.8 Gy–2.0 Gy, given in 25–28 fractions over a course of 5–6 weeks. Additional boost dose to the tumour bed was permitted in the intervention and comparator groups.	4) Acute and late radiation therapy related side effects 5) Cosmesis	HR 0.97, 95% CI 0.79 to 1.20, I^2=0.00, p=0.79 <u>2) Disease-free survival</u> HR 0.96, 95%CI 0.76 to 1.16, I^2=0.00, p = 0.67 <u>3) Overall survival</u> HR 0.95, 95% CI 0.83 to 1.09, I^2=14.79, p = 0.47) <u>4) Side effects</u> low rate of severe side effects; comparable in both treatment groups; Acute and late side effects are similar or tended to be lower after hypofractionation than after conventional fractionation <u>5) Cosmesis</u> slightly better in the moderately hypofractionated irradiation group in one	**Additional concerns about quality**: differences in the moderately hypofractionated irradiation schedules used across included studie **Quality of included studies**: All eight trials were classified as having a high risk of bias, primarily due to the lack of blinding of patients and/or outcome evaluators **Sources of funding:** No funding received

Source: GN, Marta, Riera R, Pacheco RL, Cabrera Martimbianco AL, Meattini I, Kaidar-Person O, and Poortmans P. "Moderately Hypofractionated Post-Operative Radiation Therapy for Breast Cancer: Systematic Review and Meta-Analysis of Randomized Clinical Trials." [In eng]. Breast (Edinburgh, Scotland) 62 (2022-4 2022): 84-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35131647/.

	irradiation, Comparison: Conventional radiation doses involving doses ranging from 45 to 50.4 Gy, fraction sizes up to 1.8 Gy–2.0 Gy, given in 25–28 fractions over a course of 5–6 weeks, additional boost dose to the tumour bed was permitted in the intervention and comparator groups. **Exclusion**: /			trial; no difference between cosmetic outcomes in other trials	

Abbreviations:

RT = Radiation Therapy

HR = Hazard Ratio

95% CI = 95% Confidence Interval

RCT = Randomised Controlled Trial

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.96:

Eine ultra-hypofraktionierte Radiotherapie mit 26 Gy in 5 Fraktionen über eine Woche kann nach Aufklärung über die fehlenden Langzeitdaten und das möglicherweise erhöhte Spättoxizitätsrisiko zum Einsatz kommen.

Literaturreferenzen: [107], [108], [109], [110], [111], [119], [120], [121], [122], [123], [124]

Source: F, Vicini, Broughman J, Halima A, Mayo Z, Obi E, Al-Hilli Z, Arthur D, Wazer D, and Shah C. "Delivery of Adjuvant Radiation in 5 Days or Less after Lumpectomy for Breast Cancer: A Systematic Review." [In eng]. International journal of radiation oncology, biology, physics 112, no. 5 (2022-4-1 2022): 1090-104. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34921906/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: evaluating outcomes when using ultrashort regimens (5 treatment days or less) to provide clinicians and patients with objective information regarding the status of each approach	**Design**: Systematic Review **Search date**: 2010-2021 **Searched databases**: MEDLINE **Included study designs**: randomized or prospective/registry studies, guidelines **Inclusion**: patients treated with BCT with the following	**1) Ultrashort WBI:** AWBI vs. WBI FAST-Forward trial: (1) 40 Gy in 15 daily fractions, (2) 27 Gy in 5 daily fractions, or (3) 26 Gy in 5 daily fractions 5.9y follow-up FAST trial: (1) 50 Gy/25 fractions (2) 30 Gy/5 fractions (once weekly)	Recurrence rates Toxicity	**1) Ultrashort WBI:** *Summary:* 2 RCTs supported the use of ultrashort course AWBI compared with hypofractionated WBI *Selected details* FAST-Forward Local recurrence at 5 years: 2.1% with the 40 Gy arm with a reduction	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 5 critical flaws (items 2, 4, 7, 9, 13) **Overall quality of evidence**: critically low **Additional concerns about quality**: No formal review protocol, not registered; tables don't present data of all included studies

Source: F, Vicini, Broughman J, Halima A, Mayo Z, Obi E, Al-Hilli Z, Arthur D, Wazer D, and Shah C. "Delivery of Adjuvant Radiation in 5 Days or Less after Lumpectomy for Breast Cancer: A Systematic Review." [In eng]. International journal of radiation oncology, biology, physics 112, no. 5 (2022-4-1 2022): 1090-104. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34921906/.					
	criteria: (1) randomized or prospective/registry studies; (2) radiation regimens of 5 treatment days or less; (3) RT delivered after surgery; (4) target was the whole breast or partial breast, regional nodal irradiation not required but could be included (eg, FASTForward) 7; (5) outcomes including toxicity, QOL, and/or local recurrence; and (6) initial diagnoses rather than recurrent breast cancers **Exclusion**: Studies evaluating APBI with permanent seed implants; neoadjuvant RT studies	(3) 28.5 Gy/5 fractions (once weekly) 9.9y follow-up **2) Ultrashort partial breast irradiation:** <u>APBI compared with WBI</u> Technique: External beam APBI RAPID trial: EBRT 3D-CRT WBI: 50 Gy/25 fractions or 42.5 Gy/16 fractions APBI: 38.5 Gy/10 fractions (bid) 8.6y follow-up NSABP B-39 WBI: 50 Gy/25 fractions +/- boost APBI: 38.5 Gy/10 fractions (bid, EBRT), 34		of 0.3% in the 27 Gy arm and a reduction of 0.7% in the 26 Gy arm compared with the 40 Gy arm <u>Moderate/marked normal tissue</u> effect: 40 Gy 9.9%, 27 Gy 15.4% (OR 1.55 vs 40 Gy, statistically significant), 26 Gy 11.9% (OR 1.12 vs 40 Gy, not-statistically significant) Photographic assessments worse with 27 Gy vs 40 Gy but not with 26 Gy **FAST** 9.9 Follow-up years <u>Local recurrence</u> 11 total	**Sources of funding:** No specific funding received.

Source: F, Vicini, Broughman J, Halima A, Mayo Z, Obi E, Al-Hilli Z, Arthur D, Wazer D, and Shah C. "Delivery of Adjuvant Radiation in 5 Days or Less after Lumpectomy for Breast Cancer: A Systematic Review." [In eng]. International journal of radiation oncology, biology, physics 112, no. 5 (2022-4-1 2022): 1090-104. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34921906/.					
	3 different literature searches **1) Ultrashort WBI:** Number of included studies: n=3 (2 RCTs, 1 Prospective Study) Number of included patients: RCTs: n=5,011 (FAST-Forward: n=4096 women; FAST: n=915 women; Prospective Study: n=158 patients Mean/median age: n.a. Inclusion criteria: women ≥18y, pT1-3pN0-1 Exclusion: **2) Ultrashort partial breast irradiation** Number of included studies: n=63 (n=7 RCTs,	Gy/10 fractions (brachytherapy) 10.2y follow-up <u>Brachytherapy APBI</u> Technique: Interstitial brachytherapy GEC-ESTRO WBI: 50-50.4 Gy APBI: 32 Gy/8 fractions (bid), 30.1 Gy/7 fractions (bid), 50 Gy PDR **3) IORT:** IORT compared with WBI ELIOT-trial 50 Gy/25 fractions + 10 Gy boost IORT 21 Gy with electrons TARGIT-A		50 Gy: 3 30 Gy: 4 28.5 Gy: 4 <u>Photographic breast appearance</u> change (vs 50 Gy): OR 1.65 (statistically significant) 30 Gy, 1.10 (not statistically significant) 28.5 Gy Moderate/marked normal tissue effect (vs 50 Gy): OR 2.12 (statistically significant) 30 Gy, 1.22 (not statistically significant) 28.5 Gy **2) Ultrashort partial breast irradiation** *Summary*:	

Source: F, Vicini, Broughman J, Halima A, Mayo Z, Obi E, Al-Hilli Z, Arthur D, Wazer D, and Shah C. "Delivery of Adjuvant Radiation in 5 Days or Less after Lumpectomy for Breast Cancer: A Systematic Review." [In eng]. International journal of radiation oncology, biology, physics 112, no. 5 (2022-4-1 2022): 1090-104. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34921906/.					
	n=55 prospective studies) & 1 guideline Number of included patients: 7 RCTs: n=8,528 **3) Intraoperative Radiotherapy (IORT)** Number of included studies: n=32 (2 RCTs, 26 prospective/registry studies) & 3 treatment guidelines Number of included patients: 2 RCTs: n=4,756 patients (ELIOT & TARGIT-A)	IORT (20 Gy at surface) vs WBI		Data supports short course APBI *Selected details:* RAPID Local recurrence 8 year: 2.8% WBI vs 3.0% APBI Toxicity Acute grade 2+: 45% WBI vs 28% APBI Late grade 2: 13% WBI vs 32% APBI Increased adverse cosmesis with APBI (increase of 17.7% at 7 y) NSABP B-39 Local recurrence 10 year: 3.9% WBI vs 4.6% APBI	

Source: F, Vicini, Broughman J, Halima A, Mayo Z, Obi E, Al-Hilli Z, Arthur D, Wazer D, and Shah C. "Delivery of Adjuvant Radiation in 5 Days or Less after Lumpectomy for Breast Cancer: A Systematic Review." [In eng]. International journal of radiation oncology, biology, physics 112, no. 5 (2022-4-1 2022): 1090-104. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34921906/.					
				<u>Toxicity</u> Grade 3 toxicity: 10% APBI vs 7% WBI GEC-ESTRO <u>Local recurrence</u> 0.9% WBI vs 1.4% APBI <u>Toxicity</u> Excellent/good cosmesis: 91% WBI vs 92% APBI, reduced breast pain with APBI (11.9% vs 8.4%), late grade 2-3 skin toxicity (10.7% vs 6.9%) **3) IORT** *Summary* 2 RCTs demonstrated elevated rates of recurrence with IORT compared with WBI *Selected details*	

Source: F, Vicini, Broughman J, Halima A, Mayo Z, Obi E, Al-Hilli Z, Arthur D, Wazer D, and Shah C. "Delivery of Adjuvant Radiation in 5 Days or Less after Lumpectomy for Breast Cancer: A Systematic Review." [In eng]. International journal of radiation oncology, biology, physics 112, no. 5 (2022-4-1 2022): 1090-104. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34921906/.

				ELIOT <u>Local recurrence</u> 10/15 year IBTR: 1.1%/2.4% WBI vs 8.1%/12.6% IORT <u>Toxicity</u> Reduced skin side effects (erythema, hyperpigmentation) with IORT No difference in fibrosis, retraction, pain. Increased fat necrosis with IORT TARGIT-A <u>Local recurrence</u> 5 y: 3.3% vs 1.3% 5 y (long-term not provided): 2.11% vs 0.95%	

Source: F, Vicini, Broughman J, Halima A, Mayo Z, Obi E, Al-Hilli Z, Arthur D, Wazer D, and Shah C. "Delivery of Adjuvant Radiation in 5 Days or Less after Lumpectomy for Breast Cancer: A Systematic Review." [In eng]. International journal of radiation oncology, biology, physics 112, no. 5 (2022-4-1 2022): 1090-104. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34921906/.

				5 y (long-term not provided): 3.96% vs 1.05% <u>Toxicity</u> No difference in wound complications No difference in major toxicities WBI increased grade 3-4 skin toxicities	

Abbreviations:

BCT = Breast Conserving Therapy

RT = Radiation Therapy

QoL = Quality of Life

APBI = Accelerated Partial Breast Irradiation

AWBI = Accelerated whole Breast Irradiation

WBI = Whol Breast Irradiation

IORT = Intraoperative RT

RCT = Randomized Controlled Trial

Source: F, Vicini, Broughman J, Halima A, Mayo Z, Obi E, Al-Hilli Z, Arthur D, Wazer D, and Shah C. "Delivery of Adjuvant Radiation in 5 Days or Less after Lumpectomy for Breast Cancer: A Systematic Review." [In eng]. International journal of radiation oncology, biology, physics 112, no. 5 (2022-4-1 2022): 1090-104. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34921906/.

OR = Odds Ratio

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.97:

Bei linksseitigem Tumorsitz sollte die Bestrahlung zur Herzschonung in tiefer Einatemtechnik "Deep Inspiration Breath Hold" (DIBHT) oder atemgetriggert "Gating" erfolgen.

Literaturreferenzen: [125], [126], [127], [128], [129], [130], [131], [132]

Source: Lai et al. 2020: Meta-analysis of deep inspiration breath hold (DIBH) versus free breathing (FB) in postoperative radiotherapy for left-side breast cancer https://pubmed.ncbi.nlm.nih.gov/31707586/

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Examine the difference in deep inspiration breath hold (DIBH) versus free breathing (FB) for patients receiving postoperative radiotherapy for left breast cancer	**Design**: Systematic Review and Meta-Analysis **Search date**: n.a. **Searched databases**: PubMed, Science Direct, The Cochrane Library, Web of Science; reference lists **Included study designs**: observational studies **Number of included studies**: 12	**Intervention** Deep inspiration breath hold (DIBH) - real-time position management (RPM) - active breathing coordinator (ABC) - a real-time surface tracking system (AlignRT) **Control** Free breathing (FB)	**Outcomes** Target coverage (Dmean and V95); Heart dose (Dmean, Dmax, V20, and V30); LADCA dose (Dmean, Dmax); Left lung dose	**Target coverage** (D mean and V95) No statistical significant difference Total: SMD = 0.03, 95% CI − 0.11 to 0.18, P = 0.64 Dmean SMD = 0.03, 95% CI − 0.23 to 0.29, P = 0.82, V95 SMD = 0.04, 95% CI − 0.14 to 0.21, P = 0.68 **Heart dose** DIBH group can lower heart dose more	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 5 critical flaws (items 2, 4, 7, 11, 13) **Overall quality of evidence**: critically low Additional concerns: search date not applicable; study designs of included studies not clearly described **Quality of included studies**:

Source: Lai et al. 2020: Meta-analysis of deep inspiration breath hold (DIBH) versus free breathing (FB) in postoperative radiotherapy for left-side breast cancer https://pubmed.ncbi.nlm.nih.gov/31707586/					
	Number of included patients: 1019 (576 DIBH group and 443 FB group) **Mean/median age**: n.a. **Inclusion criteria**: 1) studies that compared DIBH radiotherapy versus FB radiotherapy in patients with left breast cancer after breast-conserving surgery without metastasis 2) total number of cases greater than or equal to 40 3) at least 1 outcome indicator 4) English language articles **Exclusion**: patients with			efficiently compared to the FB group SMD = − 1.36, 95% CI − 1.64 to − 1.09, P < 0.01 Dmean SMD = − 1.23, 95% CI − 1.56 to − 0.90, P < 0.01, Dmax SMD = − 2.04, 95% CI − 2.70 to − 1.38, P < 0.01, V20 SMD = − 1.32, 95% CI − 1.94 to − 0.69, P < 0.01, V30 (SMD = − 0.70, 95% CI − 1.13 to − 0.27, P < 0.01 **LADCA dose** DIBH group can reduce LADCA dose more effectively compared to FB group SMD = − 1.45, 95% CI − 1.62 to − 1.27, P < 0.01	Most of the included studies had low risk of bias according to the Newcastle–Ottawa Scale[range 6-9] **Planned included studies**: observational studies and RCTs **Sources of funding:** grants from The First batch of Yiwu Science and Technology Project in 2019 [Grant Number: 19-3-03]

Source: Lai et al. 2020: Meta-analysis of deep inspiration breath hold (DIBH) versus free breathing (FB) in postoperative radiotherapy for left-side breast cancer https://pubmed.ncbi.nlm.nih.gov/31707586/

	comorbidities or additional treatments and non-human trials			Dmean SMD = − 1.48, 95% CI − 1.71 to − 1.25, P < 0.01 Dmax SMD = − 1.40, 95% CI − 1.68 to − 1.12, P < 0.01 **Left lung dose** DIBH group can have significantly lower left lung dose SMD = − 0.52, 95% CI − 0.81 to − 0.23, P < 0.01 Dmean SMD = − 0.54, 95% CI − 1.01 to − 0.07, P = 0.02, V5 SMD = − 0.40, 95% CI − 0.95 to 0.16, P = 0.16, V30 SMD = − 0.63, 95% CI − 1.20 to − 0.05, P = 0.03	

Abbreviations:

DIBH = Deep Inspiration Breath Hold

Source: Lai et al. 2020: Meta-analysis of deep inspiration breath hold (DIBH) versus free breathing (FB) in postoperative radiotherapy for left-side breast cancer https://pubmed.ncbi.nlm.nih.gov/31707586/

FB = Free Breathing

n.a. = not Available, not Applicable

RPM = Real-Time Position Management

ABC = Active Breathing Coordinator

AlignRT = a real-time surface tracking system

SMD = Standardized Mean Difference

95% CI = 95% Confidence Interval

RCT = Randomised Controlled Trial

Verknüpfte Empfehlungen:

Empfehlung 4.97:

Bei linksseitigem Tumorsitz sollte die Bestrahlung zur Herzschonung in tiefer Einatemtechnik "Deep Inspiration Breath Hold" (DIBHT) oder atemgetriggert "Gating" erfolgen.

Literaturreferenzen: [125], [126], [127], [128], [129], [130], [131], [132]

Source Piroth MD, Krug D, Sedlmayer F, Duma MN, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Hehr T, Souchon R, Strnad V, Sauer R; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Post-neoadjuvant treatment with capecitabine and trastuzumab emtansine in breast cancer patients-sequentially, or better simultaneously? StrahlentherOnkol. 2021 Jan;197(1): 1-7. doi: 10.1007/s00066-020-01667-z. Epub 2020 Jul 31. PMID: 32737515; PMCID: PMC7801351.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To review the evidence for sequencing postoperative radiation and chemotherapy, focusing on capecitabine and trastuzumab emtansine (T-DM1)-based regimens.	**Design**: Systematic review **Search date**: not explicitly stated; the included studies are published since 2015 **Searched databases**: **:** PubMed/MEDLINE/Web of Science **Included study designs**: prospective and retrospective	**Intervention** Postoperative systemic therapy (capecitabine, trastuzumab emtansine (T-DM1)) **Control** sequential use of radiotherapy or systemic therapy	not explicitly stated: oncological outcomes (Disease-free survival); Toxicity and tolerability	The influence of sequencing radiation therapy with maintenance capecitabine chemotherapy in the post-neoadjuvant setting is unclear. Synchronous administration of capecitabine is feasible, but reports on possible excess toxicities are partially conflicting.	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review critically low; 4 critical flaws (items 4,7,9,11) **Additional concerns about quality**: **Quality of included studies**:

Source Piroth MD, Krug D, Sedlmayer F, Duma MN, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Hehr T, Souchon R, Strnad V, Sauer R; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Post-neoadjuvant treatment with capecitabine and trastuzumab emtansine in breast cancer patients-sequentially, or better simultaneously? StrahlentherOnkol. 2021 Jan;197(1): 1-7. doi: 10.1007/s00066-020-01667-z. Epub 2020 Jul 31. PMID: 32737515; PMCID: PMC7801351.					
	Number of included studies: 6 **Number of included patients**: n.r. **Mean/median age**: n.r. **Inclusion criteria**: studies including post-neoadjuvant treatment **Exclusion**: n.r.			Dose reduction of capecitabine should be considered, especially if normofractionated radiotherapy is used. Hypofractionated schedules seem superior in terms of toxicity in concurrent settings. T-DM1 can safely be administered concurrently with radiotherapy.	heterogeneity in study designs and patient populations; **Level of evidence:** Oxford 2011: **Sources of funding**: Open Access funding provided by Projekt DEAL
Abbreviations and comment: n.r.: not reported T-DM1: trastuzumab emtansine shortcomings significantly undermine the reliability of the review's conclusions; authors appropriately discuss heterogeneity and report funding/conflicts of interest, the absence of key methodological rigor makes it difficult to have confidence in the findings					

Verknüpfte Empfehlungen:

Empfehlung 4.98:

Eine lokale Dosisaufsättigung (Boost-Bestrahlung) des Tumorbettes senkt die lokale Rezidivrate in der Brust, ohne dadurch einen signifikanten Überlebensvorteil zu bewirken.

Die Boostbestrahlung

- soll daher bei allen ≤ 50 Jahre alten Patientinnen und
- sollte bei > 50 Jahre alten Patientinnen nur bei erhöhtem lokalen Rückfallrisiko erfolgen (G3, HER2-positiv, tripelnegativ, > T1).

Empfehlung 4.99:

Die Boostbestrahlung sollte als perkutaner Boost (sequentiell oder simultan-integriert) verabreicht werden.

Empfehlung 4.101:

Die Boost-Bestrahlung kann in individuellen Fällen (z.B. tiefliegendes Tumorbett) als interstitielle Brachytherapie verabreicht werden.

Empfehlung 4.108:

Bei geplanter Teilbrustbestrahlung sollte eine intraoperative Clipmarkierung des Tumorbetts erfolgen.

Literaturreferenzen: [133], [134], [135], [136], [137]

Source: I, Kindts, Laenen A, Depuydt T, and Weltens C. "Tumour Bed Boost Radiotherapy for Women after Breast-Conserving Surgery." [In eng]. The Cochrane database of systematic reviews 11, no. 11 (2017-11-6 2017): CD011987. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29105051/.					
Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment

Source: I, Kindts, Laenen A, Depuydt T, and Weltens C. "Tumour Bed Boost Radiotherapy for Women after Breast-Conserving Surgery." [In eng]. The Cochrane database of systematic reviews 11, no. 11 (2017-11-6 2017): CD011987. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29105051/.

Aim: To assess the effects of tumour bed boost radiotherapy after breast-conserving surgery and whole-breast irradiation for the treatment of breast cancer	**Design:** Systematic review and Meta-Analyses **Search date:** 01/1980-03/2017 (Embase) 01/1966-03/2017 (all other Databases) **Searched databases**: Cochrane Breast Cancer Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, the World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov **Included study designs:** RCTs **Number of included studies:** n=5	women who had received an additional boost to the tumour bed compared with women who had not received a boost to the tumour bed. The boost could be delivered with external beam radiation (electrons or photons) or with interstitial brachytherapy. **Experimental arm** Whole-breast irradiation: · 50 Gy in 25 fractions in 5 weeks (Budapest;EORTC;Nice) · 50 Gy in 20 fractions in 5 weeks (Lyon) · 45 Gy in 25 fractions in 5 weeks (SGW) plus boost irradiation:	**Primary Outcome:** 1. Local control, defined as the time from randomization until the development of any local recurrence during follow-up time-to event outcome; local recurrence= recurrence in the ipsilateral breast (i.e. the breast in which cancer had been diagnosed), the skin and parenchyma; 2. Acute toxicity related to radiotherapy, i.e. any toxic event occurring in the breast, skin, lung, and heart within six months of completion of radiotherapy; acute toxicity to be classified according to	**Primary Outcome:** 1. Local control: 737 local recurrences in 8,315 women Administration of tumour bed boost vs. no tumour bed boost: HR 0.64, 95% CI 0.55 to 0.75; I^2=60%; p<0.00001 (5 studies, 8.315 women) <u>Sensitivity analysis:</u> HR 0.62, 95% CI 0.52 to 0.73; I^2=24%;p<0.0001 (3 studies, 6963 women) <u>Subgroup analysis</u> <u>Women >40 years</u> HR 0.65, 95% CI 0.53 to 0.81; I^2=9.82; p < 0.0001 (2 studies, 5058 women) 2. Acute toxicity No data	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 1 critical flaw (item 15 – no quantitative investigation of publication bias) **Overall quality of evidence**: low **Additional concerns about quality**: clinical heterogeneity between trials (study participants and interventions); duration of follow-up differed (3.3 to 17.2 years); treatment era – treatment approaches differed over time **Quality of included studies**: **Primary outcome:** Local control: Low quality of evidence;

Source: I, Kindts, Laenen A, Depuydt T, and Weltens C. "Tumour Bed Boost Radiotherapy for Women after Breast-Conserving Surgery." [In eng]. The Cochrane database of systematic reviews 11, no. 11 (2017-11-6 2017): CD011987. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29105051/.					
	Number of included patients: n=8,325 women (Budapest enrolled 627 women; EORTC enrolled 5569 participants, of whom 5318 were randomised between a boost and no boost; Lyon enrolled 1028 participants, Nice enrolled 664 participants; and SGW enrolled 688 participants.) Age range: Mean/median age: **Inclusion**: Women with a histological diagnosis of breast cancer for the first time (not recurrent or metastatic disease) with no prior history of malignant disease (other than basal cell carcinoma	· 16 Gy external beam (Budapest; EORTC; SGW) · high-dose-rate brachytherapy 12 to 14.25 (Budapest) · 15 Gy by means of an iridium-192 implant at a dose rate of 0.5 Gy per hour (EORTC) · 10 Gy in 4 fractions in 1 week (Lyon) · 10 Gy in 5 fractions in 1 week (Nice) The BEDs for the experimental arm were 87.8 Gy in Budapest and EORTC, 86.4 Gy in Lyon, 79.9 Gy in Nice, and 78.6 Gy in SGW. **Control arm** · Whole-breast irradiation:	the scales the authors used and, if possible, converted to the score from the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE v4.0). **Secondary Outcome**: 1. Overall survival, defined as the time from randomisation to death from any cause during follow-up. 2. Disease-free survival (time from randomisation to relapse, local or distant) during follow-up 3. Late toxicity related to radiotherapy, i.e. any toxic event	**Secondary Outcome:** 1. Overall survival 1,683 deaths in 2 studies with 6,342 women HR 1.04, 95% CI 0.94 to 1.14; I^2=43.98%; p=0.44 2. Disease free survival 2810 events in 3 studies with 6.549 women HR 0.94, 95% CI 0.87 to 1.02; I^2=76.96%; p=0.12 3. Late toxicity Data from 1,526 women in 2 Studies MD 0,38, 95% CI -0.18 to 0.93; I^2=75,42%; p=0.18 4. Cosmesis Data from 229 women with fair or poor scoring in 2 studies involving 1,116 women	sensitivity analysis because of high risk of selective reporting bias and blinding of outcome assessment bias (Nice) and inclusion of in situ tumours in SGW (studies were excluded), high quality of evidence (sensitivity analysis); subgroup analysis: high quality of evidence **Secondary outcome:** 1. Overall survival: moderate-quality evidence 2. Disease free survival: low-quality evidence 3. Late toxicity: very low quality of evidence 4. Cosmesis: low-quality evidence **Sources of funding:** n.a.

Source: I, Kindts, Laenen A, Depuydt T, and Weltens C. "Tumour Bed Boost Radiotherapy for Women after Breast-Conserving Surgery." [In eng]. The Cochrane database of systematic reviews 11, no. 11 (2017-11-6 2017): CD011987. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29105051/.

	of the skin); treated with BCS	50 Gy in 25 fractions in 5 weeks (Budapest;EORTC;Nice;SGW) · 50 Gy in 20 fractions in 5 weeks (Lyon)	occurring more than six months after radiotherapy; extracted data at 5, 10, 15, and 20 years. 4. Cosmesis, scored according to the Harvard scale in four classes: excellent, good, fair, and poor 5. Quality of life 6. Treatment costs	OR 1.41, 95% CI 1.07 to 1.86; I^2=95.93%; p=0.01 5. Quality of life No data 6. Treatment costs No data	

Abbreviations:

RCT = Randomised Controlled Trial

BCS = Breast-Conserving Surgery

HR = Hazard Ratio

OR = Odds Ratio

95% CI = 95% Confidence Interval

Verknüpfte Empfehlungen:

Empfehlung 4.99:

Die Boostbestrahlung sollte als perkutaner Boost (sequentiell oder simultan-integriert) verabreicht werden.

Empfehlung 4.100:

Wenn bereits präoperativ aufgrund der vorliegenden Informationen eine gesicherte Boost-Indikation besteht, kann eine intraoperative Boost-Bestrahlung erfolgen.

Literaturreferenzen: [133], [138], [139], [140], [141], [142], [143], [144], [145], [146]

Source: DG, Hamilton, Bale R, Jones C, Fitzgerald E, Khor R, Knight K, and Wasiak J. "Impact of Tumour Bed Boost Integration on Acute and Late Toxicity in Patients with Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 27 (2016-6 2016): 126-35. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/27113229/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: impact of concurrent boost regimes on clinical outcomes such as toxicity and cosmesis in patients with breast cancer managed with adjuvant radiotherapy	**Design:** Systematic review **Search date:** 01/2000-01/2015 **Searched databases**: Ovid MEDLINE, Ovid EMBASE and PubMed **Included study designs:** Cohort studies, case series	Use of concurrent bed boost delivery strategies in women with stage 0-III BC	**Primary Outcome:** acute skin toxicity within 12 weeks following radiation treatment; late toxicity (induration-fibrosis and telangiectasia) assessed ≥ 90 days after RT **Secondary Outcome**: long-term cosmesis	**Primary Outcome:** Techniques to deliver boost doses: En-face electron-beam (n=2), three-dimensional conformal radiotherapy (3DCRT) (n=12), intensity-modulated radiation	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 1 critical flaws (item 2) **Overall quality of evidence**: low **Additional concerns about quality**: most of studies were of a

Source: DG, Hamilton, Bale R, Jones C, Fitzgerald E, Khor R, Knight K, and Wasiak J. "Impact of Tumour Bed Boost Integration on Acute and Late Toxicity in Patients with Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 27 (2016-6 2016): 126-35. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/27113229/.					
	Number of included studies: n=17 **Number of included patients**: n=3,905; n=3,667 stratified to concurrent boost arms **Age range**: 19-89 **Mean/median age**: n.a. **Inclusion**: adult women with BC who underwent BCS and adjuvant RT with a daily concurrent boost, English language **Exclusion**: distant metastases, previous history of invasive cancer, previous radiotherapy, receiving accelerated partial breast radiotherapy, concurrent chemotherapy or those that received			therapy (IMRT) (n=6), volumetric-modulated arc therapy (VMAT) (n=1) and tomodirect (n =1) Maximum acute skin toxicity (Grade 3: n=10 studies) Range: 1%-7% N=6 studies: resolution of moderate to severe toxicities within 12 weeks Late toxicities: N=9 studies reported late breast fibrosis N=8 studies described telangiectasia Longest median follow-up: 5.1ys Incidence of moderate to severe toxicities: 1%-9% and	single-centre case series design; lack of studies with comparator arms **Quality of included studies**: Based on Newcastele-Ottawa scale: cohort study /Raza 2012 good Cohort study McDonald 2010 and Bantema-Joppe 2012: satisfactory. Case series: n=10 poor quality; n=4 good quality **Planned included studies**: randomized and non-randomized studies **Sources of funding:** no specific grant from any funding

Source: DG, Hamilton, Bale R, Jones C, Fitzgerald E, Khor R, Knight K, and Wasiak J. "Impact of Tumour Bed Boost Integration on Acute and Late Toxicity in Patients with Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 27 (2016-6 2016): 126-35. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/27113229/.

	treatment without the use of CT data to define target volumes			0%-9% for breast fibrosis and telangiectasia **Secondary Outcome:** Long-term cosmesis: 11 studies (n=1,716) patients Follow-up: 1,5 to 60 months Scale: Harvard Criteria Good Excellent scores: 65%-100% across studies	

Abbreviations:

n.a. = not Available, not Applicable

BC = Breast Cancer

BCS = Breast-Conserving Surgery

RT = Radiotherapy

CT = Computer Tomography

3D CRT = Three-Dimensional Conformal Radiotherapy

IMRT = Intensity-Modulated Radiation Therapy

VMAT = Volumetric-Modulated Arc Therapy

Verknüpfte Empfehlungen:

Empfehlung 4.104:

Die Teilbrustbestrahlung soll als perkutane Radiotherapie (moderat hypofraktionierte Radiotherapie mit 40 Gy in 15 Fraktionen über 3 Wochen oder ultra-hypofraktionierte Radiotherapie mit 30 Gy in 5 Fraktionen über 1,5 Wochen) oder als interstitielle Multikatheter-Brachytherapie durchgeführt werden.

Empfehlung 4.105:

Eine alleinige intraoperative Teilbrustbestrahlung mit niedrigenergetischen Röntgenstrahlen oder Elektronen kann nach Aufklärung über das erhöhte Lokalrezidivrisiko eingesetzt werden, wenn die intraoperative Radiotherapie im Rahmen des ersten operativen Eingriffs erfolgt.

Empfehlung 4.106:

Eine stark akzelerierte, hochdosierte perkutane Radiotherapie (2x tgl. 3,85 Gy bis 38,5 Gy) oder eine Brachytherapie mit Einzellumenkathetern sollte bei der Teilbrustbestrahlung nicht zum Einsatz kommen.

Empfehlung 4.112:

Die adjuvante Bestrahlung der regionalen Lymphabflussgebiete (Supra-/Infraklavikularregion, Mammaria interna-Region, nicht-dissezierte Anteil der Axilla) verbessert das brustkrebsspezifische Überleben und das Gesamtüberleben in Untergruppen von Patientinnen.

Literaturreferenzen: [147], [148], [149], [150], [151], [152], [153], [154], [155], [156], [157], [158], [159], [160], [161], [162], [163], [164], [165], [108], [166], [167], [168], [169], [170], [171], [172], [173], [122]

Source: M, Goldberg, Bridhikitti J, Khan AJ, McGale P, and Whelan TJ. "A Meta-Analysis of Trials of Partial Breast Irradiation." [In eng]. International journal of radiation oncology, biology, physics 115, no. 1 (2023-1-1 2023): 60-72. https: //doi.org/doi: 10.1016/j.ijrobp.2022.09.062. https: //pubmed.ncbi.nlm.nih.gov/36155214/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment

Source: M, Goldberg, Bridhikitti J, Khan AJ, McGale P, and Whelan TJ. "A Meta-Analysis of Trials of Partial Breast Irradiation." [In eng]. International journal of radiation oncology, biology, physics 115, no. 1 (2023-1-1 2023): 60-72. https: //doi.org/doi: 10.1016/j.ijrobp.2022.09.062. https: //pubmed.ncbi.nlm.nih.gov/36155214/.					
Aim: To assess the effectiveness of partial breast irradiation (PBI) and to compare the different techniques	**Design:** Meta-Analysis Search date: 1990-08/2022 Searched databases: MEDLINE (Ovid) Included study designs: RCTs Number of included studies: n=15 Number of included patients: n=16,474 Median age: ≥60y (10 trials) T1 disease (11 trials with ≥70%) grade 1 to 2 histology (12 trials with ≥75%), negative axillary nodes (11 trials with ≥85%), ER-positive cancers (9 trials with ≥90%), and were treated with adjuvant	**4 major categories of PBI techniques** 1) external beam RT without CT planning (2 trials) à RT was usually given with a direct field using electrons to the clinically identified tumor bed Dose: 40 to 55 Gy given over 8 to 20 fractions once a day over 1.5 to 5.5 weeks 2) brachytherapy (2 trials) delivered mainly using interstitial multicatheter HDR brachytherapy 3) intraoperative RT (3 trials) 4) external beam RT with CT planning (8 trials)	**Primary Outcome:** ipsilateral breast event (invasive or noninvasive) **Secondary Outcomes:** 1) True/marginal local recurrence: defined as tumor recurrence at the same site or close to the primary breast lesion 2) Elsewhere recurrence defined as tumor recurrence in the ipsilateral breast outside the area of the primary lesion 3) Regional nodal recurrence 4) Distant recurrence 5) Contralateral breast cancer 6) New second	Primary Outcome: Higher in patients treated with PBI (5.0%) compared with WBI (2.8%) RR 1.72, 95% CI 1.46 to 2.02, p<0.00001 (14 trials) (a) external beam RT without CT planning: RR 2.06, 95% CI 1.36 to 3.12; p=.0007) (b) brachytherapy: RR 1.21, 95% CI 0.65 to 2.25; p=.54) (c) intraoperative RT: RR 2.79, 95% CI 2.08 to 3.73, p<.00001) (d) external beam RT with CT planning, RR 1.25, 95% CI 0.99 to 1.58; p=.06).	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 5 critical flaws (items 2, 7, 9, 13, 15) Overall quality of evidence: critically low **Sources of funding:** n.a.

Source: M, Goldberg, Bridhikitti J, Khan AJ, McGale P, and Whelan TJ. "A Meta-Analysis of Trials of Partial Breast Irradiation." [In eng]. International journal of radiation oncology, biology, physics 115, no. 1 (2023-1-1 2023): 60-72. https: //doi.org/doi: 10.1016/j.ijrobp.2022.09.062. https: //pubmed.ncbi.nlm.nih.gov/36155214/.					
	hormone therapy (9 trials with ≥70%) Inclusion criteria: majority of trials restricted eligibility to patients at low to medium risk of recurrence: age ≥40 years (10 trials), ≤3 cm tumors (9 trials), axillary node negative or microscopic nodal involvement only (8 trials), and clear or ≥2-mm margins of excision after BCS (10 trials). Eleven of the trials permitted only patients with invasive disease, and 4 trials also permitted patients with ductal carcinoma in situ Exclusion:		Cancer 7) All-cause mortality 8) Breast cancer mortality 9) Non-breast cancer mortality 10) Cardiac mortality 11) Acute radiation toxicity 12) late (or chronic) radiation toxicity 13) Adverse breast cosmesis	Heterogeneity between the 4 different technique groups (p= .0002) and between all trials providing events (p=.02). **Secondary Outcomes:** 1) True/marginal local recurrences were uncommon (181/ 10,430, 1.7%) and similar in both treatment arms: RR 0.90, 95% CI, 0.67 to 1.21, p=.49 (7 trials) 2) Elsewhere recurrences occurred more in patients treated with PBI compared with WBI (1.6% vs 0.8%), RR 1.96, 95% CI, 1.36 to 2.82, p = .0003 (7 trials)	

Source: M, Goldberg, Bridhikitti J, Khan AJ, McGale P, and Whelan TJ. "A Meta-Analysis of Trials of Partial Breast Irradiation." [In eng]. International journal of radiation oncology, biology, physics 115, no. 1 (2023-1-1 2023): 60-72. https: //doi.org/doi: 10.1016/j.ijrobp.2022.09.062. https: //pubmed.ncbi.nlm.nih.gov/36155214/.					
				3)It was very uncommon and was increased in patients treated with PBI compared with WBI (1.0% vs 0.5%), RR 1.91, 95% CI, 1.08 to 3.39, p=.03 (9 trials) 4)Uncommon (3.2%), and no difference was observed between PBI and WBI RR 0.98, 95% CI, 0.80 to 1.19, p=.82 (10 trials) 5) Lower with PBI compared with WBI (2.5% vs 3.1%), RR 0.83, 95% CI, 0.67 to 1.03, p=.09 (8 trials) 6) No difference between PBI and WBI: (5.7% vs. 5.3%)	

Source: M, Goldberg, Bridhikitti J, Khan AJ, McGale P, and Whelan TJ. "A Meta-Analysis of Trials of Partial Breast Irradiation." [In eng]. International journal of radiation oncology, biology, physics 115, no. 1 (2023-1-1 2023): 60-72. https: //doi.org/doi: 10.1016/j.ijrobp.2022.09.062. https: //pubmed.ncbi.nlm.nih.gov/36155214/.					
				RR 1.07, 95% CI 0.91 to 1.25, p=.40 (7 trials) 7) Similar for PBI and WBI (10.6% vs 10.6%) RR 1.01, 95% CI 0.92 to 1.10, p=.87 (12 trials) 8)Similar for PBI and WBI (3.2% vs 3.0%), RR 1.08, 95% CI 0.90 to 1.30, p=0.41 (10 trials) 9) No differences between PBI and WBI (5.7% vs 6.3%) RR 0.91, 95% CI 0.79 to 1.03, p=.13 (9 trials) 10) Less with PBI compared with WBI (0.5% vs 1.0%) RR 0.54, 95% CI 0.31 to 0.92, p=0.02 (5 trials) 11) PBI: 11.6% vs. WBI: 32.7%	

Source: M, Goldberg, Bridhikitti J, Khan AJ, McGale P, and Whelan TJ. "A Meta-Analysis of Trials of Partial Breast Irradiation." [In eng]. International journal of radiation oncology, biology, physics 115, no. 1 (2023-1-1 2023): 60-72. https: //doi.org/doi: 10.1016/j.ijrobp.2022.09.062. https: //pubmed.ncbi.nlm.nih.gov/36155214/.

				RR 0.50, 95% CI 0.45 to 0.56, p<0.0001 (8 trials) 12) PBI: 28.4% vs WBI: 29.0% RR 0.90, 95% CI 0.86-0.94, p<0.0001 (13 trials) 13 PBI: 17.2% vs WBI: 15.4% RR 1.41, 95% CI 1.00 to 1.30, p=0.05 (9 trials)	

Abbreviations:

PBI = Partial Breast Irradiation

RCT = Randomised Controlled Trial

BCS = Breast Conserving Surgery

RT = Radiation Therapy

CT = Computed Tomography

HDR = High-Dose-Rate

WBI = Whole Breast Irradiation

RR = Risk Ratio

95% CI = 95% Confidence Interval

Source: M, Goldberg, Bridhikitti J, Khan AJ, McGale P, and Whelan TJ. "A Meta-Analysis of Trials of Partial Breast Irradiation." [In eng]. International journal of radiation oncology, biology, physics 115, no. 1 (2023-1-1 2023): 60-72. https: //doi.org/doi: 10.1016/j.ijrobp.2022.09.062. https: //pubmed.ncbi.nlm.nih.gov/36155214/.

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.111:

Nach primärer (neoadjuvanter) systemischer Therapie soll sich die Indikation zur Postmastektomie-Radiotherapie am prätherapeutischen klinischen Stadium orientieren; bei pCR (ypT0 und ypN0) soll die Indikation im interdisziplinären Tumorboard abhängig vom Risikoprofil festgelegt werden.

Literaturreferenzen: [174], [175], [176], [177], [178], [179], [180], [181]

Source Krug D, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Hehr T, Piroth MD, Sedlmayer F, Souchon R, Wenz F, Sauer R. Individualization of post-mastectomy radiotherapy and regional nodal irradiation based on treatment response after neoadjuvant chemotherapy for breast cancer: A systematic review. StrahlentherOnkol. 2018 Jul;194(7): 607-618. English. doi: 10.1007/s00066-018-1270-x. Epub 2018 Jan 30. PMID: 29383405.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To review the evidence regarding post-mastectomy radiotherapy (PMRT) and regional nodal irradiation (RNI) after neoadjuvant chemotherapy (NACT) for breast cancer, with a special focus on individualization of adjuvant radiotherapy based on treatment response.	**Design**: Systematic review **Search date**: last search was performed on October 29, 2017 **Searched databases**: PubMed/Medline **Included study designs**: retrospective (with a minimum of 10 patients) **Number of included studies**:	**Intervention** Post-mastectomy radiotherapy (PMRT) and regional nodal irradiation (RNI). **Control** the comparison of different approaches to PMRT and RNI based on treatment response after neoadjuvant chemotherapy	evidence regarding PMRT and RNI after NACT for breast cancer, with a special focus on individualization of adjuvant radiotherapy based on treatment response; locoregional recurrence (LRR), LRR-free survival (LRRFS), disease-free survival (DFS), and overall survival (OS).	Daveau et al. (2010) analyzed 249 cN0–2/ypN0 breast cancer patients; 63.7% received regional nodal irradiation (RNI) alongside whole-breast irradiation. RNI recipients more frequently had clinical nodal involvement (43.9% vs. 15.7%), were younger, and showed medial/central tumor locations.	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 3 critical flaws (items 2, 7,9) **Additional concerns about quality**: - **Quality of included studies**: retrospective studies, high risk of bias **Level of evidence:**

Source Krug D, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Hehr T, Piroth MD, Sedlmayer F, Souchon R, Wenz F, Sauer R. Individualization of post-mastectomy radiotherapy and regional nodal irradiation based on treatment response after neoadjuvant chemotherapy for breast cancer: A systematic review. StrahlentherOnkol. 2018 Jul;194(7): 607-618. English. doi: 10.1007/s00066-018-1270-x. Epub 2018 Jan 30. PMID: 29383405.

	13 (9 for PMRT and 5 for RNI) **Number of included patients**: n.r. **Mean/median age**: n.r. **Inclusion criteria**: Studies published since January 1, 2000. Studies with a minimum of 10 patients. Studies that provided clinical outcome data on locoregional recurrence (LRR), LRR-free survival (LRRFS), disease-free survival (DFS), or overall survival (OS). Studies published in English or German language. Studies that reported separate outcome data according to			Both univariate and multivariate analyses revealed no improvement in locoregional recurrence-free survival (LRRFS), disease-free survival (DFS), or overall survival (OS) with RNI. Bae et al. (2012) retrospectively studied 98 patients with cT3/4 or cN+ status and ypN0/1 after neoadjuvant chemotherapy; 57% underwent supraclavicular RNI. In Bae et al.'s study, no DFS or LRRFS benefit was found for ypN0 patients, while ypN1 patients treated with RNI showed significantly worse DFS. Noh et al. reported on 260 stage II/III patients (ypN0) treated with breast-conserving	Oxford 2011: **Sources of funding**: n.r.

Source Krug D, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Hehr T, Piroth MD, Sedlmayer F, Souchon R, Wenz F, Sauer R. Individualization of post-mastectomy radiotherapy and regional nodal irradiation based on treatment response after neoadjuvant chemotherapy for breast cancer: A systematic review. StrahlentherOnkol. 2018 Jul;194(7): 607-618. English. doi: 10.1007/s00066-018-1270-x. Epub 2018 Jan 30. PMID: 29383405.

	administration of RNI and/or PMRT as well as according to chemotherapy response (pCR, ypN0, ypN+). **Exclusion**: n.r.			surgery, where 52% received RNI (mainly supraclavicular) without impact on LRRFS or DFS. A Korean study focusing on internal mammary node (IMN) irradiation in 521 patients with clinically suspect lymph nodes found a significant 5-year DFS improvement. The IMN benefit was most pronounced in subgroups with cN1–2, ypN1–2, inner/central tumors, and triple-negative breast cancer. A large NCDB analysis (15,315 patients, 2003–2011) showed that adding RNI to whole-breast or post-mastectomy radiotherapy did not improve OS	

Source Krug D, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Hehr T, Piroth MD, Sedlmayer F, Souchon R, Wenz F, Sauer R. Individualization of post-mastectomy radiotherapy and regional nodal irradiation based on treatment response after neoadjuvant chemotherapy for breast cancer: A systematic review. StrahlentherOnkol. 2018 Jul;194(7): 607-618. English. doi: 10.1007/s00066-018-1270-x. Epub 2018 Jan 30. PMID: 29383405.

				regardless of nodal status or surgical method. Overall, RNI after neoadjuvant chemotherapy demonstrates limited survival benefits, except for a potential advantage when targeting the IMN in high-risk groups. A 2012 systematic review of post-mastectomy radiotherapy (PMRT) after neoadjuvant chemotherapy noted that 23 of 24 studies were retrospective; only one prospective study excluded PMRT. At MD Anderson, 106 patients achieving a pathologic complete response (pCR) showed no PMRT benefit in stage I/II disease (with 0% 10-year recurrence) but	

Source Krug D, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Hehr T, Piroth MD, Sedlmayer F, Souchon R, Wenz F, Sauer R. Individualization of post-mastectomy radiotherapy and regional nodal irradiation based on treatment response after neoadjuvant chemotherapy for breast cancer: A systematic review. StrahlentherOnkol. 2018 Jul;194(7): 607-618. English. doi: 10.1007/s00066-018-1270-x. Epub 2018 Jan 30. PMID: 29383405.

				improved outcomes in stage III. Nagar et al. observed that for cT3 cN0 patients, PMRT significantly reduced locoregional recurrence in those with occult nodal disease, although benefit in ypN0 patients was not significant. A French study of 134 stage II/III patients found no significant improvement in LRRFS, DFS, or OS with PMRT after adjusting for baseline differences. Shim et al. from Korea reported that among 151 ypN0 patients, a low (3.3%) recurrence rate was observed with numerical but non-significant improvements	

Source Krug D, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Hehr T, Piroth MD, Sedlmayer F, Souchon R, Wenz F, Sauer R. Individualization of post-mastectomy radiotherapy and regional nodal irradiation based on treatment response after neoadjuvant chemotherapy for breast cancer: A systematic review. StrahlentherOnkol. 2018 Jul;194(7): 607-618. English. doi: 10.1007/s00066-018-1270-x. Epub 2018 Jan 30. PMID: 29383405.

				in LRRFS, DFS, and OS with PMRT. Xin et al. demonstrated that in ypN1 patients, PMRT improved DFS and OS when ≤13 negative lymph nodes were removed, but not when >13 nodes were removed. Meattini et al. found that patients with pCR or significant downstaging showed no PMRT benefit regarding locoregional recurrence. In a large NCDB analysis by Rusthoven et al., among 10,283 mastectomy patients (29.6% ypN0), PMRT was associated with improved OS, particularly in patients with ypN2–3 disease.	

Source Krug D, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Hehr T, Piroth MD, Sedlmayer F, Souchon R, Wenz F, Sauer R. Individualization of post-mastectomy radiotherapy and regional nodal irradiation based on treatment response after neoadjuvant chemotherapy for breast cancer: A systematic review. StrahlentherOnkol. 2018 Jul;194(7): 607-618. English. doi: 10.1007/s00066-018-1270-x. Epub 2018 Jan 30. PMID: 29383405.

				A second NCDB study (Liu et al.) of 1,560 ypN0 stage II/III patients treated from 1998 to 2009 did not show an overall survival benefit with PMRT. In summary, the benefit of PMRT after neoadjuvant chemotherapy appears to depend on tumor stage and nodal status—with a more pronounced advantage in higher-stage or residual nodal disease patients.	

Abbreviations and comment:

PMRT: Post-mastectomy radiotherapy

RNI: regional nodal irradiation

LRR: like locoregional recurrence

LRRFS: LRR-free survival

Source Krug D, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Hehr T, Piroth MD, Sedlmayer F, Souchon R, Wenz F, Sauer R. Individualization of post-mastectomy radiotherapy and regional nodal irradiation based on treatment response after neoadjuvant chemotherapy for breast cancer: A systematic review. StrahlentherOnkol. 2018 Jul;194(7): 607-618. English. doi: 10.1007/s00066-018-1270-x. Epub 2018 Jan 30. PMID: 29383405.

DFS: disease-free survival (DFS)

OS: overall survival

There is a lack of evidence regarding the role of adjuvant radiotherapy and its individualization based on treatment response after NACT

Verknüpfte Empfehlungen:

Empfehlung 4.111:

Nach primärer (neoadjuvanter) systemischer Therapie soll sich die Indikation zur Postmastektomie-Radiotherapie am prätherapeutischen klinischen Stadium orientieren; bei pCR (ypT0 und ypN0) soll die Indikation im interdisziplinären Tumorboard abhängig vom Risikoprofil festgelegt werden.

Literaturreferenzen: [174], [175], [176], [177], [178], [179], [180], [181]

Source Nikyar N, Tegnelius E, Valachis A. Adjuvant locoregional radiation therapy in breast cancer patients with pathologic complete response after neoadjuvant chemotherapy: A systematic review and meta-analysis. Clin Transl Radiat Oncol. 2022 Jan 5;33: 45-52. doi: 10.1016/j.ctro.2021.12.010. PMID: 3036587; PMCID: PMC8749154.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
The aim of the present meta-analysis was to investigate the impact of adjuvant locoregional radiation therapy (LRRT) in breast cancer patients with clinical lymph node metastatic disease achieving ypNO after neoadjuvant chemotherapy (NACT).	**Design**: Systematic review and meta-analysis **Search date**: November 2020 (data limited to studies after 1990). **Searched databases**: PubMed **Included study designs**: **Number of included studies**: **Number of included patients**:	**Intervention** Adjuvant locoregional radiation therapy (LRRT) **Control** no adjuvant radiation therapy	**Primary Outcome**: Locoregional recurrence (LRR) **Secondary Outcome**: Disease-free survival (DFS) and overall survival (OS)	**Primary Outcome**: Adjuvant LRRT significantly reduced the risk of LRR in patients with N+ at diagnosis and ypNO (HR 0.59; 95% CI 0.42-0.81). **Secondary Outcome**: No statistically significant difference on DFS or OS was found.	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: …; 2 critical flaws (items 4,7) **Additional concerns about quality**: **Quality of included studies**: Confounding by indication and immortal time bias;

Source Nikyar N, Tegnelius E, Valachis A. Adjuvant locoregional radiation therapy in breast cancer patients with pathologic complete response after neoadjuvant chemotherapy: A systematic review and meta-analysis. Clin Transl Radiat Oncol. 2022 Jan 5;33: 45-52. doi: 10.1016/j.ctro.2021.12.010. PMID: 3036587; PMCID: PMC8749154.					
	Mean/median age: **Inclusion criteria**: studies had to include patients with clinically T3 and/or lymph node metastatic disease at diagnosis, present data on adjuvant radiotherapy in relation to PCR after NACT, and present outcome of adjuvant radiotherapy in terms of LRR and/or disease-free survival (DFS) and/or overall survival (OS); English **Exclusion**: Studies that only included patients with inflammatory breast cancer or clinically T4 disease, studies without data on whether adjuvant radiation therapy was given or data on response				ranges from very low to low, assessed using the GRADE approach **Level of evidence:** Oxford 2011: **Sources of funding**: n.r.

Source Nikyar N, Tegnelius E, Valachis A. Adjuvant locoregional radiation therapy in breast cancer patients with pathologic complete response after neoadjuvant chemotherapy: A systematic review and meta-analysis. Clin Transl Radiat Oncol. 2022 Jan 5;33: 45-52. doi: 10.1016/j.ctro.2021.12.010. PMID: 3036587; PMCID: PMC8749154.

	to chemotherapy and studies without presenting relevant outcomes				

Abbreviations and comment:

Verknüpfte Empfehlungen:

Empfehlung 4.111:

Nach primärer (neoadjuvanter) systemischer Therapie soll sich die Indikation zur Postmastektomie-Radiotherapie am prätherapeutischen klinischen Stadium orientieren; bei pCR (ypT0 und ypN0) soll die Indikation im interdisziplinären Tumorboard abhängig vom Risikoprofil festgelegt werden.

Literaturreferenzen: [174], [175], [176], [177], [178], [179], [180], [181]

Source Wang K, Jin X, Wang W, Yu X, Huang J. The role of postmastectomy radiation in patients with ypN0 breast cancer after neoadjuvant chemotherapy: a meta-analysis. BMC Cancer. 2021 Jun 25;21(1): 728. doi: 10.1186/s12885-021-08423-1. PMID: 34172014; PMCID: PMC8234630.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To evaluate whether postmastectomy radiation therapy (PMRT) improves loco-regional control and survival for breast cancer patients with pathological negative nodes (ypN0) after neoadjuvant chemotherapy (NAC).	**Design**: Meta-analysis and systematic review **Search date**: June 2019 **Searched databases**: PubMed database (and major oncology congress abstracts) **Included study designs**: observational studies **Number of included studies**: 12 **Number of included patients**: 17,747	**Intervention** Postmastectomy radiation therapy (PMRT) **Control** No postmastectomy radiation therapy	**Primary Outcome**: Local-regional recurrence (LRR) **Secondary Outcome**: Disease-free survival (DFS) and overall survival (OS)	**Primary Outcome**: PMRT was associated with a statistically significant reduction in LRR (RR, 0.38; 95% CI, 0.19–0.77, P = 0.007) This reduction in LRR was particularly significant in patients with stage III breast cancer (RR, 0.16; 95% CI, 0.07–0.37, P < 0.001) **Secondary Outcome**: No statistically significant difference in disease-free	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 5 critical flaws (items 2,4,7,9,13) **Additional concerns about quality**: Slight asymmetry in the presence of publication bias of the included literature

Source Wang K, Jin X, Wang W, Yu X, Huang J. The role of postmastectomy radiation in patients with ypN0 breast cancer after neoadjuvant chemotherapy: a meta-analysis. BMC Cancer. 2021 Jun 25;21(1): 728. doi: 10.1186/s12885-021-08423-1. PMID: 34172014; PMCID: PMC8234630.					
	Mean/median age: n.r. **Inclusion criteria**: Patients diagnosed with breast cancer. Achievement of a pathological negative node response (ypN0) to NAC. Adequate data provided for estimating the relative risk (RR) for local-regional recurrence (LRR) and survival outcome. No restrictions on histological type and breast cancer status. **Exclusion**: Studies published as systematic reviews, commentaries, letters. Studies that did not determine LRR or survival.			survival (DFS) was observed with the addition of PMRT for ypN0 patients (RR, 0.70; 95% CI, 0.21–2.27, P = 0.55). There was no statistically significant association between radiotherapy and overall survival (OS) (RR, 0.81; 95% CI, 0.64–1.04, P = 0.10)	**Quality of included studies**: **Level of evidence:** Oxford 2011: **Sources of funding**: Natural Science Foundation of Zhejiang Province (Grant No. LY18H160001).

Source Wang K, Jin X, Wang W, Yu X, Huang J. The role of postmastectomy radiation in patients with ypN0 breast cancer after neoadjuvant chemotherapy: a meta-analysis. BMC Cancer. 2021 Jun 25;21(1): 728. doi: 10.1186/s12885-021-08423-1. PMID: 34172014; PMCID: PMC8234630.

	Laboratory studies or irrelevant studies. Study sample sizes ≤ 30.				

Abbreviations and comment:

PMRT: postmastectomy radiation therapy

NAC: neoadjuvant chemotherapy

ypN0: pathological negative nodes

DFS: Disease-free survival

OS: overall survival

Verknüpfte Empfehlungen:

Empfehlung 4.113:

Bei Nachweis von 4 und mehr befallenen axillären Lymphknoten soll eine Bestrahlung der regionalen Lymphabflussgebiete durchgeführt werden.

Literaturreferenzen: [182], [183], [184], [185], [186], [187], [188], [189], [190], [191], [192]

Source Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials. Lancet. 2023 Nov 25;402(10416): 1991-2003. doi: 10.1016/S0140-6736(23)01082-6. Epub 2023 Nov 3. PMID: 37931633.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
to assess the effects of regional node radiotherapy	**Design**: meta-analysis of individual patient data from randomized trials **Search date**: **Searched databases**: MEDLINE, Embase, the Cochrane Library, and meeting abstracts **Included study designs**: RCTs **Number of included studies**: 16 (8 older trials (1961-78) used direct anterior photon beams; 8 newer	**Intervention** Regional node radiotherapy (to the internal mammary chain, supraclavicular fossa, or axilla, or any combinations of these) **Control** No regional lymph node radiotherapy	recurrence at any site, breast cancer mortality, non-breast-cancer mortality, and all-cause mortality	Four trials compared internal mammary chain radiotherapy versus no internal mammary chain radiotherapy (5,420 women). Comparisons included internal mammary chain and supraclavicular fossa radiotherapy versus no radiotherapy to these nodal regions (n=4060) and internal mammary chain, supraclavicular fossa, and axilla radiotherapy versus no	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review moderate; 0 critical flaws **Additional concerns about quality**: - **Comment:** The authors suggest the contrasting findings could reflect radiotherapy improvements since the 1980s **Level of evidence:**

Source Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials. Lancet. 2023 Nov 25;402(10416): 1991-2003. doi: 10.1016/S0140-6736(23)01082-6. Epub 2023 Nov 3. PMID: 37931633.					
	trials (1989-2008) used more tailored radiotherapy techniques) **Number of included patients**: 14,324 women **Median follow-up**: 14.0 woman-years (IQR 10.0-16.4) **Inclusion criteria**: Randomized trials of regional lymph node radiotherapy versus no regional lymph node radiotherapy in women with early breast cancer. Trials had to begin before Jan 1, 2009, with the only difference between groups being regional node radiotherapy. **Exclusion**:			radiotherapy to these nodal regions (n=3716). Three trials involved supraclavicular fossa or axilla radiotherapy or both versus no radiotherapy to these nodal regions (n=1128). 12,167 women were included in the newer trials, with a median follow-up of 13.7 woman-years (IQR 9.9-16.0) and 3,594 deaths. In newer trials (1989-2008), regional node radiotherapy significantly reduced recurrence, breast cancer mortality, and all-cause mortality. Regional node radiotherapy reduced overall breast cancer recurrence (RR 0.88, 95% CI 0.81-0.95; p=0.00083). The main	Oxford 2011: 1 **Sources of funding**: Cancer Research UK, Medical Research Council

Source Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials. Lancet. 2023 Nov 25;402(10416): 1991-2003. doi: 10.1016/S0140-6736(23)01082-6. Epub 2023 Nov 3. PMID: 37931633.					
				effect was on distant recurrence (0.86, 0.80-0.93; p=0.00026). Radiotherapy significantly reduced breast cancer mortality (0.87, 0.80-0.94; p=0.0010). There was no significant effect on non-breast-cancer mortality (0.97, 0.84-1.11; p=0.63). Regional node radiotherapy significantly reduced overall mortality (0.90, 0.84-0.96; p=0.0022). The absolute 15-year gains were 2.6% (95% CI 0.6-4.6) for any recurrence, 3.0% (1.1-4.9) for breast cancer mortality, and 3.0% (1.0-5.0) for overall mortality. In older trials (1961-1978), regional node radiotherapy had little	

Source Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials. Lancet. 2023 Nov 25;402(10416): 1991-2003. doi: 10.1016/S0140-6736(23)01082-6. Epub 2023 Nov 3. PMID: 37931633.					
				effect on breast cancer mortality but increased non-breast-cancer mortality and all-cause mortality. Eight older trials included 2,157 women, with 1,014 recurrences, 970 deaths with recurrence, and 1,541 deaths overall. Median follow-up was 25.6 woman-years (IQR 12.4-41.7).	
Abbreviations and comment: RCT – randomized controlled trial					

Verknüpfte Empfehlungen:

Empfehlung 4.116:

Bei nachgewiesenem Befall der A. mammaria interna Lymphknoten oder der supra-/infraklavikulären Lymphknoten sollte eine Bestrahlung der regionalen Lymphabflussgebiete durchgeführt werden.

Literaturreferenzen: [182], [183], [184], [185], [186], [193], [194]

Source: S, Jia, Liu Z, Zhang J, Zhao C, Zhu L, Kong J, Han H, et al. "Can Internal Mammary Lymph Nodes Irradiation Bring Survival Benefits for Breast Cancer Patients? A Systematic Review and Meta-Analysis of 12,705 Patients in 12 Studies." [In eng]. Radiation oncology (London, England) 16, no. 1 (2021-2-23 2021): 42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33622345/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Should internal mammary lymph nodes (IMLNs) be irradiated?	**Design**: Systematic review and meta-analysis **Search date**: n.a. **Searched databases**: PubMed, EMBASE, Web of Science, CNKI, Wanfang Medical Network, the Chinese Biomedical Literature Database **Included study designs**: 9 retrospective cohort studies, 1 prospective cohort study, 1 non-randomized controlled	**Intervention** Internal mammary lymph node irradiation (IMNI) **Control** Non-IMNI	**Primary Outcome**: Overall survival (OS) Disease-free survival (DFS) **Subgroup analysis:** DFS on key prognostic factors: status of axillary lymph nodes (N_0, N_+) and tumor location (medical/central, lateral) **Secondary Outcome:**	**Primary Outcome**: Overall survival HR 0.89, 95% CI 0.79 to 1.00, I^2=47.5%, p=0.047 (12 studies with 12,705 patients) Disease-free survival HR 0.62, 95% CI 0.47 to 0.82, I^2=79.2%, p=0.001 (8 studies) **Subgroup analysis**	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low;5 critical flaws (items 2, 4, 7, 11, 13) **Additional concerns about quality**: **Quality of included studies**: High-Quality: 11 articles Low-Quality: 1 article

Source: S, Jia, Liu Z, Zhang J, Zhao C, Zhu L, Kong J, Han H, et al. "Can Internal Mammary Lymph Nodes Irradiation Bring Survival Benefits for Breast Cancer Patients? A Systematic Review and Meta-Analysis of 12,705 Patients in 12 Studies." [In eng]. Radiation oncology (London, England) 16, no. 1 (2021-2-23 2021): 42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33622345/.					
	trial, 1 randomized controlled trial **Number of included studies**: n=12 **Number of included patients**: n=12,705 **Mean/median age**: n.a. **Inclusion criteria**: Patients without other tumors than BC; no distant metastasis or other complications; Follow-up time at least 5 years		Acute and late side effects	DFS of high risk group (N_+) HR 0.65, 95% CI 0.53 to 0.80, I^2=71.5%, p<0.0001 DFS in N_0 group HR 1.02, 95% CI 0.87 to 1.20, I^2=0.0%, p=0.794 Location of tumor: DFS Central/medical HR 0.55, 95% CI 0.40 to 0.78, p=0.001 Lateral HR 0.77, 95%CI 0.61 to 0.97, p=0.025 **Secondary Outcome:** Incidence of radiation pneumonitis/pulmonary fibrosis in the IMNI group (higher: 2 studies; no difference: 1 study)	**Planned included studies**: Clinical controlled study **Sources of funding:** n.a.

Source: S, Jia, Liu Z, Zhang J, Zhao C, Zhu L, Kong J, Han H, et al. "Can Internal Mammary Lymph Nodes Irradiation Bring Survival Benefits for Breast Cancer Patients? A Systematic Review and Meta-Analysis of 12,705 Patients in 12 Studies." [In eng]. Radiation oncology (London, England) 16, no. 1 (2021-2-23 2021): 42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33622345/.

				Cardiac toxicity No significant difference (5 studies=all included studies comparing cardiac toxicity) Skin reaction Slightly higher in IMNI group (1 study) Incidence of contralateral breast cancer in the long term Higher incidence in IMNI group HR 2.47, 95% CI 1.23 to 4.95	

Abbreviations:

BC = Breast Cancer

IMLNs = Internal Mammary Lymph Nodes

IMNI = Internal Mammary Lymph Node Irradiation

DFS = Disease-free survival

Source: S, Jia, Liu Z, Zhang J, Zhao C, Zhu L, Kong J, Han H, et al. "Can Internal Mammary Lymph Nodes Irradiation Bring Survival Benefits for Breast Cancer Patients? A Systematic Review and Meta-Analysis of 12,705 Patients in 12 Studies." [In eng]. Radiation oncology (London, England) 16, no. 1 (2021-2-23 2021): 42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33622345/.

OS = Overall Survival

HR = Hazard Ratio

95% CI = 95% Confidence Interval

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.116:

Bei nachgewiesenem Befall der A. mammaria interna Lymphknoten oder der supra-/infraklavikulären Lymphknoten sollte eine Bestrahlung der regionalen Lymphabflussgebiete durchgeführt werden.

Literaturreferenzen: [182], [183], [184], [185], [186], [193], [194]

Source Korzets Y, Levitas D, Grubstein A, Corn BW, Amir E, Goldvaser H. Efficacy and Safety of the Addition of Internal Mammary Irradiation to Standard Adjuvant Radiation in Early-Stage Breast Cancer: A Systematic Review and Meta-Analysis. Curr Oncol. 2022 Sep 17;29(9): 6657-6673. doi: 10.3390/curroncol29090523. PMID: 36135092; PMCID: PMC9497563.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To explore the efficacy and safety of adding IMNI (internal mammary nodal irradiation) IMNI to adjuvant radiation therapy in early-stage, high risk breast cancer.	**Design**: Systematic Review and Meta-Analysis **Search date**: January 2005 and May 2022 **Searched databases**: MEDLINE (PubMed) and EMBASE **Included study designs**: RCTs and one prospective non-randomized study **Number of included studies:** 5	**Intervention** IMNI (internal mammary nodal irradiation) added to standard adjuvant radiation **Control:** Standard adjuvant radiation	**Primary Outcome:** Overall survival (OS) **Secondary Outcome:** Breast cancer specific-survival (BCSS), disease-free survival (DFS), distant-metastasis free survival (DMFS), regional and loco-regional recurrence, non-breast cancer mortality, secondary non-breast cancer, contralateral breast cancer, and	**Primary Outcome**: IMNI was associated with significant improvement in OS HR=0.91, 95% CI, 0.82-0.98; p=0.004 **Secondary Outcome**: IMNI was associated with significant improvement in BCSS (HR=0.84, 95% CI, 0.77-0.92; p<0.001), DFS (HR=0.89, 95% CI, 0.82-0.98; p=0.01), and DMFS (HR=0.89, 95% CI, 0.81-0.98; p=0.02)	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low 4 critical flaws (items 2, 9, 13, 15) **Additional concerns about quality**: **Quality of included studies**: **Level of evidence:** Oxford 2011:

Source Korzets Y, Levitas D, Grubstein A, Corn BW, Amir E, Goldvaser H. Efficacy and Safety of the Addition of Internal Mammary Irradiation to Standard Adjuvant Radiation in Early-Stage Breast Cancer: A Systematic Review and Meta-Analysis. Curr Oncol. 2022 Sep 17;29(9): 6657-6673. doi: 10.3390/curroncol29090523. PMID: 36135092; PMCID: PMC9497563.					
	Number of included patients: 10,994 **Inclusion criteria:** Prospective studies investigating the addition of IMNI to standard irradiation in early-stage breast cancer. Studies were included if data on the efficacy or toxicity were reported. Both randomized phase 2 and phase 3 studies were included. **Exclusion:** Studies not meeting the inclusion criteria, duplicates		cardiovascular morbidity and mortality	IMNI was also associated with reduced odds for regional (OR=0.58, 95% CI, 0.44-0.75; p<0.001) and loco-regional recurrence (OR=0.85, 95% CI, 0.72-1.00; p=0.04). The odds for cardiotoxicity were not statistically significantly higher (OR=1.23, 95% CI, 0.99-1.53; p=0.07). There were comparable odds for cardiovascular mortality (OR=1.00, 95% CI, 0.69-1.46; p=1.00) non-breast cancer mortality (OR=1.05, 95% CI, 0.79-1.41; p=0.74), secondary cancer (OR=0.95, 95% CI, 0.82-1.10; p=0.51), and contra-lateral breast cancer (OR=1.07, 95% CI, 0.77-1.51, p=0.68).	**Sources of funding**:

Source Korzets Y, Levitas D, Grubstein A, Corn BW, Amir E, Goldvaser H. Efficacy and Safety of the Addition of Internal Mammary Irradiation to Standard Adjuvant Radiation in Early-Stage Breast Cancer: A Systematic Review and Meta-Analysis. Curr Oncol. 2022 Sep 17;29(9): 6657-6673. doi: 10.3390/curroncol29090523. PMID: 36135092; PMCID: PMC9497563.

Abbreviations and comment:

IMNI (internal mammary nodal irradiation)

OR: Odds ratio

Verknüpfte Empfehlungen:

Empfehlung 4.119:

Wenn bei Patientinnen mit befallenen axillären Wächterlymphknoten (> 2 mm) keine axilläre Dissektion erfolgt ist, sollte das klinische Zielvolumen der adjuvanten Strahlentherapie neben der Brust bzw. Thoraxwand die axillären Level I-IV mit erfassen.

Literaturreferenzen: [102], [103], [195], [196]

Source: Donker M, Tienhoven G, Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS) a randomised, multicenter open label, phase 3 non inferiority trial. Lancet Oncol 2014;15: 1333-10

Aim and Country	Design and participants	Intervention	Outcomes	Results	Quality and comment
Acronym of study: AMAROS trial **Aim**: Assessing whether Axillary radiotherapy provides comparable regional control with fewer side-effects compared with axillary lymph node dissection **Country**: Nine European countries	**Design**: Randomised, multicentre, open-label, phase 3 non-inferiority trial **Enrollment**: 34 hospitals, between 19.02.2001 – 29.04.2010 **Noninferiority** low event rate: primary non-inferiority test underpowered **Number of included patients**: 4,806 axillary radiotherapy: n=2,404: of those n=744	**Intervention** Axillary radiotherapy (25 fractions of 2 Gy) **Control** Axillary lymph node dissection	**Primary Outcome**: 5-year axillary recurrence **Secondary Outcome**: axillary recurrence-free survival disease-free survival (DFS) overall survival shoulder mobility lymphoedema QoL	**Primary Outcome**: 5-year axillary recurrence axillary lymph node dissection group: 0.43%; 95% CI 0.00–0.92 axillary radiotherapy group: 1.19%; 0.31–2.08 **Secondary Outcome**: axillary recurrence-free survival Because of the low number of axillary recurrences, axillary	**Quality of study** assessed with SIGN checklist for RCT: acceptable (+) **Limitations by authors** the extensive irradiation including the periclavicular area might be regarded as overtreatment an imbalance was noted in the

Source: Donker M, Tienhoven G, Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS) a randomised, multicenter open label, phase 3 non inferiority trial. Lancet Oncol 2014;15: 1333-10					
	sentinel-node-positive patients included in ITT-analysis; axillary lymph node dissection: 2,402: of those n=681 sentinel-node-positive patients included in ITT-analysis **Median Follow-up:** sentinel node positive: 6· 1 years (IQR 4· 1–8· 0) sentinel node negative: 5· 1 years (IQR 3· 9–6· 3) **Age:** Axillary radiotherapy: 55 (48-63) Axillary lymph node dissection: 56 (48-64) **Inclusion criteria**: patients with T1–2 primary, unifocal,			recurrence-free survival is analogous to overall survival <u>disease-free survival (DFS)</u> axillary lymph node dissection group: 86.9%; 95% CI 84.1–89.3 axillary radiotherapy group: 82· 7%; 95% CI 79.3–85.5) HR 1.18; 95% CI 0.93–1.51; p=0.18 <u>overall survival</u> 5-year overall survival axillary lymph node dissection group: 93· 3%; 95% CI 91.0–95.0 axillary radiotherapy group: 92.5%; 95% CI 90.0–94.4 HR 1.17, 95% CI 0.85–1.62; p=0.34 <u>shoulder mobility</u>	distribution of sentinel-node-positive patients in the two treatment groups: no suggestion of a possible bias was identified 5-year axillary recurrences were far less common than what was hypothesised and therefore the trial's primary test was underpowered **Additional concerns about quality**: none **Level of Evidence:** Oxford 2011 Level 2 **Sources of funding:** EORTC financial support from grants 2U10 CA11488-28 through

Source: Donker M, Tienhoven G, Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS) a randomised, multicenter open label, phase 3 non inferiority trial. Lancet Oncol 2014;15: 1333-10					
	invasive breast cancer, with no palpable lymphadenopathy Patients had to be fit to undergo any of the treatment procedures and be able to comply with the follow-up schedule Patients with tumours of up to 3 cm diameter <u>amendment 02/2008</u> broadened to include tumours up to 5 cm diameter or multifocal disease, or both Furthermore, sentinel nodes with only isolated tumour cells were no longer regarded as sentinel node positive **Exclusion**:			Range of motion in the four excursions (abduction, adduction, anteversion, and retroversion) did not differ significantly between the two treatment groups at both timepoints (1 year: p=0· 29; 5 years: p=0· 47) <u>lymphoedema</u> noted significantly more often after axillary lymph node dissection than after axillary radiotherapy at every measured timepoint significant at 5 years: axillary lymph node dissection group: 39 (6%) of 655 patients	5U10 CA011488-38 from the US National Cancer Institute (Bethesda, MD, USA) and donation from the Kankerbestrijding/KWF from the Netherlands through the EORTC Charitable Trust

Source: Donker M, Tienhoven G, Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS) a randomised, multicenter open label, phase 3 non inferiority trial. Lancet Oncol 2014;15: 1333-10

	medical history of previous malignancy, had received neoadjuvant systemic treatment for the primary breast cancer, or had received treatment of the axilla by surgery or radiotherapy			axillary radiotherapy group: 11 (2%) of 586 patients; received both radiation and surgery to the axilla By excluding patients who receivedboth treatments, the difference in rates of lymphoedema between the axillary lymph node dissection and axillary radiotherapy group remained significant <u>QoL</u> No statistically significant and clinically relevant differences were noted between groups for any of the selected scales	

Abbreviations:

IQR = Interquartile Range

DFS = Disease-Free Survival

Source: Donker M, Tienhoven G, Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS) a randomised, multicenter open label, phase 3 non inferiority trial. Lancet Oncol 2014;15: 1333-10

QoL = Quality of Life

RCT = Randomised Controlled Trial

HR = Hazard Ratio

95% CI = 95% Confidence Interval

Verknüpfte Empfehlungen:

Empfehlung 4.119:

Wenn bei Patientinnen mit befallenen axillären Wächterlymphknoten (> 2 mm) keine axilläre Dissektion erfolgt ist, sollte das klinische Zielvolumen der adjuvanten Strahlentherapie neben der Brust bzw. Thoraxwand die axillären Level I-IV mit erfassen.

Literaturreferenzen: [102], [103], [195], [196]

Source: Galimberti V, Cole BF, Viale G, Veronesi P, Vicini E, Intra M, Mazzarol G, Massarut S, Zgajnar J, Taffurelli M, Littlejohn D, Knauer M, Tondini C, Di Leo A, Colleoni M, Regan MM, Coates AS, Gelber RD, Goldhirsch A; International Breast Cancer Study Group Trial 23-01. **Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 tria**

l. Lancet Oncol. 2018 Oct;19(10): 1385-1393. doi: 10.1016/S1470-2045(18)30380-2. Epub 2018 Sep 5. PMID: 30196031

Aim and Country	Design and participants	Intervention	Outcomes	Results	Quality and comment
Acronym of study: IBCSG 23-01 **Aim**: 10-year follow-up results of the IBCSG 23-01 study (comparing disease-free survival in patients with breast cancer with one or more micrometastatic (≤2 mm) sentinel nodes randomly assigned to either axillary dissection or no axillary dissection)	**Design**: multicentre, randomised, controlled, open-label, non-inferiority, phase 3 trial **Enrollment**: 27 hospital and cancer centers **Number of included patients**: Randomized: n=934 Analyzed: n=931;	**Intervention** axillary dissection **Control** no axillary dissection	**Primary Outcome**: disease-free survival **Secondary Outcome**: overall survival systemic disease-free survival axillary failure assessment of sites of first failure long-term surgical complications	**Primary Outcome**: disease-free survival no axillary dissection group compared with axillary dissection group HR 0.85, 95% CI 0.65–1.11; log-rank p=0.24; p=0.0024 for non-inferiority **Secondary Outcome**:	**Quality of study** assessed with SIGN checklist for RCT: acceptable (+) **Limitations by authors** accrual was stopped before the projected number of patients was recruited study was under powered to demonstrate non-inferiority

Source: Galimberti V, Cole BF, Viale G, Veronesi P, Vicini E, Intra M, Mazzarol G, Massarut S, Zgajnar J, Taffurelli M, Littlejohn D, Knauer M, Tondini C, Di Leo A, Colleoni M, Regan MM, Coates AS, Gelber RD, Goldhirsch A; International Breast Cancer Study Group Trial 23-01. **Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 tria**

l. Lancet Oncol. 2018 Oct;19(10): 1385-1393. doi: 10.1016/S1470-2045(18)30380-2. Epub 2018 Sep 5. PMID: 30196031

Country: Australia, Belgium, Denmark, France, Italy, New Zealand, Peru, Slovenia, and Switzerland	axillary dissection: n=464 (n=447 analyzed for safety [as treated]); no axillary dissection: n=467 (n=453 analyzed for safety [as treated]) **Age group:** n.a. **Inclusion criteria**: women of any age with clinical, mammographic, ultrasonographic, or pathological diagnosis of breast cancer; diameter of 5 cm or smaller only micrometastases in the sentinel nodes **Median follow-up time:** 9.7 years (IQR 7.8-12.7) **Exclusion**:		up to 5-years after treatment	<u>overall survival</u> no axillary dissection group compared with axillary dissection group HR 0.78; 95% CI 0.53–1.14; log-rank p=0.20 <u>systemic disease-free survival</u> comparing any systemic therapy with no systemic therapy HR of 0.81 (95% CI 0.45–1.48; p=0.50) <u>axillary failure</u> 7 of the 845 patients who received breastconserving surgery (<1%) had axillary failure	analysis of this 10-year follow-up was protocol-driven, based on the 5-year follow-up analyses, it was not prespecified in the study protocol and thus was not adjusted for multiple, sequential testing 10-year results of IBCSG 23-01 are useful for estimating long-term trends, they should not be interpreted as independent confirmation of the results reported at 5 years **Additional concerns about quality**: **Level of Evidence:** Oxford 2011 Level 3

Source: Galimberti V, Cole BF, Viale G, Veronesi P, Vicini E, Intra M, Mazzarol G, Massarut S, Zgajnar J, Taffurelli M, Littlejohn D, Knauer M, Tondini C, Di Leo A, Colleoni M, Regan MM, Coates AS, Gelber RD, Goldhirsch A; International Breast Cancer Study Group Trial 23-01. **Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 tria**

l. Lancet Oncol. 2018 Oct;19(10): 1385-1393. doi: 10.1016/S1470-2045(18)30380-2. Epub 2018 Sep 5. PMID: 30196031

	previous or concomitant malignancy, pure ductal carcinoma in situ, previous systemic therapy for breast cancer, cancer chemoprevention treatment in the preceding year, distant metastases, palpable axillary nodes, or Paget's disease without invasive cancer Pregnant or lactating women			assessment of sites of first failure n.a. long-term surgical complications up to 5-years after treatment lymphoedema of any grade in 16 (4%) of 453 patients in the no axillary dissection group and 60 (13%) of 447 in the axillary dissection group, sensory neuropathy of any grade in 57 (13%) in the no axillary dissection group versus 85 (19%) in the axillary dissection group, and motor neuropathy of any grade (14 [3%] in the no axillary dissection group vs 40	(downgrade: underpowered study) **Sources of funding:** IBCSG 23-01 was supported by the centres that enrolled the women, and the International Breast Cancer Study Group (Partly funded by: the Swiss Group for Clinical Cancer Research; the Swiss Cancer League/Cancer Research Switzerland/Oncosuisse, Frontier Science and Technology Research Foundation; The Cancer Council Australia; The Australian New Zealand Breast Cancer Trials Group (National Health Medical Research Council); The Swedish

Source: Galimberti V, Cole BF, Viale G, Veronesi P, Vicini E, Intra M, Mazzarol G, Massarut S, Zgajnar J, Taffurelli M, Littlejohn D, Knauer M, Tondini C, Di Leo A, Colleoni M, Regan MM, Coates AS, Gelber RD, Goldhirsch A; International Breast Cancer Study Group Trial 23-01. **Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 tria**

l. Lancet Oncol. 2018 Oct;19(10): 1385-1393. doi: 10.1016/S1470-2045(18)30380-2. Epub 2018 Sep 5. PMID: 30196031

				[9%] in the axillary dissection group).	Cancer Society; and The Foundation for Clinical Cancer Research of Eastern Switzerland.)

Abbreviations:

RCT = Randomised Controlled Trial

IQR = Interquartile Range

HR = Hazard Ratio

95% CI = 95% Confidence Interval

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.119:

Wenn bei Patientinnen mit befallenen axillären Wächterlymphknoten (> 2 mm) keine axilläre Dissektion erfolgt ist, sollte das klinische Zielvolumen der adjuvanten Strahlentherapie neben der Brust bzw. Thoraxwand die axillären Level I-IV mit erfassen.

Empfehlung 4.120:

Sind nur 1-2 axilläre Wächterlymphknoten befallen (> 2 mm) und besteht ansonsten keine Indikation zur Lymphabflussbestrahlung, kann in dieser Situation ein Verzicht auf die Bestrahlung von Level III-IV und des kranialen Anteils von Level I-II (obere Feldgrenze des PTV bis 5 mm unterhalb der V. axillaris) erwogen werden.

Literaturreferenzen: [102], [103], [195], [196]

Source: Sávolt Á, Péley G, Polgár C, Udvarhelyi N, Rubovszky G, Kovács E, Győrffy B, Kásler M, Mátrai Z. Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial. Eur J Surg Oncol. 2017 Apr;43(4): 672-679. doi: 10.1016/j.ejso.2016.12.011. Epub 2017 Jan 16. PMID: 28139362.

Aim and Country	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: prove equivalent survival and locoregional control for patients with axillary lymph node metastasis by SLNB with reduced morbidity if treated with RNI instead of cALND **Country**: Hungary	**Design**: randomized, single centre, phase III, non-inferiority trial **Enrollment**: Between August 2002 and June 2009 (Sávolt 2013) **Number of included patients**: 474 **Mean Age (range):**	**Intervention** regional nodal irradiation (RNI) (50Gy) **Control** completion of axillary lymph node dissection (cALND)	**Primary Outcome**: axillary recurrence **Secondary Outcome**: Overall survival (OS) Disease-free survival (DFS) ***Other***	**Primary Outcome**: axillary recurrence cALND: 5 of 244(2%) RNI 4 of 230 (1.7%) p=1.00 **Secondary Outcome**: Overall survival (OS)	**Quality of study** assessed with SIGN checklist for RCT: low quality (-) **Limitations by authors** n.a. **Additional concerns about quality**:

Source: Sávolt Á, Péley G, Polgár C, Udvarhelyi N, Rubovszky G, Kovács E, Győrffy B, Kásler M, Mátrai Z. Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial. Eur J Surg Oncol. 2017 Apr;43(4): 672-679. doi: 10.1016/j.ejso.2016.12.011. Epub 2017 Jan 16. PMID: 28139362.					
	cALND: 54.7 (26-74) RNI: 55.2 (27-74) **Mean length of follow-up (range):** 97 months (54-134) cALND: 97.7 months (55-134) RNI: 95.6 months (54-133) **Inclusion criteria**: Patients with cT 3 cm, cN0 primary invasive breast cancer **Exclusion**: n.a.		Quality of life (QoL)	cALND: 190 (77.9%) RNI: 195 (84.8%) p=0.060 *8-year of follow-up* Died because of breast cancer cALND: 34 (13.9%) of 244 RNI: 20 (8.7%) Died of other reason cALND: 20 (8.2%) RNI: 15 (6.5%) Disease-free survival (DFS) cALND: 176 (72.1%) RNI: 178 (77.4%) p=0.51 ***Other*** QoL	Randomization process not described single patient characteristics differ (pathological tumor size; Arm A smaller than in Arm B) **Level of Evidence:** Oxford 2011 Level 3 (downgrade due to low quality) **Sources of funding:** n.a.

Source: Sávolt Á, Péley G, Polgár C, Udvarhelyi N, Rubovszky G, Kovács E, Győrffy B, Kásler M, Mátrai Z. Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial. Eur J Surg Oncol. 2017 Apr;43(4): 672-679. doi: 10.1016/j.ejso.2016.12.011. Epub 2017 Jan 16. PMID: 28139362.					
				No statistically significant and clinically relevant differences	

Abbreviations:

SLNB = Sentinel Lymph Node Biopsy

RNI = Regional Nodal Irradiation

cALND = completion of Axillary Lymph Node Dissection

cT = clinical Tumor Size

OS = Overall Survival

DFS = Disease-Free Survival

QoL = Quality of Life

RCT = Randomised Controlled Trial

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.119:

Wenn bei Patientinnen mit befallenen axillären Wächterlymphknoten (> 2 mm) keine axilläre Dissektion erfolgt ist, sollte das klinische Zielvolumen der adjuvanten Strahlentherapie neben der Brust bzw. Thoraxwand die axillären Level I-IV mit erfassen.

Literaturreferenzen: [102], [103], [195], [196]

Source: Alkner S; Wieslander E; Lundstedt D; Berg M; Kristensen I; Andersson Y, et al. Quality assessment of radiotherapy in the prospective randomized SENOMAC trial. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology. 2024;197: 110372

Aim and Country	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Report of RT quality assessment (QA) of the SENOMAC trial Adherence to guidelines regarding dose to targets and organs at risk (OAR) was evaluated, as well as fractionation schedule, the use of boost, intended target volumes, and concordance between data reported in the eCRF (electronic case report form) and the actual RT plan	**Design**: prospective randomized multicenter trial **Setting**: center **Enrollment**: n.a. **Number of included patients**: N=1176 N= 874 swedish N= 302 danish (randomized 1: 1) **Age group:** n.a. **Inclusion criteria**:	**Intervention** completion axillary lymph node dissection (cALND) **Control** sentinel lymph node (SLN) biopsy		3% of patients (N = 42/1271) did not receive or complete the prescribed RT Patients receiving a complete RT course, treatment plans were retrievable in 96 % (N = 1176/1229) Recommended criteria for target coverage of the breast/chest wall were fulfilled in 94 % of patients	**Quality of study** assessed with SIGN checklist for RCT: acceptable (+) **Limitations by authors** Guidelines for including level I, differed between countries and sites. Although agreement between eCRF data and the RT plan assessment was high in relation to whether regional RT had been given or not, information on whether

Source: Alkner S; Wieslander E; Lundstedt D; Berg M; Kristensen I; Andersson Y, et al. Quality assessment of radiotherapy in the prospective randomized SENOMAC trial. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology. 2024;197: 110372					
investigated how dose to level I and the humeral head was affected by whether level I was intentionally included in the target. **Country**: Sweden, Denmark	cN0 breast cancer and 1-3 SLN macrometastases **Exclusion**: n.a.			(N = 1072/1136, 40 RT plans not evaluable), and of the nodes in 97 % (N = 1097/1136) The internal mammary nodes (IMN) was included in 14 % of Swedish and > 99 % of Danish patients. Inclusion increased mean dose to the ipsilateral lung from 23.8 % to 30.0 % (p < 0.001) of the prescribed dose and mean heart dose from 0.6 Gy to 0.9 Gy (p < 0.001) in right-sided treatment. No increase in heart dose was observed for left-sided RT eCRF data agreed with the RT plan in 99 % (N = 1146/1154) regarding receipt of breast/chest wall RT 97 %	level I was an intended target was less correct. There was a systematic difference in inclusion of level I between randomization arms in Danish SENOMAC patients due to national guidelines **Additional concerns about quality**: Methodological approach is not explained in detail **Level of Evidence:** Oxford 2011 Level 2 **Sources of funding:** RT quality assessment received funding from Skåne University Hospital's Foundations, grant number: Alkner 2019-2021, and the Percy Falk's Foundation, grant number Alkner 2018

Source: Alkner S; Wieslander E; Lundstedt D; Berg M; Kristensen I; Andersson Y, et al. Quality assessment of radiotherapy in the prospective randomized SENOMAC trial. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology. 2024;197: 110372					
				(N = 1115/1154) regarding nodal RT eCRF data regarding inclusion/exclusion of level I agreed with the RT plan in 78 % of patients (N = 665/853) Danish patients: 31 % (N = 174/565) of the cALND arm had level I as an intended target and 55 % (N = 334/611) of the SLN biopsy only arm; p<0.001 Level I dose was evaluated in the 60 Swedish patients and in 210 Danish patients Median V90% for level I was 100 %, and D90% 95 % of the prescribed Dose (Due to the tangential field technique most often used in breast	The SENOMAC trial received funding from the Swedish Research Council (grant numbers 2015-00760 and 2021-02128), the Swedish Cancer Society (grant numbers CAN 2015/437 and 22 2061 Pj), the Nordic Cancer Union (grant numbers R217-A13260 and R241-A14982), and the Swedish Breast Cancer Association. The RT quality assessment received funding from Skåne University Hospital's Foundations, grant number: Alkner 2019-2021, and the Percy Falk's Foundation, grant number Alkner 2018.

Source: Alkner S; Wieslander E; Lundstedt D; Berg M; Kristensen I; Andersson Y, et al. Quality assessment of radiotherapy in the prospective randomized SENOMAC trial. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology. 2024;197: 110372

				cancer RT) a high dose coverage of level I was found also in patients where it was not an intended target level I caused a median V90% (i.e. clinically full dose) of 83 % For Danish patients, median D90% for level I was: SLN biopsy only: 95 % (IQR 94–95 %) cALND: 89 % (IQR 72–94 %) Inclusion of level I in the target volume significantly increased dose to the humeral head (p<0.001) When level I was not an intentional target, ≥50 % of the humeral	

Source: Alkner S; Wieslander E; Lundstedt D; Berg M; Kristensen I; Andersson Y, et al. Quality assessment of radiotherapy in the prospective randomized SENOMAC trial. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology. 2024;197: 110372

				head received a median of 6 % of the prescribed dose Inclusion level Idose was increased to 13 %	

Abbreviations:

QA = Quality Assessment

OAR = Organs at Risk

eCRF = Electronic Case Report Form

cALND = completion Axillary Lymph Node Dissection

SLN = Sentinel Lymph Node

RT = Radiotherapy

IMN = Internal Mammary Nodes

RCT = Randomised Controlled Trial

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.119:

Wenn bei Patientinnen mit befallenen axillären Wächterlymphknoten (> 2 mm) keine axilläre Dissektion erfolgt ist, sollte das klinische Zielvolumen der adjuvanten Strahlentherapie neben der Brust bzw. Thoraxwand die axillären Level I-IV mit erfassen.

Literaturreferenzen: [102], [103], [195], [196]

Source: Bartels SAL, Donker M, Poncet C, et al (2022) Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial. J Clin Oncol JCO2201565. https: //doi.org/10.1200/jco.22.01565

Aim and Country	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Evaluation of axillary lymph node dissection (ALND) versus axillary radiotherapy (ART) in patients with cT1-2, nodenegative breast cancer and a positive sentinel node (SN) biopsy **Country:** 9 European countries	**Design**: open-label multicenter phase III noninferiority trial **Setting**: 29 center **Enrollment**: 34 centers enrolled patients **Number of included patients**: 1,425 **Median age (Range)** [Straver et al. 2010]: ALND: 56 (24-83) ART: 55 (32-82) **Inclusion criteria**:	**Intervention** axillary lymph node dissection (ALND) **Control** axillary radiotherapy (ART) **Study flow** 10-year analysis of ARR, OS, and DFS, and an updated 5-year analysis of morbidity and quality of life	Axillary recurrence rate (ARR) Overall survival (OS) Disease-free survival (DFS) Morbidity and quality of life Locoregional recurrences Distant progression Second primary cancers	Axillary recurrence rate (ARR) Axillary recurrences occurred in 7 (0.9%) of 744 patients after ALND 11 (1.6%) of 681 patients after ART Ten-year cumulative incidence after ALND: 0.93% (95% CI, 0.18 to 1.68) ART: 1.82% (95% CI, 0.74 to 2.94) after	**Quality of study** assessed with SIGN checklist for RCT: acceptable (+) **Limitations by authors** n.a. **Additional concerns about quality**: No information found about the participating countries **Level of Evidence:** Oxford 2011 Level 2 **Sources of funding:**

Source: Bartels SAL, Donker M, Poncet C, et al (2022) Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial. J Clin Oncol JCO2201565. https: //doi.org/10.1200/jco.22.01565					
	patients with clinically node-negative cT1-2 primary breast cancer and a positive SN ALND included at least anatomic level I and II and ≥ 10 nodes **Exclusion** [Straver et al. 2010]: metastatic disease previous treatment of the axilla by surgery or radiotherapy previous treatment of cancer (except basal cell carcinoma of the skin and in situ carcinoma of the cervix) pregnancy			HR, 1.71; 95% CI, 0.67 to 4.39 <u>Overall survival (OS)</u> Ten-year OS rate ALND: 84.6% (95% CI, 81.5 to 87.1) ART: 81.4% (95% CI, 77.9 to 84.4) HR 1.17; 95% CI, 0.89 to 1.52; P=0.26 <u>Disease-free survival (DFS)</u> Ten-year DFS rate ALND: 75.0% (95% CI, 71.5 to 78.2) ART: 70.1% (95% CI, 66.2 to 73.6) HR 1.19; 95% CI, 0.97 to 1.46; P=0.11 <u>Morbidity and quality of life</u>	Sponsored by the EORTC with financial support from the Kankerbestrijding/KWF from the Netherlands through the EORTC Cancer Research Fund (ECRF)

Source: Bartels SAL, Donker M, Poncet C, et al (2022) Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial. J Clin Oncol JCO2201565. https: //doi.org/10.1200/jco.22.01565					
				Updated data (175 patients extra) show that lymphedema was observed and treated significantly more often after ALND than after ART at every measured time point, with the highest incidence at 1 year 44.2% of the patients reported lymphedema at any time point after ALND compared with 28.6% of the patients after ART Increase in arm circumference of at least 10% was also measured more frequently after	

Source: Bartels SAL, Donker M, Poncet C, et al (2022) Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial. J Clin Oncol JCO2201565. https: //doi.org/10.1200/jco.22.01565					
				ALND Shoulder mobility was measured in 159 extra patients, but was similar in the two treatment arms at both time points QoL: no statistical differences were observed For two items of the arm symptoms scale, a statistically significant difference was now observed: more swelling of the arm/hand was reported after ALND and more difficulties moving the arm were reported after ART no clinical significance <u>Locoregional recurrences</u> 10-year cumulative	

Source: Bartels SAL, Donker M, Poncet C, et al (2022) Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial. J Clin Oncol JCO2201565. https: //doi.org/10.1200/jco.22.01565

				incidence was ALND: 3.6% (95% CI, 2.1 to 5.1) ART: 4.1% (95% CI, 2.5 to 5.7) HR, 1.13; 95% CI, 0.65 to1.20; P=0.69 <u>Distant progression</u> ALND: 89 patients (12.0%) ART: 99 patients (14.5%) Most common sites of first distant progression were bone, 62 events (33.0%), and simultaneous bone and visceral metastasis, 37 events (19.7%) <u>Second primary cancers</u> 10-year cumulative incidence was ART: 12.1% (95% CI, 9.6 to 14.9)	

Source: Bartels SAL, Donker M, Poncet C, et al (2022) Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial. J Clin Oncol JCO2201565. https: //doi.org/10.1200/jco.22.01565

				ALND: 8.3% (95% CI, 6.3 to 10.7) HR 1.45; 95% CI, 1.03 to 2.04; P=0.035	

Abbreviations:

ALND = Axillary Lymph Node Dissection

ART = Axillary Radiotherapy

SN = Sentinel Node

OS = Overall survival

QoL = Quality of Life

DFS = Disease-free survival

ARR = Axillary Recurrence Rate

RCT = Randomised Controlled Trial

HR = Hazard Ratio

95% CI = 95% Confidence Interval

Verknüpfte Empfehlungen:

Empfehlung 4.120:

Sind nur 1-2 axilläre Wächterlymphknoten befallen (> 2 mm) und besteht ansonsten keine Indikation zur Lymphabflussbestrahlung, kann in dieser Situation ein Verzicht auf die Bestrahlung von Level III-IV und des kranialen Anteils von Level I-II (obere Feldgrenze des PTV bis 5 mm unterhalb der V. axillaris) erwogen werden.

Literaturreferenzen: [196], [103], [127], [197], [198], [199]

Source: Algara M, Rodriguez E, Martinez-Arcelus FJ et al. OPTimizing Irradiation through Molecular Assessment of Lymph node (OPTIMAL): a randomized clinical trial Radiother Oncol. 2022 Nov: 176: 76-82.

Aim and Country	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: To demonstrate the noninferiority of incidental irradiation of axillary nodes in comparison to intentional irradiation in terms of the 5-year DFS, in patients with early-stage BC cN0 and limited involvement of the SLN with a similar profile to Z011 trial. **Country**: Spain, Portugal, Italy	**Design**: multicentric, international, open-label, parallel group randomized clinical trial **Setting**: hospitals **Enrollment**: Radiation Oncology Departments of hospitals **Number of included patients in ITT analysis**: 442 (Intentional irradiation: n=220	**Intervention** Incidental irradiation (total dose of 50 Gy in the whole breast, but not aimed at nodal areas, with optimization of the technique, in daily fractions of 2 Gy and 5 fractions/week during 5 weeks.) **Control** Intentional irradiation (total dose of 50 Gy in the whole breast and	**Primary Outcome**: 5-years disease-free survival (DFS) **Secondary Outcome**: Locoregional recurrence (LRR) Distant recurrence (DR) Acute and chronic toxicity	**Primary Outcome**: 5-years disease-free survival INC: 93.7% INT: 93.8% with a difference of 0.1% (onesided 95% CI: <5.7%; non-inferiority p = 0.075) **Secondary Outcome**: Locoregional recurrence n= 9	**Quality of study** assessed with SIGN checklist for RCT: acceptable (+) **Limitations by authors** consequent loss of power might be the reason why it failed to show non-inferiority in terms of 5-y DFS for the pre-specified margin of 5% the median

Source: Algara M, Rodriguez E, Martinez-Arcelus FJ et al. OPTimizing Irradiation through Molecular Assessment of Lymph node (OPTIMAL): a randomized clinical trial Radiother Oncol. 2022 Nov: 176: 76-82.					
	Incidental irradiation: n=222) Trial was sized to show that INC is non-inferior to INT, with a non-inferiority margin of 1.373 for the HR, assuming 5-y DFS of 0.85 (INT) and 0.80 (INC) **Mean age (SD):** 57 (10) [both groups] **Inclusion criteria**: Patients with breast infiltrating ductal carcinoma in stages T1 or T2 and cN0, treated with BCS (tumorectomy or quadrantectomy) without lymphadenectomy 18 years or older had SLN assessed by OSNA, with TTL in the range of 250 –	nodal areas (axillary I, II, III, and supraclavicular) with optimization of the technique, in daily fractions of 2 Gy and 5 fractions/week during 5 weeks)		5-years Incidence of LRR: INC: 3.5% INT: 3.4% difference of 0.1% (one-sided 95% CI: <4.8%; non-inferiority p = 0.021) <u>Distant recurrence</u> n= 11 5-years Incidence DR INC: 5% INT: 3.5% difference of 1.4% (one-sided 95% CI: <6.0%; non-inferiority p = 0.101) <u>Acute toxicity</u> INC: 199 (89.6%) INT: 191 (86.8%) chi-square test, p = 0.55 Most acute toxicity	follow-up length was 3.7 years, with less than 100 patients per group followed for more than 3 years some randomized patients had to be excluded from the analysis due to a lack of follow-up data, and post-randomization exclusions can be a source of bias **Additional concerns about quality**: trial was prematurely terminated due to low recruitment before the first interim analysis, and therefore a single (final) analysis was done using the usual 5% significance level (max. sample size of 1422 patients was

Source: Algara M, Rodriguez E, Martinez-Arcelus FJ et al. OPTimizing Irradiation through Molecular Assessment of Lymph node (OPTIMAL): a randomized clinical trial Radiother Oncol. 2022 Nov: 176: 76-82.					
	15,000 copies/IL a Karnofsky Index ≥70% consented to participate **Exclusion**: other types of BC or bilateral BC males mastectomy or axillary homolateral LN dissection previous thoracic radiotherapy neoadjuvant therapies, contraindications for radiotherapy (pregnancy, severe collagen diseases) other neoplasms severe associated comorbidities that could interfere with the study evaluations			events were mild or moderate (CTCAE grades 1or 2) Grade 3 dermatitis radiation occurred in INC: 13 (5.86%) INT: 21 (9.55%) <u>5-y cumulative Incidence of chronic toxicity</u> INC: 19.2% INT: 26.9% HR: 1.39; 95% CI 0.92-2.10; log-rank p = 0.11	anticipated to provide 80% power) **Level of Evidence:** Oxford 2011 Level 3 (downgraded due to low recruting and sample size) **Sources of funding:** Sysmex Europe and Sysmex España S.L. provide technical and financial support.
Abbreviations:					

Source: Algara M, Rodriguez E, Martinez-Arcelus FJ et al. OPTimizing Irradiation through Molecular Assessment of Lymph node (OPTIMAL): a randomized clinical trial Radiother Oncol. 2022 Nov: 176: 76-82.

DFS = Disease-Free Survival

BC = Breast Cancer

SLN = Sentinel Lymph Node

SD = Mean

OSNA = One-Step Nucleic Acid Amplification

TTL = Total Tumor Load

LN = Lymph Nodes

DR = Distant recurrence

LRR = Locoregional recurrence

INC = Incidental

INT = Intentional

ITT = Intention-To-Treat

RCT = Randomised Controlled Trial

HR = Hazard Ratio

95% CI = 95% Confidence Interval

Verknüpfte Empfehlungen:

Empfehlung 4.120:

Sind nur 1-2 axilläre Wächterlymphknoten befallen (> 2 mm) und besteht ansonsten keine Indikation zur Lymphabflussbestrahlung, kann in dieser Situation ein Verzicht auf die Bestrahlung von Level III-IV und des kranialen Anteils von Level I-II (obere Feldgrenze des PTV bis 5 mm unterhalb der V. axillaris) erwogen werden.

Literaturreferenzen: [196], [103], [127], [197], [198], [199]

Source: Jagsi R, Manjoet C, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) trial. J Clin Oncol 2014;Nov 10;32(32): 3600-6					
Aim and Country	Design and participants	Intervention	Outcomes	Results	Quality and comment
Acronym of study: ACOSOG Z0011 **Aim**: Review the radiotherapy (RT) treatment records to determine if there were differences in RT delivery based on extent of axillary surgery **Country**: USA	**Design**: multicenter, randomized phase 3 noninferiority trial **Enrollment**: 05/1999-12/2004 **Number of included patients**: n=891; allocated to ALND: n=445 (n=420 primary trial analysis); allocated to SLND: n=446 (n=436 primary trial analysis) **Mean age (SD)**	**Intervention** ALND **Control** SLND	**Primary Outcome**: n.a. **Secondary Outcome**: n.a.	n= 228 patients with detailed RT records ductal tumors in this subgroup: ALND 76.5% SLND: 86.9% P=0.047 High-tangent RT fields ALND: 50.0% (33 of 66) SLND: 52.6% (40 of 76) Patients receiving nodal RT had a greater number of lymph nodes involved	**Quality of study** assessed with SIGN checklist for RCT: acceptable (+) **Limitations by authors** Detailed RT records were only available for approximately one third of patients known to have received RT Long time elapsed since treatment: retrieval of these records, loss

Source: Jagsi R, Manjoet C, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) trial. J Clin Oncol 2014;Nov 10;32(32): 3600-6					
	ALND: 56.1 (11.2) SLND: 54.9 (10.6) **Inclusion criteria**: women with clinical T1-T2 invasive breast cancer 5cm or less, no palpable adenopathy, and 1 to 2 SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section **Exclusion**: 3 or more positive SLNs, matted nodes, or gross extranodal disease, received neoadjuvant hormonal therapy or chemotherapy			than those who did not (p<0.001) 0 nodes: n=3 (all SLND arm) One of them: received directed nodal RT; using at least one third supraclavicular field 1 node: n= 140 ALND: n= 55 SLND: n= 85 2 nodes: n=44 ALND: n= 19 SLND: n= 25 3 nodes: n=9 ALND: n= 6 SLND: n= 3 4 nodes: n= 16 ALND: n= 14 SLND: n= 2	of archived records, inability to reach treating physicians (moved/died) Three-dimensional treatment planning was not performed for all patients **Additional concerns about quality**: Randomization process not described **Level of Evidence:** Oxford 2011 Level 2 **Sources of funding:** AbbVie: Pharmaceutical Research & Development
Abbreviations:					

Source: Jagsi R, Manjoet C, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) trial. J Clin Oncol 2014;Nov 10;32(32): 3600-6

RT = Radiotherapy

ALND = Axillary Lymph Node Dissection

SLN = Sentinel Lymph Nodes

SLND = Sentinel Lymph Node Dissection

SD = Standard Deviation

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.125:

Eine adjuvante endokrine Therapie kann unabhängig von der Radiotherapie eingeleitet werden.

Literaturreferenzen: [200], [201], [202], [203], [204], [205], [206], [207], [208]

Source: C, Matuschek, Bölke E, Haussmann J, Mohrmann S, Nestle-Krämling C, Gerber PA, Corradini S, et al. "The Benefit of Adjuvant Radiotherapy after Breast Conserving Surgery in Older Patients with Low Risk Breast Cancer- a Meta-Analysis of Randomized Trials." [In eng]. Radiation oncology (London, England) 12, no. 1 (2017-3-23 2017): 60. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/28335784/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: to investigate the importance of additional adjuvant radiotherapy in patients with low risk breast cancer	**Design**: Systematic Review and Meta-Analysis **Search date**: n.a. **Searched databases**: PubMed **Included study designs**: RCT **Number of included studies**: 5 **Number of included patients**: 3,766 **Mean/median age**: n.a. **Inclusion criteria**:	**Intervention** Addition of whole breast radiotherapy to endocrine therapy after breast conserving therapy **Control** Endocrine therapy without radiotherapy	**Primary Outcome**: Local tumor relapse; Death from any cause **Secondary Outcome**: side effects	**Primary Outcome**: **Local tumor relapse** Follow-up: 10-20 years Tamoxifen alone: shorter time to local relapse compared to combination (tamoxifen + RT) HR: 6.8, 95% CI: 4.23-10.93, p<0.0001 **Death from any cause** OR: 1.09, 95% CI 0.81-1.48, p=0.57 **Secondary Outcome**:	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 7 critical flaws (items 2, 4, 7, 9, 11, 13, 15) **Overall quality of evidence**: critically low **Sources of funding:** Thomas and Kim Speer, Germany

Source: C, Matuschek, Bölke E, Haussmann J, Mohrmann S, Nestle-Krämling C, Gerber PA, Corradini S, et al. "The Benefit of Adjuvant Radiotherapy after Breast Conserving Surgery in Older Patients with Low Risk Breast Cancer- a Meta-Analysis of Randomized Trials." [In eng]. Radiation oncology (London, England) 12, no. 1 (2017-3-23 2017): 60. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/28335784/.

	Mostly elderly women; early stage breast cancer			Side effects Summary: RT is well tolerated and does not impair quality of life	

Abbreviations:

RT = Radiation Therapy

RCT = Randomised Controlled Trial

OR = Odds Ratio

HR = Hazard Ratio

95% CI = 95% Confidence Interval

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.125:

Eine adjuvante endokrine Therapie kann unabhängig von der Radiotherapie eingeleitet werden.

Literaturreferenzen: [200], [201], [202], [203], [204], [205], [206], [207], [208]

Source: SF, McGee, Mazzarello S, Caudrelier JM, Lima MAG, Hutton B, Sienkiewicz M, Stober C, et al. "Optimal Sequence of Adjuvant Endocrine and Radiation Therapy in Early-Stage Breast Cancer - a Systematic Review." [In eng]. Cancer treatment reviews 69 (2018-9 2018): 132-42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30014951/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Does the sequence of adjuvant endocrine and radiation therapy in early-stage breast cancer impact on clinical outcomes including, treatment efficacy, disease recurrence, overall survival or treatment-related toxicity?	**Design**: Systematic review **Search date**: 1946 - 2017 **Searched databases**: PubMed, Ovid Medline, EMBASE, Cochrane CENTRAL, clinicaltrials.gov (until 01/2018) **Included study designs**: prospective (n= prospective randomized, n= prospective) and retrospective (n=)	**Intervention** Surgery, radiation, chemotherapy, and endocrine therapy **Control**	**Primary Outcome**: local, regional and distant recurrence, disease free survival (DFS) and overall survival (OS) **Secondary Outcome**: frequency of radiation and/or endocrine therapy treatment-related toxicity that included dermatitis, pneumonitis, skin and lung fibrosis	**Primary Outcome**: Treatment efficacy No evidence that concurrent aromataseinhibitors and radiotherapy had a detrimental impact on local recurrence, DFS, OS **Secondary Outcome**: Toxicity No evidence of increased treatment-realted toxicity with concurrent	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 3 critical flaws (items 4, 7, 13) **Overall quality of evidence**: critically low **Additional concerns about quality**: lack of prospective studies, only 1 phase 2 RCT available, many retrospective studies of poor quality, confounding factors

Source: SF, McGee, Mazzarello S, Caudrelier JM, Lima MAG, Hutton B, Sienkiewicz M, Stober C, et al. "Optimal Sequence of Adjuvant Endocrine and Radiation Therapy in Early-Stage Breast Cancer - a Systematic Review." [In eng]. Cancer treatment reviews 69 (2018-9 2018): 132-42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30014951/.					
	Number of included studies: n=13 **Number of included patients**: n=7,569 **Mean/median age**: n.a. **Inclusion criteria**: Women with early-stage, operable, breast cancer, post primary surgical management, and planned for both adjuvant radiation, and endocrine therapy. No restrictions regarding age, menopausal status, type of surgery, type of radiotherapy (including optional regional nodal irradiation and/or provision of a tumour bed boost), or endocrine therapy (tamoxifen or aromatase			aromatase inhibitors and radiotherapy Incidence of radiation dermatitis No difference with treatment sequence Clinical pneumotitis, alterations in pulmonary function testing, image detected pulmonary fibrosis No difference with sequence of treatment	frequently not controlled for; Duration of follow-up not sufficient for the assessment of recurrence or survival events in estrogen receptor positive breast cancer; Heterogeneity of outcome and toxicity endpoints hindering cross-study comparisons **Sources of funding:** No funding received.

Source: SF, McGee, Mazzarello S, Caudrelier JM, Lima MAG, Hutton B, Sienkiewicz M, Stober C, et al. "Optimal Sequence of Adjuvant Endocrine and Radiation Therapy in Early-Stage Breast Cancer - a Systematic Review." [In eng]. Cancer treatment reviews 69 (2018-9 2018): 132-42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30014951/.					
	inhibitor); The interventions included surgery, radiation, chemotherapy, and endocrine therapy; English language **Exclusion:** Studies in which concurrent radiation and endocrine therapy were compared with radiotherapy alone were excluded				

Abbreviations:

n.a. = not Available, not Applicable

OS = Overall Survival

DFS = Disease Free Survival

RCT = Randomised Controlled Trial

Verknüpfte Empfehlungen:

Empfehlung 4.129:

Eine Therapie mit Inhibitoren Cyclin-abhängiger Kinasen (CDK) oder der Poly(ADP-ribose)-Polymerase (PARP) sollte während der adjuvanten Strahlentherapie vermieden werden, da ausreichende Daten zur Sicherheit fehlen.

Literaturreferenzen: [209], [206]

Source Becherini C, Visani L, Caini S, Bhattacharya IS, Kirby AM, Nader Marta G, Morgan G, Salvestrini V, Coles CE, Cortes J, Curigliano G, de Azambuja E, Harbeck N, Isacke CM, Kaidar-Person O, Marangoni E, Offersen B, Rugo HS, Morandi A, Lambertini M, Poortmans P, Livi L, Meattini I. Safety profile of cyclin-dependent kinase (CDK) 4/6 inhibitors with concurrent radiation therapy: A systematic review and meta-analysis. Cancer Treat Rev. 2023 Sep;119: 102586. doi: 10.1016/j.ctrv.2023.102586. Epub 2023 Jun 15. PMID: 37336117.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To evaluate the safety profile of combining CDK4/6i with palliative and ablative RT in both metastatic and early breast cancer settings.	**Design**: Systematic review and meta-analysis **Search date**: January 1, 2000, to November 1, 2022 **Searched databases**: **:** Medline, Scopus, and Embase **Included study designs**: Retrospective **Number of included studies**: 11	CDK4/6i (palbociclib, ribociclib, or abemaciclib) combined with radiation therapy (RT)	**Primary Outcome**: Safety of the combination of RT and CDK4/6i in HR+/HER2- breast cancer patients, assessed based on the occurrence of toxicities of grade 3 or higher **Secondary Outcome**: Evaluation of the association between RT and any grade of toxicity, the rate of CDK4/6i dose reduction, and the rate of	Pooled incidence of all grade 3+ toxicity was 22% (95% CI, 0.08-0.39). Pooled incidence of grade 3+ hematologic toxicity was 14% (95% CI, 0.03-0.30). Pooled incidence of grade 3+ non-hematologic toxicity was 3% (95% CI, 0.01-0.05).	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: …; X critical flaws (items …) **Additional concerns about quality**: **Quality of included studies**: Most studies were judged at moderate overall risk of bias.

Source Becherini C, Visani L, Caini S, Bhattacharya IS, Kirby AM, Nader Marta G, Morgan G, Salvestrini V, Coles CE, Cortes J, Curigliano G, de Azambuja E, Harbeck N, Isacke CM, Kaidar-Person O, Marangoni E, Offersen B, Rugo HS, Morandi A, Lambertini M, Poortmans P, Livi L, Meattini I. Safety profile of cyclin-dependent kinase (CDK) 4/6 inhibitors with concurrent radiation therapy: A systematic review and meta-analysis. Cancer Treat Rev. 2023 Sep;119: 102586. doi: 10.1016/j.ctrv.2023.102586. Epub 2023 Jun 15. PMID: 37336117.

	Number of included patients: 382 **Median age (range)**: 57 years (30-91) **Inclusion criteria**: Cohorts of breast cancer patients with more than five consecutive patients. Studies investigating the administration of CDK4/6i in combination with either palliative or ablative RT. RT delivered for intracranial or extracranial disease. Study focused on the adjuvant or metastatic setting **Exclusion**: n.r.		CDK4/6i treatment discontinuation		**Level of evidence:** Oxford 2011: **Sources of funding**:

Abbreviations and comment:

Kapitel 4.5: Beeinflussbare Lebensstilfaktoren

Verknüpfte Empfehlungen:

Empfehlung 4.136:

Patientinnen sollten dahingehend beraten werden, dass Alkoholkonsum vor oder nach Diagnosestellung ein erhebliches Brustkrebsrisiko beziehungsweise Rezidivrisiko birgt. Bei einem übermäßigen Alkoholkonsum steigt das relative Risiko der Gesamtsterblichkeit. Patientinnen sollten einen täglichen Alkoholkonsum von >6g/Tag vermeiden.

Literaturreferenzen: [210], [211], [212], [213], [214]

Source: Nomura T, Kawai M, Fukuma Y, Koike Y, Ozaki S, Iwasaki M, Yamamoto S, Takamatsu K, Okamura H, Arai M, Ootani S, Iwata H, Saji S. Alcohol consumption and breast cancer prognosis after breast cancer diagnosis: a systematic review and meta-analysis of the Japanese Breast Cancer Society Clinical Practice Guideline, 2022 edition. Breast Cancer. 2023 Jul;30(4): 519-530. doi: 10.1007/s12282-023-01455-4. Epub 2023 Apr 8. PMID: 37029889; PMCID: PMC10284729.

Aim	Design and participants	Exposure	Outcomes	Results	Quality and comment
Aim: association of alcohol consumption and breast cancer recurrence	**Design**: Systematic Review and Meta-Analysis **Search date**: up to March 2021 **Searched databases**: PubMed, Cochrane Library, Ichushi Web Databases **Included study designs**: Cohort studies, case-control studies	Alcohol consumption	Breast cancer recurrence, breast cancer-specific death, all-cause and cardiovascular disease mortality	4,638 cases of recurrence, 12,209 cases of breast cancer-related mortality, 21,945 cases of all-cause mortality, and 7,727 cases of cardiovascular disease mortality	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low 5 critical flaws (items 2, 7, 11, 13, 15) **Quality of included studies**: Assessed with the Cochrane Risk of Bias Tool [taking into account

Source: Nomura T, Kawai M, Fukuma Y, Koike Y, Ozaki S, Iwasaki M, Yamamoto S, Takamatsu K, Okamura H, Arai M, Ootani S, Iwata H, Saji S. Alcohol consumption and breast cancer prognosis after breast cancer diagnosis: a systematic review and meta-analysis of the Japanese Breast Cancer Society Clinical Practice Guideline, 2022 edition. Breast Cancer. 2023 Jul;30(4): 519-530. doi: 10.1007/s12282-023-01455-4. Epub 2023 Apr 8. PMID: 37029889; PMCID: PMC10284729.					
	Number of included studies: 33 studies – of those: 32 cohorts 1 case-control study Of those: 24 studies pre-diagnosis alcohol consumption 7 post-diagnosis alcohol consumption and 2 pre- and post-diagnosis studies (not included in Meta-analysis) **Alcohol exposure:** varied from over 4 g/day to over 30 g/day **Number of included patients à** range: 149 and 251,420 **Mean/median age**: n.a.			Breast cancer recurrence, breast cancer-specific death, all-cause and cardiovascular disease mortality **1) Association between alcohol consumption and breast cancer recurrence** <u>7 pre-diagnosed studies</u> HR 1.02, 95% CI 0.77-1.37, p=0.88, I^2=69% <u>3 post-diagnosis studies</u> HR 0.96, 95% CI 0.85-1.10, p=0.57, I^2=0% **2) Association between alcohol consumption and breast cancer-related mortality** <u>21 pre-diagnosis studies</u> HR 1.02, 95% CI 0.93-1.11, p=0.69, I^2=60%	that all studies are observational, this might not be the best choice] Selection bias: unclear risk of bias (RoB) in 31 studies, high RoB in 2 studies Adjustment of confounding factors: unclear RoB in 5 studies, high RoB in 7 studies Attrition bias: unclear RoB in 5 studies, high RoB in 1 study Some studies did not account for confounding factors such as age, BMI, stage of initial breast cancer; alcohol consumption status was mainly based on questionnaire surveys – the exact amount and frequency of alcohol consumption are not

Source: Nomura T, Kawai M, Fukuma Y, Koike Y, Ozaki S, Iwasaki M, Yamamoto S, Takamatsu K, Okamura H, Arai M, Ootani S, Iwata H, Saji S. Alcohol consumption and breast cancer prognosis after breast cancer diagnosis: a systematic review and meta-analysis of the Japanese Breast Cancer Society Clinical Practice Guideline, 2022 edition. Breast Cancer. 2023 Jul;30(4): 519-530. doi: 10.1007/s12282-023-01455-4. Epub 2023 Apr 8. PMID: 37029889; PMCID: PMC10284729.					
	Median Follow-up: 31.56 months **Inclusion criteria**: n.a. **Exclusion**: breast cancer incidence, very low population numbers, and articles with missing outcome data			9 post-diagnosis studies HR 0.96, 95% CI 0.77-1.19, p=0.70, I²=38% *Subgroup analysis:* **Estrogen receptor (ER) expression status** 3 pre-diagnosis studies and 2 post-diagnosis studies **ER-positive cases:** HR 0.77, 95% CI 0.59-1.00, p=0.05, I²=0% **ER-negative cases:** HR 0.79, 95% CI 0.56-1.11, p=0.17, I²=39% **3) Association between alcohol consumption and all-cause mortality** 18 pre-diagnosis studies HR 0.90, 95% CI 0.82-0.98, p=0.02, I²=37%	known à possibility of underreporting High heterogeneity between pre-diagnosis alcohol consumption and breast cancer recurrence and breast cancer-related mortality: may be due to insufficient follow-up period in several studies and variability in the number of events; number of participants in included studies varied substantially **Level of Evidence:** Oxford 2011: Level of Evidence 3 **Sources of funding:** n.a.

Source: Nomura T, Kawai M, Fukuma Y, Koike Y, Ozaki S, Iwasaki M, Yamamoto S, Takamatsu K, Okamura H, Arai M, Ootani S, Iwata H, Saji S. Alcohol consumption and breast cancer prognosis after breast cancer diagnosis: a systematic review and meta-analysis of the Japanese Breast Cancer Society Clinical Practice Guideline, 2022 edition. Breast Cancer. 2023 Jul;30(4): 519-530. doi: 10.1007/s12282-023-01455-4. Epub 2023 Apr 8. PMID: 37029889; PMCID: PMC10284729.

				<u>7 post-diagnosis studies</u> HR 0.88, 95% CI 0.77-1.02, p=0.08, I^2=67% *Subgroup analysis:* Estrogen receptor (ER) expression status **ER-positive cases:** HR 0.79, 95% CI 0.68-0.92, p=0.003, I^2=4% **ER-negative cases:** HR 0.68, 95% CI 0.50-0.91, p=0.01 I^2=32% **4) Association between alcohol consumption and cardiovascular disease mortality** <u>2 post-diagnosis studies</u> HR, 0.47, 95% CI 0.28-0.79, p=0.005, I^2=0%	

Abbreviations:

Source: Nomura T, Kawai M, Fukuma Y, Koike Y, Ozaki S, Iwasaki M, Yamamoto S, Takamatsu K, Okamura H, Arai M, Ootani S, Iwata H, Saji S. Alcohol consumption and breast cancer prognosis after breast cancer diagnosis: a systematic review and meta-analysis of the Japanese Breast Cancer Society Clinical Practice Guideline, 2022 edition. Breast Cancer. 2023 Jul;30(4): 519-530. doi: 10.1007/s12282-023-01455-4. Epub 2023 Apr 8. PMID: 37029889; PMCID: PMC10284729.

ER = Estrogen receptor

HR = Hazard Ratio

95% CI = 95% Confidence Interval

RoB = Risk of Bias

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.136:

Patientinnen sollten dahingehend beraten werden, dass Alkoholkonsum vor oder nach Diagnosestellung ein erhebliches Brustkrebsrisiko beziehungsweise Rezidivrisiko birgt. Bei einem übermäßigen Alkoholkonsum steigt das relative Risiko der Gesamtsterblichkeit. Patientinnen sollten einen täglichen Alkoholkonsum von >6g/Tag vermeiden.

Literaturreferenzen: [210], [211], [212], [213], [214]

Source: Simapivapan P, Boltong A, Hodge A. To what extent is alcohol consumption associated with breast cancer recurrence and second primary breast cancer?: A systematic review. Cancer Treat Rev. 2016 Nov;50: 155-167. doi: 10.1016/j.ctrv.2016.09.010. Epub 2016 Sep 20. PMID: 27693930.

Aim	Design and participants	Exposure	Outcomes	Results	Quality and comment
Aim: association of alcohol intake and breast cancer recurrence or development of second primary breast cancer (BC) in the survivor population	**Design**: Systematic Review **Search date**: up to January 2016 **Searched databases**: Cochrane Library, Embase, MEDLINE, PubMed, Scopus and Web of Science **Included study designs**: Cohort studies, case-control studies	Alcohol intake	Breast cancer recurrence, Development of second primary breast cancer	**Breast cancer recurrence** *11 studies* – of those: 5 studies: no significant association between alcohol intake and breast cancer recurrence; 2 studies: modest, but statistically significant association between pre-diagnosis alcohol intake and BC recurrence; 2 publications by Kwan: regular consumption of	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 2 critical flaws (items 4, 7) **Additional concerns about quality**: n.a. **Quality of included studies**: *Rated with Newcastle-Ottawa Scale for non-randomised studies:*

Source: Simapivapan P, Boltong A, Hodge A. To what extent is alcohol consumption associated with breast cancer recurrence and second primary breast cancer?: A systematic review. Cancer Treat Rev. 2016 Nov;50: 155-167. doi: 10.1016/j.ctrv.2016.09.010. Epub 2016 Sep 20. PMID: 27693930.					
	Number of included studies: 16 14 cohort studies, 2 case-control studies **Number of included patients**: 35,690 **Mean/median age**: n.a. **Follow-up:** Between 5 and 18 years (time first BC diagnosis until recurrence) TNM stages: 0-IV **Inclusion criteria**: Peer-reviewed, English language articles; original data or secondary data with original analyses involving adult (age≥18 years) human			≥three alcoholic drinks (1 drink = 13.7 g of alcohol) per week or 6g of alcohol per day post-diagnosis to be associated with increased risk of breast cancer recurrence, particularly amongst postmenopausal and overweight/ obese women; 1 study (second breast cancer diagnosis): small positive association for post-diagnosis alcohol intake of at least 1 drink/day (12g alcohol) **Development of second primary breast cancer** *5 studies – of those:* 3 studies: no significant association between pre-diagnosis alcohol intake and second primary BC; 2 case-control studies: modest positive	16 studies seven were rated high quality, eight were rated fair quality, and one study was rated poor quality items most commonly assigned no stars were: method of assessing alcohol exposure (e.g. lack of validated tools), method of defining cancer status (e.g. self-reported as opposed to medical records), and adequacy of follow-up of cohorts **Sources of funding**: no specific funding

Source: Simapivapan P, Boltong A, Hodge A. To what extent is alcohol consumption associated with breast cancer recurrence and second primary breast cancer?: A systematic review. Cancer Treat Rev. 2016 Nov;50: 155-167. doi: 10.1016/j.ctrv.2016.09.010. Epub 2016 Sep 20. PMID: 27693930.

	participants **Exclusion**: n.a.			associations between pre and post-diagnosis alcohol exposure	

Abbreviations:

BC = Breast Cancer

n.a. = not Available, not Applicable

e.g. = Exempli Gratia

Kapitel 4.6: Systemische Therapie frühes Mammakarzinom

Kapitel 4.6.1: Allgemeine Empfehlungen und Therapieentscheidungen

Verknüpfte Empfehlungen:

Empfehlung 4.137:

Zytostatika können zeitlich simultan oder sequenziell verabreicht werden (entsprechend evidenzbasierter Protokolle).

Bei hohem tumorbedingtem Mortalitätsrisiko und dafür geeigneten Patientinnen sollten dosisdichte Therapien eingesetzt werden.

Empfehlung 4.139:

Ist eine Chemotherapie indiziert, kann diese vor der Operation (neoadjuvant) oder danach (adjuvant) durchgeführt werden. Beide Verfahren sind hinsichtlich des Gesamtüberlebens gleichwertig.

Die neoadjuvante Therapie kann zu einer höheren Rate an brusterhaltenden Therapien führen und erlaubt basierend auf das Therapieansprechen eine risikoadaptierte postneoadjuvante Therapie. Diese kann mit einem Überlebensvorteil assoziiert sein.

Literaturreferenzen: [215], [216]

Source: AJ, Kerr, Dodwell D, McGale P, Holt F, Duane F, Mannu G, Darby SC, and Taylor CW. "Adjuvant and Neoadjuvant Breast Cancer Treatments: A Systematic Review of Their Effects on Mortality." [In eng]. Cancer treatment reviews 105 (2022-4 2022): 102375. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35367784/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: to estimate proportional benefits and risks of modern adjuvant and neoadjuvant treatment options	**Design**: Systematic Review **Search date**:	**Intervention** anthracycline, taxane + anthracycline, trastuzumab, timing of	**Outcome** Breast cancer mortality	**Breast cancer mortality** Chemotherapy Patients: all women	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review:

Source: AJ, Kerr, Dodwell D, McGale P, Holt F, Duane F, Mannu G, Darby SC, and Taylor CW. "Adjuvant and Neoadjuvant Breast Cancer Treatments: A Systematic Review of Their Effects on Mortality." [In eng]. Cancer treatment reviews 105 (2022-4 2022): 102375. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35367784/.					
recommended in current clinical guidelines for early breast cancer	Guidelines: 2016-2021 Studies: 2008 onwards **Searched databases**: Embase, Medline **Included study designs**: US, European and UK Guidelines; Meta-analysis; Randomized trials **Number of included studies**: 16 Guidelines 21 Studies **Number of included patients**: n.a. **Mean/median age**: n.a. **Inclusion criteria**: Studies which compared treatment effects on breast cancer or non-breast-cancer	systemic therapy, 5 years of tamoxifen and extended tamoxifen (ER positive cancer) **Control** AI versus tamoxifen (in premenopausal women with ovarian suppression or ablation and in postmenopausal women, both with ER positive cancer) and tamoxifen/AI versus tamoxifen alone (postmenopausal women with ER positive cancer); and bisphosphonates (postmenopausal women)	Non-breast-cancer mortality	Anthracycline vs no chemotherapy RR 0.79, 95% CI 0.72 to 0.85 Patients: all women Taxane+anthracycline vs anthracycline RR 0.86, 95% CI 0.79 to 0.93 <u>Anti-HER2 therapy (HER2 positive cancer)</u> Trastuzumab vs. not RR 0.67, 95% CI 0.61 to 0.73 <u>Neoadjuvant vs. adjuvant chemotherapy</u> RR 1.06, 95% CI 0.95-1.18 <u>Endocrine therapy in ER+ disease</u> Patients: women of any age	critically low; 4 critical flaws (items 2,7,9,13) **Additional concerns about quality**: only the mortality benefits and risks of breast cancer treatments, not their effects on breast cancer recurrence or on side-effects that are not usually fatal even using all available randomised evidence, there were few events for reliable assessment of rare side-effects **Quality of included studies**: No RoB Assessment Ranking of search results enabled identification of the highest quality estimates, with the least risk of bias and the

Source: AJ, Kerr, Dodwell D, McGale P, Holt F, Duane F, Mannu G, Darby SC, and Taylor CW. "Adjuvant and Neoadjuvant Breast Cancer Treatments: A Systematic Review of Their Effects on Mortality." [In eng]. Cancer treatment reviews 105 (2022-4 2022): 102375. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35367784/.

	mortality, included at least 3 years median follow-up and were pub lished 2008 and onwards, as earlier studies would inevitably assess the effects of older treatment regimens <u>Inclusion criteria If a search identified more than one eligible meta-analysis:</u> 1. Individual patient data meta-analysis including all relevant randomised trials, both published and unpublished. 2. Individual patient data meta-analysis omitting some relevant randomised trials. 3. Published data meta-analysis including all relevant randomised trials.			Tamoxifen vs not 5 years RR 0.70, 95% CI 0.64 to 0.75 Patients: women of any age Extended tamoxifen ≥10 vs 5 years RR 0.88, 95% CI 0.80 to 0.97 Patients: post-menopausal AI vs tamoxifen 5 years RR 0.85, 95% CI 0.75 to 0.96 Patients: post-menopausal Tamoxifen □ AI vs tamoxifen 5 years total	greatest number of women randomised **Planned included studies**: Guidelines Meta-analysis Randomized trials **Sources of funding:** no specific funding

Source: AJ, Kerr, Dodwell D, McGale P, Holt F, Duane F, Mannu G, Darby SC, and Taylor CW. "Adjuvant and Neoadjuvant Breast Cancer Treatments: A Systematic Review of Their Effects on Mortality." [In eng]. Cancer treatment reviews 105 (2022-4 2022): 102375. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35367784/.

	4. Published data meta-analysis omitting some relevant randomised trials. **Exclusion**: Non-randomised studies comparing different treatments Studies of patients with metastatic disease, or other cancer types			RR 0.84, 95% CI 0.72 to 0.96 <u>Biphosphonates</u> Patients: Postmenopausal Biphosphonate vs not <1-5 years RR 0.82, 95% CI 0.73 to 0.93 <u>Radiotherapy</u> Patients: After breast conserving surgery Whole breast RT vs not RR 0.82, 95% CI 0.75 to 0.90 Patients: After mastectomy and axillary dissection in node positive cancer Chest wall and regional node RT vs not RR 0.84, 95% CI 0.76 to 0.94	

Source: AJ, Kerr, Dodwell D, McGale P, Holt F, Duane F, Mannu G, Darby SC, and Taylor CW. "Adjuvant and Neoadjuvant Breast Cancer Treatments: A Systematic Review of Their Effects on Mortality." [In eng]. Cancer treatment reviews 105 (2022-4 2022): 102375. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35367784/.

				Patients: Any surgery, target or nodes Regional node RT vs not RR 0.81, 95% CI 0.70 to 0.94 **Non-breast-cancer mortality** <u>Endocrine therapy in ER+ disease</u> Patients: post-menopausal Tamoxifen □ AI vs tamoxifen 5 years total RR 0.79, 95% CI 0.67 to 0.93 <u>Neoadjuvant vs. adjuvant chemotherapy</u> RR 0.94, 95% CI 0.73-1.22	

Abbreviations:

Source: AJ, Kerr, Dodwell D, McGale P, Holt F, Duane F, Mannu G, Darby SC, and Taylor CW. "Adjuvant and Neoadjuvant Breast Cancer Treatments: A Systematic Review of Their Effects on Mortality." [In eng]. Cancer treatment reviews 105 (2022-4 2022): 102375. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35367784/.

n.a. = not Available, not Applicable

AI = Aromatase Inhibitors

RR = Rate Ratio

95% CI = 95% Confidence Interval

Verknüpfte Empfehlungen:

Empfehlung 4.137:

Zytostatika können zeitlich simultan oder sequenziell verabreicht werden (entsprechend evidenzbasierter Protokolle).

Bei hohem tumorbedingtem Mortalitätsrisiko und dafür geeigneten Patientinnen sollten dosisdichte Therapien eingesetzt werden.

Empfehlung 4.153:

Sofern bei Patientinnen mit triple-negativem Mammakarzinom (TNBC) die Indikation zu einer alleinigen anthrazyklin-/taxanhaltigen Chemotherapie besteht, sollte diese dosisdicht erfolgen.

Literaturreferenzen: [215], [216]

Source: Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet. 2019 Apr 6;393(10179): 1440-1452. doi: 10.1016/S0140-6736(18)33137-4. Epub 2019 Feb 8. PMID: 30739743; PMCID: PMC6451189.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Clarify the relative benefits and risks of dose-intense and standard-schedule chemotherapy in early breast cancer	**Design**: Meta-Analysis **Search date**: up to 03/2018 **Searched databases**: MEDLINE, Embase, the Cochrane Library **Included study designs**:	**Intervention** 2-weekly dose-dense chemotherapy of sequential anthracycline and taxane chemotherapy	Recurrence of invasive breast cancer (distant, locoregional, or new primary in the contralateral breast) Breast cancer Mortality	**Dose-dense (2-weekly) chemotherapy versus the same chemotherapy given 3-weekly** 10,004 women, 71% are N+. RR=rate ratio 10-year cumulative risk of any recurrence (A)	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: moderate **Additional concerns about quality**: Heterogeneity between trial designs makes it

Source: Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet. 2019 Apr 6;393(10179): 1440-1452. doi: 10.1016/S0140-6736(18)33137-4. Epub 2019 Feb 8. PMID: 30739743; PMCID: PMC6451189.					
	Randomized controlled trials **Number of included studies**: 26 (26 of 33 relevant trials provided individual patient data) **Number of included patients**: 37,298 **Median follow-up:** 7.4 years (IQR: 5.9-10.3) **Inclusion criteria**: n.a. Trials of adjuvant or neoadjuvant chemotherapy; began before 2008 **Exclusion**: Trials of dose fractionation (e.g., giving drugs once weekly at approximately a third of the dose used in a 3-weekly regimen)	**Control** standard 3-weekly or 4-weekly administration concurrent anthracycline and taxane chemotherapy		RR 0.83, 95% CI 0.76 to 0.91 Log-rank 2p<0.0001 10-year gain 4.3%, 95% CI 2.1 to 6.4 <u>Breast cancer mortality (B)</u> RR 0.86, 95% CI 0.77 to 0.96 Log-rank 2p=0.005 10-year gain 2.8%, 95% CI 0.8 to 4.8 <u>Death without recurrence (C)</u> RR 0.96, 95% CI 0.76 to 1.20 Log-rank 2p=0.71 10-year loss 0.6%, 95% CI 1.0 to 2.1 <u>All-cause mortality (D)</u>	difficult to identify reliably more or less effective dose-intensification strategies **Quality of included studies**: n.a. **Sources of funding**: Cancer Research UK, Medical Research Council **Oxford 2011 level of evidence**: 1

Source: Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet. 2019 Apr 6;393(10179): 1440-1452. doi: 10.1016/S0140-6736(18)33137-4. Epub 2019 Feb 8. PMID: 30739743; PMCID: PMC6451189.					
				RR 0.88, 95% CI 0.80 to 0.97 Log-rank 2p=0.007 10-year gain 2.3%, 95% CI 0.0 to 4.5 **10-year risk of any recurrence (left) and breast cancer death (right) for all trials (confounded and unconfounded)** (A) Dose-dense (2-weekly) versus standard schedule (3-weekly)chemotherapy 15 512 women, 65% are N+ **Any recurrence:** RR 0.84, 95% CI 0.78 to 0.90 Log-rank 2p<0.0001	

Source: Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet. 2019 Apr 6;393(10179): 1440-1452. doi: 10.1016/S0140-6736(18)33137-4. Epub 2019 Feb 8. PMID: 30739743; PMCID: PMC6451189.					
				10-year gain 4.4%, 95% CI 2.6 to 6.3 **Breast cancer mortality:** RR 0.86, 95% CI 0.79 to 0.93 Log-rank 2p=0.0004 10-year gain 2.9%, 95% CI 1.2 to 4.6) <u>(B) Sequential versus concurrent chemotherapy (both 3-weekly)</u> 11 028 women, 91% are N+ **Any recurrence:** RR 0.87, 95% CI 0.80 to 0.94 Log-rank 2p=0.0006 10-year gain 3.2%, 95% CI 0.8 to 5.6 **Breast cancer mortality:**	

Source: Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet. 2019 Apr 6;393(10179): 1440-1452. doi: 10.1016/S0140-6736(18)33137-4. Epub 2019 Feb 8. PMID: 30739743; PMCID: PMC6451189.					
				RR 0.89, 95% CI 0.80 to 0.99 Log-rank 2p=0.030 10-year gain 2.1%, 95% CI 0.1 to 4.1 <u>(C) Sequential (2-weekly) versus concurrent (3-weekly) therapy</u> 6532 women, 90% are N+ **Any recurrence:** RR 0.82, 95% CI 0.74 to 0.90 Log-rank 2p<0.0001 10-year gain 4.6%, 95% CI 1.1 to 8.1 **Breast cancer mortality:** RR 0.82, 95% CI 0.73 to 0.92 Log-rank 2p=0.0009 10-year gain 4.0%, 95% CI 0.6 to 7.5	

Kapitel 4.6.2: Hormonrezeptor-positives Mammakarzinom (HR+)

Verknüpfte Empfehlungen:

Empfehlung 4.142:

Die alleinige Ovarialsuppression kann entweder durch Gabe eines GnRHa oder durch eine bilaterale Ovarektomie für prämenopausale Frauen mit einem Östrogenrezeptor-positiven-Mammakarzinom erwogen werden, die kein Tamoxifen erhalten können oder wollen.

Literaturreferenzen: [217]

Source. Aromatase Inhibitors Versus Tamoxifen in Premenopausal Women with Oestrogen Receptor-Positive Early-Stage Breast Cancer Treated with Ovarian Suppression: A Patient-Level Meta-Analysis of 7030 Women from Four Randomised Trials. [In eng]. The Lancet. Oncology 23, no. 3 (2022-3 2022): 382-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35123662/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: To better define the benefits and risks of aromatase inhibitors compared with tamoxifen in women who have their ovarian function suppressed.	**Design**: Individual Patient-Level Meta-Analysis **Search date**: database inception to July 31, 2020 **Searched databases**: MEDLINE, Embase, the Cochrane Library, meeting abstracts **Included study designs**:	**Intervention** aromatase inhibitor plus ovarian function suppression **Control** tamoxifen plus ovarian function suppression	**Primary Outcomes**: any recurrence of invasive breast cancer (distant, locoregional, or new primary in the contralateral breast) Breast cancer mortality, death without recurrence, and all-cause mortality. **Secondary Outcomes**: Incidence and site of second primary cancers (including endometrial	**Any recurrence** 10 years: lower in women allocated to an aromatase inhibitor than women assigned to tamoxifen RR 0.79 95% CI 0.69–0.90 Main benefit in years 0–4: RR 0.68, 99% CI 0.55–0.85 years 5–9	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: moderate **Additional concerns about quality**: n.a. **Quality of included studies**: n.a. **Sources of funding:** project grant from Cancer Research UK, with

Source. Aromatase Inhibitors Versus Tamoxifen in Premenopausal Women with Oestrogen Receptor-Positive Early-Stage Breast Cancer Treated with Ovarian Suppression: A Patient-Level Meta-Analysis of 7030 Women from Four Randomised Trials. [In eng]. The Lancet. Oncology 23, no. 3 (2022-3 2022): 382-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35123662/.					
	RCTs **Number of included studies**: 4 (ABCSG XII, TEXT, SOFT, HOBOE) **Number of included patients**: 7030 **Population** premenopausal women receiving ovarian suppression **Inclusion criteria**: Trials began before Jan 1, 2010, and randomly assigned premenopausal women with oestrogen receptor (ER)-positive operable breast cancer (defined as ER expression in at least 1% of tumour cells, by immunohistochemistry in SOFT, TEXT, and HOBOE; ABCSG XII used Reiner		cancer), and bone fracture.	RR 0.98, 99% CI 0.73–1.33; p=0.89 *Subgroup analysis (overall follow-up time):* <u>Nodal status:</u> NO: RR 0.71, 99 % CI 0.54-0.95 N1-3: RR 0.71, 99 % CI 0.53-0.96 N4+: RR 1.03, 99 % CI 0.73-1.46 <u>Tumour diameter, mm</u> 1-20: RR 0.80, 99 % CI 0.62-1.03 21-50: RR 0.81, 99 % CI 0.81-1.06 >50: RR 0.50, 99 % CI 0.21-1.14 <u>Tumour grade</u> Well differentiated:	additional support from core funding to the Clinical Trial Service Unit and the Population Health Research Unit, Nuffield Department of Population Health, University of Oxford from Cancer Research UK, and the UK Medical Research Council

Source. Aromatase Inhibitors Versus Tamoxifen in Premenopausal Women with Oestrogen Receptor-Positive Early-Stage Breast Cancer Treated with Ovarian Suppression: A Patient-Level Meta-Analysis of 7030 Women from Four Randomised Trials. [In eng]. The Lancet. Oncology 23, no. 3 (2022-3 2022): 382-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35123662/.					
	score for staining of tumour-cell nuclei to define ER positivity [score ≥3; ie, ≥10% cells are positive]) to an aromatase inhibitor plus ovarian function suppression versus tamoxifen plus ovarian function suppression **Excluded from Meta-Analysis:** Women with ER-negative, progesterone receptor (PR)-positive tumours			RR 0.75, 99% CI 0.42-1.32 Moderately: RR 0.87, 99% CI 0.68-1.12 Poorly: RR 0.73, 99% CI 0.55-0.97 <u>HER2 status</u> HER2 positive RR 1.08, 99% CI 0.65-1.80 HER2 negative RR 0.65, 99% CI 0.52-0.82 HER2 unknown RR 1.06, 99% CI 0.74-1.51 **Distant recurrence**	

Source. Aromatase Inhibitors Versus Tamoxifen in Premenopausal Women with Oestrogen Receptor-Positive Early-Stage Breast Cancer Treated with Ovarian Suppression: A Patient-Level Meta-Analysis of 7030 Women from Four Randomised Trials. [In eng]. The Lancet. Oncology 23, no. 3 (2022-3 2022): 382-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35123662/.					
				Reduced in the aromatase inhibitor group vs the tamoxifen group: RR 0.83, 95% CI 0.71−0.97 Years 0-4 RR 0.78, 95% CI 0.65−0.95 Years 5–9 RR 0.91, 95% CI 0.68−1.22 ≥10 years RR 7.86, 95% CI 0.72−85.91 **Breast cancer mortality** RR 1.01, 95% CI 0.82–1.24 Years 0–4 RR 1.25, 99% CI 0.85–1.85 Years 5–9	

Source. Aromatase Inhibitors Versus Tamoxifen in Premenopausal Women with Oestrogen Receptor-Positive Early-Stage Breast Cancer Treated with Ovarian Suppression: A Patient-Level Meta-Analysis of 7030 Women from Four Randomised Trials. [In eng]. The Lancet. Oncology 23, no. 3 (2022-3 2022): 382-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35123662/.

				RR 0.80, 99% CI 0.54–1.19 <u>≥10 years</u> RR, 1.45, 95% CI 0.33–6.44 **All-cause mortality** RR 1.04, 95% CI 0.86–1.27 The rate ratio for breast cancer mortality after being treated with an aromatase inhibitor compared with being treated with tamoxifen was <u>Years 0–4</u> RR 1.33, 95% CI 1.00–1.76 <u>Years 5–9</u> RR 0.84, 95% CI 0.64–1.11 <u>≥10 years</u>	

Source. Aromatase Inhibitors Versus Tamoxifen in Premenopausal Women with Oestrogen Receptor-Positive Early-Stage Breast Cancer Treated with Ovarian Suppression: A Patient-Level Meta-Analysis of 7030 Women from Four Randomised Trials. [In eng]. The Lancet. Oncology 23, no. 3 (2022-3 2022): 382-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35123662/.

				RR 0.64, 95% CI 0.18−2.24 **Secondary Outcome**: There were more **bone fractures** with aromatase inhibitor than with tamoxifen RR 1.27, 95% CI 1.04–1.54; p=0· 017). **Non-breast cancer deaths** (30 [0.9%] vs 24 [0.7%]; RR 1.30; 95% CI [0.75–2.25]; p=0.36) and **endometrial cancer** (seven [0.2%] vs 15 [0.3%]; RR 0.52; 95% CI [0.22–1.23]; p=0.14) were rare **Subgroup analysis** **1. Any first recurrence** (including locoregional recurrence, distant recurrence, and new	

Source. Aromatase Inhibitors Versus Tamoxifen in Premenopausal Women with Oestrogen Receptor-Positive Early-Stage Breast Cancer Treated with Ovarian Suppression: A Patient-Level Meta-Analysis of 7030 Women from Four Randomised Trials. [In eng]. The Lancet. Oncology 23, no. 3 (2022-3 2022): 382-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35123662/.					
				contralateral disease) **in premenopausal women** This outcome was in the following subgroups significant: Follow-up period of 2-4 years: RR 0· 60, 95% CI 0.46–0.79 Ageof 45−54 RR 0.71, 95% CI 0.51–0.98 BMI 20–24 RR 0.75, 95% CI 0.57–0.98 Nodal status N0: RR 0.71, 95% CI 0.54–0.95 N1−3: RR 0.71, 95% CI 0.53–0.96 PR positive	

Source. Aromatase Inhibitors Versus Tamoxifen in Premenopausal Women with Oestrogen Receptor-Positive Early-Stage Breast Cancer Treated with Ovarian Suppression: A Patient-Level Meta-Analysis of 7030 Women from Four Randomised Trials. [In eng]. The Lancet. Oncology 23, no. 3 (2022-3 2022): 382-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35123662/.					
				RR 0.79, 95% CI 0.66–0.95 Poorly differentiated tumor RR 0.73, 95% CI 0.55–0.97 Ductal carcinoma RR 0.78, 95% CI 0.64–0.95 HER2 negative RR 0.65, 95% CI 0.52–0.82 Chemotherapy use: yes RR 0.74, 95% CI 0.59–0.93 Bisphosphonate use RR: 0· 77, 95% CI (0· 64–0· 93) Nodal status N0 RR: 0.49, 95% CI (0.32–0.73)	

Source. Aromatase Inhibitors Versus Tamoxifen in Premenopausal Women with Oestrogen Receptor-Positive Early-Stage Breast Cancer Treated with Ovarian Suppression: A Patient-Level Meta-Analysis of 7030 Women from Four Randomised Trials. [In eng]. The Lancet. Oncology 23, no. 3 (2022-3 2022): 382-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35123662/.					
				N1−3 RR: 0.56, 95% CI (0.38–0.83) HER2 negative RR: 0.56,95% CI (0.43–0.73)	

Abbreviations:

RCT = Randomised Controlled Trial

RR = Rate Ratio

95% CI = 95% Confidence Interval

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.146:

Eine adjuvante endokrine Therapie sollte bei prämenopausalen Patientinnen mit erhöhten Rezidivrisiko eine ovarielle Suppression (2-5 Jahre in Kombination mit Tamoxifen oder 5 Jahre in Kombination mit einem Aromataseinhibitor) beinhalten.

Literaturreferenzen: [218]

Source: Bui, KT, ML Willson, S Goel, J Beith, and A Goodwin. "Ovarian Suppression for Adjuvant Treatment of Hormone Receptor-Positive Early Breast Cancer." Cochrane Database of Systematic Reviews, no. 3 (2020 2020). https: //doi.org/doi: 10.1002/14651858.CD013538. http: //dx.doi.org/10.1002/14651858.CD013538.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: assess effects of ovarian function suppression (OFS) for treatment of premenopausal women with hormone receptor-positive early breast cancer	**Design**: Systematic Review **Search date**: 17 September 2018 top-up search on 26 September 2019 **Searched databases**: Specialised Register of the Cochrane Breast Cancer Group, MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL; 2019,	**Intervention** OFS (± other treatment) **Control** no OFS (± other treatment) **In detail -** **studies that compared:** (1) OFS versus observation (2) OFS + chemotherapy versus chemotherapy (3) OFS + tamoxifen versus tamoxifen (4 studies)	**Primary Outcome**: Overall survival (OS) Disease-free survival (DFS) **Secondary Outcome**: Toxicity (hot flushes, contralateral breast cancer) Contralateral breast cancer Second malignancy Quality of life	**OFS + tamoxifen vs tamoxifen (=subgroup analysis)** **Primary Outcome**: **Overall survival (OS)** HR 0.74, 95% CI 0.59 to 0.93, I^2=0; (4 RCTs [ABCTCG; E-3193, INT-0142; SOFT; Yang 2013], 3299 patients) Median follow-up (FU): ABCTCG: 5,9 years (y)	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: high; 0 critical flaws **Certainty of the evidence (GRADE)** OS: high DFS: high Toxicity (hot flushes): low Contralateral breast cancer: moderate

Source: Bui, KT, ML Willson, S Goel, J Beith, and A Goodwin. "Ovarian Suppression for Adjuvant Treatment of Hormone Receptor-Positive Early Breast Cancer." Cochrane Database of Systematic Reviews, no. 3 (2020 2020). https: //doi.org/doi: 10.1002/14651858.CD013538. http: //dx.doi.org/10.1002/14651858.CD013538.

	Issue 8), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov **Included study designs**: RCT **Number of included studies**: 15 Of those: 6 studies comparing OFS+ tamoxifen vs tamoxifen (ABCTCG; E-3193, INT-0142; SOFT; Yang 2013; Yi 2016; ZBCSG Trial B) **Number of included patients**: 11,538 **Inclusion criteria**: RCTs assessing any method of OFS: oophorectomy, radiation-induced ovarian ablation, or luteinising hormone releasing hormone	(4) OFS + chemotherapy + tamoxifen versus chemotherapy + tamoxifen		E-3193, INT-0142: 9.9 y SOFT: 8 y Yang 2013: 6 y **Disease-free survival (DFS)** HR 0.76, 95% CI 0.63 to 0.92, I^2=0%; (3 RCTs [E-3193, INT-0142; SOFT; Yang 2023], 2461 patients) Median follow-up (FU): E-3193, INT-0142: 9.9 y SOFT: 8 y Yang 2013: 6 y **Secondary Outcome**: Toxicity: hot flushes RR 1.99, 95% CI 1.56 to 2.55; I^2=74.01%	**Risk of included studies**: ABCTCG: unsure detection bias (blinding outcome assessment) for outcome toxicity and QoL; E-3193, INT-0142 and SOFT: unsure detection bias (blinding outcome assessment) for outcome QoL Yang 2013: unsure about random sequence generation Yi 2016: unsure about random sequence generation; allocation concealment and blinding outcome assessment) for outcome toxicity ZBCSG Trial B: unsure about random sequence generation; allocation concealment; blinding of outcome assessment

Source: Bui, KT, ML Willson, S Goel, J Beith, and A Goodwin. "Ovarian Suppression for Adjuvant Treatment of Hormone Receptor-Positive Early Breast Cancer." Cochrane Database of Systematic Reviews, no. 3 (2020 2020). https: //doi.org/doi: 10.1002/14651858.CD013538. http: //dx.doi.org/10.1002/14651858.CD013538.					
	(LHRH) agonists, as adjuvant treatment for premenopausal women with early-stage breast cancer **Types of participants:** Premenopausal women with a histological diagnosis of hormone receptor-positive early breast cancer; 'early breast cancer' is defined as tumour-node-metastasis (TNM) stage I, II, and III; 'premenopausal' is defined by the studies, usually as menses in the last 3 to 12 months and/or oestradiol levels in premenopausal ranges			(3 studies [E-3193, INT-0142; SOFT; ZBCSG Trial B], 2468 patients) Contralateral breast cancer RR 0.56, 95% CI 0.29 to 1.07; I^2=n.a. (1 study [SOFT], 2033 patients) Second malignancy RR 0.96, 95% CI 0.55 to 1.67; I^2=n.a. (1 study [SOFT], 2033 patients)	(toxicity, QoL) and selective reporting **Sources of funding:** National Institute for Health Research (NIHR) Cochrane Incentive Award 2018 (NIHR 128381)
Abbreviations: OFS = Ovarian Function Suppression RCT = Randomised Controlled Trial					

Source: Bui, KT, ML Willson, S Goel, J Beith, and A Goodwin. "Ovarian Suppression for Adjuvant Treatment of Hormone Receptor-Positive Early Breast Cancer." Cochrane Database of Systematic Reviews, no. 3 (2020 2020). https: //doi.org/doi: 10.1002/14651858.CD013538. http: //dx.doi.org/10.1002/14651858.CD013538.

LHRH = Luteinising Hormone Releasing Hormone

TNM = Tumour-Node-Metastasis

OS = Overall survival

DFS = Disease-free survival

QoL = Quality of Life

HR = Hazard Ratio

RR = Risk Ratio

95% CI = 95% Confidence Interval

FU = Follow-Up

y = years

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.148:

Bei postmenopausalen Patientinnen soll die Aromatasehemmer-haltigen endokrinen Therapie mindestens 5 Jahre und bei Patientinnen mit einem erhöhten Rezidivrisiko bis zu 7-8 Jahre betragen. Eine über diesen Zeitraum hinausgehende endokrine Therapie ist lediglich mit einem geringeren Risiko für das Auftreten eines kontralateralen Mammakarzinoms assoziiert.

Literaturreferenzen: [219]

Source: X, Qian, Li Z, Ruan G, Tu C, and Ding W. "Efficacy and Toxicity of Extended Aromatase Inhibitors after Adjuvant Aromatase Inhibitors-Containing Therapy for Hormone-Receptor-Positive Breast Cancer: A Literature-Based Meta-Analysis of Randomized Trials." [In eng]. Breast cancer research and treatment 179, no. 2 (2020-1 2020): 275-85. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31606823/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: to assess the differences in efficacy and toxicity of the extended adjuvant aromatase inhibitors (AIs) therapy after completing the initial standard AIs-containing therapy	**Design**: Systematic review and meta-analysis **Search date**: n.a. **Searched databases**: PubMed, Embase, and Cochrane Library, abstracts and presentations reported from annual meetings of the American Society of Clinical Oncology (ASCO)	**Intervention** extended adjuvant AIs therapy after completing the initial standard AIs-containing therapy **Control** placebo **Population** Postmenopausal women, hormone-receptor-positive early or locally advanced breast cancer	**Outcomes** Disease-free survival (DFS) Overall survival (OS) Local recurrence Distant recurrence Contralateral breast cancer Non-breast cancer-related death Toxicity	**Outcomes** **Disease-free survival** RR 0.79, 95% CI 0.68–0.91; p=0.003; I^2=68% (8 RCTs, 15609 patients) **Overall survival** RR, 1.00, 95% CI 0.99–1.01; p=0.84; I^2=0% (7 RCTs, 12168 patients) **Local recurrence**	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 5 critical flaws (items 2,4,7,13,15) **Additional concerns about quality**: follow-up times are different among the trials, and in particular they are shorter for AIs; heterogeneity of the outcome measures

Source: X, Qian, Li Z, Ruan G, Tu C, and Ding W. "Efficacy and Toxicity of Extended Aromatase Inhibitors after Adjuvant Aromatase Inhibitors-Containing Therapy for Hormone-Receptor-Positive Breast Cancer: A Literature-Based Meta-Analysis of Randomized Trials." [In eng]. Breast cancer research and treatment 179, no. 2 (2020-1 2020): 275-85. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31606823/.					
	or the San Antonio Breast Cancer Symposium (SABCS) **Included study designs**: RCTs **Number of included studies**: 8 ABCSG16 ABCSG6a AERAS DATA IDEAL LATER MA17R NSABP42 **Number of included patients**: 15,966 postmenopausal patients **Inclusion criteria**:			RR, 0.82 95% CI 0.64–1.06; p=0.14; I²=42% (7 RCTs, 12168 patients) **Distant recurrence** RR, 0.75; 95% CI 0.58–0.96; p=0.03; I²=58% (7 RCTs, 12168 patients) **Contralateral breast cancer** RR 0.53, 95% CI 0.40–0.70; p=0.90; I²=0% (7 RCTs, 12168 patients) **Non-breast cancer-related death** RR, 1.16, 95% CI 0.96–1.41; p=0.13; I²=0% (5 RCTs, 8717 patients) **Subgroup analysis** The following subgroups would get a greater DFS	definitions across the trials **Quality of included studies**: For allocation concealment, the risk of bias was unclear in 3 RCTs with an allocation scheme that was not mentioned in the trials; in 1 study the risk of bias was low, whereas in the other 5 studies the risk of bias was high; for the performance bias, the risk of bias was unclear in 3 RCT studies and high in another one; For the detection bias, the risk was unclear in 1 study **Sources of funding:** n.a.

Source: X, Qian, Li Z, Ruan G, Tu C, and Ding W. "Efficacy and Toxicity of Extended Aromatase Inhibitors after Adjuvant Aromatase Inhibitors-Containing Therapy for Hormone-Receptor-Positive Breast Cancer: A Literature-Based Meta-Analysis of Randomized Trials." [In eng]. Breast cancer research and treatment 179, no. 2 (2020-1 2020): 275-85. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31606823/.

	published in English; patients of any age with hormone receptor-positive early or locally advanced breast cancer; RCTs investigating the outcomes of extended adjuvant AIs-containing therapy in postmenopausal women who had remained free of breast cancer after completing AIs-containing therapy			benefit with extended AIs: **Tumor size** <u>>2 cm (T2 and T3/4):</u> HR 0.74, 95% CI 0.54-1.00; RD −0.31, 95% CI -0.61—0.00; P=0.05 <u>vs. T1:</u> HR 0.85, 95% CI 0.66-1.09; RD −0.16, 95% CI -0.41-0.09; P = 0.20) **Nodal status** <u>Node positive status</u> HR 0.77, 95% CI 0.67-0.87 RD −0.27, 95% CI -0.40, -0.14; P = <0.0001 <u>vs. node negative</u> HR 0.89, 95% CI 0.75-1.06	

Source: X, Qian, Li Z, Ruan G, Tu C, and Ding W. "Efficacy and Toxicity of Extended Aromatase Inhibitors after Adjuvant Aromatase Inhibitors-Containing Therapy for Hormone-Receptor-Positive Breast Cancer: A Literature-Based Meta-Analysis of Randomized Trials." [In eng]. Breast cancer research and treatment 179, no. 2 (2020-1 2020): 275-85. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31606823/.					
				RD −0.12, 95% CI -0.29-0.06; P = 0.19 **Previous chemotherapy use** Yes: HR 0.75, 95% CI 0.62-0.91 RD −0.29, 95% CI -0.49, -0.10; P = 0.003 vs. No: HR 0.91, 95% CI 0.71-1.16 RD −0.10, 95% CI -0.34 – 0.15; P = 0.44 The benefits of extended AIs therapy were statistically significant regardless of whether the initial endocrine therapy includes tamoxifen TAM-AI:	

Source: X, Qian, Li Z, Ruan G, Tu C, and Ding W. "Efficacy and Toxicity of Extended Aromatase Inhibitors after Adjuvant Aromatase Inhibitors-Containing Therapy for Hormone-Receptor-Positive Breast Cancer: A Literature-Based Meta-Analysis of Randomized Trials." [In eng]. Breast cancer research and treatment 179, no. 2 (2020-1 2020): 275-85. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31606823/.					
				HR 0.82, 95% CI 0.70 – 0.96 RD = −0.20, 95% CI -0.35, -0.04; P = 0.01 vs. AI: HR 0.81, 95% CI 0.69-0.94 RD −0.21, 95% CI -0.37, -0.06 P = 0.0002 Longer treatment with AIs was associated with an increased risk ratio of the following outcomes: Bone pain (RR=1.26, RD = 0.04, P = 0.003), Bone fractures (RR=1.59, RD = 0.02, P = 0.002) Osteoporosis (RR=1.53, RD = 0.07, P = 0.005)	

Source: X, Qian, Li Z, Ruan G, Tu C, and Ding W. "Efficacy and Toxicity of Extended Aromatase Inhibitors after Adjuvant Aromatase Inhibitors-Containing Therapy for Hormone-Receptor-Positive Breast Cancer: A Literature-Based Meta-Analysis of Randomized Trials." [In eng]. Breast cancer research and treatment 179, no. 2 (2020-1 2020): 275-85. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31606823/.

				Myalgia (RR=1.26, RD = 0.04, P = 0.02) Treatment discontinuation for adverse events (RR=1.51, RD = 0.06, P = 0.0009) Longer duration of ALs had nostatistically significant effectin RR of following outcomes: Cardiovascular events (RR = 1.07, RD = 0, P = 0.41, I 2 = 12%) Hypertension (RR = 0.99, RD = 0, P = 0.92, I 2 = 32%)	

Abbreviations:

AI = Aromatase Inhibitors

RCT = Randomised Controlled Trial

n.a. = not Available, not Applicable

DFS = Disease-Free Survival

Source: X, Qian, Li Z, Ruan G, Tu C, and Ding W. "Efficacy and Toxicity of Extended Aromatase Inhibitors after Adjuvant Aromatase Inhibitors-Containing Therapy for Hormone-Receptor-Positive Breast Cancer: A Literature-Based Meta-Analysis of Randomized Trials." [In eng]. Breast cancer research and treatment 179, no. 2 (2020-1 2020): 275-85. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31606823/.

OS = Overall survival

TAM-AI = Tamoxifen - Aromatase Inhibitors

RR = Risk Ratio

HR = Hazard Ratio

RD = Risk Difference

95% CI = 95% Confidence Interval

Verknüpfte Empfehlungen:

Empfehlung 4.148:

Bei postmenopausalen Patientinnen soll die Aromatasehemmer-haltigen endokrinen Therapie mindestens 5 Jahre und bei Patientinnen mit einem erhöhten Rezidivrisiko bis zu 7-8 Jahre betragen. Eine über diesen Zeitraum hinausgehende endokrine Therapie ist lediglich mit einem geringeren Risiko für das Auftreten eines kontralateralen Mammakarzinoms assoziiert.

Literaturreferenzen: [219]

Source: SP, Corona, Roviello G, Strina C, Milani M, Madaro S, Zanoni D, Allevi G, et al. "Efficacy of Extended Aromatase Inhibitors for Hormone-Receptor-Positive Breast Cancer: A Literature-Based Meta-Analysis of Randomized Trials." [In eng]. Breast (Edinburgh, Scotland) 46 (2019-8 2019): 19-24. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31051411/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: To evaluate the real impact of extended adjuvant therapy with aromatase inhibitors (AIs) on disease-free survival (DFS) through a meta-analysis.	**Design**: Systematic review and meta-analysis **Search date**: n.a. **Searched databases**: PubMed, Central Registry of Controlled Trials of the Cochrane Library **Included study designs**: RCTs	**Intervention** an extended treatment with aromatase inhibitors in the experimental arm (defined as adjuvant treatment prolonged after 5 years) **Control** placebo or observation **Population** participants with hormone receptor BC	**Primary Outcome**: disease-free survival (DFS) **Secondary Outcome**: overall survival (OS)	**Primary Outcome**: **DFS** after a median follow-up of 64.1 months, extended endocrine therapy with AIs improved DFS when compared to control: HR0.78, 95% CI 0.68-0.90; P=0.0006; I^2=64%; (all included RCTs [n=8])	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low;5 critical flaws (items 2,7,9,13,15) **Additional concerns about quality**: heterogeneity of the outcome measures definitions across the trials

Source: SP, Corona, Roviello G, Strina C, Milani M, Madaro S, Zanoni D, Allevi G, et al. "Efficacy of Extended Aromatase Inhibitors for Hormone-Receptor-Positive Breast Cancer: A Literature-Based Meta-Analysis of Randomized Trials." [In eng]. Breast (Edinburgh, Scotland) 46 (2019-8 2019): 19-24. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31051411/.					
	Number of included studies: 8 RCTs (name with median FU-time in months) ABCSG Trial 6a (62.3); DATA (49.2); MA-17 (30); MA-17R (75); NSABP B-33 (30); NSABP B-42 (82.8); IDEAL (78); ABCSG-16 (SALSA) (106.2) **Number of included patients**: 19,345 **Mean/median age**: n.a. **Inclusion criteria**:	treated with adjuvant endocrine therapy		**DFS among node positive patients** HR 0.67, 95% CI 0.57-0.79; P<0.00001;I²=8% (5 RCTs [ABCSG Trial 6a; DATA; IDEAL; MA 17; NSABP B-33]) **DFS among node negative patients** HR 0.80, 95% CI 0.48-1.35; P=0.41; I²=74% (4 RCTs [ABCSG Trial 6a; DATA; IDEAL; MA 17] **Total:** HR 0.70, 95% CI 0.57-0.87; P=0.0009; I²=0 **Secondary Outcome**: The pooled analysis revealed no improvement in OS with extended AIs endocrine therapy	**Quality of included studies**: Overall quality of the studies was high (assess with Jadad instrument) - half of the studies had the score of 5, and half of them had the score of 4 out of 5 possible score **Sources of funding:** No external funding.

Source: SP, Corona, Roviello G, Strina C, Milani M, Madaro S, Zanoni D, Allevi G, et al. "Efficacy of Extended Aromatase Inhibitors for Hormone-Receptor-Positive Breast Cancer: A Literature-Based Meta-Analysis of Randomized Trials." [In eng]. Breast (Edinburgh, Scotland) 46 (2019-8 2019): 19-24. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31051411/.

	1) participants with BC treated with adjuvant endocrine therapy; 2) an extended treatment in the experimental arm (defined as adjuvant treatment prolonged after 5 years), 3) a primary outcome of DFS expressed as hazard ratio (HR) and secondary outcome of OS expressed as HR			HR0.99, 95% CI 0.87-1.12;P=0.84;I^2=22%;	

Abbreviations:

AI = Aromatase Inhibitors

DFS = Disease-Free Survival

OS = Overall Survival

RCT = Randomised Controlled Trial

n.a. = not Available, not Applicable

FU = Follow-Up

BC = Breast Cancer

Source: SP, Corona, Roviello G, Strina C, Milani M, Madaro S, Zanoni D, Allevi G, et al. "Efficacy of Extended Aromatase Inhibitors for Hormone-Receptor-Positive Breast Cancer: A Literature-Based Meta-Analysis of Randomized Trials." [In eng]. Breast (Edinburgh, Scotland) 46 (2019-8 2019): 19-24. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31051411/.

HR = Hazard Ratio

95% CI = 95% Confidence Interval

Verknüpfte Empfehlungen:

Empfehlung 4.149:

Bei Patientinnen mit HR+/HER2-Mammakarzinom und hohem Rückfallrisiko (bei N2-3 oder N1 mit G3 oder Tumorgröße >/= 5cm) sollte Abemaciclib für 2 Jahre in Kombination mit der endokrinen Standard-Therapie oder Ribociclib (bei N+, oder N0 T3/T4, oder N0 T2 G3 oder N0 T2 G2 und (Ki-67 ≥ 20 % oder high-risk Genexpression)) für 3 Jahre in Kombination mit einem Aromatasehemmer (+ OFS bei prämenopausalen Patientinnen) durchgeführt werden. Beide Medikamente führen zur Senkung der Rezidivwahrscheinlichkeit.

Literaturreferenzen: [220]

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Abemaciclib (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, früh mit hohem Rezidivrisiko, Adjuvanz, Kombination mit endokriner Therapie)			
Wirkstoff	Abemaciclib	**Handelsname**	Verzenios
Pharmazeutischer Unternehmer	Lilly Deutschland GmbH	**Beschlussdatum**	20.10.2022
Anwendungsgebiet	Mammakarzinom		

Abemaciclib (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, früh mit hohem Rezidivrisiko, Adjuvanz, Kombination mit endokriner Therapie)			
Wirkstoff	Abemaciclib	**Handelsname**	Verzenios
Pharmazeutischer Unternehmer	Lilly Deutschland GmbH	**Beschlussdatum**	20.10.2022
Anwendungsgebiet	Mammakarzinom		

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung eines neuen Anwendungsgebietes für den Wirkstoff Abemaciclib in Kombination mit endokriner Therapie. Das hier bewertete Anwendungsgebiet lautet:
Abemaciclib ist in Kombination mit einer endokrinen Therapie angezeigt für die adjuvante Behandlung von erwachsenen Patientinnen und Patienten mit HR-positivem, HER2-negativem, nodal-positivem Brustkrebs im frühen Stadium mit einem hohen Rezidivrisiko. Bei prä- oder perimenopausalen Frauen sollte die endokrine Aromatasehemmer-Therapie mit einem LHRH-Agonisten (LHRH= Luteinising Hormone Releasing Hormone) kombiniert werden.
In dem zu betrachtenden Anwendungsgebiet wurden drei Patientengruppen unterschieden:
a1) Prämenopausale Frauen mit einem Hormonrezeptor-positiven, HER2-negativen Mammakarzinom im Frühstadium mit hohem Rezidivrisiko
Als zweckmäßige Vergleichstherapie wurde vom G-BA Tamoxifen (ggf. zusätzlich mit einer Ausschaltung der Ovarialfunktion) bestimmt.
Für diese Patientengruppe legt der pharmazeutische Unternehmer die RCT MONARCH-E vor, in der Abemaciclib + endokrine Therapie mit alleiniger endokriner Therapie verglichen wurde. Es wurden nur Patientinnen bei der Bewertung berücksichtigt, bei denen die zweckmäßige Vergleichstherapie adäquat umgesetzt wurde.
Beim Endpunkt Gesamtüberleben zeigte sich kein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen.
Für den Endpunkt Rezidive, dargestellt als Rezidivrate und krankheitsfreies Überleben, zeigen sich statistisch signifikant weniger Rezidive für Abemaciclib + endokrine Therapie.
Hinsichtlich Symptomatik und Lebensqualität zeigen sich statistisch signifikante Unterschiede zum Nachteil von Abemaciclib + endokrine Therapie. Es lässt sich jedoch nicht ableiten, dass die beobachteten Effekte relevant sind. Beim Gesundheitszustand liegt weder ein Vorteil noch ein Nachteil vor.
Dem relevanten Vorteil bei den Rezidiven stehen in der Kategorie Nebenwirkungen bedeutsame Nachteile von Abemaciclib + endokrine Therapie insbesondere bei den Endpunkten schwerwiegende unerwünschte Ereignisse (SUE), schwere unerwünschte Ereignisse (UE, CTCAE-Grad ≥ 3) und Abbruch wegen UE gegenüber, die jedoch die Vorteile beim Endpunkt Rezidive vor dem Hintergrund der essentiellen Bedeutung der Vermeidung von Rezidiven in der kurativen Therapiesituation nicht grundsätzlich infrage stellen.
Das Verzerrungspotenzial auf Studienebene wird aufgrund des bedeutsamen Anteils an Patientinnen, die nicht in die Analysen eingeschlossen wurden, als hoch eingestuft. Zudem resultiert aus der kurzen medianen Beobachtungsdauer in der Studie eine relevante Unsicherheit hinsichtlich der Aussagesicherheit, weshalb diese als Anhaltspunkt eingestuft wird.
In der Gesamtschau wird daher ein Anhaltspunkt für einen geringen Zusatznutzen von Abemaciclib in Kombination mit endokriner Therapie gegenüber endokriner Therapie festgestellt.
Der Beschluss ist für diese Patientengruppe bis zum 01.07.2025 befristet.

Abemaciclib (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, früh mit hohem Rezidivrisiko, Adjuvanz, Kombination mit endokriner Therapie)			
Wirkstoff	Abemaciclib	**Handelsname**	Verzenios
Pharmazeutischer Unternehmer	Lilly Deutschland GmbH	**Beschlussdatum**	20.10.2022
Anwendungsgebiet	Mammakarzinom		

Abemaciclib (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, früh mit hohem Rezidivrisiko, Adjuvanz, Kombination mit endokriner Therapie)			
Wirkstoff	Abemaciclib	**Handelsname**	Verzenios
Pharmazeutischer Unternehmer	Lilly Deutschland GmbH	**Beschlussdatum**	20.10.2022
Anwendungsgebiet	Mammakarzinom		

Abemaciclib (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, früh mit hohem Rezidivrisiko, Adjuvanz, Kombination mit endokriner Therapie)			
Wirkstoff	Abemaciclib	**Handelsname**	Verzenios
Pharmazeutischer Unternehmer	Lilly Deutschland GmbH	**Beschlussdatum**	20.10.2022
Anwendungsgebiet	Mammakarzinom		

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung eines neuen Anwendungsgebietes für den Wirkstoff Abemaciclib in Kombination mit endokriner Therapie. Das hier bewertete Anwendungsgebiet lautet:

Abemaciclib ist in Kombination mit einer endokrinen Therapie angezeigt für die adjuvante Behandlung von erwachsenen Patientinnen und Patienten mit HR-positivem, HER2-negativem, nodal-positivem Brustkrebs im frühen Stadium mit einem hohen Rezidivrisiko. Bei prä- oder perimenopausalen Frauen sollte die endokrine Aromatasehemmer-Therapie mit einem LHRH-Agonisten (LHRH= Luteinising Hormone Releasing Hormone) kombiniert werden.

In dem zu betrachtenden Anwendungsgebiet wurden drei Patientengruppen unterschieden:

a2) Postmenopausale Frauen mit einem Hormonrezeptor-positiven, HER2-negativen Mammakarzinom im Frühstadium mit hohem Rezidivrisiko

Als zweckmäßige Vergleichstherapie wurde vom G-BA ein Aromataseinhibitor (Anastrozol oder Letrozol) allein, ggf. Tamoxifen falls Aromataseinhibitoren nicht geeignet sind, oder ein Aromataseinhibitor (Anastrozol oder Exemestan) in Sequenz nach Tamoxifen bestimmt.

Für diese Patientengruppe legt der pharmazeutische Unternehmer die RCT MONARCH-E vor, in der Abemaciclib + endokrine mit alleiniger endokriner Therapie verglichen wurde. Es wurden nur Patientinnen bei der Bewertung berücksichtigt, bei denen die zweckmäßige Vergleichstherapie adäquat umgesetzt wurde.

Beim Endpunkt Gesamtüberleben zeigte sich kein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen.

Für den Endpunkt Rezidive, dargestellt als Rezidivrate und krankheitsfreies Überleben, zeigen sich statistisch signifikant weniger Rezidive für Abemaciclib + endokrine Therapie.

Hinsichtlich Symptomatik, Gesundheitszustand und Lebensqualität zeigen sich statistisch signifikante Unterschiede zum Nachteil von Abemaciclib + endokrine Therapie. Es lässt sich jedoch nicht ableiten, dass die Effekte relevant sind.

Dem Vorteil bei den Rezidiven stehen in der Kategorie Nebenwirkungen überwiegend Nachteile von Abemaciclib + endokrine Therapie insbesondere bei den Endpunkten schwerwiegende unerwünschte Ereignisse (SUE), schwere unerwünschte Ereignisse (UE, CTCAE-Grad ≥ 3) und Abbruch wegen UE gegenüber. Vor dem Hintergrund der beobachteten Effektstärke bei dem Endpunkt Rezidive stellen die bedeutsamen Nebenwirkungen den Vorteil beim Endpunkt Rezidive infrage. Dabei wurde berücksichtigt, dass die Aussagekraft der Ergebnisse zum Endpunkt Rezidive in der vorliegenden Therapiesituation aufgrund der kurzen medianen Beobachtungsdauer limitiert ist.

In der Gesamtschau wird daher festgestellt, dass ein Zusatznutzen von Abemaciclib in Kombination mit endokriner Therapie gegenüber endokriner Therapie, nicht belegt ist.

Der Beschluss ist für diese Patientengruppe bis zum 01.07.2025 befristet.

Das Studiendesign der Studie MONARCH-E (NCT03155997) ist unter Population A beschrieben.

Abemaciclib (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, früh mit hohem Rezidivrisiko, Adjuvanz, Kombination mit endokriner Therapie)			
Wirkstoff	Abemaciclib	**Handelsname**	Verzenios
Pharmazeutischer Unternehmer	Lilly Deutschland GmbH	**Beschlussdatum**	20.10.2022
Anwendungsgebiet	Mammakarzinom		

Abemaciclib (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, früh mit hohem Rezidivrisiko, Adjuvanz, Kombination mit endokriner Therapie)			
Wirkstoff	Abemaciclib	**Handelsname**	Verzenios
Pharmazeutischer Unternehmer	Lilly Deutschland GmbH	**Beschlussdatum**	20.10.2022
Anwendungsgebiet	Mammakarzinom		

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung eines neuen Anwendungsgebietes für den Wirkstoff Abemaciclib in Kombination mit endokriner Therapie. Das hier bewertete Anwendungsgebiet lautet:

Abemaciclib ist in Kombination mit einer endokrinen Therapie angezeigt für die adjuvante Behandlung von erwachsenen Patientinnen und Patienten mit HR-positivem, HER2-negativem, nodal-positivem Brustkrebs im frühen Stadium mit einem hohen Rezidivrisiko. Bei prä- oder perimenopausalen Frauen sollte die endokrine Aromatasehemmer-Therapie mit einem LHRH-Agonisten (LHRH= Luteinising Hormone Releasing Hormone) kombiniert werden.

In dem zu betrachtenden Anwendungsgebiet wurden drei Patientengruppen unterschieden:

a3) Männer mit einem Hormonrezeptor-positiven, HER2-negativen Mammakarzinom im Frühstadium mit hohem Rezidivrisiko

Als zweckmäßige Vergleichstherapie wurde vom G-BA Tamoxifen bestimmt.

Aufgrund der geringen Anzahl an Patienten in der Studie MONARCH-E besteht keine ausreichende Datengrundlage zur Bewertung des Zusatznutzens.

Somit ist ein Zusatznutzen für Abemaciclib in Kombination mit endokriner Therapie nicht belegt.

Das Studiendesign der Studie MONARCH-E (NCT03155997) ist unter Population A beschrieben.

Verknüpfte Empfehlungen:

Empfehlung 4.149:

Bei Patientinnen mit HR+/HER2-Mammakarzinom und hohem Rückfallrisiko (bei N2-3 oder N1 mit G3 oder Tumorgröße >/= 5cm) sollte Abemaciclib für 2 Jahre in Kombination mit der endokrinen Standard-Therapie oder Ribociclib (bei N+, oder N0 T3/T4, oder N0 T2 G3 oder N0 T2 G2 und (Ki-67 ≥ 20 % oder high-risk Genexpression)) für 3 Jahre in Kombination mit einem Aromatasehemmer (+ OFS bei prämenopausalen Patientinnen) durchgeführt werden. Beide Medikamente führen zur Senkung der Rezidivwahrscheinlichkeit.

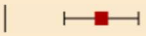
Literaturreferenzen: [220]

A phase iii multi-center, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, her2-negative early breast cancer (new adjuvant trial with ribociclib [lee011]: natalee) (Nct03701334)							
Short Name	Design	Population	Intervention	Comparator	Outcomes		
NATALEE	Randomized, Parallel, PHASE3 Open Label study	Patients with Stage 3 Early Breast Cancer	1. Ribociclib + endocrine therapy (N=2549)[1] 2. Ribociclib + Anastrozol oder Letrozol (N=1115)[2] 3. Ribociclib + Anastrozol oder Letrozol (N=1424)[3]	1. Endocrine therapy (N=2552)[4] 2. Anastrozol oder Letrozol (N=1123)[5] 3. Anastrozol oder Letrozol (N=1420)[6]			
Notes - Study							

A phase iii multi-center, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, her2-negative early breast cancer (new adjuvant trial with ribociclib [lee011]: natalee) (Nct03701334)						
Open Label Study						
Notes - Study Arms						
1: Participants will receive ribociclib 400 mg once daily on days 1-21 of a 28-day cycle and endocrine therapy once daily continuously 2: Prämenopausale Frauen im Interventionsarm 3: Postmenopausale Frauen im Interventionsarm 4: Participants will receive endocrine therapy only once daily continuously 5: Prämenopausale Frauen im Kontrollarm 6: Postmenopausale Frauen im Kontrollarm						
Outcome	Ribociclib + Anastrozol oder Letrozol N=1115		Anastrozol oder Letrozol N=1123		Effect Estimate	GRADE
Ribociclib + Anastrozol oder Letrozol vs. Anastrozol oder Letrozol zur adjuvanten Behandlung von prämenopausalen Frauen mit einem HR-positiven,HER2-negativen Mammakarzinom im Frühstadium mit hohem Rezidivrisiko: Studie NATALEE (Datenschnitt 29.04.2024)						
Dichotomous Outcomes						
Overall Survival, Time To Event[1,2,3]	N=1115	[;] 31 (2.8%)	N=1123	[;] 46 (4.1%)	HR 0.63 [0.4; 1] p=0.049		⊕⊕⊖⊖[a,b]

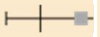
A phase iii multi-center, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, her2-negative early breast cancer (new adjuvant trial with ribociclib [lee011]: natalee) (Nct03701334)							
Disease-Free Survival, Time To Event[4,5,6]	N=1115	[;] 99 (8.9%)	N=1123	[;] 136 (12.1%)	HR 0.67 [0.52; 0.87] p=0.002		⊕⊕⊖⊖[a,c,a,c]
Recurrence Rate[12,13]	N=1115	99 (8.9%)	N=1123	136 (12.1%)	RR 0.73 [0.57; 0.93] p=0.012		⊕⊕⊖⊖[a,c]
Adverse Events[6,22]	N=1108	1093 (98.7%)	N=1070	964 (90.1%)	RR 1.09 [1.07; 1.12] p< 0.001		⊕⊕⊖⊖[a,c]
Severe Adverse Events (Total) [6,23]	N=1108	734 (66.2%)	N=1070	200 (18.7%)	RR 3.54 [3.11; 4.04] p< 0.001		⊕⊕⊕⊖[a]
Serious Adverse Events[6,24,25]	N=1108	145 (13.1%)	N=1070	105 (9.8%)	RR 1.33 [1.05; 1.69] p=0.017		⊕⊕⊕⊖[a]

A phase iii multi-center, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, her2-negative early breast cancer (new adjuvant trial with ribociclib [lee011]: natalee) (Nct03701334)							
AE-Disc[6,26,27]	N=1108	190 (17.1%)	N=1070	60 (5.6%)	RR 3.06 [2.32; 4.04] p< 0.001		⊕⊕⊖⊖[a,d]
Adverse Events: Erkrankungen der Haut und des Unterhautgewebes[6,28]	N=1108	416 (37.5%)	N=1070	227 (21.2%)	RR 1.77 [1.54; 2.03] p< 0.001		⊕⊕⊖⊖[a,c]
Adverse Events: Erkrankungen der Atemwege, des Brustraums und des Mediastinums[6,29]	N=1108	339 (30.6%)	N=1070	186 (17.4%)	RR 1.76 [1.5; 2.06] p< 0.001		⊕⊕⊖⊖[a,c]

A phase iii multi-center, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, her2-negative early breast cancer (new adjuvant trial with ribociclib [lee011]: natalee) (Nct03701334)							
Adverse Events: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort (CTCAE ≥3) [6,30]	N=1108	24 (2.2%)	N=1070	9 (0.8%)	RR 2.58 [1.2; 5.51] p=0.012		⊕⊕⊖⊖[a,b]
Adverse Events: Erkrankungen des Gastrointestinaltrakts (CTCAE ≥3) [6,31]	N=1108	24 (2.2%)	N=1070	9 (0.8%)	RR 2.58 [1.2; 5.51] p=0.012		⊕⊕⊖⊖[a,b]
Adverse Events: Hepatobiliäre Toxizität (CTCAE ≥3) [6,32]	N=1108	75 (6.8%)	N=1070	21 (2.0%)	RR 3.45 [2.14; 5.55] p< 0.001		⊕⊕⊕⊖[a]

A phase iii multi-center, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, her2-negative early breast cancer (new adjuvant trial with ribociclib [lee011]: natalee) (Nct03701334)							
Adverse Events: Infektionen und parasitäre Erkrankungen (CTCAE ≥3) [6,33]	N=1108	57 (5.1%)	N=1070	29 (2.7%)	RR 1.9 [1.22; 2.94] p=0.004		⊕⊕⊕⊖[a]
Adverse Events: Neutropenie (CTCAE ≥3) [6,34]	N=1108	335 (30.2%)	N=1070	9 (0.8%)	RR 35.95 [18.64; 69.32] p< 0.001		⊕⊕⊖⊖[a,e]
Continuous Outcomes							
EORTC QLQ-BR23 (SA) [7,8,9]	N=1054	-0.3 ±0.4	N=1000	-2.1 ±0.5	LSMD 1.78 [0.54; 3.03] p=0.005		⊕⊕⊖⊖[a,c]
EORTC QLQ-BR23 (SCA) [7,8,10]	N=1052	-4.8 ±0.4	N=1001	-5.8 ±0.4	LSMD 1.01 [0.04; 1.99] p=0.041		⊕⊕⊖⊖[a,c]

A phase iii multi-center, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, her2-negative early breast cancer (new adjuvant trial with ribociclib [lee011]: natalee) (Nct03701334)							
EORTC QLQ-BR23 (SEST) [7,8,11]	N=1060	5.8 ±0.4	N=1003	3.3 ±0.4	LSMD 2.52 [1.53; 3.52] p< 0.001		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Constipation) [7,8,14]	N=1055	4.6 ±0.5	N=1004	3.1 ±0.5	LSMD 1.54 [0.16; 2.93] p=0.029		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Diarrhea) [7,8]	N=1055	2.1 ±0.3	N=1003	1.7 ±0.3	LSMD 0.37 [-0.54; 1.27] p=0.427		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Dyspnea) [7,8]	N=1057	3.5 ±0.5	N=1004	2.6 ±0.5	LSMD 0.93 [-0.34; 2.2] p=0.150		⊕⊕⊖⊖[a,c]

A phase iii multi-center, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, her2-negative early breast cancer (new adjuvant trial with ribociclib [lee011]: natalee) (Nct03701334)							
EORTC QLQ-C30 (Fatigue) [7,8,15]	N=1059	4.1 ±0.5	N=1004	1.3 ±0.5	LSMD 2.81 [1.4; 4.21] p< 0.001		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Insomnia) [7,8]	N=1060	2.7 ±0.7	N=1005	2.6 ±0.7	LSMD 0.09 [-1.74; 1.91] p=0.927		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Lack of Appetite) [7,8]	N=1059	2.2 ±0.4	N=1005	1.7 ±0.4	LSMD 0.53 [-0.56; 1.63] p=0.339		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Nausea) [7,8,16]	N=1059	2.3 ±0.2	N=1005	1.3 ±0.2	LSMD 1.02 [0.39; 1.66] p=0.002		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Pain) [7,8]	N=1060	3.3 ±0.5	N=1004	2.5 ±0.5	LSMD 0.78 [-0.66; 2.23] p=0.288		⊕⊕⊖⊖[a,c]

A phase iii multi-center, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, her2-negative early breast cancer (new adjuvant trial with ribociclib [lee011]: natalee) (Nct03701334)							
EQ-5D (VAS) [7,17]	N=1051	-1.2 ±0.4	N=999	-0.5 ±0.4	LSMD -0.64 [-1.7; 0.41] p=0.232		⊕⊕⊖⊖[a,c]
EORTC QLQ-BR23 (Body Image) [7,17]	N=1060	2.1 ±0.6	N=1000	3.5 ±0.6	LSMD -1.35 [-2.98; 0.29] p=0.106		⊕⊕⊖⊖[a,c]
EORTC QLQ-BR23 (Future Perspective) [7,17]	N=1058	10.0 ±0.7	N=997	11.3 ±0.7	LSMD -1.32 [-3.21; 0.58] p=0.174		⊕⊕⊖⊖[a,c]
EORTC QLQ-BR23 (Sexual Activity) [7,17]	N=1047	-5.0 ±0.4	N=994	-4.42 ±0.46	LSMD -0.57 [-1.82; 0.68] p=0.372		⊕⊕⊖⊖[a,c]

A phase iii multi-center, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, her2-negative early breast cancer (new adjuvant trial with ribociclib [lee011]: natalee) (Nct03701334)							
EORTC QLQ-C30 (Cognitive Function) [7,17]	N=1056	-6.2 ±0.5	N=1003	-5.2 ±0.5	LSMD -1.05 [-2.49; 0.38] p=0.150		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Emotional Function) [7,17]	N=1056	-5.8 ±0.5	N=1003	-5.4 ±0.5	LSMD -0.48 [-1.85; 0.89] p=0.494		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Global Health Status) [7,17,18]	N=1056	-3.5 ±0.4	N=1003	-2.4 ±0.4	LSMD -1.16 [-2.31; -0.02] p=0.047		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Physical Function) [7,17,19]	N=1060	-1.5 ±0.3	N=1003	-0.3 ±0.3	LSMD -1.22 [-2.15; -0.3] p=0.010		⊕⊕⊖⊖[a,c]

A phase iii multi-center, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, her2-negative early breast cancer (new adjuvant trial with ribociclib [lee011]: natalee) (Nct03701334)							
EORTC QLQ-C30 (Role Function) [7,17,20]	N=1059	-2.9 ±0.5	N=1004	-1.3 ±0.5	LSMD -1.64 [-3.06; -0.22] p=0.023		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Social Function) [7,17,21]	N=1056	-0.2 ±0.5	N=1002	1.9 ±0.5	LSMD -2.08 [-3.52; -0.64] p=0.005		⊕⊕⊖⊖[a,c]
1: Medianes Gesamtüberleben nicht erreicht 2: Absolute Differenz der Todesfälle: 1,3% 3: Todesfälle 4: Invasiv-krankheitsfreies Überleben (iDFS, Berücksichtigung der Ereignisse Tod aufgrund jeglicher Ursache, lokales Brustkrebsrezidiv, regionäres invasives Brustkrebsrezidiv, kontralateraler invasiver Brustkrebs, Fernrezidiv, sekundäres Primärkarzinom (kein Brustkrebs)) 5: Mediane Zeit bis zum Ereignis nicht erreicht 6: Ereignisrate 7: Mittlere Änderung im Studienverlauf 8: Niedrigere (abnehmende) Werte bedeuten bessere Symptomatik, negative Effekte (Intervention minus Vergleich) bedeuten einen Vorteil für die Intervention (Skala: 0-100). 9: SMD 0.12 [0.04; 0.21] 10: SMD 0.09 [0.00; 0.18] 11: SMD 0.22 [0.13; 0.31] 12: Rezidivrate (umfasst die Ereignisse Tod aufgrund jeglicher Ursache, lokales Brustkrebsrezidiv, regionäres invasives Brustkrebsrezidiv, kontralateraler invasiver Brustkrebs, Fernrezidiv, sekundäres Primärkarzinom (kein Brustkrebs)) 13: AD = 3.2 % 14: SMD 0.10 [0.01; 0.18] 15: SMD 0.17 [0.09; 0.26] 16: SMD 0.14 [0.05; 0.23] 17: Höhere (zunehmende) Werte bedeuten besseren Gesundheitszustand bzw. gesundheitsbezogene Lebensqualität, positive Effekte (Intervention minus Vergleich) bedeuten einen Vorteil für die Intervention (Skala: 0-100). 18: SMD - 0.09 [-0.17; -0.00] 19: SMD -0.11 [-0.20; -0.03] 20: SMD -0.10 [-0.19; -0.01] 21: SMD -0.12 [-0.21; -0.04] 22: UE jeglichen Schweregrades - Gesamt 23: AD = 47.5 % 24: Schwerwiegende UE - Gesamt 25: AD = 3.3 % 26: Therapieabbruch aufgrund von UE 27: AD = 11.5 % 28: AD = 16. 3 % 29: AD = 13.2 % 30: AD = 1.4 % 31: AD =1.4 % 32: AD = 4.8 % 33: AD = 2.4 % 34: AD = 29.4 %							

A phase iii multi-center, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, her2-negative early breast cancer (new adjuvant trial with ribociclib [lee011]: natalee) (Nct03701334)							
a: Hohes endpunktübergreifendes Verzerrungspotential: Kontinuierlich im Studienverlauf auftretender hoher Anteil an Zensierungen aus potenziell informativen Gründen. Es wird angenommen, dass die Zensierungen weitgehend auf Studienabbrüche zurückzuführen sind. Die genauen Gründe für die meisten Studienabbrüche sind jedoch nicht beschrieben. b: geringe Anzahl an aufgetretenen Ereignissen c: fehlende Verblindung bei subjektiver Endpunkterhebung d: fehlende Verblindung bei subjektiver Entscheidung zum Therapieabbruch (für nicht schwere / nicht schwerwiegende UEs) e: ungenaue Effektschätzung (breites Konfidenzintervall)							
AE: Adverse Events; **CTCAE ≥3**: Common Terminology Criteria for Adverse Events, Grade ≥3; **DFS**: Disease-Free Survival ; **EQ-5D**: European Quality of Life 5 Dimensions; **OS**: Overall Survival; **SA**: Symptoms in the arm area; **SAE**: Serious Adverse Events; **SCA**: Symptoms in the chest area; **SEST**: Side effects of systemic therapy; **VAS**: Visual Analogue Scale							
Quelle: G-BA 2025. Nutzenbewertungsverfahren zum Wirkstoff Ribociclib (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, früh mit hohem Rezidivrisiko, adjuvante Therapie, Kombination mit Aromatasehemmer) - Gemeinsamer Bundesausschuss.							

Verknüpfte Empfehlungen:

Empfehlung 4.149:

Bei Patientinnen mit HR+/HER2-Mammakarzinom und hohem Rückfallrisiko (bei N2-3 oder N1 mit G3 oder Tumorgröße >/= 5cm) sollte Abemaciclib für 2 Jahre in Kombination mit der endokrinen Standard-Therapie oder Ribociclib (bei N+, oder N0 T3/T4, oder N0 T2 G3 oder N0 T2 G2 und (Ki-67 ≥ 20 % oder high-risk Genexpression)) für 3 Jahre in Kombination mit einem Aromatasehemmer (+ OFS bei prämenopausalen Patientinnen) durchgeführt werden. Beide Medikamente führen zur Senkung der Rezidivwahrscheinlichkeit.

Literaturreferenzen: [220]

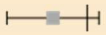
Outcome	Ribociclib + Anastrozol oder Letrozol N=1424		Anastrozol oder Letrozol N=1420		Effect Estimate		GRADE
Ribociclib + Anastrozol oder Letrozol vs. Anastrozol oder Letrozol zur adjuvanten Behandlung von postmenopausalen Frauen mit einem HR-positiven, HER2-negativen Mammakarzinom im Frühstadium mit hohem Rezidivrisiko: Studie NATALEE (Datenschnitt 29.04.2024)							
Dichotomous Outcomes							
Overall Survival, Time To Event[1,2]	N=1424	[;] 74 (5.2%)	N=1420	[;] 75 (5.3%)	HR 0.94 [0.68; 1.3] p=0.724		⊕⊕⊖⊖[a,b]
Disease-Free Survival, Time To Event[3,4,5]	N=1424	[;] 164 (11.5%)	N=1420	[;] 203 (14.3%)	HR 0.75 [0.61; 0.92] p=0.005		⊕⊕⊖⊖[a,c]

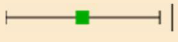
Outcome	Ribociclib + Anastrozol oder Letrozol N=1424		Anastrozol oder Letrozol N=1420		Effect Estimate		GRADE
Recurrence Rate[9,10]	N=1424	164 (11.5%)	N=1420	203 (14.3%)	RR 0.81 [0.67; 0.98] p=0.027		⊕⊕⊖⊖[a,c]
Adverse Events[5,15]	N=1409	1376 (97.7%)	N=1362	1183 (86.9%)	RR 1.12 [1.1; 1.15] p<0.001		⊕⊕⊖⊖[a,c]
Severe Adverse Events (Total) [5,16]	N=1409	883 (62.7%)	N=1362	280 (20.6%)	RR 3.05 [2.73; 3.41] p< 0.001		⊕⊕⊕⊖[a]
Serious Adverse Events[5,17,18]	N=1409	229 (16.3%)	N=1362	162 (11.9%)	RR 1.37 [1.13; 1.65] p< 0.001		⊕⊕⊕⊖[a]
AE-Disc[5,19,20]	N=1409	340 (24.1%)	N=1362	68 (5.0%)	RR 4.83 [3.77; 6.2] p< 0.001		⊕⊕⊖⊖[a,d]

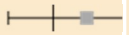
Outcome	Ribociclib + Anastrozol oder Letrozol N=1424		Anastrozol oder Letrozol N=1420		Effect Estimate		GRADE
Adverse Events: Erkrankungen des Haut und des Unterhautgewebes[5,21]	N=1409	536 (38.0%)	N=1362	274 (20.1%)	RR 1.89 [1.67; 2.14] p< 0.001		⊕⊕⊖⊖[a,c]
Adverse Events: Erkrankungen des Gastrointestinaltrakts[5,22]	N=1409	760 (53.9%)	N=1362	384 (28.2%)	RR 1.91 [1.74; 2.11] p< 0.001		⊕⊕⊖⊖[a,c]
Adverse Events: Erkrankungen des Nervensystems (CTCAE ≥3) [5,23]	N=1409	40 (2.8%)	N=1362	16 (1.2%)	RR 2.42 [1.36; 4.29] p=0.002		⊕⊕⊖⊖[a,b]

Outcome	Ribociclib + Anastrozol oder Letrozol N=1424		Anastrozol oder Letrozol N=1420		Effect Estimate		GRADE
Adverse Events: Ermüdung (CTCAE ≥3) [5,24]	N=1409	15 (1.1%)	N=1362	3 (0.2%)	RR 4.83 [1.4; 16.66] p=0.006		⊕⊕⊖⊖[a,b]
Adverse Events: Hepatobiliäre Toxizität (CTCAE ≥3) [5,25]	N=1409	142 (10.1%)	N=1362	21 (1.5%)	RR 6.54 [4.16; 10.27] p< 0.001		⊕⊕⊕⊖[a]
Adverse Events: Infektionen und parasitäre Erkrankungen (CTCAE ≥3) [5,26]	N=1409	89 (6.3%)	N=1362	51 (3.7%)	RR 1.69 [1.21; 2.36] p=0.002		⊕⊕⊖⊖[a,b]
Adverse Events: Neutropenie (CTCAE ≥3) [5,27]	N=1409	374 (26.5%)	N=1362	4 (0.3%)	RR 90.38 [33.84; 241.39] p< 0.001		⊕⊕⊖⊖[a,e]

Outcome	Ribociclib + Anastrozol oder Letrozol N=1424		Anastrozol oder Letrozol N=1420		Effect Estimate		GRADE
Adverse Events: Nierentoxizität (CTCAE ≥3) [5,28]	N=1409	7 (0.5%)	N=1362	0 (0.0%)	RR 14.5 [0.83; 253.63] p=0.009		⊕⊕⊖⊖[a,e]
Serious Adverse Events: Erkrankungen der Atemwege des Brustraums und des Mediastinums[5,29]	N=1409	34 (2.4%)	N=1362	16 (1.2%)	RR 2.05 [1.14; 3.7] p=0.015		⊕⊕⊖⊖[a,b]
Continuous Outcomes							
EORTC QLQ-BR23 (SA) [6,7]	N=1323	0.3 ±0.4	N=1261	-0.3 ±0.4	LSMD 0.58 [-0.58; 1.74] p=0.329		⊕⊕⊖⊖[a,c]
EORTC QLQ-BR23 (SCA) [6,7]	N=1322	-5.5 ±0.3	N=1259	-5.5 ±0.3	LSMD 0.01 [-0.87; 0.89] p=0.981		⊕⊕⊖⊖[a,c]

Outcome	Ribociclib + Anastrozol oder Letrozol N=1424		Anastrozol oder Letrozol N=1420		Effect Estimate		GRADE
EORTC QLQ-BR23 (SEST) [6,7,8]	N=1329	4.2 ±0.3	N=1257	3.0 ±0.3	LSMD 1.22 [0.37; 2.07] p=0.005		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Constipation) [6,7,11]	N=1323	4.1 ±0.4	N=1263	1.3 ±0.4	LSMD 2.78 [1.57; 3.98] p< 0.001		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Diarrhea) [6,7]	N=1322	1.2 ±0.3	N=1259	1.8 ±0.3	LSMD -0.58 [-1.36; 0.2] p=0.144		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Dyspnea) [6,7]	N=1322	3.5 ±0.4	N=1260	3.4 ±0.4	LSMD 0.11 [-1.08; 1.3] p=0.853		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Fatigue) [6,7]	N=1325	2.8 ±0.4	N=1263	2.7 ±0.4	LSMD 0.05 [-1.13; 1.22] p=0.939		⊕⊕⊖⊖[a,c]

Outcome	Ribociclib + Anastrozol oder Letrozol N=1424		Anastrozol oder Letrozol N=1420		Effect Estimate		GRADE
EORTC QLQ-C30 (Insomnia) [6,7]	N=1322	2.2 ±0.5	N=1261	3.4 ±0.6	LSMD -1.22 [-2.75; 0.3] p=0.116		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Lack of Appetite) [6,7]	N=1325	1.1 ±0.4	N=1261	0.6 ±0.4	LSMD 0.47 [-0.51; 1.44] p=0.349		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Nausea) [6,7,12]	N=1325	2.0 ±0.2	N=1263	1.1 ±0.2	LSMD 0.88 [0.33; 1.44] p=0.002		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Pain) [6,7,13]	N=1328	3.0 ±0.5	N=1263	4.5 ±0.5	LSMD -1.52 [-2.82; -0.21] p=0.022		⊕⊕⊖⊖[a,c]
EQ-5D (VAS) [6,14]	N=1323	-1.6 ±0.3	N=1259	-1.3 ±0.3	LSMD -0.27 [-1.13; 0.59] p=0.540		⊕⊕⊖⊖[a,c]

Outcome	Ribociclib + Anastrozol oder Letrozol N=1424		Anastrozol oder Letrozol N=1420		Effect Estimate		GRADE
EORTC QLQ-BR23 (Body Image) [6,14]	N=1327	2.7 ±0.5	N=1254	2.1 ±0.5	LSMD 0.57 [-0.76; 1.9] p=0.401		⊕⊕⊖⊖[a,c]
EORTC QLQ-BR23 (Future Perspective) [6,14]	N=1327	9.1 ±0.5	N=1252	8.1 ±0.5	LSMD 0.94 [-0.55; 2.43] p=0.215		⊕⊕⊖⊖[a,c]
EORTC QLQ-BR23 (Sexual Activity) [6,14]	N=1297	-1.9 ±0.4	N=1221	-2.1 ±0.4	LSMD 0.12 [-0.88; 1.13] p=0.808		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Cognitive Function) [6,14]	N=1322	-4.5 ±0.4	N=1260	-5.1 ±0.4	LSMD 0.62 [-0.5; 1.75] p=0.278		⊕⊕⊖⊖[a,c]

Outcome	Ribociclib + Anastrozol oder Letrozol N=1424		Anastrozol oder Letrozol N=1420		Effect Estimate		GRADE
EORTC QLQ-C30 (Emotional Function) [6,14]	N=1323	-2.8 ±0.4	N=1259	-3.8 ±0.4	LSMD 0.98 [-0.14; 2.1] p=0.088		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Global Health Status) [6,14]	N=1322	-2.8 ±0.4	N=1258	-2.4 ±0.4	LSMD -0.43 [-1.4; 0.54] p=0.388		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Physical Function) [6,14]	N=1326	-2.2 ±0.3	N=1264	-2.8 ±0.3	LSMD 0.64 [-0.27; 1.56] p=0.168		⊕⊕⊖⊖[a,c]
EORTC QLQ-C30 (Role Function) [6,14]	N=1325	-3.0 ±0.4	N=1264	-3.5 ±0.4	LSMD 0.57 [-0.63; 1.78] p=0.353		⊕⊕⊖⊖[a,c]

Outcome	Ribociclib + Anastrozol oder Letrozol N=1424		Anastrozol oder Letrozol N=1420		Effect Estimate		GRADE
EORTC QLQ-C30 (Social Function) [6,14]	N=1323	0.4 ±0.3	N=1259	0.5 ±0.3	LSMD -0.05 [-0.9; 0.8] p=0.911		⨁⨁⊖⊖[a,c]

1: Medianes Gesamtüberleben nicht erreicht 2: Todesfälle 3: Invasiv-krankheitsfreies Überleben (iDFS, Berücksichtigung der Ereignisse Tod aufgrund jeglicher Ursache, lokales Brustkrebsrezidiv, regionäres invasives Brustkrebsrezidiv, kontralateraler invasiver Brustkrebs, Fernrezidiv, sekundäres Primärkarzinom (kein Brustkrebs)) 4: Mediane Zeit bis zum Ereignis nicht erreicht 5: Ereignisrate 6: Mittlere Änderung im Studienverlauf 7: Niedrigere (abnehmende) Werte bedeuten bessere Symptomatik, negative Effekte (Intervention minus Vergleich) bedeuten einen Vorteil für die Intervention (Skala: 0-100). 8: SMD 0.11 [0.03; 0.19] 9: Rezidivrate (umfasst die Ereignisse Tod aufgrund jeglicher Ursache, lokales Brustkrebsrezidiv, regionäres invasives Brustkrebsrezidiv, kontralateraler invasiver Brustkrebs, Fernrezidiv, sekundäres Primärkarzinom (kein Brustkrebs)) 10: AD 2.8 % 11: SMD 0.18 [0.10; 0.26] 12: SMD 0.12 [0.05; 0.20] 13: SMD -0.09 [-0.17; -0.01] 14: Höhere (zunehmende) Werte bedeuten besseren Gesundheitszustand bzw. gesundheitsbezogene Lebensqualität, positive Effekte (Intervention minus Vergleich) bedeuten einen Vorteil für die Intervention (Skala: 0-100). 15: UE jeglichen Schweregrades - Gesamt 16: AD = 42.1 % 17: Schwerwiegende UE - Gesamt 18: AD = 4.4 % 19: Therapieabbruch aufgrund von UE (Abbruch einer Therapiekomponente) 20: AD = 19.1 % 21: AD = 17.9 % 22: AD = 25,7 % 23: AD = 1.6 % 24: AD = 0.9 % 25: AD = 8.6 % 26: AD = 2.6 % 27: AD = 26.2 % 28: AD = 0.5 % 29: AD = 1.2 %

a: Hohes endpunktübergreifendes Verzerrungspotential: Kontinuierlich im Studienverlauf auftretender hoher Anteil an Zensierungen aus potenziell informativen Gründen. Es wird angenommen, dass die Zensierungen weitgehend auf Studienabbrüche zurückzuführen sind. Die genauen Gründe für die meisten Studienabbrüche sind jedoch nicht beschrieben. b: geringe Anzahl an aufgetretenen Ereignissen c: fehlende Verblindung bei subjektiver Endpunkterhebung d: fehlende Verblindung bei subjektiver Entscheidung zum Therapieabbruch (für nicht schwere / nicht schwerwiegende UEs) e: ungenaue Effektschätzung (breites Konfidenzintervall)

Outcome	Ribociclib + Anastrozol oder Letrozol N=1424	Anastrozol oder Letrozol N=1420	Effect Estimate		GRADE
AE: Adverse Events; **CTCAE ≥3**: Common Terminology Criteria for Adverse Events, Grade ≥3; **DFS**: Disease-Free Survival ; **EQ-5D**: European Quality of Life 5 Dimensions; **OS**: Overall Survival; **SA**: Symptoms in the arm area; **SAE**: Serious Adverse Events; **SCA**: Symptoms in the chest area; **SEST**: Side effects of systemic therapy; **VAS**: Visual Analogue Scale					
Quelle: G-BA 2025. Nutzenbewertungsverfahren zum Wirkstoff Ribociclib (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, früh mit hohem Rezidivrisiko, adjuvante Therapie, Kombination mit Aromatasehemmer) - Gemeinsamer Bundesausschuss.					

Verknüpfte Empfehlungen:

Empfehlung 4.156:

Patientinnen mit einem triple-negativem Mammakarzinom (TNBC) und pathogener *BRCA-1* oder *BRCA-2* Keimbahnmutation, die nach neoadjuvanter Chemotherapie keine pCR erreicht haben oder die ein hohes Risiko nach primärer Operation aufweisen (> pT2, und/oder >pN1), sollten Olaparib über 1 Jahr erhalten.

Empfehlung 4.150:

Bei Patientinnen mit Hormonrezeptor-positivem und HER2/neu negativem Mammacarcinom mit hohem Rückfallrisiko (z.B. N2-3 oder CPS Score ≥3 nach neoadjuvanter Chemotherapie) und einer Keimbahn BRCA1/2 Mutation sollte Olaparib für 1 Jahr in Kombination mit der endokrinen Standard-Therapie durchgeführt werden.

Literaturreferenzen: [220]

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Olaparib (Neues Anwendungsgebiet: Mammakarzinom, HER2-, BRCA1/2-Mutation, vorbehandelt, hohes Rezidivrisiko, Adjuvanz, Monotherapie oder Kombination mit endokriner Therapie)			
Wirkstoff	Olaparib	**Handelsname**	Lynparza
Pharmazeutischer Unternehmer	AstraZeneca GmbH	**Beschlussdatum**	16.02.2023
Anwendungsgebiet	Mammakarzinom		

Olaparib (Neues Anwendungsgebiet: Mammakarzinom, HER2-, BRCA1/2-Mutation, vorbehandelt, hohes Rezidivrisiko, Adjuvanz, Monotherapie oder Kombination mit endokriner Therapie)			
Wirkstoff	Olaparib	**Handelsname**	Lynparza
Pharmazeutischer Unternehmer	AstraZeneca GmbH	**Beschlussdatum**	16.02.2023
Anwendungsgebiet	Mammakarzinom		

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung eines neuen Anwendungsgebietes für den Wirkstoff Olaparib als Monotherapie oder in Kombination mit einer endokrinen Therapie zur adjuvanten Behandlung von Erwachsenen mit Keimbahn-BRCA1/2-Mutationen, die ein HER2-negatives Mammakarzinom im Frühstadium mit hohem Rezidivrisiko haben und zuvor mit neoadjuvanter oder adjuvanter Chemotherapie behandelt wurden.
Als zweckmäßige Vergleichstherapie wurde „Beobachtendes Abwarten“ bestimmt.
Für den Nachweis des Zusatznutzens wurden Ergebnisse aus der doppelblinden, randomisierten, kontrollierten Studie OlympiA zu den Endpunktkategorien Mortalität, Morbidität, Lebensqualität und Nebenwirkungen vorgelegt.
Für den Endpunkt Gesamtüberleben zeigt sich ein statistisch signifikanter Unterschied zum Vorteil von Olaparib gegenüber beobachtendem Abwarten.
In der Kategorie Morbidität zeigen sich statistisch signifikant weniger Rezidive unter Behandlung mit Olaparib im Vergleich zum beobachtenden Abwarten. In der vorliegenden kurativen Therapiesituation stellt die Vermeidung von Rezidiven ein essentielles Therapieziel dar. Das Ausmaß der Vermeidung von Rezidiven wird vorliegend als relevanter Vorteil bewertet.
Hinsichtlich der patientenberichteten Symptomatik sowie zur gesundheitsbezogenen Lebensqualität zeigen sich insgesamt keine bewertungsrelevanten Unterschiede.
Bei den Nebenwirkungen zeigen sich statistisch signifikante Nachteile von Olaparib gegenüber beobachtendem Abwarten bei den Endpunkten schwere UE (CTCAE-Grad ≥ 3) und Abbruch wegen UE sowie im Detail bei spezifischen unerwünschten Ereignissen.
In der Gesamtbetrachtung stehen somit den Vorteilen – Verbesserung im Gesamtüberleben und Vermeidung von Rezidiven – Nachteile bei den Nebenwirkungen gegenüber. Die Nachteile bei den Nebenwirkungen werden vor dem Hintergrund des vorliegenden kurativen Therapieanspruches gewichtet. Insgesamt überwiegen die Vorteile die Nachteile, womit ein Zusatznutzen festzustellen ist. Für die Beurteilung des Ausmaßes des Zusatznutzens ist insbesondere der vorliegende Effekt hinsichtlich der Vermeidung von Rezidiven leitend. Unter Berücksichtigung der Rezidivraten in beiden Behandlungsgruppen und der absoluten Differenz in den Rezidivraten gelangt der G-BA zu der Beurteilung, dass in der Gesamtbewertung im vorliegenden Fall nicht mit hinreichender Sicherheit von dem Ausmaß eines beträchtlichen Zusatznutzens ausgegangen werden kann.

Somit wird für Olaparib ein geringer Zusatznutzen gegenüber beobachtendem Abwarten festgestellt.
Die Aussagesicherheit wird insbesondere aufgrund des niedrigen Verzerrungspotenzials auf Studienebene und bei den für die Bewertungsentscheidung maßgeblichen Endpunkten in die Kategorie „Hinweis“ eingestuft.

Olaparib (Neues Anwendungsgebiet: Mammakarzinom, HER2-, BRCA1/2-Mutation, vorbehandelt, hohes Rezidivrisiko, Adjuvanz, Monotherapie oder Kombination mit endokriner Therapie)			
Wirkstoff	Olaparib	**Handelsname**	Lynparza
Pharmazeutischer Unternehmer	AstraZeneca GmbH	**Beschlussdatum**	16.02.2023
Anwendungsgebiet	Mammakarzinom		

Olaparib (Neues Anwendungsgebiet: Mammakarzinom, HER2-, BRCA1/2-Mutation, vorbehandelt, hohes Rezidivrisiko, Adjuvanz, Monotherapie oder Kombination mit endokriner Therapie)			
Wirkstoff	Olaparib	**Handelsname**	Lynparza
Pharmazeutischer Unternehmer	AstraZeneca GmbH	**Beschlussdatum**	16.02.2023
Anwendungsgebiet	Mammakarzinom		

Olaparib (Neues Anwendungsgebiet: Mammakarzinom, HER2-, BRCA1/2-Mutation, vorbehandelt, hohes Rezidivrisiko, Adjuvanz, Monotherapie oder Kombination mit endokriner Therapie)			
Wirkstoff	Olaparib	**Handelsname**	Lynparza
Pharmazeutischer Unternehmer	AstraZeneca GmbH	**Beschlussdatum**	16.02.2023
Anwendungsgebiet	Mammakarzinom		

Kapitel 4.6.3: Chemotherapie Triple-negatives Mammakarzinom (TNBC)

Verknüpfte Empfehlungen:

Empfehlung 4.154:

Patientinnen mit einem triple-negativem Mammakarzinom (TNBC) größer 2 cm oder mit Lymphknotenbefall sollten den ICPi Pembrolizumab in Kombination mit einer neoadjuvanten Chemotherapie mit Anthrazyklin/Taxan/Carboplatin erhalten.

Das Therapie sollte postoperativ mit 9 Zyklen adjuvant Pembrolizumab fortgesetzt werden.

Literaturreferenzen: [220]

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Pembrolizumab (Neues Anwendungsgebiet: Mammakarzinom, triple-negativ, PD-L1-Expression ≥ 10 (CPS), Kombination mit Chemotherapie)			
Wirkstoff	Pembrolizumab	**Handelsname**	Keytruda
Pharmazeutischer Unternehmer	MSD Sharp & Dohme GmbH	**Beschlussdatum**	05.05.2022
Anwendungsgebiet	Mammakarzinom		

Pembrolizumab (Neues Anwendungsgebiet: Mammakarzinom, triple-negativ, PD-L1-Expression ≥ 10 (CPS), Kombination mit Chemotherapie)			
Wirkstoff	Pembrolizumab	**Handelsname**	Keytruda
Pharmazeutischer Unternehmer	MSD Sharp & Dohme GmbH	**Beschlussdatum**	05.05.2022

Pembrolizumab (Neues Anwendungsgebiet: Mammakarzinom, triple-negativ, PD-L1-Expression ≥ 10 (CPS), Kombination mit Chemotherapie)	
Anwendungsgebiet	Mammakarzinom

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung eines neuen Anwendungsgebietes für den Wirkstoff Pembrolizumab. Das hier bewertete Anwendungsgebiet lautet:
„Keytruda ist in Kombination mit Chemotherapie zur Behandlung des lokal rezidivierenden nicht resezierbaren oder metastasierenden triple-negativen Mammakarzinoms mit PD-L1-exprimierenden Tumoren (Combined Positive Score [CPS] ≥ 10) bei Erwachsenen, die keine vorherige Chemotherapie zur Behandlung der metastasierenden Erkrankung erhalten haben, angezeigt."
Der Bewertung liegt die Studie KEYNOTE 355 zugrunde, in der Pembrolizumab in Kombination mit Paclitaxel oder nab-Paclitaxel oder Gemcitabin/Carboplatin im Vergleich zu Paclitaxel oder nab-Paclitaxel oder Gemcitabin/Carboplatin untersucht worden ist. Die Bewertung basiert auf Auswertungen zu einer Teilpopulation von Patientinnen und Patienten mit PL1-exprimierenden Tumor (CPS ≥ 10) entsprechend der Zulassung und der Zuordnung zu einer Taxan-Chemotherapie (Paclitaxel oder nab-Paclitaxel) vor Randomisierung.
Da der Bewertung allein Daten für Pembrolizumab in Kombination mit nab-Paclitaxel oder Paclitaxel vorliegen, jedoch nicht in Kombination mit einer anderen Chemotherapie, werden diesbezüglich getrennte Aussagen zum Zusatznutzen vorgenommen:

- Pembrolizumab in Kombination mit nab-Paclitaxel oder Paclitaxel
- Pembrolizumab in Kombination mit einer anderen Chemotherapie als nab-Paclitaxel oder Paclitaxel

Bewertung des Zusatznutzens für a)
Für die Bewertung liegen Ergebnisse zum Gesamtüberleben, zur Morbidität, Lebensqualität und zu Nebenwirkungen vor.
Für den Endpunkt Gesamtüberleben zeigt sich ein statistisch signifikanter Unterschied zugunsten von Pembrolizumab in Kombination mit nab-Paclitaxel oder Paclitaxel. Das Ausmaß des Effektes wird als eine deutliche Verbesserung bewertet.
In den Endpunktkategorien Morbidität und gesundheitsbezogene Lebensqualität zeigen sich insgesamt keine relevanten Unterschiede.
In der Gesamtschau der Ergebnisse zu den Nebenwirkungen lässt sich für Pembrolizumab in Kombination mit nab-Paclitaxel oder Paclitaxel im Vergleich zu nab-Paclitaxel oder Paclitaxel weder ein Vorteil noch ein Nachteil feststellen.
Im Ergebnis stellt der G-BA einen beträchtlicher Zusatznutzen fest.
Die Aussagesicherheit für den festgestellten Zusatznutzen wird als Anhaltspunkt eingestuft.

Pembrolizumab (Neues Anwendungsgebiet: Mammakarzinom, triple-negativ, PD-L1-Expression ≥ 10 (CPS), Kombination mit Chemotherapie)			
Wirkstoff	Pembrolizumab	**Handelsname**	Keytruda
Pharmazeutischer Unternehmer	MSD Sharp & Dohme GmbH	**Beschlussdatum**	05.05.2022
Anwendungsgebiet	Mammakarzinom		

Pembrolizumab (Neues Anwendungsgebiet: Mammakarzinom, triple-negativ, PD-L1-Expression ≥ 10 (CPS), Kombination mit Chemotherapie)			
Wirkstoff	Pembrolizumab	**Handelsname**	Keytruda
Pharmazeutischer Unternehmer	MSD Sharp & Dohme GmbH	**Beschlussdatum**	05.05.2022
Anwendungsgebiet	Mammakarzinom		

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung eines neuen Anwendungsgebietes für den Wirkstoff Pembrolizumab. Das hier bewertete Anwendungsgebiet lautet:

„Keytruda ist in Kombination mit Chemotherapie zur Behandlung des lokal rezidivierenden nicht resezierbaren oder metastasierenden triple-negativen Mammakarzinoms mit PD-L1-exprimierenden Tumoren (Combined Positive Score [CPS] ≥ 10) bei Erwachsenen, die keine vorherige Chemotherapie zur Behandlung der metastasierenden Erkrankung erhalten haben, angezeigt.“

Der Bewertung liegt die Studie KEYNOTE 355 zugrunde, in der Pembrolizumab in Kombination mit Paclitaxel oder nab-Paclitaxel oder Gemcitabin/Carboplatin

im Vergleich zu Paclitaxel oder nab-Paclitaxel oder Gemcitabin/Carboplatin untersucht worden ist. Die Bewertung basiert auf Auswertungen zu einer Teilpopulation von Patientinnen und Patienten mit PL1-exprimierenden Tumor (CPS ≥ 10) entsprechend der Zulassung und der Zuordnung zu einer Taxan-Chemotherapie (Paclitaxel oder nab-Paclitaxel) vor Randomisierung.

Da der Bewertung allein Daten für Pembrolizumab in Kombination mit nab-Paclitaxel oder Paclitaxel vorliegen, jedoch nicht in Kombination mit einer anderen Chemotherapie, werden diesbezüglich getrennte Aussagen zum Zusatznutzen vorgenommen:

- Pembrolizumab in Kombination mit nab-Paclitaxel oder Paclitaxel
- Pembrolizumab in Kombination mit einer anderen Chemotherapie als nab-Paclitaxel oder Paclitaxel

Bewertung des Zusatznutzens für b)

Es liegen keine Daten vor, die eine Bewertung des Zusatznutzens ermöglichen. Ein Zusatznutzen ist somit nicht belegt.

Verknüpfte Empfehlungen:

Empfehlung 4.154:

Patientinnen mit einem triple-negativem Mammakarzinom (TNBC) größer 2 cm oder mit Lymphknotenbefall sollten den ICPi Pembrolizumab in Kombination mit einer neoadjuvanten Chemotherapie mit Anthrazyklin/Taxan/Carboplatin erhalten.

Das Therapie sollte postoperativ mit 9 Zyklen adjuvant Pembrolizumab fortgesetzt werden.

Literaturreferenzen: [220]

Pembrolizumab (Neues Anwendungsgebiet: Mammakarzinom, triple-negativ, hohes Rezidivrisiko, neoadjuvante und adjuvante Therapie, Monotherapie oder Kombination mit Chemotherapie)			
Wirkstoff	Pembrolizumab	**Handelsname**	Keytruda
Pharmazeutischer Unternehmer	MSD Sharp & Dohme GmbH	**Beschlussdatum**	15.12.2022
Anwendungsgebiet	Mammakarzinom		

Pembrolizumab (Neues Anwendungsgebiet: Mammakarzinom, triple-negativ, hohes Rezidivrisiko, neoadjuvante und adjuvante Therapie, Monotherapie oder Kombination mit Chemotherapie)			
Wirkstoff	Pembrolizumab	**Handelsname**	Keytruda
Pharmazeutischer Unternehmer	MSD Sharp & Dohme GmbH	**Beschlussdatum**	15.12.2022
Anwendungsgebiet	Mammakarzinom		

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung eines neuen Anwendungsgebietes für den Wirkstoff Pembrolizumab + Chemotherapie zur neoadjuvanten und anschließend nach Operation als Monotherapie zur adjuvanten Behandlung. Das hier bewertete Anwendungsgebiet lautet:
Keytruda ist in Kombination mit Chemotherapie zur neoadjuvanten und anschließend nach Operation als Monotherapie zur adjuvanten Behandlung des lokal fortgeschrittenen oder frühen triple-negativen Mammakarzinoms mit hohem Rezidivrisiko bei Erwachsenen angezeigt.
Da der Bewertung allein Daten aus der Studie KEYNOTE 522 für Pembrolizumab + Paclitaxel + Carboplatin gefolgt von Pembrolizumab + Doxorubicin oder Epirubicin + Cyclophosphamid (neoadjuvant) und Pembrolizumab (adjuvant) vorliegen, jedoch nicht in Kombination mit einer anderen Chemotherapie, werden diesbezüglich getrennte Aussagen zum Zusatznutzen vorgenommen:

- Pembrolizumab + Paclitaxel + Carboplatin gefolgt von Pembrolizumab + Doxorubicin/Epirubicin + Cyclophosphamid (neoadjuvant) und Pembrolizumab (adjuvant)
- Pembrolizumab + andere Chemotherapie als Paclitaxel und Carboplatin gefolgt von Pembrolizumab + andere Chemotherapie als Doxorubicin oder Epirubicin + Cyclophosphamid (neoadjuvant) und Pembrolizumab (adjuvant)

Bewertung des Zusatznutzens für a)
Beim Endpunkt Gesamtüberleben zeigt sich kein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen.
In der Betrachtung der Rezidive, operationalisiert über die Rezidivrate und das ereignisfreie Überleben, zeigt sich ein statistisch signifikanter Vorteil für Patientinnen und Patienten, welche im Interventionsarm behandelt wurden.
Für die Endpunkte Symptomatik und Gesundheitszustand liegen keine bewertbaren Daten vor.
Für die Kategorie Lebensqualität liegen ebenfalls keine bewertbaren Daten vor.
Dem relevanten Vorteil bei den Rezidiven stehen in der Kategorie Nebenwirkungen Nachteile der Interventionsbehandlung insbesondere bei den Endpunkten schwerwiegende unerwünschte Ereignisse (SUE) und Abbruch wegen UE gegenüber, die jedoch die Vorteile bei den Rezidiven vor dem Hintergrund der essentiellen Bedeutung der Vermeidung von Rezidiven in der kurativen Therapiesituation nicht grundsätzlich infrage stellen.
Die Aussagesicherheit wird insgesamt als Anhaltspunkt eingestuft. Dies ergibt sich daraus, dass eine platin-basierte Chemotherapie nicht für alle Patientinnen und Patienten eine geeignete Behandlung darstellt. Zudem sind Arzneimittel mit einem Platin-Wirkstoff für die vorliegende Therapiesituation nicht zugelassen. Gemäß dem vorliegenden Anwendungsgebiet wären auch weitere Chemotherapiekombinationen möglich.
In der Gesamtschau wird daher ein Anhaltspunkt für einen geringen Zusatznutzen von Pembrolizumab + Paclitaxel + Carboplatin gefolgt von Pembrolizumab + Doxorubicin/Epirubicin + Cyclophosphamid (neoadjuvant) und Pembrolizumab (adjuvant) festgestellt.
Der Beschluss ist für diese Patientengruppe bis zum 01.10.2024 befristet, da weitere klinische Daten aus der Studie KEYNOTE 522 erwartet werden.

Pembrolizumab (Neues Anwendungsgebiet: Mammakarzinom, triple-negativ, hohes Rezidivrisiko, neoadjuvante und adjuvante Therapie, Monotherapie oder Kombination mit Chemotherapie)			
Wirkstoff	Pembrolizumab	**Handelsname**	Keytruda
Pharmazeutischer Unternehmer	MSD Sharp & Dohme GmbH	**Beschlussdatum**	15.12.2022
Anwendungsgebiet	Mammakarzinom		

Pembrolizumab (Neues Anwendungsgebiet: Mammakarzinom, triple-negativ, hohes Rezidivrisiko, neoadjuvante und adjuvante Therapie, Monotherapie oder Kombination mit Chemotherapie)			
Wirkstoff	Pembrolizumab	**Handelsname**	Keytruda
Pharmazeutischer Unternehmer	MSD Sharp & Dohme GmbH	**Beschlussdatum**	15.12.2022
Anwendungsgebiet	Mammakarzinom		

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung eines neuen Anwendungsgebietes für den Wirkstoff Pembrolizumab + Chemotherapie zur neoadjuvanten und anschließend nach Operation als Monotherapie zur adjuvanten Behandlung. Das hier bewertete Anwendungsgebiet lautet:

Keytruda ist in Kombination mit Chemotherapie zur neoadjuvanten und anschließend nach Operation als Monotherapie zur adjuvanten Behandlung des lokal fortgeschrittenen oder frühen triple-negativen Mammakarzinoms mit hohem Rezidivrisiko bei Erwachsenen angezeigt.

Da der Bewertung allein Daten aus der Studie KEYNOTE 522 für Pembrolizumab + Paclitaxel + Carboplatin gefolgt von Pembrolizumab + Doxorubicin oder Epirubicin + Cyclophosphamid (neoadjuvant) und Pembrolizumab (adjuvant) vorliegen, jedoch nicht in Kombination mit einer anderen Chemotherapie, werden diesbezüglich getrennte Aussagen zum Zusatznutzen vorgenommen:

- Pembrolizumab + Paclitaxel + Carboplatin gefolgt von Pembrolizumab + Doxorubicin/Epirubicin + Cyclophosphamid (neoadjuvant) und Pembrolizumab (adjuvant)
- Pembrolizumab + andere Chemotherapie als Paclitaxel und Carboplatin gefolgt von Pembrolizumab + andere Chemotherapie als Doxorubicin oder Epirubicin + Cyclophosphamid (neoadjuvant) und Pembrolizumab (adjuvant)

Bewertung des Zusatznutzens für b)

Es liegen keine Daten vor, die eine Bewertung des Zusatznutzens ermöglichen. Ein Zusatznutzen ist somit nicht belegt.

Der Beschluss ist für diese Patientengruppe bis zum 01.10.2024 befristet.

Verknüpfte Empfehlungen:

Empfehlung 4.155:

Patientinnen mit einem triple-negativem Mammakarzinom (TNBC) mit non-pCR nach anthrazyklin- / taxanhaltiger Chemotherapie sollten adjuvant Capecitabin für 6-8 Zyklen erhalten.

Literaturreferenzen: [221]

Source: MT, van Mackelenbergh, Seither F, Möbus V, O'Shaughnessy J, Martin M, Joensuu H, Untch M, et al. "Effects of Capecitabine as Part of Neo-/Adjuvant Chemotherapy - a Meta-Analysis of Individual Breast Cancer Patient Data from 13 Randomised Trials Including 15,993 Patients." [In eng]. European journal of cancer (Oxford, England: 1990) 166 (2022-5 2022): 185-201. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35305453/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: effect of capecitabine on DFS, distant DFS and OS in early breast cancer (EBC)	**Design**: Systematic review and meta-analysis of individual breast cancer patient data **Search date**: 13th August 2020 **Searched databases**: PubMed, clinicaltrials.gov **Included study designs**: Multicenter randomised controlled trials	**Intervention** capecitabine in addition to another therapy **Control** capecitabine instead ofanother therapy	**Primary Outcome**: Disease-free survival (DFS) **Secondary Outcome**: Overall survival (OS) Distant disease-free survival (DDFS) Pathological complete response (pCR)	**Primary Outcome**: **DFS among TNBC:** 1) Overall cohort: HR: 0.89, 95% CI 0.79-0.99; p=0.040 2) Capecitabine in addition to another therapy: HR: 0.82, 95% CI 0.71-0.94; p=0.004 3) Capecitabine instead ofanother therapy:	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 6 critical flaws (item 2,4,7,9,13,15) **Additional concerns about quality**: Results from CBCSG010 trial were not included in this meta-analysis (published after the initial search)

Source: MT, van Mackelenbergh, Seither F, Möbus V, O'Shaughnessy J, Martin M, Joensuu H, Untch M, et al. "Effects of Capecitabine as Part of Neo-/Adjuvant Chemotherapy - a Meta-Analysis of Individual Breast Cancer Patient Data from 13 Randomised Trials Including 15,993 Patients." [In eng]. European journal of cancer (Oxford, England: 1990) 166 (2022-5 2022): 185-201. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35305453/.					
	Number of included studies: 8 studies when capecitabine addedto and 5 studies when used instead of other treatments **Number of included patients**: 15,993; 8,253 received capecitabine during the course of their treatment, and 7,740 in control arms **Distribution of biological subtypes:** TNBC: 3,979 (26.1%) 8,907 HR+/HER2- (58.5%) HER2+ 2,336 (15.4%) **Median age**: at primary diagnosis: 53 years **Median follow-up:**			HR: 1.07, 95% CI 0.86-1.33; p=0.531 **Secondary Outcome**: **Overall survival (OS) among TNBC:** 1) Overall cohort: OR: 0.83, 95% CI 0.72-0.95; p=0.008 2) Capecitabine in addition to another therapy: HR: 0.78, 95% CI 0.66-0.92; p=0.004 3) Capecitabine instead ofanother therapy HR: 0.95, 95%CI 0.74, 1.21; p=0.655 **Distant disease-free survival (DDFS) among TNBC:** 1) Overall cohort:	**Quality of included studies**: n.a. **Sources of funding:** German Breast Group

Source: MT, van Mackelenbergh, Seither F, Möbus V, O'Shaughnessy J, Martin M, Joensuu H, Untch M, et al. "Effects of Capecitabine as Part of Neo-/Adjuvant Chemotherapy - a Meta-Analysis of Individual Breast Cancer Patient Data from 13 Randomised Trials Including 15,993 Patients." [In eng]. European journal of cancer (Oxford, England: 1990) 166 (2022-5 2022): 185-201. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35305453/.					
	79.4 months (0 to 193.2 months) **Inclusion criteria**: Multicenter randomised controlled trials conducted in EBC in the adjuvant or neoadjuvant setting with N > 100 patients and outcome data available were selected **Exclusion**: patients participating in the GeparTrio study who had a complete or partial response or were not randomised after two cycles of TAC and patients participating in the GeparQuattro study who were not randomised after four cycles of EC			OR: 0.88, 95%CI 0.78-1.00; p= 0.051 2) Capecitabine in addition to another therapy: HR: 0.84, 95% CI 0.72-0.97; p=0.019 3) Capecitabine instead of another therapy HR: 0.99, 95%CI 0.79-1.25; p=0.945 **Pathological complete response (pCR)** **pCR rates among TNBC patients** pCR rates were not altered by the administration of capecitabine in TNBC patients: OR 0.78; CI 0.58-1.06; p= 0.116	

Source: MT, van Mackelenbergh, Seither F, Möbus V, O'Shaughnessy J, Martin M, Joensuu H, Untch M, et al. "Effects of Capecitabine as Part of Neo-/Adjuvant Chemotherapy - a Meta-Analysis of Individual Breast Cancer Patient Data from 13 Randomised Trials Including 15,993 Patients." [In eng]. European journal of cancer (Oxford, England: 1990) 166 (2022-5 2022): 185-201. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35305453/.

Abbreviations:

DFS = Disease-Free Survival

OS = Overall Survival

DDFS = Distant Disease-Free Survival

pCR = pathological Complete Response

BC = Breast Cancer

HR = Hazard Ratio

OR = Odds Ratio

95% CI = 95% Confidence Interval

Kapitel 4.6.4: HER2-positives Mammakarzinom (HER2+)

Verknüpfte Empfehlungen:

Empfehlung 4.157:

Patientinnen mit HER2-positiven Mammakarzinomen (immunhistochemisch Score 3+ oder Score 2+ und ISH-positiv) mit einem Durchmesser >1 cm sollen eine Chemotherapie mit einer anti-HER2-gerichteten Therapie erhalten

Literaturreferenzen: [222]

Source: Trastuzumab for Early-Stage, Her2-Positive Breast Cancer: A Meta-Analysis of 13 864 Women in Seven Randomised Trials. [In eng]. The Lancet. Oncology 22, no. 8 (2021-8 2021): 1139-50. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34339645/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Long-term benefits and risks of adjuvant trastuzumab on breast cancer recurrence and cause-specific mortality.	**Design**: Meta-Analysis of individual patient data from RCTs **Search date**: until March 31, 2020 **Searched databases**: MEDLINE, Embase, Cochrane Library **Included study designs**: RCTs **Number of included studies**: 7 FinHER trial	**Intervention** Chemotherapy (adjuvant or neoadjuvant) plus trastuzumab **Control** Same chemotherapy [as in intervention] alone	**Primary Outcomes**: Any recurrence of invasive breast cancer (distant, loco-regional, or new primary in the contralateral breast), breast cancer mortality, and all-cause mortality **Prespecified primary subgroup investigations:** Site of recurrence, concurrent or sequential trastuzumab and	**Primary Outcome**: **Effect of trastuzumab versus control on recurrence and mortality** **Breast cancer mortality** 13,864 women RR 0.66 (95% CI 0.62-0.71) 10-year gain 9.0% (95% CI 7.4 to 10.7)	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: moderate **Sources of funding:** Cancer Research UK, UK Medical Research Council

Source: Trastuzumab for Early-Stage, Her2-Positive Breast Cancer: A Meta-Analysis of 13 864 Women in Seven Randomised Trials. [In eng]. The Lancet. Oncology 22, no. 8 (2021-8 2021): 1139-50. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34339645/.

	NSABP trial B-31 NCCTG trial N9831 HERA trial PACS 04 BCIRG 006 NOAH trial **Number of included patients**: 13,864 women **Inclusion criteria**: Trials were eligible if they began before Jan 1, 2010, and randomly assigned women with node-negative or node-positive, operable breast cancer to either chemotherapy (adjuvant or neoadjuvant) plus trastuzumab or to the same chemotherapy alone **Exclusion**: Trials of trastuzumab added to other biological		chemotherapy, level of HER2 amplification, age, ER status, PR status, nodal status, tumour diameter (grade, histology [ie, ductal or lobular], BMI, proliferation index (Ki-67 <10%, 10-19%, or ≥20%), follow-up period (years 0-1, 2-4, 5-9, ≥10)	**Death without any recurrence** 13,864 RR 0.67 (95% CI 0.61 to 0.73) 10-year gain 6.4% (95% CI 4.9 to 7.8) **Death from any cause** 13,854 women RR 0.90 (95% CI 0.72 to 1.12) 10-year gain 0.4% (95% CI −0.3 to 1.1) **Breast cancer mortality rates** 13,864 women RR 0.69 (95% CI 0.64 to 0.75) 10 year gain 6.5% (95% CI 5.0 to 8.0) **Subgroup analysis**	

Source: Trastuzumab for Early-Stage, Her2-Positive Breast Cancer: A Meta-Analysis of 13 864 Women in Seven Randomised Trials. [In eng]. The Lancet. Oncology 22, no. 8 (2021-8 2021): 1139-50. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34339645/.					
	therapies (eg, trials comparing lapatinib, pertuzumab, or neratinib with or without trastuzumab) were not eligible			**Effect of trastuzumab versus control on recurrence by ER status** Recurrence analyses include any loco-regional or distant recurrence, but exclude contralateral disease <u>ER-negative:</u> 6,837 women 0.62 (95% CI 0.56–0.69) 10-year gain 10.1% (95% CI 7.7–12.5) <u>ER-positive:</u> 7,018 women RR 0.67 (95% CI 0.60–0.74) 10-year gain 7.8% (95% CI 5.5–10.0) **Effect of trastuzumab versus control on recurrence by nodal status**	

Source: Trastuzumab for Early-Stage, Her2-Positive Breast Cancer: A Meta-Analysis of 13 864 Women in Seven Randomised Trials. [In eng]. The Lancet. Oncology 22, no. 8 (2021-8 2021): 1139-50. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34339645/.					
				Recurrence analyses include any loco-regional or distant recurrence, but exclude contralateral disease N0 2,803 women RR 0.67 (99% CI 0.54–0.83) 5-year gain 5.7% (99% CI 3.1–8.3) N1-3 5,335 women RR 0.61 (99% CI 0.53–0.69) 5-year gain 6.8% (99% CI 4.7–9.0) N4+ 4,690 women RR 0.67 (99% CI 0.60–0.74)	

Source: Trastuzumab for Early-Stage, Her2-Positive Breast Cancer: A Meta-Analysis of 13 864 Women in Seven Randomised Trials. [In eng]. The Lancet. Oncology 22, no. 8 (2021-8 2021): 1139-50. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34339645/.

				5-year gain 10.7% (9% CI 7.7–13.6) **Effect of trastuzumab versus control on recurrence by tumour diameter** 1-10 mm (T1a+b) RR 0.61 (99% CI 0.38-0.99) 11-20 mm (T1c) RR 0.65 (99% CI 0.54-0.79) 21-50 mm (T2) RR 0.63 (99% CI 0.55-0.72) >50 mm (T3 or T4) RR 0.69 (99% CI 0.50-0.94)	

Abbreviations:

RCT = Randomised Controlled Trial

RR = Rate Ratio

Source: Trastuzumab for Early-Stage, Her2-Positive Breast Cancer: A Meta-Analysis of 13 864 Women in Seven Randomised Trials. [In eng]. The Lancet. Oncology 22, no. 8 (2021-8 2021): 1139-50. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34339645/.

95% CI = 95% Confidence Interval

Verknüpfte Empfehlungen:

Empfehlung 4.160:

Patientinnen mit HER2-positiven Mammakarzinomen (immunhistochemisch Score 3+ oder 2+ und ISH-positiv) und klinischer Tumorgrösse ≤ 2cm sowie klinisch und sonographisch negativem axillären Lymphknotenstatus kann eine primäre Operation angeboten werden, um eine Deeskalation der Systemtherapie in Form von Paclitaxel in Kombination mit Trastuzumab über 12 Wochen zu ermöglichen. Trastuzumab soll über eine Gesamtdauer von einem Jahr verabreicht werden.

Literaturreferenzen: [223]

Source: Tolaney et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial.Lancet Oncology, Lancet Oncol 2023; 24: 273–85, DOI: https: //doi.org/10.1016/S1470-2045(23)00051-7

Aim and Country	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: to report on long-term outcomes of patients with small, node-negative, HER2-positive breast cancer treated with adjuvant paclitaxel and trastuzumab and to establish potential biomarkers to predict prognosis **Country**: USA	**Study designs**: multicenter *(16 institutions in 13 US-cities)*, single-arm, phase 2 trial **Number of included patients**: n=406 (405 female, 1 male) **Mean age**: 55 years (SD 10.5) – at enrolment **Follow-up time:** 10 years **Inclusion criteria**:	**Intervention** weekly intravenous paclitaxel 80 mg/m² plus weekly intravenous trastuzumab (loading dose of 4 mg/kg, subsequent doses 2 mg/kg) for 12 weeks; thereafter, patients were given either weekly trastuzumab (2 mg/kg) or trastuzumab once every 3 weeks (6 mg/kg) for 40 weeks to complete 1 year of adjuvant	**Primary Outcome**: invasive disease-free survival = time from study enrolment to first of the following events: locoregional ipsilateral invasive recurrence (or ipsilateral invasive new primary), contralateral invasive breast cancer,	**Primary Outcome**: 10-year invasive disease-free survival: 91% (95% CI 88.3-94.4) 10-year recurrence-free interval: 96.3% (95% CI 94.3-98.3) 13 recurrence-free interval events occurred (including 6 locoregional ipsilateral recurrences, 6	**Concerns about quality**: single-arm design there was no standard treatment in patients with small, node-negative, HER2-positive breast cancer at the time the trial was designed randomized trial would require several thousand patients given the low event rate with therapy **Level of Evidence:**

Source: Tolaney et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial.Lancet Oncology, Lancet Oncol 2023; 24: 273–85, DOI: https: //doi.org/10.1016/S1470-2045(23)00051-7					
	≥18 years, HER2 positive breast cancer (3+ intensity or amplification of the HER2 gene of 2.0 or higher on fluorescence in-situ hybridisation); primary invasice tumour ≤ 3.0cm in the greatest dimension; node-negative (until June 2, 2009 [188 had been enrolled] – protocol amended to allow a single micrometastatic node); left ventricular ejection fraction of at least 50%; an Eastern Cooperative Oncology Group performance status of 0 or 1; no previous myocardial infarction or uncontrolled hypertension; no neuropathy worse than grade 1; no history of invasive BC; no previous malignancy within 5 years before study entry	therapy per investigator choice. Patients who had breast-conserving surgery received either partial breast irradiation before the start of protocol therapy or whole breast irradiation after the completion of paclitaxel Patients with hormone receptor-positive disease were allowed to receive adjuvant endocrine therapy after the completion of paclitaxel. **Control** - (single arm study)	distant recurrence, or death from any cause **post-hoc survival endpoints:** recurrence-free interval (time from study enrolment to disease recurrence, including invasive locoregional recurrence and distant recurrence, or death due to breast cancer), breast cancer-specific survival (time from study enrolment until death from breast cancer), overall survival (time from study enrolment until death from any cause)	distant recurrences, and 1 breast-cancer-death) 10-year overall survival: 94.3% (95% CI 91.8-96.8) with 19 deaths being recorded 10-year breast cancer specific survival: 98.8% (95% CI 97.6-100) with 4 deaths due to breast cancer 10-year breast cancer specific survival accounting for competing risks of death: 98.8% (95% CI 97.7-100)	Oxford 2011 Level 4 **Sources of funding:** Genentech

Source: Tolaney et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial.Lancet Oncology, Lancet Oncol 2023; 24: 273–85, DOI: https: //doi.org/10.1016/S1470-2045(23)00051-7					
	(except for early-stage tumours of the skin or cervix with curative intent); Surgery with modified radical mastectomy or lumpectomy, with either a sentinel node biopsy or axillary dissection; Up to 4 weeks of adjuvant endocrine treatment; no previous chemotherapy or trastuzumab therapy permitted **Exclusion**: - **additional information about population:** 76 (18.7%) of 406 patients were premenopausal at baseline (self-reported) of whom 15 (20%) hat surgically induced menopause during trial and 3 (4%) received				

Source: Tolaney et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial.Lancet Oncology, Lancet Oncol 2023; 24: 273–85, DOI: https: //doi.org/10.1016/S1470-2045(23)00051-7					
	ovarian suppressing medications				

Abbreviations:

95% CI = 95% Confidence Interval

Verknüpfte Empfehlungen:

Empfehlung 4.161:

Patientinnen mit HER2-positiven Mammakarzinomen (immunhistochemisch Score 3+ oder 2+ und ISH-positiv) mit einem Durchmesser > 2 cm und/oder positivem Nodalstatus (klinisch bzw. sonographisch oder bioptisch) sollten eine neoadjuvante Chemotherapie in Kombination mit Trastuzumab und Pertuzumab erhalten.

Literaturreferenzen: [224], [225]

Source: S, Chen, Liang Y, Feng Z, and Wang M. "Efficacy and Safety of Her2 Inhibitors in Combination with or without Pertuzumab for Her2-Positive Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. BMC cancer 19, no. 1 (2019-10-21 2019): 973. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31638935/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: to assess the efficacy and safety of H (trastuzumab or trastuzumab emtansine ± chemotherapy) + P (pertuzumab) versus H in the (neo)adjuvant treatment of operable HER2+ breast cancer (in neoadjuvant and metastatic setting)	**Design**: Systematic Review and meta-Analysis **Search date**: published between 2005 (based on the first reported trial of pertuzumab efficacy in humans) and Dec 30, 2018 **Searched databases**: PubMed, Cochrane, Science Direct, Embase, the clinical trial registry **Included study designs**:	**Intervention** trastuzumab or trastuzumab emtansine ± chemotherapy + pertuzumab **Control** trastuzumab or trastuzumab emtansine ± chemotherapy	**Primary Outcome**: Pathologic complete response (pCR); *Progression-free survival (PFS);* *Overall survival (OS) only in metastatic setting* **Secondary Outcome**: Safety (rash, diarrhea, myalgia, epistaxis, mucosal inflammation, cardiac toxicity [LVEF decline])	**Neoadjuvant setting** **Primary Outcome**: **pCR** 4 single-arm studies; included 205 patients; treated with H+P pCR range: 0.27 to 0.62: absolute pCR rate: 0.56; 95% CI, 0.45–0.68; Significant heterogeneity was observed (I^2 = 82.4%; P < 0.001)	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 4 critical flaws (7, 9, 11, 13) **Additional concerns about quality**: several of the controlled trials lacked complete data and included nonrandomized controlled trials, and

Source: S, Chen, Liang Y, Feng Z, and Wang M. "Efficacy and Safety of Her2 Inhibitors in Combination with or without Pertuzumab for Her2-Positive Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. BMC cancer 19, no. 1 (2019-10-21 2019): 973. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31638935/.					
	Prospective, retrospective, controlled trials **Number of included studies and patients**: 38 trials in qualitative synthesis; 26 trials for meta-analysis Of those: 14 single-arm trials with 1,098 patients (included 13 studies: pertuzumab combined with trastuzumab; 1 study: pertuzumab combined with T-DM1); 12 controlled trials with 8,774 participants (included 7 studies: pertuzumab combined with trastuzumab vs trastuzumab alone; 4 studies: pertuzumab + T-DM1 vs T-DM1 alone) **Mean/median age**: n.a.			Sensitivity analysis 0.59; 95% CI, 0.36–0.63; (after removing the studies conducted by Luca Gianni and Jasmeet C. Singh) 4 controlled trials; included 1.448 patients pCR in H+P group significantly higher than in the H group: 1.33; 95% CI 1.08 - 1.63; P = 0.006 I^2 = 0.0%; P = 0.78 **Secondary Outcome**: AEs grade ≥3 (common) Neutropenia, diarrhea, anemia In controlled trials, the rates of diarrhea and anemia in the experimental	fewer samples were included in the single-arm trials **Level of Evidence:** Oxford 2011 Level 3 (downgrade due to methodology flaws and included study designs) **Sources of funding:** none

Source: S, Chen, Liang Y, Feng Z, and Wang M. "Efficacy and Safety of Her2 Inhibitors in Combination with or without Pertuzumab for Her2-Positive Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. BMC cancer 19, no. 1 (2019-10-21 2019): 973. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31638935/.

	Inclusion criteria: assessed the effectiveness and safety of H + P versus H in patients with HER2+ breast cancer, irrespective of the trial phase, the cohorts (whether prospectively or retrospectively defined), the choice of chemotherapy, and the stage of the HER2+ breast cancer patients **Exclusion**: Studies lacked original data			group were significantly higher than those in the controlledgroup [(OR = 2.42; 95% CI, 1.94–3.02; P = 0.0001) and (OR = 1.43, 95% CI, 1.14–1.79, P = 0.002), respectively]. significant difference was not observed in neutropenia: (OR = 0.99, 95% CI, 0.86–1.13, P = 0.814) Cardiac toxicity: controlled trials: H + P did not increase the incidence of LVEF compared with the effect of H (OR = 1.26; 95% CI, 0.81–1.95; P = 0.309)	

Abbreviations:

pCR = Pathologic Complete Response

Source: S, Chen, Liang Y, Feng Z, and Wang M. "Efficacy and Safety of Her2 Inhibitors in Combination with or without Pertuzumab for Her2-Positive Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. BMC cancer 19, no. 1 (2019-10-21 2019): 973. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31638935/.

PFS = Progression-Free Survival

OS = Overall Survival

LVEF = Left Ventricular Ejection Fraction

OR = Odds Ratio

95% CI = 95% Confidence Interval

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.164:

Trastuzumab sollte insgesamt für 12 Monate verabreicht werden. Eine kürzere Dauer von 6 Monaten kann im Falle von niedrigem Risiko oder kardialen Komorbiditäten erwogen werden.

Source: L, Chen, Zhou W, Hu X, Yi M, Ye C, and Yao G. "Short-Duration Versus 1-Year Adjuvant Trastuzumab in Early Her2 Positive Breast Cancer: A Meta-Analysis of Randomized Controlled Trials." [In eng]. Cancer treatment reviews 75 (2019-5 2019): 12-19. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30856373/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: to investigate the efficacy and toxicity of shorter courses of trastuzumab	**Design**: systematic review and meta-analysis (aggregated data) **Search date**: up to December 2018 **Searched databases**: PubMed/MEDLINE, Cochrane library, and EMBASE **Included study designs**: RCTs **Number of included studies**: 6	**Intervention** short duration (<1 year) trastuzumab **Control** 1 year of trastuzumab	**Outcomes**: Disease free survival Overall survival	**Disease free survival** <1year vs 1 year HR 1.13, 95% CI 1.03-1.25; p=0.01; I²=0% 9 or 12 weeks vs 1 year HR 1.23, 95% CI 1.03-1.48 6 months vs 1 year HR 1.09, 95% CI 0.97-1.23 **Overall survival** <1year vs 1 year HR 1.16, 95% CI 1.01-1.32; p=0.03; I²=0%	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 2 critical flaws (items 2, 7) **Additional concerns about quality**: Meta-analysis based on aggregated data; differences in study design, inconsistent margins set for non-inferiority; different follow-up durations **Sources of funding:** grant from the Natural

Source: L, Chen, Zhou W, Hu X, Yi M, Ye C, and Yao G. "Short-Duration Versus 1-Year Adjuvant Trastuzumab in Early Her2 Positive Breast Cancer: A Meta-Analysis of Randomized Controlled Trials." [In eng]. Cancer treatment reviews 75 (2019-5 2019): 12-19. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30856373/.					
	(PERSEPHONE, Short-HER, SOLD, PHARE, HORG, E 2198) **Number of included patients**: 11,496 **Inclusion criteria**: Early stage breast cancer patients with positive HER2 status			9 or 12 weeks vs 1 year HR 1.23, 95% CI 0.93-1.63 6 months vs 1 year HR 1.14, 95% CI 0.98-1.33; p=0.65 **Subgroup analysis** **Disease free survival** **Estrogen receptor status** significant improvement in ER- patients ER+ HR 1.10, 95% CI 0.97-1.25; p=0.14; I^2=20% ER- HR 1.23, 95% CI1.07-1.41; p=0.004; I^2=0% Total: HR 1.16, 95% CI 1.05-1.27; p=0.002; I^2=9%	Science Foundation of Guangdong Province, China [grant number 2017A030313563]

Source: L, Chen, Zhou W, Hu X, Yi M, Ye C, and Yao G. "Short-Duration Versus 1-Year Adjuvant Trastuzumab in Early Her2 Positive Breast Cancer: A Meta-Analysis of Randomized Controlled Trials." [In eng]. Cancer treatment reviews 75 (2019-5 2019): 12-19. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30856373/.

				Nodal status significant improvement in node positive patients <u>Node positive</u> HR 1.18, 95% CI 1.01-1.38; p=0.04; I^2=26% <u>Node negative</u> HR 1.11, 95% CI 0.93-1.32; p=0.24; I^2=11% <u>Total:</u> HR 1.15, 95% CI 1.02-1.29; p=0.02; I^2=12%	

Abbreviations:

RCT = Randomised Controlled Trial

HR = Hazard Ratio

95% CI = 95% Confidence Interval

Verknüpfte Empfehlungen:

Empfehlung 4.164:

Trastuzumab sollte insgesamt für 12 Monate verabreicht werden. Eine kürzere Dauer von 6 Monaten kann im Falle von niedrigem Risiko oder kardialen Komorbiditäten erwogen werden.

Source: BC, Wang, Xiao BY, Fan JQ, Lin GH, Wang C, Liu Q, and Zhao YX. 6 Versus 12 Months of Adjuvant Trastuzumab in Her2+ Early Breast Cancer: A Systematic Review and Meta-Analysis. Vol. 100, 2021-3-12, 2021. doi: doi: . https: //pubmed.ncbi.nlm.nih.gov/33725875/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: To synthesize the published data and to find whether 6 months treatment of trastuzumab does show non-inferiority versus 12 months treatment.	**Design**: systematic review and meta-analysis **Search date**: Up to Jan 14, 2020 **Searched databases**: PubMed, Cochrane Library, Web of Science, and EMBASE **Included study designs**: RCTs **Number of included studies**: 3 PERSEPHONE	**Intervention** 6 months adjuvant trastuzumab treatment **Control** 12 months adjuvant trastuzumab treatment	**Primary Outcome**: Disease-free survival (DFS) **Secondary Outcome**: Overall survival (OS)	**Primary Outcome**: **Disease-free survival (DFS)** 6 months treatment had an 18% higher risk of disease progression compared to the 12 months treatment: adjusted HR 1.18, 95% CI 0.97–1.44, P=.09 (95% CIs included the prespecified non-inferiority margin of 1.20) □ 6 months treatment was not non-inferior to 12 months treatment in improving the DFS	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 6 critical flaws (items 2, 4, 7, 11, 13, 15) **Additional concerns about quality**: factors such as age, nodal status, tumor size, endocrine receptors status, and chemotherapy type might impact results; Ki-67 proliferative index could influence treatment

Source: BC, Wang, Xiao BY, Fan JQ, Lin GH, Wang C, Liu Q, and Zhao YX. 6 Versus 12 Months of Adjuvant Trastuzumab in Her2+ Early Breast Cancer: A Systematic Review and Meta-Analysis. Vol. 100, 2021-3-12, 2021. doi: doi: . https: //pubmed.ncbi.nlm.nih.gov/33725875/.					
	PHARE HORG **Median Follow-up time:** PERSEPHONE: 5.4 years PHARE: 7.5 years HORG: 6 months group: 4.3 years 12 months group: 3.9 years **Number of included patients**: 3974 patients in 6 months group and 3976 in 12months group. **Mean age range**: 54 to 56 **Inclusion criteria**: (1) RCTs (2) patients were diagnosed as early-stage HER2+ breast cancer;			**Secondary Outcome**: **Overall survival (OS)** 14% higher risk of death in patients treated with 6 months versus 12 months trastuzumab HR 1.14, 95% CI 0.98–1.32, P=.08 □ the prespecified non-inferiority margin of 1.43 was not comprised in the 95% CIs (=non-inferiority of the 6-month adjuvant trastuzumab treatment)	strategy selection (was not shown in studies); all eligible studies were open-label, potentially affecting therapeutic efficacy; **Quality of included studies**: included studies had high risk of bias in domains blinding of participants and blinding of outcome assessor **Sources of funding:** n.a.

Source: BC, Wang, Xiao BY, Fan JQ, Lin GH, Wang C, Liu Q, and Zhao YX. 6 Versus 12 Months of Adjuvant Trastuzumab in Her2+ Early Breast Cancer: A Systematic Review and Meta-Analysis. Vol. 100, 2021-3-12, 2021. doi: doi: . https: //pubmed.ncbi.nlm.nih.gov/33725875/.					
	(3) 6 months versus 12 months adjuvant trastuzumab treatment (4) studies were full-text articles and published in English **Exclusion**: n.a.				

Abbreviations:

RCT = Randomised Controlled Trail

n.a. = not Available, not Applicable

DFS = Disease-free survival

OS = Overall Survival

HR = Hazard Ratio

95% CI = 95% Confidence Interval

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 4.164:

Trastuzumab sollte insgesamt für 12 Monate verabreicht werden. Eine kürzere Dauer von 6 Monaten kann im Falle von niedrigem Risiko oder kardialen Komorbiditäten erwogen werden.

Source: S, Gulia, Kannan S, Badwe R, and Gupta S. "Evaluation of 1-Year Vs Shorter Durations of Adjuvant Trastuzumab among Patients with Early Breast Cancer: An Individual Participant Data and Trial-Level Meta-Analysis." [In eng]. JAMA network open 3, no. 8 (2020-8-3 2020): e2011777. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/32833018/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: To compare shorter durations with 1 year of adjuvant trastuzumab for patients with early breast cancer.	**Design**: IPD and trial-level meta-analyses (important: to assess noninferiority of shorter duration of trastuzumab compared with 1y based on the **primary outcome DFS** □ noninferiority margin: 1.3; range 1.15-1.53; one-sided DFS p<0.025 was considered significant for including noninferiority of shorter duration) **Search date**: January 1, 2005 to June 30, 2019	**Intervention** short duration (<1 year) trastuzumab duration of trastuzumab: PERSEPHONE: 6 mo, Short-HER: 9 wk, SOLD: 9 wk, PHARE: 6 mo, HORG: 6 mo, E 2198: 12 wk **Control** 1 year trastuzumab	**Primary Outcome**: Disease-free survival (DFS) **Secondary Outcome**: Overall survival (OS) and cardiac toxic effects	**Primary Outcome**: **Disease-free survival** 5 RCTs: IPD analysis Shorter duration vs. 1 year trastuzumab 5 year DFS: Shorter duration group: 85.42% (95% CI, 84.41%-86.38%) 1-year trastuzumab group: 87.12% (95% CI, 86.15%-88.02%)	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low;4 critical flaws (items 2,7,13,15) **Additional concerns about quality**: **Quality of included studies**: Different study designs of included studies, variable noninferiority margins, varying durations of trastuzumab in the experimental arm,

Source: S, Gulia, Kannan S, Badwe R, and Gupta S. "Evaluation of 1-Year Vs Shorter Durations of Adjuvant Trastuzumab among Patients with Early Breast Cancer: An Individual Participant Data and Trial-Level Meta-Analysis." [In eng]. JAMA network open 3, no. 8 (2020-8-3 2020): e2011777. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/32833018/.					
	Searched databases: PubMed, Embase, The Cochrane Library; meeting abstracts and virtual meeting presentations; reference lists **Included study designs**: RCTs **Number of included studies**: 6 (PERSEPHONE, Short-HER, SOLD, PHARE, HORG, E 2198) **Number of included patients**: 11,376 (IPD analysis) **Mean/median age**: **Inclusion criteria**: Randomized, compared short duration (<1 year) with 1 year of trastuzumab; early			HR, 1.14, 95% CI, 1.03-1.25; I²=14%; test for noninferiority (one sided p=0.0042) **DFS: Subgroup analysis** Shorter duration vs. 1 year trastuzumab DFS by age (50y) 4 RCTs <=50y HR, 1.08, 95% CI 0.92-1.27; I²=0% >50y HR, 1.25, 95% CI 1.01-1.55; I²=60% Total: HR, 1.16, 95% CI 1.03-1.31; I²=25% DFS by estrogen receptor status 5 RCTs	different chemotherapeutic regimes and schedules, different timing of randomisation, HRs based on variable follow-up durations **Sources of funding:** n.a.

Source: S, Gulia, Kannan S, Badwe R, and Gupta S. "Evaluation of 1-Year Vs Shorter Durations of Adjuvant Trastuzumab among Patients with Early Breast Cancer: An Individual Participant Data and Trial-Level Meta-Analysis." [In eng]. JAMA network open 3, no. 8 (2020-8-3 2020): e2011777. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/32833018/.					
	(nonmetastatic) breast cancer			ER positive: HR, 1.10, 95% CI 0.96-1.27; I²=19% ER negative: HR, 1.23, 95% CI 1.07-1.41; I²=0% Total: HR, 1.16, 95% CI 1.05-1.27; I²=10% <u>DFS by nodal status</u> 4 RCTs N0 HR, 1.12, 95% CI 0.92-1.37; I²=5% N1-2 HR, 1.30, 95% CI 0.94-1.79; I²=45% N3 HR, 1.24, 95% CI 0.77-2.00; I²=76%	

Source: S, Gulia, Kannan S, Badwe R, and Gupta S. "Evaluation of 1-Year Vs Shorter Durations of Adjuvant Trastuzumab among Patients with Early Breast Cancer: An Individual Participant Data and Trial-Level Meta-Analysis." [In eng]. JAMA network open 3, no. 8 (2020-8-3 2020): e2011777. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/32833018/.					
				Total HR, 1.21, 95% CI 1.01-1.45; I^2=50% DFS by stage (2 RCTs) Stage 1 HR, 1.17, 95% CI 0.73-1.85; I^2=54% Stage 2 HR, 1.23, 95% CI 0.77-1.95; I^2=72% Stage 3 HR, 1.43, 95% CI 0.99-2.07; I^2=31% Total HR, 1.28, 95% CI 1.04-1.57; I^2=37% DFS by timing of trastuzumab Sequential (2 RCTs)	

Source: S, Gulia, Kannan S, Badwe R, and Gupta S. "Evaluation of 1-Year Vs Shorter Durations of Adjuvant Trastuzumab among Patients with Early Breast Cancer: An Individual Participant Data and Trial-Level Meta-Analysis." [In eng]. JAMA network open 3, no. 8 (2020-8-3 2020): e2011777. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/32833018/.					
				HR, 0.96, 95% CI 0.73-1.27; I²=68% Concomitant (6 RCTs) HR, 1.26, 95% CI 1.09-1.45; I²=27% Total HR, 1.17, 95% CI 1.00-1.36; I²=58% **Secondary Outcome**: **OS** < 1 year of trastuzumab 92.39% (95% CI, 91.61%-93.10%) 1 year of trastuzumab, overall survival was 93.46% (95% CI, 92.73%-94.13%) HR, 1.17; 95% CI, 1.02-1.34 **Cardiac Toxic Effects**	

Source: S, Gulia, Kannan S, Badwe R, and Gupta S. "Evaluation of 1-Year Vs Shorter Durations of Adjuvant Trastuzumab among Patients with Early Breast Cancer: An Individual Participant Data and Trial-Level Meta-Analysis." [In eng]. JAMA network open 3, no. 8 (2020-8-3 2020): e2011777. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/32833018/.					
				Developing CHF: lower among those receiving shorter duration of trastuzumab compared with those receiving 1 year (3.9% vs 6.9%; RR 0.53; 95% CI 0.38-0.74; p<0.001) Developing asymptomatic LVEF decline: lower among those receiving shorter duration of trastuzumab compared with those receiving 1 year (5% vs 7%; RR 0.71; 95% CI 0.50-1.00; p=0.049)	
Abbreviations: IPD = Individual Patient Data DFS = Disease-Free Survival OS = Overall Survival CHF = Congestive Heart Failure					

Source: S, Gulia, Kannan S, Badwe R, and Gupta S. "Evaluation of 1-Year Vs Shorter Durations of Adjuvant Trastuzumab among Patients with Early Breast Cancer: An Individual Participant Data and Trial-Level Meta-Analysis." [In eng]. JAMA network open 3, no. 8 (2020-8-3 2020): e2011777. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/32833018/.

RCT = Randomised Controlled Trial

mo = month

wk = week

y = year

HR = Hazard Ratio

95% CI = 95% Confidence Interval

Verknüpfte Empfehlungen:

Empfehlung 4.165:

Patientinnen mit HER2-positiven Mammakarzinomen (immunhistochemisch Score 3+ oder 2+ und ISH-positiv) und nicht erreichter histologischer Komplettremission (non-pCR) nach einem Anthrazyklin- oder Taxan-basierten Chemotherapieschema in Kombination mit anti-HER2 gerichteter Therapie sollen als postneoadjuvante Therapie 14 Zyklen Trastuzumab-Emtansin erhalten.

Literaturreferenzen: [226]

Source Geyer CE Jr, Untch M, Huang CS, Mano MS, Mamounas EP, Wolmark N, Rastogi P, Schneeweiss A, Redondo A, Fischer HH, D'Hondt V, Conlin AK, Guarneri V, Wapnir IL, Jackisch C, Arce-Salinas C, Fasching PA, DiGiovanna MP, Crown JP, Wuelfing P, Shao Z, Rota Caremoli E, Bonnefoi HR, Hennessy BT, Stamatovic L, Castro-Salguero H, Brufsky AM, Knott A, Siddiqui A, Lambertini C, Boulet T, Nyawira B, Restuccia E, Loibl S; KATHERINE Study Group. Survival with Trastuzumab Emtansine in Residual HER2-Positive Breast Cancer. N Engl J Med. 2025 Jan 16;392(3): 249-257. doi: 10.1056/NEJMoa2406070. PMID: 39813643.

Aim and Country	Design and participants	Intervention	Outcomes	Results	Quality and comment
To evaluate whether**trastuzumab emtansine (T-DM1)**, compared to**trastuzumab alone,** improves**invasive disease-free survival (IDFS)** and**overall survival (OS)** in patients with **HER2-positive early breast cancer**	**Design**: RCT (phase III) **Setting:** 273 sites **Number of included patients**: 1,486 Intention-to-treat: 743 patients per group Safety population: T-DM1: 740 patients Trastuzumab: 720 **Age, n (groups)**: total	**Intervention** **T-DM1** (3.6 mg per kilogram of body weight intravenously every 3 weeks) **Control** **trastuzumab** (6 mg per kilogram intravenously every 3 weeks) for 14 cycles	**Primary Outcome**: Invasive disease-free survival (time from randomization until the first occurrence of one of the following events: ipsilateral invasive disease, ipsilateral locoregional invasive disease, contralateral invasive breast cancer, distant	clinical cutoff date (October 5, 2023), patients alive: T-DM1: 521 patients (70.1%) Trastuzumab: 461 patients (62.0%) Deaths: T-DM1: 89 (12.0%)	Quality of study assessed with SIGN checklist for RCT: high quality (++) **Level of evidence:** Oxford 2011: 2 **Sources of funding:** Supported by F. Hoffmann-La Roche/Genentech.

Source Geyer CE Jr, Untch M, Huang CS, Mano MS, Mamounas EP, Wolmark N, Rastogi P, Schneeweiss A, Redondo A, Fischer HH, D'Hondt V, Conlin AK, Guarneri V, Wapnir IL, Jackisch C, Arce-Salinas C, Fasching PA, DiGiovanna MP, Crown JP, Wuelfing P, Shao Z, Rota Caremoli E, Bonnefoi HR, Hennessy BT, Stamatovic L, Castro-Salguero H, Brufsky AM, Knott A, Siddiqui A, Lambertini C, Boulet T, Nyawira B, Restuccia E, Loibl S; KATHERINE Study Group. Survival with Trastuzumab Emtansine in Residual HER2-Positive Breast Cancer. N Engl J Med. 2025 Jan 16;392(3): 249-257. doi: 10.1056/NEJMoa2406070. PMID: 39813643.

who have residual invasive disease in the breast or axilla after**neoadjuvant systemic therapy**(including taxane-based chemotherapy and trastuzumab). **Acronym:** KATHERINE **Country:** 28 countries	<40: 296 40-64: 1,064 ≥65: 126 **Median follow-up:** T-DM1: 101.4 months (range, 0.1 to 123.3) Trastuzumab: 100.8 months (range, 0.1 to 122.8) **Inclusion criteria**: HER2-positive early breast cancer, received a minimum of six cycles of neoadjuvant chemotherapy comprising a minimum of 9 weeks of taxane-based therapy combined with a	(1: 1 ratio)	recurrence, or death from any cause) **Secondary Outcome**: disease-free survival (including non- invasive breast cancers), overall survival (time from randomization until the date of death from any cause), distant recurrence–free survival, and safety (included all the patients who received at least one dose of a trial drug)	Trastuzumab: 126 (17.0%) **Primary Outcome**: **7-year invasive disease-free survival** T-DM1: 80.8% Trastuzumab: 67.1% (difference: 13.7 percentage points) *Subgroup analysis:* *IHC 3+ group* T-DM1: 82.8% Trastuzumab: 66.5% HR 0.47, 95% CI 0.37-0.60 *IHC 2+ group* T-DM1: 72.4% Trastuzumab: 68.8%	

Source Geyer CE Jr, Untch M, Huang CS, Mano MS, Mamounas EP, Wolmark N, Rastogi P, Schneeweiss A, Redondo A, Fischer HH, D'Hondt V, Conlin AK, Guarneri V, Wapnir IL, Jackisch C, Arce-Salinas C, Fasching PA, DiGiovanna MP, Crown JP, Wuelfing P, Shao Z, Rota Caremoli E, Bonnefoi HR, Hennessy BT, Stamatovic L, Castro-Salguero H, Brufsky AM, Knott A, Siddiqui A, Lambertini C, Boulet T, Nyawira B, Restuccia E, Loibl S; KATHERINE Study Group. Survival with Trastuzumab Emtansine in Residual HER2-Positive Breast Cancer. N Engl J Med. 2025 Jan 16;392(3): 249-257. doi: 10.1056/NEJMoa2406070. PMID: 39813643.

	minimum of 9 weeks of trastuzumab (a second HER2-targeted agent was allowed), and had residual invasive cancer in the breast or resected axillary nodes at surgery **Exclusion**: gross residual disease remaining after mastec- tomy or positive margins after breast-conserving surgery; progressive disease during neoadjuvant therapy; and cardiopulmonary dysfunction, in- cluding heart failure of New York Heart Asso- ciation (NYHA) class II (mild symptoms and			HR 0.84, 95% CI 0.56-1.25 **Secondary Outcome**: Death: T-DM1: 89 (12.0%) Trastuzumab: 126 (17.0%) **7-year overall survival** T-DM1: 89.1% Trastuzumab: 84.4% □ absolute difference: 4.7 percentage points HR for death: HR 0.66, 95% CI 0.51-0.87, p=0.003 **Safety** *Adverse events grade 3 or higher:*	

Source Geyer CE Jr, Untch M, Huang CS, Mano MS, Mamounas EP, Wolmark N, Rastogi P, Schneeweiss A, Redondo A, Fischer HH, D'Hondt V, Conlin AK, Guarneri V, Wapnir IL, Jackisch C, Arce-Salinas C, Fasching PA, DiGiovanna MP, Crown JP, Wuelfing P, Shao Z, Rota Caremoli E, Bonnefoi HR, Hennessy BT, Stamatovic L, Castro-Salguero H, Brufsky AM, Knott A, Siddiqui A, Lambertini C, Boulet T, Nyawira B, Restuccia E, Loibl S; KATHERINE Study Group. Survival with Trastuzumab Emtansine in Residual HER2-Positive Breast Cancer. N Engl J Med. 2025 Jan 16;392(3): 249-257. doi: 10.1056/NEJMoa2406070. PMID: 39813643.

	function limitation) or higher or a history of a reduction in the left ventricular ejection fraction to less than 40% with previous therapy [von Minckwitz 2019, NEJM]			T-DM1: 193 of 740 patients (26.1%) Trastuzumab: 113 of 720 patients (15.7%) *Serious adverse events:* T-DM1: 94 patients (12.7%) Trastuzumab: 58 patients (8.1%)	

Abbreviations:

HR: Hazard Ratio

RCT = Randomised Controlled Trial

95% CI = 95% Confidence Interval

Verknüpfte Empfehlungen:

Empfehlung 4.166:

Patientinnen mit hormonrezeptor-positiven, HER2-positiven Mammakarzinomen (immunhistochemisch Score 3+ oder 2+ und ISH-positiv) im Stadium II bis III kann nach adjuvanter anti-HER2-gerichteten Therapie mit Trastuzumab allein eine erweiterte (postneo-) adjuvante Therapie mit Neratinib für ein Jahr angeboten werden. Patientinnen mit Tumoren unter 2 cm sollten nicht mit Neratinib behandelt werden.

Literaturreferenzen: [220]

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Neratinib (Mammakarzinom, HR+, HER2+, adjuvante Therapie)			
Wirkstoff	Neratinib	**Handelsname**	Nerlynx
Pharmazeutischer Unternehmer	Pierre Fabre Pharma	**Beschlussdatum**	14.05.2020
Anwendungsgebiet	Mammakarzinom		

Neratinib (Mammakarzinom, HR+, HER2+, adjuvante Therapie)			
Wirkstoff	Neratinib	**Handelsname**	Nerlynx
Pharmazeutischer Unternehmer	Pierre Fabre Pharma	**Beschlussdatum**	14.05.2020
Anwendungsgebiet	Mammakarzinom		

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung des neuen Arzneimittels Nerlynx® mit dem Wirkstoff Neratinib.
Neratinib ist indiziert für die erweiterte adjuvante Behandlung von erwachsenen Patienten mit Hormonrezeptor-positivem, HER2-überexprimiertem/amplifiziertem Brustkrebs in einem frühen Stadium, die vor weniger als einem Jahr eine Trastuzumab-basierte adjuvante Therapie abgeschlossen haben.
Als zweckmäßige Vergleichstherapie wurde das beobachtende Abwarten vom G-BA bestimmt.
Für die Bewertung legt der pharmazeutische Unternehmer die Ergebnisse der randomisierten, kontrollierten, doppelblinden Phase III-Studie ExteNET vor, in der Neratinib mit Placebo verglichen wird. Basierend auf der in der Studie durchgeführten Nachsorgestrategie stellt der Vergleich mit Placebo eine geeignete Umsetzung der zweckmäßigen Vergleichstherapie „beobachtendes Abwarten“ dar. Für die Bewertung sind die Ergebnisse der Teilpopulation der Patientinnen mit Hormonrezeptor-positivem Brustkrebs und deren Trastuzumab-Therapie seit weniger als 1 Jahr abgeschlossen ist, entsprechend dem zugelassenen Anwendungsgebiet von Neratinib, aus dem ersten Datenschnitt vom 7. Juli 2014 relevant.
Neratinib zeigt im Vergleich zum beobachtenden Abwarten einen deutlichen, klinisch relevanten Vorteil in der Vermeidung von Rezidiven. Die Vermeidung von Rezidiven stellt ein essentielles Therapieziel in der vorliegenden kurativen Therapiesituation dar.
Es liegen keine Daten zum Gesamtüberleben vor. Zum Gesundheitszustand und zur Lebensqualität zeigen sich keine statistisch signifikanten Unterschiede.
Dem Vorteil in Bezug auf die Vermeidung der Rezidive stehen Nachteile durch eine Zunahme an schwerwiegende unerwünschte Ereignisse sowie deutliche Nachteile durch eine Zunahme an schweren unerwünschten Ereignissen (CTCAE-Grad ≥ 3) und Therapieabbrüchen aufgrund von unerwünschten Ereignissen, gegenüber. Die Nachteile werden vor dem Hintergrund des vorliegenden kurativen Therapieanspruches gewichtet.
Es verbleiben Unsicherheiten bei der Interpretation der Ergebnisse zu den Rezidiven aufgrund der geringen Ereigniszahlen.
In der Gesamtschau wird ein Anhaltspunkt für einen geringen Zusatznutzen von Neratinib gegenüber dem beobachtenden Abwarten festgestellt.

Neratinib (Mammakarzinom, HR+, HER2+, adjuvante Therapie)			
Wirkstoff	Neratinib	**Handelsname**	Nerlynx
Pharmazeutischer Unternehmer	Pierre Fabre Pharma	**Beschlussdatum**	14.05.2020
Anwendungsgebiet	Mammakarzinom		

Neratinib (Mammakarzinom, HR+, HER2+, adjuvante Therapie)			
Wirkstoff	Neratinib	**Handelsname**	Nerlynx
Pharmazeutischer Unternehmer	Pierre Fabre Pharma	**Beschlussdatum**	14.05.2020
Anwendungsgebiet	Mammakarzinom		

Neratinib (Mammakarzinom, HR+, HER2+, adjuvante Therapie)			
Wirkstoff	Neratinib	**Handelsname**	Nerlynx
Pharmazeutischer Unternehmer	Pierre Fabre Pharma	**Beschlussdatum**	14.05.2020
Anwendungsgebiet	Mammakarzinom		

Kapitel 4.6.5: Knochengerichtete Therapie

Verknüpfte Empfehlungen:

Empfehlung 4.172:

Bei Patientinnen mit endokriner Therapie, die einen therapieassoziierten Knochenmasseverlust hervorruft, sollte eine Therapie mit Denosumab oder Bisphosphonaten zur Risikoreduzierung von Frakturen durchgeführt werden.

Literaturreferenzen: [227], [228]

Source: Mei M, Xiang Z, Yang J, Xiang R. Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials. Curr Probl Cancer. 2020;44(2): 100507.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Assessing the efficacy of zoledronic acid (ZA) at different skeletal sites in premenopausal and post-menopausal patients respectively	**Design**: Systematic Review and Meta-Analysis **Search date**: before 09/2018 **Searched databases**: PubMed, Embase, Cochrane **Included study designs**: RCT **Number of included studies**: 13	**Intervention** Upfront ZA **Control** 6 studies: placebo or no treatment 7 studies were delayed-start ZA groups, which received ZA when (lumbar spine) LS or total hip (TH) T score decreased to less than −2.0 or when a nontraumatic fracture occurred	Efficacy of ZA for prevention of bone loss Adverse events	Efficacy of ZA for prevention of bone loss Effect of ZA on LS, TH, and FN BMD in premenopausal subgroup 5 trials investigated LS BMD ZA compared with non-ZA mean difference: 0.06 g/cm^2, 95% CI 0.05 to0.08, $p < 0.00001$	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 4 critical flaws (items 2, 7, 13, 15) **Overall quality of evidence**: critically low **Additional concerns about quality**: 4 trials from the same author (suspected some

Source: Mei M, Xiang Z, Yang J, Xiang R. Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials. Curr Probl Cancer. 2020;44(2): 100507.					
	Number of included patients: 7,375 **Mean/median age**: n.a. **Inclusion criteria**: (1) controlled trials that randomized early BC patients receiving adjuvant endocrine therapy and/or chemotherapy to undergo intravenous ZA treatment (upfront ZA or ZA) or non-ZA treatment (delayed ZA or placebo or no treatment) (2) the dosage of ZA was 4 mg every several months and the most common period is every 6 months (3) the trials defined bone loss by assessing bone mineral density (BMD) at LS, and/or TH, and/or (femoral neck) FN with			3 trials investigated TH BMD no significant difference between ZA group and non-ZA group 0.02 g/cm^2, 95% CI −0.00 to 0.05, p= 0.05 3 trials investigated FN BMD no significant difference between ZA group and non-ZA group 0.03 g/cm^2, 95% CI −0.00 to 0.06, p = 0.05 <u>Effect of ZA on LS, TH, and FN BMD in postmenopausal subgroup</u> 8 trials investigated LS BMD ZA compared with non-ZA	participants may be the same ones) 2 trials were double-blinded, can lead to increased risk of performance bias or detection bias number of participants evaluated the FN BMD were small **Quality of included studies**: moderate **Sources of funding:** National Natural Science Foundation of China (grant numbers 81700993 , 81570993); and the Beijing Natural Science Foundation (grant number 7162100)

Source: Mei M, Xiang Z, Yang J, Xiang R. Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials. Curr Probl Cancer. 2020;44(2): 100507.

	dual-energy x-ray absorptiometry devices (4) early BC patients were premenopausal or postmenopausal **Exclusion**: (1) performed on cell line (2) nonrandomized trials (3) The focus was pathologic analysis, survival outcomes, dosing frequency or cost-effectiveness (4) Review, conference abstract, editorial, letter, case report, or expert opinion			mean difference: 0.06 g/cm^2, 95% CI 0.05 to 0.07, p< 0.00001 8 trials investigated TH BMD meta-analysis mean difference 0.04 g/cm^2, 95% CI 0.03 to 0.04, p < 0.00001 2 trials investigated FN BMD 0.04 g/cm^2, 95% CI −0.01 to 0.08, p= 0.1 <u>Adverse events</u> In contrast to con- trol group, ZA significantly increased the occurrence rate of pyrexia, bone pain, chills, fever headache, influenza-like illness, and myalgia in early BC	

Source: Mei M, Xiang Z, Yang J, Xiang R. Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials. Curr Probl Cancer. 2020;44(2): 100507.

				patients receiving adjuvant therapy ZA greatly decreased the occurrence rate of cough, depression, and sleep disorders Out of the 8 trials, 1 trial reported a case of osteonecrosis of the jaw (ONJ) in ZA group No fracture and other severe adverse events were reported	

Abbreviations:

ZA = Zoledronic Acid

RCT = Randomised Controlled Trial

BC = Breast Cancer

BMD = Bone Mineral Density

FN = Femoral Neck

LS = Lumbar Spine

TH = Total Hip

Source: Mei M, Xiang Z, Yang J, Xiang R. Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials. Curr Probl Cancer. 2020;44(2): 100507.

ONJ = Osteonecrosis of the Jaw

n.a. = not Available, not Applicable

95% CI = 95% Confidence Interval

Kapitel 5: Das rezidivierte oder metastasierte Mammakarzinom

Kapitel 5.1: Das lokale/lokoregionale Rezidiv

Kapitel 5.1.1: Therapie des lokalen/lokoregionalen Rezidivs

Kapitel 5.1.1.1: Lokales (intramammäres) Rezidiv

Verknüpfte Empfehlungen:

Empfehlung 5.10:

Vor einer erneuten brusterhaltenden Operation sollte die Möglichkeit einer Re-Bestrahlung (Teilbrustbestrahlung) geprüft, in einer interdisziplinären Tumorkonferenz diskutiert und die Patientin ggf. einem Strahlentherapeuten vorgestellt werden.

Empfehlung 5.11:

Bei brusterhaltender Operation soll die Patientin auf ein erhöhtes Risiko für ein erneutes intramammäres Rezidiv hingewiesen werden.

Empfehlung 5.8:

Beim intramammären Rezidiv (DCIS/invasives Karzinom) wird durch die sekundäre Mastektomie die höchste lokale Tumorkontrolle erzielt.

Die Radikalität des operativen Vorgehens beim lokalen und lokoregionären Rezidiv beeinflusst ebenso wie beim Primärkarzinom nicht das Überleben der Patientin.

Empfehlung 5.9:

Bei günstiger Ausgangssituation, z. B. DCIS oder invasives Karzinom mit langem rezidivfreiem Intervall und fehlendem Hautbefall, kann nach sorgfältiger Aufklärung erneut brusterhaltend operiert werden.

Literaturreferenzen: [229], [230], [231], [232], [233]

Source: CJEF, Walstra, Schipper RJ, Poodt IGM, van Riet YE, Voogd AC, van der Sangen MJC, and Nieuwenhuijzen GAP. "Repeat Breast-Conserving Therapy for Ipsilateral Breast Cancer Recurrence: A Systematic Review." [In eng]. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 45, no. 8 (2019-8 2019): 1317-27. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30795956/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: to provide an overview of the latest insights on breast-preserving treatment options for ipsilateral breast tumour recurrence(IBTR), focusing on oncological safety, morbidity, cosmesis and QoL. And to answer the following questions. 1. Which repeat breast conserving therapy (BCT)regimens are currently used for IBTR? 2. What is the IBTR-free, distant metastasis-free and overall survival after repeat BCT in the various treatment regimens?	**Design**: systematic review **Search date**: In June 2018 **Searched databases**: PubMed **Included study designs**: non- RCTs **Number of included studies**: 34 **Number of included patients**: NR **Mean/median age**: NR **Inclusion criteria**: All studies concerning BCT options for IBTR after previous BCT were included. ***Exclusion**:*	**Intervention** repeat BCT regimes followed by radiotherapy **Control** No comparison	**Primary Outcome**: 1. distant disease-free survival 2. overall survival 3. acute and late toxicities and cosmetic outcome (for studies investigating repeat radiotherapy) 4.local control	**Primary Outcome**: **1. local control**: Weighted estimates of 5-year and 10-year local control for repeat BCS followed by re-irradiation were 89%, and 93 respectively. The 5-year local control rate was reported in only one study for whole-breast irradiation (68%), in two studies for IORT (weighted estimate 91%) and in three studies for brachytherapy (weighted estimate 89%). **2.Distant-metastasis free survival**: Weighted estimates of 5-year distant-metastasis free survival for repeat	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 5 critical flaws (items2, 4, 7, 9, 13) **Overall quality of evidence**: critically low **Additional concerns about quality**: 1. Due to the scarce information on the specific inclusion criteria, high heterogeneity and different endpoints in the included studies, it was not possible to perform an adequate meta-analysis. The second best option was to calculate a weighted estimate for all available outcomes.

Source: CJEF, Walstra, Schipper RJ, Poodt IGM, van Riet YE, Voogd AC, van der Sangen MJC, and Nieuwenhuijzen GAP. "Repeat Breast-Conserving Therapy for Ipsilateral Breast Cancer Recurrence: A Systematic Review." [In eng]. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 45, no. 8 (2019-8 2019): 1317-27. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30795956/.					
3. Which patients with IBTR are considered eligible for repeat BCT? 4. What are the acute and late toxicity rates of re-irradiation of the breast in various radiotherapy regimens for IBTR? 5. How is the cosmetic outcome after repeat BCT for IBTR? 6. What do we know about QoL in patients with IBTR treated with repeat BCT in comparison to salvage mastectomy?	studies with patients who underwent primary BCS without radiotherapy, review articles, duplicate publications, comments, editorials, and letters to the editor			BCS followed by re-irradiation was 86.64% (86.18, 87.10%) (6 studies) and Weighted estimates of 10-year distant-metastasis free survival was 78% (77.29, 78.27) (2 studies) **3.Overall survival**: Weighted estimates of 5-year overall survival for repeat BCS followed by re-irradiation was 87.31% (86.93, 87.71%) (9 studies) and Weighted estimates of 10-year overall survival was 79% (78.73, 79.71%) (2 studies): Weighted estimates for 5-year overall survival per re-irradiation technique were 76% for whole-breast irradiation (based on two studies), 89% for brachytherapy (based on	However, some estimates (for example the 10-year IBTR-free survival after repeat BCS alone) are based on a single study with a limited number of patients. Therefore, the weighted estimates should be interpreted with caution. 2. There is also risk of selection bias due to the retrospective design of the studies and the lack of randomized controlled trials. 3. Some authors stated that they included patients who refused a mastectomy for various reasons. The pooled estimates in this study for local control, distant disease-free and overall survival after repeat BCS followed by re-irradiation

Source: CJEF, Walstra, Schipper RJ, Poodt IGM, van Riet YE, Voogd AC, van der Sangen MJC, and Nieuwenhuijzen GAP. "Repeat Breast-Conserving Therapy for Ipsilateral Breast Cancer Recurrence: A Systematic Review." [In eng]. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 45, no. 8 (2019-8 2019): 1317-27. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30795956/.

				five studies) and 89% for IORT (based on two studies). 4**. Ipsilateral breast tumor recurrence -free survival(IBTR-FS)** Weighted estimates of 5-year IBTR-FS for repeat BCS followed by re-irradiation was 88.56 (87.91, 89.20%) (6 studies), the 10-year IBTR-FS was 93%(1 study) **5.Toxicity** Sixteen studies reported toxicity rates after repeat radiotherapy. In five of these, no grade III to IV toxicities occurred, and 11 studies had toxicity rates varying from 2 to 21%. Seven articles reported	were non-inferior or better compared to salvage mastectomy. However, this comparison is susceptible to selection bias, since tumors that are considered eligible for repeat BCS are generally smaller and have better prognostic features (longer time to IBTR, clinically lymph node-negative). 4. Another contributing factor in possible selection bias is the inclusion of patients with primary breast cancer. Some studies included patients with a breast tumour after previous radiation on the chest for another malignancy and thus strictly had no IBTR. This may have led to an overestimation of local control and overall

Source: CJEF, Walstra, Schipper RJ, Poodt IGM, van Riet YE, Voogd AC, van der Sangen MJC, and Nieuwenhuijzen GAP. "Repeat Breast-Conserving Therapy for Ipsilateral Breast Cancer Recurrence: A Systematic Review." [In eng]. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 45, no. 8 (2019-8 2019): 1317-27. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30795956/.

				separately on acute and late toxicities, whereas most toxicities tend to occur late rather than acute. Taken acute and late toxicity together, weighted estimates for grade III and IV complications were 11% for whole-breast re-irradiation, 9% for external PBI, 9% for interstitial brachytherapy and 18% for IORT(intra-operative radiotherapy **6.Cosmetic** Twelve studies reported on cosmesis after repeat lumpectomy followed by radiotherapy. Overall, the cosmesis was “excellent to	survival. However, these studies focused on toxicity as primary endpoint rather than oncological safety. **Quality of included studies:** NR **Planned included studies** Due to non-RCT nture of included studies, we propose to downgrade the **level of evidence** to **2a** **Sources of funding:** None

Source: CJEF, Walstra, Schipper RJ, Poodt IGM, van Riet YE, Voogd AC, van der Sangen MJC, and Nieuwenhuijzen GAP. "Repeat Breast-Conserving Therapy for Ipsilateral Breast Cancer Recurrence: A Systematic Review." [In eng]. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 45, no. 8 (2019-8 2019): 1317-27. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30795956/.

				good" in 29e100% of patients with a weighted estimate of 75% (77% for brachytherapy, 62% for IORT and 75% for whole-breast reirradiation). Cosmesis was described as unacceptable in four studies (Kauer-Dorner 4%, Adkison 18%, Hannoun-Levi 2013 2%, Smanyko 18%, all multi-catheter brachytherapy). The weighted estimate of overall unacceptable cosmesis in IBTwas 3%. **7.Overall conclusion**: Repeat BCT seems to be a feasible alternative to salvage mastectomy in selected patients with IBTR. With the use of	

Source: CJEF, Walstra, Schipper RJ, Poodt IGM, van Riet YE, Voogd AC, van der Sangen MJC, and Nieuwenhuijzen GAP. "Repeat Breast-Conserving Therapy for Ipsilateral Breast Cancer Recurrence: A Systematic Review." [In eng]. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 45, no. 8 (2019-8 2019): 1317-27. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30795956/.

				irradiation, lower local recurrence rates are reported compared to repeat BCS alone with acceptable toxicity. Partial breast re-irradiation seems to be the preferable option, but it is not clear whether one specific technique is superior. Available data show good disease-free and overall survival rates, at least within relatively short follow-up. The long-term effects of re-irradiation of the breast are yet unknown.	

Abbreviations:

IBTR = Ipsilateral Breast Tumour Recurrence

IBTR-FS = Ipsilateral Breast Tumor Recurrence-Free Survival

QoL = Quality of Life

BCT = Breast Conserving Therapy

Source: CJEF, Walstra, Schipper RJ, Poodt IGM, van Riet YE, Voogd AC, van der Sangen MJC, and Nieuwenhuijzen GAP. "Repeat Breast-Conserving Therapy for Ipsilateral Breast Cancer Recurrence: A Systematic Review." [In eng]. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 45, no. 8 (2019-8 2019): 1317-27. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30795956/.

BCS = Breast-Conserving Surgery

IORT = Intraoperative Radiotherapy

PBI = Partial Breast Irradiation

RCT = Randomized Controlled Trial

NR = not Reported

Kapitel 5.1.1.2: Axilläres Lymphknotenrezidiv

Kapitel 5.2: Systemische Therapie metastasiertes Mammakarzinom

Kapitel 5.2.1: Systemische Therapie HER2-positives Mammakarzinom

Verknüpfte Empfehlungen:

Empfehlung 5.25:

Bei einem metastasierten HER2-positiven Mammakarzinom sollte in der Erstlinientherapie eine duale Blockade mit Trastuzumab / Pertuzumab und einem Taxan eingesetzt werden.

Literaturreferenzen: [234], [235], [236]

Source: BJ, Xie, Zhu LN, Ma C, Li JB, Dong L, Zhu ZN, Ding T, and Gu XS. "A Network Meta-Analysis on the Efficacy of Her2-Targeted Agents in Combination with Taxane-Containing Regimens for Treatment of Her2-Positive Metastatic Breast Cancer." [In eng]. Breast cancer (Tokyo, Japan) 27, no. 2 (2020-3 2020): 186-96. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31529262/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: to compare the effectiveness of different combination options and to identify the best strategy for HER2+MBC	**Design**: Systematic Review and Network Meta-Analysis **Search date**: 04/2018 **Searched databases**: PubMed, Embase,	Effectiveness of different combination options: 2665 patients were included in the **single-HER2-targetedagent+a taxane group**	**Overall Survival** **Overall response rate** **PFS** **Abbreviations** T Taxane	**Overall Survival** Effects on 1-year OS rate were reported in 12 studies including 9 regimens “Ranking analysis based on their P-scores	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 5 critical flaws (items 2, 7, 9, 13, 15)

Source: BJ, Xie, Zhu LN, Ma C, Li JB, Dong L, Zhu ZN, Ding T, and Gu XS. "A Network Meta-Analysis on the Efficacy of Her2-Targeted Agents in Combination with Taxane-Containing Regimens for Treatment of Her2-Positive Metastatic Breast Cancer." [In eng]. Breast cancer (Tokyo, Japan) 27, no. 2 (2020-3 2020): 186-96. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31529262/.					
	Cochrane Library and ClinicalTrials.gov **Included study designs**: Randomized controlled trials (phase II or III) **Number of included studies**: 13 **Number of included patients**: 4.941 **Mean/median age**: n.a. **Inclusion criteria**: phase II or III randomized controlled trials (RCTs) including patients with HER2+ MBC treatment with taxanes (paclitaxel, docetaxel, or nab-paclitaxel) plus with HER2-targeted agents at any line	808 patients were included in the **doublet-HER2-targeted agent+a taxane group** 1468 patients were included in the **single-HER2-targeted agent+taxane-based doublets group**	T+Tra Taxane+Trastuzumab T+Lap Taxane+Lapatinib T+Ner Taxane+Neratinib T-DM1 Trastuzumab emtansine T+Tra+Car Taxane+Trastuzumab+ Carboplatin T+Tra+Cap Taxane+Trastuzumab+ Capecitabine T+Tra+Bev Taxane+Trastuzumab+ Bevacizumab T+Tra+NPLD Taxane+Trastuzumab+ Nonpegylated liposomal doxorubicin	best treatment T+Tra+Per vs. T OR 3.80 (95% CI 2.00-7.22) followed by T+Tra+Cap vs. T OR 3.36 (95% CI 1.34-8.44) T+Tra+Car vs. T OR 2.62 (95% CI 1.31-5.25) T+Tra+NPLD vs. T OR 2.07 (95% CI 1.05-4.05) Effects on 2-year OS rate were reported in 12 studies including 9 regimens “Ranking analysis based on their P-scores suggested that T+Tra+Per	**Overall quality of evidence**: critically low **Additional concerns about quality**: 10 different regimens: therefore, only data extracted from 1 or 2 studies were synthesized in view of each pair of comparators Limited size of patients and lack of head to head comparisons might undermine the credibility and autenticity of this assessment Chose the suitable trials without consideration of whether the trial was first-line or not because of lack of sufficient trials Authors did not consider the cost-effectiveness of

Source: BJ, Xie, Zhu LN, Ma C, Li JB, Dong L, Zhu ZN, Ding T, and Gu XS. "A Network Meta-Analysis on the Efficacy of Her2-Targeted Agents in Combination with Taxane-Containing Regimens for Treatment of Her2-Positive Metastatic Breast Cancer." [In eng]. Breast cancer (Tokyo, Japan) 27, no. 2 (2020-3 2020): 186-96. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31529262/.					
	sufficient data provided about efficacy if multiple publications of the same trial were retrieved, only the most recent publication was included. **Exclusion**: NR		T+Tra+Per Taxane+Trastuzumab+Pertuzumab	was the best treatment for 2-year OS rate" Effects on median OS were reported in 12 studies including 9 regimens Ranking analysis based on their P-scores suggested that T+Tra+Per was the best treatment for median OS **Overall response rate** 13 studies including 10 Regimens "Ranking analysis based on their P-scores suggested that T+Tra+Per was the best treatment for ORR" **PFS** 12 studies including	taxanes combination with HER2-targeted therapies To reduce heterogeneity and inconsistency, the authors excluded studies using sequential combination therapy, which reduced the number of studies and may have impacted the accuracy of the results **Quality of included studies**: n.a. **Planned included studies**: Randomized controlled trials (phase II or III) **Sources of funding:** This study was funded by the Natural Science Foundation of China (81773828, 81273600), the Natural

Source: BJ, Xie, Zhu LN, Ma C, Li JB, Dong L, Zhu ZN, Ding T, and Gu XS. "A Network Meta-Analysis on the Efficacy of Her2-Targeted Agents in Combination with Taxane-Containing Regimens for Treatment of Her2-Positive Metastatic Breast Cancer." [In eng]. Breast cancer (Tokyo, Japan) 27, no. 2 (2020-3 2020): 186-96. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31529262/.

				10 regimens: "Ranking analysis based on their P-scores suggested that T+Tra+Per was the best treatment for PFS" –	Science Foundation of Hebei Province (C2011206145, C2018206297), Key Project of Medical Science Research of Hebei Province (ZD20140163), the Research Project of Education Department, Hebei Province (ZD2016010),the Project Medical Science Research of Hebei Health and Family Planning Commission (20160402), and the Research Project of Hebei Health and Family Planning Commission (20160234).

Abbreviations:

n.a. = not Available, not Applicable

MBC = Metastatic Breast Cancer

PFS = Progression-Free Survival

Source: BJ, Xie, Zhu LN, Ma C, Li JB, Dong L, Zhu ZN, Ding T, and Gu XS. "A Network Meta-Analysis on the Efficacy of Her2-Targeted Agents in Combination with Taxane-Containing Regimens for Treatment of Her2-Positive Metastatic Breast Cancer." [In eng]. Breast cancer (Tokyo, Japan) 27, no. 2 (2020-3 2020): 186-96. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31529262/.

OS = Overall Survival

ORR = Overall Response Rate

RCT = Randomised Controlled Trial

OR = Odds Ratio

95% CI = 95% Confidence Interval

n.a. = not Available, not Applicable

NR = not Reported

Verknüpfte Empfehlungen:

Empfehlung 5.26:

Bei Patientinnen mit einem HER2-positiven metastasierten Mammakarzinom sollte in der Zweitlinientherapie bevorzugt eine Therapie mit Trastuzumab-Deruxtecan oder alternativ die Kombination Tucatinib + Trastuzumab + Capecitabin eingesetzt werden.

Literaturreferenzen: [237]

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Trastuzumab deruxtecan (Mammakarzinom, HER2+, nach 1 Vortherapie)			
Wirkstoff	Trastuzumab deruxtecan	**Handelsname**	Enhertu
Pharmazeutischer Unternehmer	Daiichi Sankyo Deutschland GmbH	**Beschlussdatum**	02.02.2023
Anwendungsgebiet	Mammakarzinom		

Trastuzumab deruxtecan (Mammakarzinom, HER2+, nach 1 Vortherapie)			
Wirkstoff	Trastuzumab deruxtecan	**Handelsname**	Enhertu
Pharmazeutischer Unternehmer	Daiichi Sankyo Deutschland GmbH	**Beschlussdatum**	02.02.2023
Anwendungsgebiet	Mammakarzinom		

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung eines neuen Anwendungsgebietes für den Wirkstoff Trastuzumab-Deruxtecan. Enhertu wurde unter besonderen Bedingungen zugelassen.
Trastuzumab-Deruxtecan ist zugelassen als Monotherapie zur Behandlung von erwachsenen Patienten mit inoperablem oder metastasiertem HER2-positivem Brustkrebs, die bereits mindestens eine gegen HER2 gerichtete Vorbehandlung erhalten haben.
Hier wurde das Anwendungsgebiet zur Behandlung von erwachsenen Patienten mit inoperablem oder metastasiertem HER2-positivem Brustkrebs, die bereits eine gegen HER2 gerichtete Vorbehandlungen erhalten haben, bewertet.
Als zweckmäßige Vergleichstherapie wurde vom G-BA Trastuzumab Emtansin bestimmt.
Für die Bewertung des Zusatznutzens liegen aus der offenen, randomisierten, kontrollierten Studie DESTINY-Breast03 Ergebnisse im Vergleich zu Trastuzumab Emtansin zur Mortalität, Morbidität, Lebensqualität und zu Nebenwirkungen vor.
Für das Gesamtüberleben zeigt sich ein statistisch signifikanter Vorteil. Aufgrund einer Effektmodifikation durch das Merkmal Alter, die sich in Subgruppenanalysen zeigt (≥ 65 Jahre; < 65 Jahre), in Verbindung mit zusätzlichen Limitationen der Studie hinsichtlich der erfolgten Vortherapien verbleibt eine Unsicherheit in Bezug auf die Quantifizierung des Ausmaßes des Zusatznutzens für die gesamte Studienpopulation.
Hinsichtlich der Morbidität und der Lebensqualität liegt kein eindeutiger Vor- oder Nachteil von Trastuzumab-Deruxtecan im Vergleich zu Trastuzumab Emtansin vor.
Für die Endpunkte SUE und schwere UE wird ein Vorteil festgestellt. Bei dem Endpunkt Abbruch wegen UE liegt kein Unterschied vor. In Bezug auf spezifische unerwünschte Ereignisse bestehen sowohl Vor- als auch Nachteile. Insgesamt zeigen die Endpunkte der Nebenwirkungen überwiegend Vorteile für Trastuzumab-Deruxtecan.
Aufgrund der Effektmodifikation durch das Merkmal Alter besteht eine Unsicherheit in Bezug auf die Quantifizierung des Ausmaßes des Zusatznutzens für die gesamte Studienpopulation. Ferner liegen Unsicherheiten bezüglich der Vortherapien der in die Studie DESTINY-Breast03 eingeschlossenen Patientinnen und Patienten vor. Aus diesen Gründen lässt sich Ausmaß des Zusatznutzens in der Gesamtbetrachtung nicht sicher quantifizieren.
Hinsichtlich der Aussagesicherheit wird insgesamt ein Hinweis für den festgestellten Zusatznutzen abgeleitet. In der Gesamtbetrachtung wird ein Hinweis auf einen nicht quantifizierbaren Zusatznutzen für Trastuzumab-Deruxtecan im Vergleich zu Trastuzumab Emtansin festgestellt.

Trastuzumab deruxtecan (Mammakarzinom, HER2+, nach 1 Vortherapie)			
Wirkstoff	Trastuzumab deruxtecan	**Handelsname**	Enhertu
Pharmazeutischer Unternehmer	Daiichi Sankyo Deutschland GmbH	**Beschlussdatum**	02.02.2023
Anwendungsgebiet	Mammakarzinom		

Trastuzumab deruxtecan (Mammakarzinom, HER2+, nach 1 Vortherapie)			
Wirkstoff	Trastuzumab deruxtecan	**Handelsname**	Enhertu
Pharmazeutischer Unternehmer	Daiichi Sankyo Deutschland GmbH	**Beschlussdatum**	02.02.2023
Anwendungsgebiet	Mammakarzinom		

Verknüpfte Empfehlungen:

Empfehlung 5.27:

Bei einem metastasierten HER2-positiven Mammakarzinom sollte, sofern noch nicht angewandt, in der Drittlinientherapie bevorzugt eine Therapie mit Tucatinib + Trastuzumab + Capecitabin, T-DXd oder T-DM1 eingesetzt werden.

Literaturreferenzen: [238], [239], [240], [241], [242], [237]

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Tucatinib (Mammakarzinom, HER2+, mind. 2 Vortherapien, Kombination mit Trastuzumab und Capecitabin)			
Wirkstoff	Tucatinib	**Handelsname**	Tukysa
Pharmazeutischer Unternehmer	Seagen Germany GmbH	**Beschlussdatum**	02.09.2021
Anwendungsgebiet	Mammakarzinom		

Tucatinib (Mammakarzinom, HER2+, mind. 2 Vortherapien, Kombination mit Trastuzumab und Capecitabin)			
Wirkstoff	Tucatinib	**Handelsname**	Tukysa
Pharmazeutischer Unternehmer	Seagen Germany GmbH	**Beschlussdatum**	02.09.2021
Anwendungsgebiet	Mammakarzinom		

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung des neuen Arzneimittels Tukysa in Kombination mit Trastuzumab und Capecitabin. Tukysa ist zugelassen in Kombination mit Trastuzumab und Capecitabin zur Behandlung von erwachsenen Patienten mit HER2-positivem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die zuvor mindestens 2 gegen HER2 gerichtete Behandlungsschemata erhalten haben.
Als zweckmäßige Vergleichstherapie wurde eine Therapie nach ärztlicher Maßgabe bestimmt.
Im Rahmen der Therapie nach ärztlicher Maßgabe wurden die Behandlungsoptionen Lapatinib in Kombination mit Capecitabin, Lapatinib in Kombination mit Trastuzumab (nur für Patienten mit Hormonrezeptor-negativem Mammakarzinom) und Trastuzumab in Kombination mit Capecitabin als geeignete Komparatoren benannt.
Der pharmazeutische Unternehmer legt für die Nutzenbewertung die Ergebnisse der noch laufenden, doppelblinden randomisierten und kontrollierten Studie HER2CLIMB vor.
In der Endpunktkategorie Mortalität zeigen die vorliegenden Ergebnisse zum Endpunkt Gesamtüberleben eine statistisch signifikante Verlängerung der Überlebenszeit durch eine Behandlung mit Tucatinib + Trastuzumab + Capecitabin gegenüber einer Behandlung mit Trastuzumab + Capecitabin, die im Ausmaß als eine deutliche Verbesserung bewertet wird.
Für die Endpunktkategorie Morbidität zeigen sich in Bezug auf den Endpunkt Gesundheitszustand weder positive noch negative Effekte einer Behandlung mit Tucatinib + Trastuzumab + Capecitabin gegenüber einer Behandlung mit Trastuzumab + Capecitabin.
Hinsichtlich der gesundheitsbezogenen Lebensqualität liegen keine Daten vor, da in der Studie HER2CLIMB keine Daten zur gesundheitsbezogenen Lebensqualität erhoben wurden.
Hinsichtlich der Nebenwirkungen kann für Tucatinib + Trastuzumab + Capecitabin im Vergleich zu Trastuzumab + Capecitabin weder ein Vorteil noch ein Nachteil festgestellt werden. Allein bei den spezifischen unerwünschten Ereignissen liegen statistisch signifikante Unterschiede vor, die sowohl ein Vorteil als auch Nachteile aufzeigen.
In der Gesamtbetrachtung der vorliegenden Ergebnisse zu den patientenrelevanten Endpunkten stehen dem Vorteil im Gesamtüberleben keine Nachteile bei der Morbidität und den Nebenwirkungen gegenüber.
Im Ergebnis stellt der G-BA für Tucatinib + Trastuzumab + Capecitabin zur Behandlung von Patienten mit HER2-positivem, lokal fortgeschrittenem oder metastasiertem Brustkrebs, die zuvor mindestens zwei HER2-gerichtete Therapieregime erhalten haben, im Vergleich zur zweckmäßigen Vergleichstherapie einen beträchtlichen Zusatznutzen fest.
Es liegen keine Daten zur krankheitsspezifischen Symptomatik und zur gesundheitsbezogenen Lebensqualität aus der Studie HER2CLIMB vor. Diese Limitationen führen insgesamt dazu, dass die Aussagesicherheit für den festgestellten Zusatznutzen als „Anhaltspunkt“ eingestuft wird.
Im Ergebnis stellt der G-BA für Tucatinib in Kombination mit Trastuzumab und Capecitabin einen Anhaltspunkt für einen beträchtlichen Zusatznutzen gegenüber der zweckmäßigen Vergleichstherapie fest.

Tucatinib (Mammakarzinom, HER2+, mind. 2 Vortherapien, Kombination mit Trastuzumab und Capecitabin)			
Wirkstoff	Tucatinib	**Handelsname**	Tukysa
Pharmazeutischer Unternehmer	Seagen Germany GmbH	**Beschlussdatum**	02.09.2021
Anwendungsgebiet	Mammakarzinom		

Tucatinib (Mammakarzinom, HER2+, mind. 2 Vortherapien, Kombination mit Trastuzumab und Capecitabin)			
Wirkstoff	Tucatinib	**Handelsname**	Tukysa
Pharmazeutischer Unternehmer	Seagen Germany GmbH	**Beschlussdatum**	02.09.2021
Anwendungsgebiet	Mammakarzinom		

Verknüpfte Empfehlungen:

Empfehlung 5.27:

Bei einem metastasierten HER2-positiven Mammakarzinom sollte, sofern noch nicht angewandt, in der Drittlinientherapie bevorzugt eine Therapie mit Tucatinib + Trastuzumab + Capecitabin, T-DXd oder T-DM1 eingesetzt werden.

Literaturreferenzen: [238], [239], [240], [241], [242], [237]

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Trastuzumab deruxtecan (Mammakarzinom, HER2+, mind. 2 Vortherapien)			
Wirkstoff	Trastuzumab deruxtecan	**Handelsname**	Enhertu
Pharmazeutischer Unternehmer	Daiichi Sankyo Deutschland GmbH	**Beschlussdatum**	02.02.2023
Anwendungsgebiet	Mammakarzinom		

Trastuzumab deruxtecan (Mammakarzinom, HER2+, mind. 2 Vortherapien)			
Wirkstoff	Trastuzumab deruxtecan	**Handelsname**	Enhertu
Pharmazeutischer Unternehmer	Daiichi Sankyo Deutschland GmbH	**Beschlussdatum**	02.02.2023
Anwendungsgebiet	Mammakarzinom		

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung des neuen Arzneimittels Enhertu mit dem Wirkstoff Trastuzumab-Deruxtecan. Enhertu wurde unter besonderen Bedingungen zugelassen.
Trastuzumab-Deruxtecan ist zugelassen als Monotherapie zur Behandlung von erwachsenen Patienten mit inoperablem oder metastasiertem HER2-positivem Brustkrebs, die bereits mindestens eine gegen HER2 gerichtete Vorbehandlung erhalten haben.
Das hier bewertete Anwendungsgebiet lautet:
Trastuzumab-Deruxtecan wird angewendet als Monotherapie zur Behandlung von erwachsenen Patienten mit inoperablem oder metastasiertem HER2-positivem Brustkrebs, die bereits mindestens zwei gegen HER2 gerichtete Vorbehandlungen erhalten haben.
Als zweckmäßige Vergleichstherapie wurde eine Therapie nach ärztlicher Maßgabe bestimmt. Im Rahmen der Therapie nach ärztlicher Maßgabe wurden die Behandlungsoptionen Lapatinib in Kombination mit Capecitabin, Lapatinib in Kombination mit Trastuzumab (nur für Patienten mit Hormonrezeptor-negativem Mammakarzinom), Trastuzumab in Kombination mit Capecitabin und Tucatinib in Kombination mit Trastuzumab und Capecitabin als geeignete Komparatoren benannt.
Der pharmazeutische Unternehmer legt für die Nutzenbewertung die Ergebnisse der noch laufenden, offenen, randomisierten und kontrollierten Phase III-Studie DESTINY-Breast02 vor.
In der Endpunktkategorie Mortalität zeigt sich im Endpunkt Gesamtüberleben eine statistisch signifikante Verlängerung der Überlebenszeit durch eine Behandlung mit Trastuzumab-Deruxtecan gegenüber der Therapie nach ärztlicher Maßgabe, die als eine deutliche Verbesserung bewertet wird.
In der Kategorie Morbidität lässt sich für den Endpunkt Gesundheitszustand ein Vorteil für die Behandlung mit Trastuzumab-Deruxtecan feststellen, der als eine deutliche Verbesserung des Gesundheitszustandes gewertet wird. In der Gesamtschau liegt hinsichtlich der Symptomatik ein Vorteil von Trastuzumab-Deruxtecan vor.
Für die gesundheitsbezogene Lebensqualität ergibt sich ebenfalls ein Vorteil von Trastuzumab-Deruxtecan im Vergleich zur Therapie nach ärztlicher Maßgabe.
In der Gesamtschau der Ergebnisse zu den Nebenwirkungen ergeben sich keine für die Nutzenbewertung relevanten Unterschiede zwischen den Behandlungsarmen.
In der Gesamtbetrachtung kommt der G-BA zu dem Ergebnis, dass insbesondere aufgrund des Ausmaßes der Verlängerung der Überlebensdauer und in Anbetracht der positiven Effekte auf die Morbidität und Lebensqualität für Trastuzumab-Deruxtecan in der Behandlung von erwachsenen Patientinnen und Patienten mit inoperablem oder metastasiertem HER2-positivem Brustkrebs, die bereits mindestens zwei gegen HER2-gerichtete Vorbehandlungen erhalten haben, ein beträchtlicher Zusatznutzen gegenüber einer Therapie nach ärztlicher Maßgabe vorliegt.
Die Aussagekraft wird als Hinweis eingestuft.
Im Ergebnis stellt der G-BA für Trastuzumab-Deruxtecan einen Hinweis auf einen beträchtlichen Zusatznutzen gegenüber der zweckmäßigen Vergleichstherapie fest.

Trastuzumab deruxtecan (Mammakarzinom, HER2+, mind. 2 Vortherapien)			
Wirkstoff	Trastuzumab deruxtecan	**Handelsname**	Enhertu
Pharmazeutischer Unternehmer	Daiichi Sankyo Deutschland GmbH	**Beschlussdatum**	02.02.2023
Anwendungsgebiet	Mammakarzinom		

Trastuzumab deruxtecan (Mammakarzinom, HER2+, mind. 2 Vortherapien)			
Wirkstoff	Trastuzumab deruxtecan	**Handelsname**	Enhertu
Pharmazeutischer Unternehmer	Daiichi Sankyo Deutschland GmbH	**Beschlussdatum**	02.02.2023
Anwendungsgebiet	Mammakarzinom		

Verknüpfte Empfehlungen:

Empfehlung 5.27:

Bei einem metastasierten HER2-positiven Mammakarzinom sollte, sofern noch nicht angewandt, in der Drittlinientherapie bevorzugt eine Therapie mit Tucatinib + Trastuzumab + Capecitabin, T-DXd oder T-DM1 eingesetzt werden.

Literaturreferenzen: [238], [239], [240], [241], [242], [237]

C, Omarini, Piacentini F, Sperduti I, Cerma K, Barbolini M, Canino F, Nasso C, et al. "T-Dm1 Efficacy in Trastuzumab-Pertuzumab Pre-Treated Her2 Positive Metastatic Breast Cancer Patients: A Meta-Analysis." [In eng]. BMC cancer 22, no. 1 (2022-6-7 2022): 623. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35672679/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
To investigate the efficacy of T-DM1 after the combination of trastuzumab-pertuzumab (TP) in HER2 positive metastatic breast cancer patients (MBC). Focus on the activity of T-DM1 in 2nd line setting following TP and taxane 1st line treatment.	**Design**: Systematic review and Meta-Analysis **Search date**: until December 31st 2020 **Searched databases**: PubMed, Embase, Cochrane Library, Web of Science **Included study designs**: observational studies (7 retrospective, 1 non-comparative randomized open label phase II trial [PERNETTA trial])	**Intervention** T-DM1 in 2nd line setting following TP and taxane 1st line treatment **Control** EMILIA trial (phase III RCT): no TP pre-treated patients (patients were pretreated with trastuzumab and taxane)	1 year progression-free survival (PFS)	1 year progression-free survival (PFS) T-DM1 in 2nd or further line of treatment Risk difference for T-DM1 efficacy: -0.1222, 95% CI -0.253 to 0.010, p=0.07, I²=0.001% T-DM1 in 2ndlinetreatment Risk difference: -0.034, 95% CI -0.207 to 0.139, p=0.701, I²=0.01%	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 5 critical flaws (item 2,7,9,11,13) **Overall quality of evidence**: critically low **Additional concerns about quality:** of the SR Article would have benefitted from careful prove reading, e.g. label of Fig. 2 includes the TH3ERESA trial, the text

C, Omarini, Piacentini F, Sperduti I, Cerma K, Barbolini M, Canino F, Nasso C, et al. "T-Dm1 Efficacy in Trastuzumab-Pertuzumab Pre-Treated Her2 Positive Metastatic Breast Cancer Patients: A Meta-Analysis." [In eng]. BMC cancer 22, no. 1 (2022-6-7 2022): 623. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/35672679/.					
	Number of included studies: 10 studies on T-DM1 in TP pre-treated patients; 7 (Meta-Analysis) Of those: 5 studies on T-DM1 in 2nd line setting **Number of included patients**: 1,152 **Mean/median age**: n.a. **Inclusion criteria**: not specifically stated				focused only on the EMILIA trial as a comparison; text states that 8 studies are included in the MA, but there are only 7 trials included in the MA; authors describe that they included 5 studies on T-DM1 2nd line therapy, but there are only 4 studies; maybe they counted the phase II PERNETTA trial as 2 studies **Quality of included studies**: only aggregated results of formal quality assessment; included retrospective studies + 1 phase II study **Sources of funding**: none

Verknüpfte Empfehlungen:

Empfehlung 5.27:

Bei einem metastasierten HER2-positiven Mammakarzinom sollte, sofern noch nicht angewandt, in der Drittlinientherapie bevorzugt eine Therapie mit Tucatinib + Trastuzumab + Capecitabin, T-DXd oder T-DM1 eingesetzt werden.

Literaturreferenzen: [238], [239], [240], [241], [242], [237]

Source: R, Martin Huertas, Fernández Abad M, Corral de la Fuente E, Serrano Domingo JJ, and Martínez Jáñez N. "Prolonged Responses with Trastuzumab Emtasine Treatment of Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Refractory to Trastuzumab and Pertuzumab: Systematic Review of Evidence." [In eng]. Clinical breast cancer 21, no. 5 (2021-10 2021): 391-98. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33549470/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: we summarize published evidence on efficacy and prolonged responses with trastuzumab emtansine (T-DM1) after first-line trastuzumab plus pertuzumab and provide possible factors related to prolonged responses to T-DM1.	**Design**: Systematic review **Search date**: between July 1, 2012 and December 31, 2019 **Searched databases**: PubMed **Included study designs**: Non-experimental studies: retrospective and prospective cohort **Number of included studies**: 7	**Intervention** T-DM1 in the second or later lines of MBC after pertuzumab treatment **Control** Findings of two phase III trials including EMILIA and TH3RESA.	Overall response rate; Progression-free survival	Less efficacy in terms of responses (overall response rate, 18%-33%) and progression-free survival (4-6 months) with second-line T-DM1, in patients pretreated with pertuzumab, was shown (if compared with the EMILIA trial). The results are more similar to those of the TH3RESA trial (very pretreated population). Prolonged treatments (6 months or more) were observed in at least 17%	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 5 critical flaws (item 2,4,7,9,13) **Overall quality of evidence**: critically low **Additional concerns about quality**: these results should be interpreted with caution because of the retro-spective nature of studies, the small sample

Source: R, Martin Huertas, Fernández Abad M, Corral de la Fuente E, Serrano Domingo JJ, and Martínez Jáñez N. "Prolonged Responses with Trastuzumab Emtasine Treatment of Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Refractory to Trastuzumab and Pertuzumab: Systematic Review of Evidence." [In eng]. Clinical breast cancer 21, no. 5 (2021-10 2021): 391-98. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33549470/.					
	Number of included patients: 796 **Mean/median age**: n.a. **Inclusion criteria**: We included articles that specifically reported efficacy data of T-DM1 in the second or later lines of MBC after pertuzumab treatment and articles about long survival or prolonged responses with T-DM1 alone. **Exclusion**: articles that exclusively referred to early breast cancer and T-DM1 treatment in the neoadjuvant or adjuvant setting, articles that evaluated combinations of T-DM1 with other drugs; articles focused on other anti-HER2 treatments for MBC, and			of cases. The efficacy of T-DM1 after a previous pertuzumab treatment is lower than if pertuzumab is not given, although prolonged responses are observed in this setting. The efficacy of T-DM1 after a previous pertuzumab treatment is lower than if pertuzumab is not given, although prolonged responses are observed in this setting. Prolonged responses are observed in a significant proportion of patients: 30% of total patients maintained T-DM1 for more than 6 months, and more than 14% of patients maintained treatment for 1 year of more. The possible factors that can condition long and durable	size, and the different comparisons made; not all patients had received prior pertuzumab, and this fact can be considered a limitation of some of the studies, because a comparison of the efficacy of T-DM1 according to whether patients had previously received or not pertuzumab is not possible. Also, there are differences in the line in which T-DM1 is administered. **Sources of funding**: no funding

Source: R, Martin Huertas, Fernández Abad M, Corral de la Fuente E, Serrano Domingo JJ, and Martínez Jáñez N. "Prolonged Responses with Trastuzumab Emtasine Treatment of Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Refractory to Trastuzumab and Pertuzumab: Systematic Review of Evidence." [In eng]. Clinical breast cancer 21, no. 5 (2021-10 2021): 391-98. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33549470/.					
	articles that included only patients with brain metastasis (BM) as the reference population			responses are ECOG PS 0, late recurrence after adjuvant trastuzumab, no visceral disease, and good response to prior treatment with pertuzumab	

Verknüpfte Empfehlungen:

Empfehlung 5.28:

Ist bei Patientinnen mit asymptomatischen HER2-positiven Hirnmetastasen, nach interdisziplinärer Diskussion unter Berücksichtigung der Patientinnenpräferenz, eine Systemtherapie geplant, sollte entweder T-DXd oder eine Dreierkombination Tucatinib + Capecitabin + Trastuzumab angeboten werden.

Literaturreferenzen: [239], [243], [241]

Source: Kendra DeBusk, Shaun Abeysinghe, Adrian Vickers, Anubhav Nangia, Judith Bell, Chiemeka Ike, Andres Forero-Torres & Matthew T Blahna (2021) Efficacy of Tucatinib for HER2-Positive Metastatic Breast Cancer After HER2-Targeted Therapy: A Network Meta-Analysis, Future Oncology, 17: 33, 4635-4647, DOI: 10.2217/fon-2021-0742

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Indirect comparison of tucatinib with other therapies in patients with HER2+ MBC after ≥1 prior HER2-directed therapy (or ≥1 prior chemotherapy, for trials assessing eribulin in a mixed population of MBC patients that included a HER2+ subgroup)	**Design**: Systematic literature review and network meta-analysis **Search date**: conducted 23.11.2020 **Searched databases**: PubMed, Embase, Cochrane Library **Included study designs**: RCT **Number of included studies**: 12	**Intervention** T-DM1 (trastuzumab emtansine) **Control** Other therapies (capecitabine, eribulin, vinorelbine, lapatinib, neratinib, margetuximab, pertuzumab, T-DM1 and tucatinib, including any combination therapy	Progression-free survival (PFS) Overall survival (OS)	**Progression-free survival (PFS)** tucatinib plus trastuzumab with capecitabine as the most likely therapy to be ranked first for improving T-DM1 monotherapy and neratinib were the next most effective therapies for improving PFS **Overall survival (OS)**	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 5 critical flaws (items 2, 7, 9, 13, 15) **Overall quality of evidence**: critically low **Additional concerns about quality**: Some trials could not be connected to the evidence network or did

Source: Kendra DeBusk, Shaun Abeysinghe, Adrian Vickers, Anubhav Nangia, Judith Bell, Chiemeka Ike, Andres Forero-Torres & Matthew T Blahna (2021) Efficacy of Tucatinib for HER2-Positive Metastatic Breast Cancer After HER2-Targeted Therapy: A Network Meta-Analysis, Future Oncology, 17: 33, 4635-4647, DOI: 10.2217/fon-2021-0742					
	Number of included patients: n.a. **Mean/median age**: n.a. **Inclusion criteria**: Randomized controlled trials of patients receiving therapy for HER2+ MBC after ≥1 prior HER2-directed therapy (or chemotherapy, for trials assessing eribulin in a mixed population of MBC patients that included a HER2+ subgroup) that reported efficacy or safety data	with trastuzumab and/or capecitabine)		tucatinib plus trastuzumab with capecitabine as the most likely therapy to be ranked first for improving T-DM1 monotherapy and pertuzumab plus trastuzumab with capecitabine were the next most effective therapies for improving OS	not meet inclusion criteria two publications reporting trials assessing pyrotinib (with capecitabine) were excluded in the main analysis owing to data immaturity, a high proportion of treatment switching and being conducted solely in Asian patients Several trials permitted treatment switching. To account for this, such studies were included if RPSFTM-adjusted Kaplan–Meier data could be found In some cases, details such as the number of patients at risk throughout follow-up were not reported; however, errors from the

Source: Kendra DeBusk, Shaun Abeysinghe, Adrian Vickers, Anubhav Nangia, Judith Bell, Chiemeka Ike, Andres Forero-Torres & Matthew T Blahna (2021) Efficacy of Tucatinib for HER2-Positive Metastatic Breast Cancer After HER2-Targeted Therapy: A Network Meta-Analysis, Future Oncology, 17: 33, 4635-4647, DOI: 10.2217/fon-2021-0742

					reconstructed RPSFTM-adjusted data were less than those presented in the original, unadjusted charts **Quality of included studies**: Low: 8 trials High: 4 trials **Sources of funding:** Sponsored by Seagen Inc. K DeBusk, C Ike, A Forero-Torres and MT Blahna are employees and stockholders of Seagen Inc. S Abeysinghe, A Vickers, A Nangia and J Bell are employees of RTI Health Solutions, which received funding from Seagen Inc.

Source: Kendra DeBusk, Shaun Abeysinghe, Adrian Vickers, Anubhav Nangia, Judith Bell, Chiemeka Ike, Andres Forero-Torres & Matthew T Blahna (2021) Efficacy of Tucatinib for HER2-Positive Metastatic Breast Cancer After HER2-Targeted Therapy: A Network Meta-Analysis, Future Oncology, 17: 33, 4635-4647, DOI: 10.2217/fon-2021-0742

					for the analyses reported in this manuscript Medical writing assistance was provided by M Bell of Curo (part of Envision Pharma Group), and was funded by Seagen Inc.

Abbreviations:

MBC = Metastatic Breast Cancer

RCT = Randomised Controlled Trial

n.a. = not Available, not Applicable

PFS = Progression-free survival

OS = Overall survival

Kapitel 5.2.2: Systemische Therapie bei prä- und perimenopausalen Patientinnen und positivem Hormonrezeptorstatus und negativem HER2-Status

Verknüpfte Empfehlungen:

Empfehlung 5.30:

Bei prä- und perimenopausalen Patientinnen soll bei positivem Hormonrezeptorstatus und negativem HER2-Status eine endokrine Therapie, bevorzugt kombiniert mit einer zielgerichteten Therapie mit einem CDK4/6-Inhibitor angeboten werden.

Empfehlung 5.34:

Bei postmenopausalen Patientinnen soll die endokrin-basierte Therapie mit einem CDK4/6-Inhibitor in Abhängigkeit von der Vortherapie in Kombination mit einem Aromatasehemmer, Fulvestrant oder Tamoxifen (Tamoxifen nicht in Kombination mit Ribociclib) erfolgen.

Empfehlung 5.36:

Sofern in der Erstlinie noch kein CDK4/6-Inhibitor eingesetzt worden war, sollte er in weiteren endokrin-basierten Therapielinien eingesetzt werden.

Empfehlung 5.31:

Bei prämenopausalen Patientinnen soll die endokrin-basierte Therapie mit einem CDK4/6-Inhibitor unter Ausschaltung der Ovarialfunktion und in Abhängigkeit von der Vortherapie in Kombination mit einem Aromatasehemmer, Fulvestrant oder Tamoxifen (Tamoxifen nicht in Kombination mit Ribociclib) erfolgen.

Empfehlung 5.33:

Die Kombinationstherapie eines Aromatasehemmers oder Fulvestrant mit CDK 4/6-Inhibitoren soll als Erstlinientherapie oder spätestens ab der Zweitlinie durchgeführt werden, sofern diese Substanzgruppe noch nicht eingesetzt wurde.

Literaturreferenzen: [244], [245]

Source: F, Schettini, Giudici F, Giuliano M, Cristofanilli M, Arpino G, Del Mastro L, Puglisi F, et al. "Overall Survival of Cdk4/6-Inhibitor-Based Treatments in Clinically Relevant Subgroups of Metastatic Breast Cancer: Systematic Review and Meta-Analysis." [In eng]. Journal of the National Cancer Institute 112, no. 11 (2020-11-1 2020): 1089-97. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/32407488/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Identifying patients that might benefit most from CDK4/6-inhibitors, in different clinically relevant subgroups of HR+/HER2-negative MBC.	**Design**: Systematic review and meta-analysis **Search date**: end of October 2019 **Searched databases**: PubMed (+ European Society for medical Oncology (ESMO) and American Society and Clinical Oncology meetings and San Antonio Breast Cancer Symposium online databases) **Included study designs**: Phase II or III RCT **Number of included studies**: 6 papers reporting OS results:	**Intervention** Palbociclib + letrozole (PALOMA 1) Palbociclib + fulvestrant (PALOMA 3, MONALEESA 3) Ribociclib + letrozole (MONALEESA 2) Ribociclib + tamoxifen or AI + GnRHa (MONALEESA 7) Abemaciclib + fulvestrant (MONARCH 2) **Control** letrozole (PALOMA 1; MONALEESA 2) fulvestrant (PALOMA 3; MONALEESA 3)	**Primary Outcome**: Overall survival **Secondary Outcome**: n.a.	**Primary Outcome**: Overall survival Benefit for CDK4/6-inhibitors combinations compared with standard ET: HR 0.76, 95% CI 0.68-0.85, I^2=0.0% **Secondary Outcome**: n.a. **Subgroup analysis** visceral disease (yes vs no) HR 0.73, 95% CI 0.65-0.83, P<0.001, I^2=0.0% bone-only disease (yes vs no) HR 0.74, 95% CI 0.62-0.89, P<0.001, I^2=0.0%	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 4 critical flaws (items 2, 4, 7, 15) (no information about review protocol no comprehensive search strategy no list of excluded studies no adequate investigation of publication bias) **Overall quality of evidence**: critically low **Quality of included studies**:

Source: F, Schettini, Giudici F, Giuliano M, Cristofanilli M, Arpino G, Del Mastro L, Puglisi F, et al. "Overall Survival of Cdk4/6-Inhibitor-Based Treatments in Clinically Relevant Subgroups of Metastatic Breast Cancer: Systematic Review and Meta-Analysis." [In eng]. Journal of the National Cancer Institute 112, no. 11 (2020-11-1 2020): 1089-97. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/32407488/.					
	PALOMA 1 / 3 MONALEESA 2 / 7 / 3 MONARCH 2 **Number of included patients**: 3,421 for OS **Mean/median age**: n.a. **Inclusion criteria**: HR+/HER2-neg metastatic breast cancer; first- or second line	fulvestrant [+ GnRHa in pre/peri pts] (MONARCH 2) tamoxifen or AI + GnRHa (MONALEESA 7)		number of metastatic sites (<3 sites vs ≥3) HR 0.77, 95% CI 0.65-0.91, P<0.002, I^2=0.0% endocrine sensitivity and resistance (yes vs no), HR 0.77, 95% CI 0.68-0.86, P<0.001, I^2=0.0% previous CT for the metastatic setting (yes vs no), HR 0.77, 95% CI 0.62-0.94, P<0.01, I^2=0.0% age (<65 vs ≥65 years) HR 0.77, 95%CI 0.66-0.88, P<0.001, I^2=12.0% menopausal status (pre-perimenopausal vs postmenopausal) HR 0.75, 95% CI 0.67-0.84, P<0.001, I^2=0.0%	Assessed with the Cochrane Collaboration's Risk of Bias tool **Sources of funding:** no funding

Source: F, Schettini, Giudici F, Giuliano M, Cristofanilli M, Arpino G, Del Mastro L, Puglisi F, et al. "Overall Survival of Cdk4/6-Inhibitor-Based Treatments in Clinically Relevant Subgroups of Metastatic Breast Cancer: Systematic Review and Meta-Analysis." [In eng]. Journal of the National Cancer Institute 112, no. 11 (2020-11-1 2020): 1089-97. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/32407488/.

Abbreviations:

MBC = Metastatic Breast Cancer

RCT = Randomised Controlled Trial

OS = Overall Survival

CT = Chemotherapy

n.a. = not Available, not Applicable

HR = Hazard Ratio

95% CI = 95% Confidence Interval

Verknüpfte Empfehlungen:

Empfehlung 5.30:

Bei prä- und perimenopausalen Patientinnen soll bei positivem Hormonrezeptorstatus und negativem HER2-Status eine endokrine Therapie, bevorzugt kombiniert mit einer zielgerichteten Therapie mit einem CDK4/6-Inhibitor angeboten werden.

Empfehlung 5.34:

Bei postmenopausalen Patientinnen soll die endokrin-basierte Therapie mit einem CDK4/6-Inhibitor in Abhängigkeit von der Vortherapie in Kombination mit einem Aromatasehemmer, Fulvestrant oder Tamoxifen (Tamoxifen nicht in Kombination mit Ribociclib) erfolgen.

Empfehlung 5.36:

Sofern in der Erstlinie noch kein CDK4/6-Inhibitor eingesetzt worden war, sollte er in weiteren endokrin-basierten Therapielinien eingesetzt werden.

Empfehlung 5.31:

Bei prämenopausalen Patientinnen soll die endokrin-basierte Therapie mit einem CDK4/6-Inhibitor unter Ausschaltung der Ovarialfunktion und in Abhängigkeit von der Vortherapie in Kombination mit einem Aromatasehemmer, Fulvestrant oder Tamoxifen (Tamoxifen nicht in Kombination mit Ribociclib) erfolgen.

Empfehlung 5.33:

Die Kombinationstherapie eines Aromatasehemmers oder Fulvestrant mit CDK 4/6-Inhibitoren soll als Erstlinientherapie oder spätestens ab der Zweitlinie durchgeführt werden, sofern diese Substanzgruppe noch nicht eingesetzt wurde.

Literaturreferenzen: [244], [245]

Source: J, Li, Huo X, Zhao F, Ren D, Ahmad R, Yuan X, Du F, and Zhao J. "Association of Cyclin-Dependent Kinases 4 and 6 Inhibitors with Survival in Patients with Hormone Receptor-Positive Metastatic Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. JAMA network open 3, no. 10 (2020-10-1 2020): e2020312. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33048129/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
The primary objective was to evaluate the association of CDK4/6 inhibitors plus ET, compared with ET alone, with OS in patients with HR-positive, ERBB2-negative metastatic breast cancers. The secondary objective was to assess the association of PFS, objective response rate (ORR), adverse events (AEs), and grade 3 or grade 4 (grade 3/4) AEs with treatment of CDK4/6 inhibitors plus ET vs ET alone among patients with HR-positive, ERBB2-negative metastatic breast cancer	**Design**: Systematic Review and Meta-analysis **Search date**: up to 30/03/2020 **Searched databases**: PubMed and Embase **Included study designs**: RCTs **Number of included studies**: 9 MONALEESA-2 / -3 / -7 PALOMA-1 / -2 / -3 MONARCH-2 / -3 / -plus **Number of included patients**: 5043 (HR+ metastatic BC) **Inclusion criteria**: (1) phase 2 or 3 randomized clinical trials	**Intervention** CDK4/6 inhibitors plus ET **Control** ET	**Primary Outcome**: Overall Survival (OS) **Secondary Outcome**: Progression-Free Survival (PFS) Objective Response Rate (ORR) Grade 3/4 Adverse Events (AEs)	**Primary Outcome**: **Overall Survival(OS)** HR, 1.33; 95% CI, 1.19-1.48; P < .001 **Secondary Outcome**: **Progression-Free Survival** HR, 1.84; 95% CI, 1.70-1.98; P < .001 **Objective Response Rate** OR, 2.02; 95% CI, 1.61-2.53; P < .001 **Grade 3/4 AEs** The combination of CDK4/6 inhibitors plus ET was associated with increased cases of:	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 6 critical flaws (items 2, 4, 7, 9, 13, 15) **Overall quality of evidence**: **Limitations**: studies included in search were only in English; all data were extracted from published literature, and no individual patient data were used in this study; some studies in this meta-analysis included randomized clinical trials, but the subgroup analysis did not include all of those studies àfor

Source: J, Li, Huo X, Zhao F, Ren D, Ahmad R, Yuan X, Du F, and Zhao J. "Association of Cyclin-Dependent Kinases 4 and 6 Inhibitors with Survival in Patients with Hormone Receptor-Positive Metastatic Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. JAMA network open 3, no. 10 (2020-10-1 2020): e2020312. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33048129/.					
	of HR-positive, ERBB2-negative metastatic breast cancer (2) with patients randomly assigned to receive CDK4/6 inhibitors plus ET or ET alone, (3) having OS or PFS outcomes **Exclusion**: (1) phase 1 trials, (2) retrospective studies, or (3) studies without survival outcomes			**Neutropenia** (HR, 57.05; 95% CI, 38.26-85.05; P < .001), **Leukopenia** (HR, 36.36; 95% CI, 19.35-68.34; P < .001 **Diarrhea** (HR, 4.97; 95% CI, 2.84-8.69; P < .001), **Subgroup analysis** **First- and Second-Line Therapy Subgroups** The combination of CDK4/6 inhibitors plus ET vs ET alone was associated with improved OS for the first-line therapy subgroup (HR, 1.35; 95% CI, 1.18-1.54; P < .001), as well as for the second-line therapy subgroup (HR, 1.30; 95% CI, 1.09-1.54; P = .004)	example, in the age subgroup analysis, some studies used 40 years as the cut point, whereas other studies used 65 years as the cut point **Quality of included studies**: n.a. **Sources of funding:** supported by a grant from the Innovation Team for the Study of Pathogenesis and Anti-tumor Mechanism of Chinese-Tibetan Medicine in the Qinghai area (Talent Highland Program) and grant 2018-ZJ-T02 from the Qinghai province Medical Gene Detection Technology Platform

Source: J, Li, Huo X, Zhao F, Ren D, Ahmad R, Yuan X, Du F, and Zhao J. "Association of Cyclin-Dependent Kinases 4 and 6 Inhibitors with Survival in Patients with Hormone Receptor-Positive Metastatic Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. JAMA network open 3, no. 10 (2020-10-1 2020): e2020312. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33048129/.

				Premenopausal and Postmenopausal Subgroups Treatment with CDK4/6 inhibitors plus ET was associated with improved OS for both the premenopausal subgroup (HR, 1.32; 95% CI, 1.04-1.66; P = .02), and for the postmenopausal subgroup (HR, 1.34; 95% CI, 1.18-1.52; P < .001). **Visceral Metastasis and Bone-Only Metastasis Subgroups** Treatment with CDK4/6 inhibitors plus ET was associated with improved OS for the visceral metastasis subgroup (HR, 1.31; 95% CI, 1.12-1.53; P < .001). Treatment with CDK4/6 inhibitors plus ET was not	

Source: J, Li, Huo X, Zhao F, Ren D, Ahmad R, Yuan X, Du F, and Zhao J. "Association of Cyclin-Dependent Kinases 4 and 6 Inhibitors with Survival in Patients with Hormone Receptor-Positive Metastatic Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. JAMA network open 3, no. 10 (2020-10-1 2020): e2020312. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33048129/.					
				associated with improved OS for the bone-only metastasis subgroup (HR, 1.22; 95% CI, 0.88-1.68; P = .23). **Age Subgroups** Treatment with CDK4/6 inhibitors plus ET was associated with improved OS both for the younger patient subgroup (HR, 1.25; 95% CI, 1.06-1.49; P = .010), and for the older patient subgroup (HR, 1.38; 95% CI, 1.11-1.72; P = .003)	
Abbreviations: ET = Endocrine Therapy OS = Overall Survival PFS = Progression-Free Survival ORR = Objective Response Rate AE = Adverse Event					

Source: J, Li, Huo X, Zhao F, Ren D, Ahmad R, Yuan X, Du F, and Zhao J. "Association of Cyclin-Dependent Kinases 4 and 6 Inhibitors with Survival in Patients with Hormone Receptor-Positive Metastatic Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. JAMA network open 3, no. 10 (2020-10-1 2020): e2020312. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33048129/.

BC = Breast Cancer

RCT = Randomised Controlled Trial

HR = Hazard Ratio

OR = Odds Ratio

95% CI = 95% Confidence Interval

n.a. = not Available, not Applicable

Kapitel 5.2.3: Erstlinientherapie

Verknüpfte Empfehlungen:

Empfehlung 5.34:

Bei postmenopausalen Patientinnen soll die endokrin-basierte Therapie mit einem CDK4/6-Inhibitor in Abhängigkeit von der Vortherapie in Kombination mit einem Aromatasehemmer, Fulvestrant oder Tamoxifen (Tamoxifen nicht in Kombination mit Ribociclib) erfolgen.

Empfehlung 5.36:

Sofern in der Erstlinie noch kein CDK4/6-Inhibitor eingesetzt worden war, sollte er in weiteren endokrin-basierten Therapielinien eingesetzt werden.

Empfehlung 5.33:

Die Kombinationstherapie eines Aromatasehemmers oder Fulvestrant mit CDK 4/6-Inhibitoren soll als Erstlinientherapie oder spätestens ab der Zweitlinie durchgeführt werden, sofern diese Substanzgruppe noch nicht eingesetzt wurde.

Literaturreferenzen: [244], [245], [246], [247]

Source: Q, Tian, Gao H, Zhou Y, and Yang J. "Overall Survival and Progression-Free Survival with Cyclin-Dependent Kinase 4/6 Inhibitors Plus Endocrine Therapy in Breast Cancer: An Updated Meta-Analysis of Randomized Controlled Trials." [In eng]. European review for medical and pharmacological sciences 25, no. 23 (2021-12 2021): 7252-67. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34919224/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: to better define the efficacy and safety of CDK4/6i in HR+, Her2- ABC (advanced breast cancer) patients and aimed to identify a	**Design**: updated meta-analysis **Search date**: 01/2014 to 01/2020	**Intervention** CDK4/6i plus ET **Control** ET alone	**Primary Outcome**: Overall survival (OS) Progression-free survival (PFS)	**Overall survival** HR: 0.76 (95% CI: 0.67–0.84) **Progression-free survival**	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 3

Source: Q, Tian, Gao H, Zhou Y, and Yang J. "Overall Survival and Progression-Free Survival with Cyclin-Dependent Kinase 4/6 Inhibitors Plus Endocrine Therapy in Breast Cancer: An Updated Meta-Analysis of Randomized Controlled Trials." [In eng]. European review for medical and pharmacological sciences 25, no. 23 (2021-12 2021): 7252-67. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34919224/.					
suitable patient population for CDK4/6i therapy through subgroup analysis	**Searched databases**: MEDLINE, EMBASE and the Cochrane Library databases **Included study designs**: RCT phase 2 or 3 **Number of included studies**: 8 RCT (6 RCT for OS and 8 RCT for PFS) PALOMA 1 / 2 / 3 MONALESA 2 / 3 / 7 MONARCH 2 / 3 **Number of included patients**: 4,580 **Inclusion criteria**: 1) phase 2 or 3 RCTs designed to evaluate the efficacy and safety of CDK4/6i plus ET vs. ET alone in HR+, Her2- ABC patients and		Objective response rate (ORR) Adverse events (AEs)	HR 0.55 (95% CI: 0.50–0.59) **Objective response rate** CDK4/6i meaningfully improved the ORR in both the intention-to-treat population (RR=1.47; 95% CI: 1.29–1.67) and patients with measurable disease (RR=1.47; 95% CI: 1.30– 1.67) **Adverse events (AEs)** RR=2.69; (95% CI: 2.43–2.97) **Subgroup analysis** **1) Subgroup analysis of Overall survival as outcome** **Types of drug** The addition of ribociclib (HR=0.72; 95% CI: 0.60-0.84) and abemaciclib (HR=0.76; 95% CI: 0.59-	critical flaws (items 2, 7, 11) **Quality of included studies**: Most studies had low risk of bias in most domains. Two studies had high risk of bias in domain blinding and one studie had high risk of attrition bias. **Sources of funding:** no funding received

Source: Q, Tian, Gao H, Zhou Y, and Yang J. "Overall Survival and Progression-Free Survival with Cyclin-Dependent Kinase 4/6 Inhibitors Plus Endocrine Therapy in Breast Cancer: An Updated Meta-Analysis of Randomized Controlled Trials." [In eng]. European review for medical and pharmacological sciences 25, no. 23 (2021-12 2021): 7252-67. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34919224/.

	2) the hazard ratios (HRs) for the PFS and OS outcomes were reported. **Exclusion**: Non/randomized prospective studies, retrospective studies, single-arm studies, reviews, meta-analyses and case			0.93) to ET resulted in a numerically larger improvement in OS benefits than the addition of palbociclib (HR=0.83; 95% CI: 0.66-1.00). **Combinations** The combination treatment improved OS outcomes in patients with treatment-naïve advanced disease (HR=0.74; 95% CI: 0.61–0.87) and in patients who had received up to one line of prior endocrine therapy for advanced disease (HR=0.77; 95% CI: 0.66–0.88). **Menopausal status** Consistent treatment effects on OS outcomes were observed in both postmenopausal patients (HR=0.75; 95% CI: 0.66–	

Source: Q, Tian, Gao H, Zhou Y, and Yang J. "Overall Survival and Progression-Free Survival with Cyclin-Dependent Kinase 4/6 Inhibitors Plus Endocrine Therapy in Breast Cancer: An Updated Meta-Analysis of Randomized Controlled Trials." [In eng]. European review for medical and pharmacological sciences 25, no. 23 (2021-12 2021): 7252-67. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34919224/.

				0.85) and pre-, perimenopausal patients (HR=0.74; 95% CI: 0.56–0.91). **Metastasis site** A numerically larger effect was observed in patients with visceral disease (HR=0.74; 95% CI: 0.58–0.91) compared to the effect on those with non-visceral disease (HR=0.79; 95% CI: 0.56–1.01) or bone-only disease (HR=0.76; 95% CI: 0.50–1.03). **Endocrine resistance** The subgroup analysis of patients with primary vs. secondary endocrine resistance showed a statistically significant OS benefit in patients with secondary endocrine resistance (HR=0.75; 95%	

Source: Q, Tian, Gao H, Zhou Y, and Yang J. "Overall Survival and Progression-Free Survival with Cyclin-Dependent Kinase 4/6 Inhibitors Plus Endocrine Therapy in Breast Cancer: An Updated Meta-Analysis of Randomized Controlled Trials." [In eng]. European review for medical and pharmacological sciences 25, no. 23 (2021-12 2021): 7252-67. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34919224/.					
				CI: 0.61–0.89) compared to that in patients with primary resistance (HR=0.85; 95% CI: 0.42–1.27). **2) Subgroup analysis of Progression-free survival as outcome** Improvements in PFS outcomes were consistent among all subgroups. **Types of drug** Three CDK4/6 inhibitors, palbociclib (HR=0.53; 95% CI: 0.45–0.60), ribociclib (HR=0.59; 95% CI: 0.50–0.64), and abemaciclib (HR=0.54; 95% CI: 0.46–0.62), showed similar PFS benefits when combined with ET **Treatment line** The PFS advantage was obtained regardless of	

Source: Q, Tian, Gao H, Zhou Y, and Yang J. "Overall Survival and Progression-Free Survival with Cyclin-Dependent Kinase 4/6 Inhibitors Plus Endocrine Therapy in Breast Cancer: An Updated Meta-Analysis of Randomized Controlled Trials." [In eng]. European review for medical and pharmacological sciences 25, no. 23 (2021-12 2021): 7252-67. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34919224/.

				whether the treatments were applied as first-line (HR=0.55; 95% CI: 0.49–0.61) or subsequent-line (HR=0.53; 95% CI: 0.46–0.60) therapies **Race** The addition of CD-K4/6i to ET showed a numerically larger effect in the Asian population (HR=0.42; 95% CI: 0.33-0.52) than in the non-Asian population (HR=0.56; 95% CI: 0.47-0.64) **PR status** PR-negative patients (HR=0.43; 95% CI: 0.33-0.53) obtained a greater PFS benefit from the combination treatment than PR-positive patients (HR=0.57; 95% CI: 0.50-0.64).	

Source: Q, Tian, Gao H, Zhou Y, and Yang J. "Overall Survival and Progression-Free Survival with Cyclin-Dependent Kinase 4/6 Inhibitors Plus Endocrine Therapy in Breast Cancer: An Updated Meta-Analysis of Randomized Controlled Trials." [In eng]. European review for medical and pharmacological sciences 25, no. 23 (2021-12 2021): 7252-67. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34919224/.

				Menopausal status the PFS advantage was significant in postmenopausal patients (HR=0.55; 95% CI: 0.50–0.60) and pre-, perimenopausal patients (HR=0.52; 95% CI: 0.41–0.62) **Metastasis site** Analysis by metastasis site indicated consistent PFS benefits for visceral (HR=0.52; 95% CI: 0.45–0.58), nonvisceral (HR=0.48; 95% CI: 0.40–0.56) and bone-only (HR=0.48; 95% CI: 0.38–0.57) metastases: **Endocrine resistance status** Subgroup analysis by endocrine resistance status indicated consistent PFS	

Source: Q, Tian, Gao H, Zhou Y, and Yang J. "Overall Survival and Progression-Free Survival with Cyclin-Dependent Kinase 4/6 Inhibitors Plus Endocrine Therapy in Breast Cancer: An Updated Meta-Analysis of Randomized Controlled Trials." [In eng]. European review for medical and pharmacological sciences 25, no. 23 (2021-12 2021): 7252-67. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34919224/.

				improvements among patients with both primary (HR=0.48; 95% CI: 0.34–0.63) and secondary (HR=0.49; 95% CI: 0.35–0.63) ET resistance	

Abbreviations:

ET = Endocrine Therapy

PFS = Progression-Free Survival

OS = Overall Survival

ORR = Objective Response Rate

AE = Adverse Events

HR = Hazard Ratio

RR = Risk Ratio

95% CI = 95% Confidence Interval

RCT = Randomised Controlled Trial

Kapitel 5.2.4: Systemische Therapie bei postmenopausalen Patientinnen und positivem Hormonrezeptorstatus und negativem HER2-Status

Kapitel 5.2.4.1: Zweit- und Folgelinientherapie

Verknüpfte Empfehlungen:

Empfehlung 5.38:

Postmenopausale Patientinnen mit HR-positivem / HER2-negativem fortgeschrittenem oder metastasiertem Mammakarzinom und einer aktivierenden ESR1-Mutation nach mindestens einer endokrinen Therapielinien, einschließlich eines CDK 4/6-Inhibitors, sollten mit Elacestrant behandelt werden.

Literaturreferenzen: [248], [237]

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Elacestrant (Mammakarzinom, ER+, HER2-, mit ESR1-Mutation, nach min. 1 Vortherapie)			
Wirkstoff	Elacestrant	**Handelsname**	Orserdu
Pharmazeutischer Unternehmer	Stemline Therapeutics B.V.	**Beschlussdatum**	02.05.2024
Anwendungsgebiet	Mammakarzinom		

Elacestrant (Mammakarzinom, ER+, HER2-, mit ESR1-Mutation, nach min. 1 Vortherapie)			
Wirkstoff	Elacestrant	**Handelsname**	Orserdu

Elacestrant (Mammakarzinom, ER+, HER2-, mit ESR1-Mutation, nach min. 1 Vortherapie)			
Pharmazeutischer Unternehmer	Stemline Therapeutics B.V.	**Beschlussdatum**	02.05.2024
Anwendungsgebiet	Mammakarzinom		

Für die Bewertung des Zusatznutzens von Elacestrant bei Patientinnen ER-positivem, HER2-negativem, lokal fortgeschrittenem oder metastasiertem Brustkrebs mit einer aktivierenden ESR1-Mutation; mit Krankheitsprogression nach mindestens einer endokrinen Therapielinie einschließlich eines CDK4/6-Inhibitors liegen Ergebnisse zur Mortalität, Morbidität, gesundheitsbezogener Lebensqualität und Nebenwirkungen aus der randomisierten, offenen, multizentrischen, kontrollierten Studie EMERALD vor. In der Studie EMERALD wurde Elacestrant gegenüber einer Therapie nach ärztlicher Maßgabe unter Auswahl von Fulvestrant, Anastrozol, Letrozol und Exemestan verglichen. Die Bewertung basiert auf den Datenschnitten vom 08. 07. 2022 bzw. vom 02. 09. 2022. In den Subgruppenanalysen zu dem Merkmal "Anzahl vorheriger endokriner Therapielinien im fortgeschrittenen/metastasierten Stadium" (1 vs. 2) zeigte sich für den Endpunkt Gesamtüberleben ein deutlich unterschiedlicher Effekt in Abhängigkeit von der Anzahl vorheriger Therapielinien. Aufgrund dieser Effektmodifikation wird eine separate Bewertung des Zusatznutzens für Patientinnen mit 1 vorherigen endokrinen Therapielinie und mit 2 vorherigen endokrinen Therapielinien vorgenommen. a1) Postmenopausale Frauen mit 1 vorherigen endokrinen Therapielinie Für Patientinnen mit einer vorherigen endokrinen Therapielinie ergibt sich in der Endpunktkategorie Gesamtüberleben kein statistisch signifikanter Unterschied zwischen den Behandlungsarmen. In der Kategorie Morbidität ergibt sich insgesamt weder ein Vorteil noch ein Nachteil für die Behandlung mit Elacestrant. Im Detail zeigt sich für die Gesamtpopulation ein Nachteil im Endpunkt Appetitverlust (erhoben mittels EORTC QLQ-C30) und für Patientinnen mit 1 vorherigen endokrinen Therapielinie ein Vorteil für den Endpunkt Schlaflosigkeit (erhoben mittels EORTC QLQ-C30). Für die gesundheitsbezogene Lebensqualität ergibt sich weder ein Vorteil noch ein Nachteil für die Behandlung mit Elacestrant. Für die Endpunktkategorie Nebenwirkungen lässt sich für Elacestrant gegenüber einer Therapie nach ärztlicher Maßgabe insgesamt weder ein Vorteil noch ein Nachteil feststellen. Im Detail zeigen sich in der Gesamtpopulation Nachteile bei spezifischen UE. In der Gesamtbetrachtung der Ergebnisse ergeben sich weder Vor- noch Nachteile in allen Endpunktkategorien. Für Patientinnen mit ER-positivem, HER2-negativem, lokal fortgeschrittenem oder metastasiertem Brustkrebs mit einer aktivierenden ESR1-Mutation und 1 vorherigen Therapielinie ist ein Zusatznutzen von Elacestrant gegenüber einer Therapie nach ärztlicher Maßgabe daher nicht belegt. a2) Postmenopausale Frauen mit 2 vorherigen endokrinen Therapielinien Für Patientinnen mit 2 vorherigen endokrinen Therapielinien ergibt sich in der Endpunktkategorie Gesamtüberleben ein statistisch signifikanter Unterschied zum Vorteil von Elacestrant. Das Ausmaß der erzielten Verlängerung im Gesamtüberleben wird als eine deutliche Verbesserung bewertet. In der Kategorie Morbidität ergibt sich insgesamt weder ein Vorteil noch ein Nachteil für die Behandlung mit Elacestrant. Im Detail zeigt sich für die Gesamtpopulation ein Nachteil im Endpunkt Appetitverlust (erhoben mittels EORTC QLQ-C30). Für die gesundheitsbezogene Lebensqualität ergeben sich weder ein Vorteil noch ein Nachteil für die Behandlung mit Elacestrant. Für die Endpunktkategorie Nebenwirkungen lässt sich für Elacestrant gegenüber einer

Therapie nach ärztlicher Maßgabe insgesamt weder ein Vorteil noch ein Nachteil feststellen. Im Detail zeigen sich in der Gesamtpopulation Nachteile bei spezifischen UE. In der Gesamtschau zeigt sich ein Vorteil in der Mortalität. In den weiteren Endpunktkategorien zeigen sich insgesamt weder Vor- noch Nachteile. In der Gesamtbewertung wird ein beträchtlicher Zusatznutzen von Elacestrant gegenüber einer Therapie nach ärztlicher Maßgabe für Patientinnen mit ER-positivem, HER2-negativem, lokal fortgeschrittenem oder metastasiertem Brustkrebs mit einer aktivierenden ESR1-Mutation und 2 vorherigen Therapielinien festgestellt. Aussagesicherheit (Wahrscheinlichkeit des Zusatznutzens) Die vorliegende Bewertung basiert auf den Ergebnissen der offenen randomisierten Phase III Studie EMERALD. Aufgrund des relevanten Unterschieds von nicht in die Auswertung eingehenden Patientinnen zwischen den Behandlungsarmen liegt in Bezug auf die gesamte Studienpopulation ein hohes endpunktübergreifendes Verzerrungspotenzial vor. In der vorliegenden Datensituation zeigt sich für die Subgruppe der Patientinnen mit 2 vorherigen endokrinen Therapielinien jedoch, dass nur eine Patientin nicht in die Auswertung eingeht. Damit liegt für diese Subgruppe für die Ergebnisse zum Endpunkt Gesamtüberleben ein niedriges Verzerrungspotenzial vor. Eine relevante Limitation ergibt sich aufgrund der geringen Patientenzahl in der vorliegenden Subgruppe der Patientinnen mit 2 vorherigen endokrinen Therapielinien. Zusammenfassend leitet der G-BA hinsichtlich der Aussagesicherheit einen Anhaltspunkt für den festgestellten Zusatznutzen ab

Elacestrant (Mammakarzinom, ER+, HER2-, mit ESR1-Mutation, nach min. 1 Vortherapie)			
Wirkstoff	Elacestrant	**Handelsname**	Orserdu
Pharmazeutischer Unternehmer	Stemline Therapeutics B.V.	**Beschlussdatum**	02.05.2024
Anwendungsgebiet	Mammakarzinom		

Elacestrant (Mammakarzinom, ER+, HER2-, mit ESR1-Mutation, nach min. 1 Vortherapie)			
Wirkstoff	Elacestrant	**Handelsname**	Orserdu
Pharmazeutischer Unternehmer	Stemline Therapeutics B.V.	**Beschlussdatum**	02.05.2024
Anwendungsgebiet	Mammakarzinom		

Verknüpfte Empfehlungen:

Empfehlung 5.39:

Patientinnen mit vorbehandeltem HR-positivem / HER2-negativem fortgeschrittenem oder metastasiertem Mammakarzinom mit einer oder mehrerer PIK3CA/AKT1/PTEN-Alteration sollten mit Capivasertib und Fulvestrant behandelt werden.

Literaturreferenzen: [249]

A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)							
Short Name	Design	Population	Intervention	Comparator	Outcomes		
CAPItello 291	Randomized, Parallel, PHASE3 quadruple-blind study	Patients with Stage 3 Locally Advanced (Inoperable) or Metastatic Breast Cancer	1. Capivasertib + fulvestrant (N=426)[1] 2. Capivasertib + Fulvestrant (N=16)[2] 3. Capivasertib + Fulvestrant (N=156)[3] 4. Capivasertib + Fulvestrant (Metaanalyse) (N=195)[4]	1. Placebo + fulvestrant (N=416)[5] 2. Placebo + Fulvestrant (N=28)[6] 3. Placebo + Fulvestrant (N=124)[7] 4. Placebo + Fulvestrant (Metaanalyse) (N=161)[8]	• Primary: Progression-Free Survival (PFS) in the overall population and in the PIK3CA/AKT1/PTEN-altered subgroup		

A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)							
					• Secondary: Overall Survival (OS) in the overall population and in the PIK3CA/AKT1/PTEN-altered subgroup. • Secondary: ocurrence/frequency of AEs and its relationship to study drugs		

A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)							
					(safety and tolerability) in the overall population and in the PIK3CA/AKT1/PTEN-altered subgroup • Secondary: EORTC QLQ BR23(European Organisation for Research and Treatment of Cancer		

A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)							
					Quality of Life Questionnaire breast cancer specific module) in the overall population and in the PIK3CA/AKT1/PTEN-altered subgroup where applicable • Secondary: The EORTC QLQ-C30 (Europea		

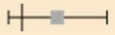
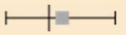
A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)							
					n Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items) in the overall population and in the PIK3CA/AKT1/PTEN-altered subgroup where		

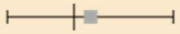
A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)							
					applicable		
Notes - Study Arms							
1: Fulvestrant: 2 intramuscular injections of 500 mg given on day 1 of weeks 1 and 3 of cycle 1, and then on day 1, week 1 of each cycle thereafter. capivasertib: 400 mg (2 oral tablets) bd given on an intermittent weekly dosing schedule. dosed on days 1 to 4 in each week of a 28-day treatment cycle. 2: Teilpopulation im Interventionsarm: Patientinnen mit PIK3CA/AKT1/PTEN-Alteration(en) und mit einer (neo-)adjuvanten endokrinen Vortherapie, die bisher keine Therapie im lokal fortgeschrittenen oder metastasierten Stadium erhalten haben 3: Teilpopulation im Interventionsarm: Patientinnen mit nachgewiesener PIK3CA/AKT1/PTEN-Alteration, die zuvor eine endokrine Therapie im lokal fortgeschrittenen oder metastasierten Stadium erhalten haben 4: Interventionsarm der Metaanalyse von Studie CAPItello 291 und FRAKTION: Patientinnen mit nachgewiesener PIK3CA/AKT1/PTEN-Alteration, die zuvor eine endokrine Therapie im lokal fortgeschrittenen oder metastasierten Stadium erhalten haben 5: Fulvestrant: 2 intramuscular injections of 500 mg given on day 1 of weeks 1 and 3 of cycle 1, and then on day 1, week 1 of each cycle thereafter. placebo: 400 mg (2 oral tablets) bd given on an intermittent weekly dosing schedule. dosed on days 1 to 4 in each week of a 28-day treatment cycle. 6: Teilpopulation im Kontrollarm: Patientinnen mit PIK3CA/AKT1/PTEN-Alteration(en) und mit einer (neo-)adjuvanten endokrinen Vortherapie, die bisher keine Therapie im lokal fortgeschrittenen oder metastasierten Stadium erhalten haben 7: Teilpopulation im Kontrollarm: Patientinnen mit nachgewiesener PIK3CA/AKT1/PTEN-Alteration, die zuvor eine endokrine Therapie im lokal fortgeschrittenen oder metastasierten Stadium erhalten haben 8: Kontrollarm der Metaanalyse von Studie CAPItello 291 und FRAKTION: Patientinnen mit nachgewiesener PIK3CA/AKT1/PTEN-Alteration, die zuvor eine endokrine Therapie im lokal fortgeschrittenen oder metastasierten Stadium erhalten haben							
Outcome	Capivasertib + Fulvestrant N=16	Placebo + Fulvestrant N=28	Effect Estimate		GRADE		

A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)							
a1) Capivasertib + Fulvestrant versus Placebo + Fulvestrant zur Behandlung von Frauen mit ER-positivem, HER2-negativem, lokal fortgeschrittenem oder metastasiertem Mammakarzinom mit PIK3CA/AKT1/PTEN-Alteration(en), nach Wiederauftreten der Erkrankung während oder nach einer (neo-)adjuvanten endokrinen Therapie, bisher keine Behandlung im lokal fortgeschrittenen oder metastasierten Stadium: Studie CAPItello 291							
Dichotomous Outcomes							
Overall Survival, Time To Event[1,2,3]	N=16	[;] 3 (18.8%)	N=28	[;] 3 (10.7%)	HR 1.09 [0.19; 6.1] p=0.921		⊕⊕⊖⊖[a]
Progression-Free Survival, Time To Event[2,4,5,6]	N=16	11.5 [6.3;] 11 (68.8%)	N=28	3.7 [1.8; 7.4] 24 (85.7%)	HR 0.36 [0.16; 0.77] p=0.0078		⊕⊕⊖⊖[a]
EORTC QLQ-BR23 (SA) - TTC[2,7,8]	N=14	4.7 [1;] 9 (64.3%)	N=24	2.7 [1; 16.5] 14 (58.3%)	HR 1.41 [0.55; 3.56] p=0.452		⊕⊖⊖⊖[a,b,c]

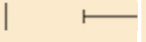
A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)							
EORTC QLQ-BR23 (SCA) - TTC[2,7,8]	N=14	12.9 [1.9;] 7 (50.0%)	N=24	[;] 7 (29.2%)	HR 1.39 [0.43; 4.52] p=0.573		⊕⊖⊖⊖[a,b,c]
EORTC QLQ-BR23 (SEST) - TTC[2,7,8]	N=14	2.8 [1.1; 16.6] 10 (71.4%)	N=24	10.2 [3.7;] 10 (41.7%)	HR 2.33 [0.85; 6.61] p=0.092		⊕⊖⊖⊖[a,b,c]
EORTC QLQ-C30 (Constipation) - TTC[2,7,8,9]	N=14	16.6 [7.4;] 6 (42.9%)	N=24	12.9 [3.6;] 6 (25.0%)	HR 1.18 [0.33; 3.97] p=0.789		⊕⊖⊖⊖[a,b,c]
EORTC QLQ-C30 (Diarrhea) - TTC[2,7,8,9,10]	N=14	2.7 [1; 3.7] 12 (85.7%)	N=24	12.8 [3.7;] 8 (33.3%)	HR 4.05 [1.54; 11.48] p=0,004		⊕⊖⊖⊖[a,b,c]

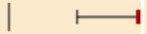
A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)							
EORTC QLQ-C30 (Dyspnea) - TTC[2,7,8,9]	N=14	9.2 [1; 14.1] 10 (71.4%)	N=24	3.6 [1;] 12 (50.0%)	HR 0.97 [0.39; 2.31] p=0.959		⊕⊖⊖⊖[a,b,c]
EORTC QLQ-C30 (Fatigue) - TTC[2,7,8,9]	N=14	1.5 [0.9; 11.9] 11 (78.6%)	N=24	2.8 [1;] 14 (58.3%)	HR 1.33 [0.56; 3.07] p=0.484		⊕⊖⊖⊖[a,b,c]
EORTC QLQ-C30 (Insomnia) - TTC[2,7,8,9]	N=14	6.9 [1; 16.6] 10 (71.4%)	N=24	6.5 [1.9;] 11 (45.8%)	HR 1.05 [0.42; 2.57] p=0.901		⊕⊖⊖⊖[a,b,c]
EORTC QLQ-C30 (Lack of Appetite) - TTC[2,7,8,9]	N=14	2.3 [1; 15.6] 12 (85.7%)	N=24	8.3 [2.8;] 10 (41.7%)	HR 2.05 [0.83; 5.07] p=0.134		⊕⊖⊖⊖[a,b,c]

A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)							
EORTC QLQ-C30 (Nausea) - TTC[2,7,8,9]	N=14	6.0 [1.1; 14.7] 11 (78.6%)	N=24	[;] 9 (37.5%)	HR 1.87 [0.71; 5.2] p=0.22		⊕⊖⊖⊖[a,b,c]
EORTC QLQ-C30 (Pain) - TTC[2,7,8,9]	N=14	3.3 [1; 7.4] 13 (92.9%)	N=24	6.0 [1;] 12 (50.0%)	HR 1.86 [0.79; 4.45] p=0.14		⊕⊖⊖⊖[a,b,c]
EQ-5D (VAS) - TTC[2,11,12]	N=14	7.5 [1.8;] 8 (57.1%)	N=24	10.2 [1.9;] 11 (45.8%)	HR 1.42 [0.51; 3.77] p=0.507		⊕⊖⊖⊖[a,b,c]
EORTC QLQ-BR23 (Body Image) - TTC[2,7,8]	N=14	4.6 [1.9;] 8 (57.1%)	N=24	2.8 [1.8;] 13 (54.2%)	HR 1.26 [0.47; 3.2] p=0.63		⊕⊖⊖⊖[a,b,c]

A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)							
EORTC QLQ-BR23 (Future Perspective) - TTC[2,7,8]	N=14	[;] 5 (35.7%)	N=24	6.5 [1.8;] 12 (50.0%)	HR 0.65 [0.2; 1.82] p=0.447		⊕⊖⊖⊖[a,b,c]
EORTC QLQ-BR23 (Sexual Activity) - TTC[2,8,13]	N=14	[;] 4 (28.6%)	N=24	[;] 4 (16.7%)	HR 1.34 [0.31; 5.72] p=0.684		⊕⊖⊖⊖[a,b,c]
EORTC QLQ-C30 (Cognitive Function) - TTD[2,7,8,9]	N=14	6.5 [1.1; 16.5] 10 (71.4%)	N=24	2.7 [1.8;] 15 (62.5%)	HR 0.78 [0.32; 1.83] p=0.573		⊕⊖⊖⊖[a,b,c]
EORTC QLQ-C30 (Emotional Function) - TTD[2,7,8,9]	N=14	12.0 [6.4;] 6 (42.9%)	N=24	[;] 8 (33.3%)	HR 0.98 [0.32; 2.88] p=0.974		⊕⊖⊖⊖[a,b,c]

A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)							
EORTC QLQ-C30 (Global Health Status) - TTC[2,7,8,9]	N=14	1.5 [1;] 10 (71.4%)	N=24	3.6 [1.9; 7.4] 16 (66.7%)	HR 1.5 [0.62; 3.47] p=0.384		⊕⊖⊖⊖[a,b,c]
EORTC QLQ-C30 (Physical Function) - TTD[2,7,8,9]	N=14	4.6 [3.7;] 9 (64.3%)	N=24	6.4 [2.8;] 12 (50.0%)	HR 0.83 [0.32; 2.05] p=0.632		⊕⊖⊖⊖[a,b,c]
EORTC QLQ-C30 (Role Function) - TTD[2,7,8,9]	N=14	7.3 [1.1; 11.1] 10 (71.4%)	N=24	2.8 [1.8; 6.5] 15 (62.5%)	HR 0.8 [0.34; 1.83] p=0.63		⊕⊕⊖⊖[a,b,c]
EORTC QLQ-C30 (Social Function) - TTD[2,7,8,9]	N=14	[;] 6 (42.9%)	N=24	1.9 [1; 7.9] 15 (62.5%)	HR 0.5 [0.17; 1.3] p=0.177		⊕⊖⊖⊖[a,b,c]

A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)							
Adverse Events - TTE[2,14,15,16,17]	N=16	0.1 [0; 0.3] 16 (100.0%)	N=28	0.5 [0.5; 1.8] 22 (78.6%)	[;]		⊕⊕⊖⊖[a]
Severe Adverse Events (Total) - TTE[2,15,17]	N=16	[;] 7 (43.8%)	N=28	17.5 [14;] 2 (7.1%)	HR 3.46 [0.85; 14.03] p=0.083		⊕⊖⊖⊖[a,b]
Serious Adverse Events - TTE[2,15,17,18]	N=16	[;] 3 (18.8%)	N=28	16.0 [16;] 2 (7.1%)	HR 1.96 [0.31; 12.26] p=0.474		⊕⊖⊖⊖[a,b]
Adverse Events: Ausschlag makulo papulös - TTE[2,17,19]	N=16	[;] 6 (37.5%)	N=28	[;] 0 (0.0%)	HR 21.64 [3.92; 119.57] p< 0.001		⊕⊖⊖⊖[a,b]

A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)							
Adverse Events: Diarrhö - TTE[2,15,17]	N=16	1.1 [0.1; 9.2] 11 (68.8%)	N=28	[;] 3 (10.7%)	HR 10.47 [3.31; 33.1] p< 0.001		⊕⊖⊖⊖[a,b]
Adverse Events: Stomatitis - TTE[2,17,19]	N=16	[;] 4 (25.0%)	N=28	[;] 0 (0.0%)	HR 13.39 [1.76; 101.87] p=0.012		⊕⊖⊖⊖[a,b]
Adverse Events: Erkrankungen des Gastrointestinaltrakts (CTCAE ≥3) - TTE[2,17,19]	N=16	[;] 3 (18.8%)	N=28	[;] 0 (0.0%)	HR 17.25 [1.61; 184.64] p=0.019		⊕⊖⊖⊖[a,b]
Continuous Outcomes							

1: Medianes Gesamtüberleben nicht erreicht 2: Gemeinsame Auswertung der beiden Kohorten der Studie CAPItello-291 (globale Kohorte: Datenschnitt 15.08.2022, Erweiterungskohorte: Datenschnitt 08.05.2023) 3: Todesfälle 4: Medianes progressionsfreies Überleben (Monate) 5: AD = 7.8 Monate 6: Anteil der Personen mit PFS-

A phase iii double-blind randomised study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant as treatment for locally advanced (inoperable) or metastatic hormone receptor positive, human epidermal growth factor receptor 2 negative (hr+/her2-) breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor (Nct04305496)		
Ereignis 7: Mediane Zeit bis zur 1. Verschlechterung um ≥ 10 Punkte (Monate) 8: Anteil der Personen mit Verschlechterung um ≥ 10 Punkte 9: Score range 0-100 10: AD = 10.1 Monate 11: Mediane Zeit bis zur 1. Verschlechterung um ≥ 15 Punkte (Monate) 12: Anteil der Personen mit Verschlechterung um ≥ 15 Punkte 13: Mediane Zeit bis zur Verschlechterung um ≥ 10 Punkte nicht erreicht 14: UE jeglichen Schweregrades - Gesamt 15: Mediane Zeit bis zum ersten Ereignis (Monate) 16: Angaben zum HR nicht verfügbar 17: Ereignisrate 18: Schwerwiegende UE - Gesamt 19: Mediane Zeit bis zum Ereignis nicht erreicht		
a: Sehr geringe Stichprobengröße b: Unvollständige Beobachtungen aus potenziell informativen Gründen bei unterschiedlich langen Bachbeobachtungszeiten c: Hoher Anteil an Patientinnen (> 10 %), die nicht in der Auswertung berücksichtigt wurden		
AE: Adverse Events; **CTCAE ≥3**: Common Terminology Criteria for Adverse Events, Grade ≥3; **EQ-5D**: European Quality of Life 5 Dimensions; **OS**: Overall Survival; **PFS**: Progression-Free Survival; **SA**: Symptoms in the arm area; **SAE**: Serious Adverse Events; **SCA**: Symptoms in the chest area; **SEST**: Side effects of systemic therapy; **TTC**: Time To Change ; **TTD**: Time to Deterioration ; **TTE**: Time To Event ; **VAS**: Visual Analogue Scale		
Quellen: G-BA 2025. Nutzenbewertungsverfahren zum Wirkstoff Capivasertib (Mammakarzinom, ER+, HER2-, PIK3CA/AKT1/PTEN-Alteration(en), nach Vortherapie, Kombination mit Fulvestrant) - Gemeinsamer Bundesausschuss. G-BA 2025. Nutzenbewertungsverfahren zum Wirkstoff Capivasertib (Mammakarzinom, ER+, HER2-, PIK3CA/AKT1/PTEN-Alteration(en), nach Vortherapie, Kombination mit Fulvestrant) - Gemeinsamer Bundesausschuss.		

Verknüpfte Empfehlungen:

Empfehlung 5.39:

Patientinnen mit vorbehandeltem HR-positivem / HER2-negativem fortgeschrittenem oder metastasiertem Mammakarzinom mit einer oder mehrerer PIK3CA/AKT1/PTEN-Alteration sollten mit Capivasertib und Fulvestrant behandelt werden.

Literaturreferenzen: [249]

Outcome	Capivasertib + Fulvestrant (Metaanalyse) N=195		Placebo + Fulvestrant (Metaanalyse) N=161		Effect Estimate		GRADE
b1) Capivasertib + Fulvestrant versus Placebo + Fulvestrant zur Behandlung von Frauen mit ER-positivem, HER2-negativem, lokal fortgeschrittenem oder metastasiertem Mammakarzinom mit PIK3CA/AKT1/PTEN-Alteration(en), mit einer Progression der Erkrankung während oder nach einer endokrinen Therapie, welche im lokal fortgeschrittenen oder metastasierten Stadium erfolgte: Metaanalyse (CAPItello 291 + FAKTION)							
Dichotomous Outcomes							
Overall Survival, Time To Event[1]	N=195	[;]	N=161	[;]	HR 0.57 [0.41; 0.79]		⊕⊕⊕⊕
Progression-Free Survival, Time To Event[1]	N=195	[;]	N=161	[;]	HR 0.5 [0.4; 0.64]		⊕⊕⊕⊕
Continuous Outcomes							

Outcome	Capivasertib + Fulvestrant (Metaanalyse) N=195	Placebo + Fulvestrant (Metaanalyse) N=161	Effect Estimate		GRADE
1: p-Wert: keine Angabe.					
OS: Overall Survival; **PFS**: Progression-Free Survival					
Quelle: G-BA 2025. Nutzenbewertungsverfahren zum Wirkstoff Capivasertib (Mammakarzinom, ER+, HER2-, PIK3CA/AKT1/PTEN-Alteration(en), nach Vortherapie, Kombination mit Fulvestrant) - Gemeinsamer Bundesausschuss.					

Outcome	Capivasertib + Fulvestrant (Metaanalyse) N=195	Placebo + Fulvestrant (Metaanalyse) N=161	Effect Estimate		GRADE
b1) Capivasertib + Fulvestrant versus Placebo + Fulvestrant zur Behandlung von Frauen mit ER-positivem, HER2-negativem, lokal fortgeschrittenem oder metastasiertem Mammakarzinom mit PIK3CA/AKT1/PTEN-Alteration(en), mit einer Progression der Erkrankung während oder nach einer endokrinen Therapie, welche im lokal fortgeschrittenen oder metastasierten Stadium erfolgte: Metaanalyse (CAPItello 291 + FAKTION)					
Dichotomous Outcomes					

Outcome	Capivasertib + Fulvestrant (Metaanalyse) N=195		Placebo + Fulvestrant (Metaanalyse) N=161		Effect Estimate		GRADE
Overall Survival, Time To Event[1]	N=195	[;]	N=161	[;]	HR 0.57 [0.41; 0.79]		⊕⊕⊕⊕
Progression-Free Survival, Time To Event[1]	N=195	[;]	N=161	[;]	HR 0.5 [0.4; 0.64]		⊕⊕⊕⊕
Continuous Outcomes							
1: p-Wert: keine Angabe.							
OS: Overall Survival; **PFS**: Progression-Free Survival							
Quelle: G-BA 2025. Nutzenbewertungsverfahren zum Wirkstoff Capivasertib (Mammakarzinom, ER+, HER2-, PIK3CA/AKT1/PTEN-Alteration(en), nach Vortherapie, Kombination mit Fulvestrant) - Gemeinsamer Bundesausschuss.							

Outcome	Capivasertib + Fulvestrant (Metaanalyse) N=195		Placebo + Fulvestrant (Metaanalyse) N=161		Effect Estimate		GRADE
b1) Capivasertib + Fulvestrant versus Placebo + Fulvestrant zur Behandlung von Frauen mit ER-positivem, HER2-negativem, lokal fortgeschrittenem oder metastasiertem Mammakarzinom mit PIK3CA/AKT1/PTEN-Alteration(en), mit einer Progression der Erkrankung während oder nach einer endokrinen Therapie, welche im lokal fortgeschrittenen oder metastasierten Stadium erfolgte: Metaanalyse (CAPItello 291 + FAKTION)							
Dichotomous Outcomes							
Overall Survival, Time To Event[1]	N=195	[;]	N=161	[;]	HR 0.57 [0.41; 0.79]		⊕⊕⊕⊕
Progression-Free Survival, Time To Event[1]	N=195	[;]	N=161	[;]	HR 0.5 [0.4; 0.64]		⊕⊕⊕⊕
Continuous Outcomes							
1: p-Wert: keine Angabe.							

Outcome	Capivasertib + Fulvestrant (Metaanalyse) N=195		Placebo + Fulvestrant (Metaanalyse) N=161		Effect Estimate		GRADE
OS: Overall Survival; **PFS**: Progression-Free Survival							
Quelle: G-BA 2025. Nutzenbewertungsverfahren zum Wirkstoff Capivasertib (Mammakarzinom, ER+, HER2-, PIK3CA/AKT1/PTEN-Alteration(en), nach Vortherapie, Kombination mit Fulvestrant) - Gemeinsamer Bundesausschuss.							

Kapitel 5.2.5: Therapie des HR+ HER2- metastasierten Mammakarzinoms mit Antikörper-Wirkstoff-Konjugaten (ADC)

Verknüpfte Empfehlungen:

Empfehlung 5.42:

Patientinnen mit HR-positivem / HER2-low fortgeschrittenem oder metastasiertem Mammakarzinom, die eine Chemotherapie in der metastasierten Situation erhalten haben oder bei denen während oder innerhalb von 6 Monaten nach Beendigung der adjuvanten Chemotherapie ein Rezidiv aufgetreten ist sollten mit Trastuzumab Deruxtecan behandelt werden.

Literaturreferenzen: [250], [237]

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Trastuzumab deruxtecan (Neues Anwendungsgebiet: Mammakarzinom, HER2-low, vorbehandelt)			
Wirkstoff	Trastuzumab deruxtecan	**Handelsname**	Enhertu
Pharmazeutischer Unternehmer	Daiichi Sankyo Deutschland GmbH	**Beschlussdatum**	20.07.2023
Anwendungsgebiet	Mammakarzinom		

Trastuzumab deruxtecan (Neues Anwendungsgebiet: Mammakarzinom, HER2-low, vorbehandelt)			
Wirkstoff	Trastuzumab deruxtecan	**Handelsname**	Enhertu
Pharmazeutischer Unternehmer	Daiichi Sankyo Deutschland GmbH	**Beschlussdatum**	20.07.2023

Trastuzumab deruxtecan (Neues Anwendungsgebiet: Mammakarzinom, HER2-low, vorbehandelt)	
Anwendungsgebiet	Mammakarzinom

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung eines neuen Anwendungsgebietes für den Wirkstoff Trastuzumab-Deruxtecan:
„Enhertu wird angewendet als Monotherapie zur Behandlung von erwachsenen Patienten mit inoperablem oder metastasiertem HER2-low-Brustkrebs, die bereits eine Chemotherapie in der metastasierten Situation erhalten haben oder bei denen während oder innerhalb von 6 Monaten nach Beendigung der adjuvanten Chemotherapie ein Rezidiv aufgetreten ist.“
Enhertu wurde unter besonderen Bedingungen zugelassen.
Als zweckmäßige Vergleichstherapie wurde vom G-BA Capecitabin oder Eribulin oder Vinorelbin oder eine Anthrazyklin- oder Taxan-haltige Therapie (nur für Patientinnen und Patienten, die noch keine Anthrazyklin- und/oder Taxan-haltige Therapie erhalten haben oder die für eine erneute Anthrazyklin- oder Taxan-haltige Behandlung infrage kommen.) bestimmt.
Für die Bewertung liegt die offene RCT DESTINY-Breast04 vor, in welcher Trastuzumab-Deruxtecan mit einer Therapie nach ärztlicher Maßgabe unter Auswahl von Capecitabin, Eribulin, Gemcitabin, Paclitaxel oder Nab-Paclitaxel vergleichen wird.
Die Bewertung basiert auf Auswertungen zu einer Teilpopulation, die vor der Randomisierung einer Behandlung mit Capecitabin, Eribulin, Paclitaxel oder Nab-Paclitaxel zugeordnet wurde.
Für den Endpunkt Gesamtüberleben zeigt sich eine statistisch signifikante Verlängerung der Überlebenszeit durch Trastuzumab-Deruxtecan, die als eine deutliche Verbesserung bewertet wird.
Hinsichtlich der Symptomatik wird in der Gesamtschau der Ergebnisse kein überwiegender Vor- oder Nachteil von Trastuzumab-Deruxtecan festgestellt.
Hinsichtlich des Gesundheitszustands zeigen sich weder positive noch negative Effekte.
In Bezug auf die Lebensqualität liegen Vorteile für Trastuzumab-Deruxtecan vor.
Bei den Nebenwirkungen zeigen sich Vorteile von Trastuzumab-Deruxtecan bei den schwerwiegenden UE und schweren UE. Im Detail zeigen sich bei den spezifischen UE sowohl Vor- als auch Nachteile.
Insgesamt ist die Datengrundlage insbesondere angesichts der fehlenden Verblindung mit Unsicherheiten behaftet. Diese werden jedoch nicht als derart hoch beurteilt, als dass eine Herabstufung der Aussagesicherheit für die Gesamtbewertung gerechtfertigt wäre.
Im Ergebnis stellt der G-BA insbesondere aufgrund der deutlichen positiven Effekte auf die Verlängerung der Überlebensdauer und in Anbetracht der Vorteile hinsichtlich der Lebensqualität und der Nebenwirkungen für Trastuzumab-Deruxtecan einen Hinweis auf einen beträchtlichen Zusatznutzen gegenüber Capecitabin, Eribulin, Paclitaxel oder Nab-Paclitaxel fest.

Trastuzumab deruxtecan (Neues Anwendungsgebiet: Mammakarzinom, HER2-low, vorbehandelt)			
Wirkstoff	Trastuzumab deruxtecan	**Handelsname**	Enhertu
Pharmazeutischer Unternehmer	Daiichi Sankyo Deutschland GmbH	**Beschlussdatum**	20.07.2023
Anwendungsgebiet	Mammakarzinom		

Trastuzumab deruxtecan (Neues Anwendungsgebiet: Mammakarzinom, HER2-low, vorbehandelt)			
Wirkstoff	Trastuzumab deruxtecan	**Handelsname**	Enhertu
Pharmazeutischer Unternehmer	Daiichi Sankyo Deutschland GmbH	**Beschlussdatum**	20.07.2023
Anwendungsgebiet	Mammakarzinom		

Verknüpfte Empfehlungen:

Empfehlung 5.44:

Patientinnen mit HR-positivem / HER2-negativem fortgeschrittenem oder metastasiertem Mammakarzinom nach Vorbehandlung mit endokrin-basierter Therapie und mindestens 2 zusätzlichen systemischen Therapien bei fortgeschrittener Erkrankung sollten mit Sacituzumab Govitecan behandelt werden.

Literaturreferenzen: [251], [235], [237]

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Sacituzumab govitecan (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, mind. 3 Vortherapien)			
Wirkstoff	Sacituzumab govitecan	**Handelsname**	Trodelvy
Pharmazeutischer Unternehmer	Gilead Sciences GmbH	**Beschlussdatum**	15.02.2024
Anwendungsgebiet	Mammakarzinom		

Sacituzumab govitecan (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, mind. 3 Vortherapien)			
Wirkstoff	Sacituzumab govitecan	**Handelsname**	Trodelvy
Pharmazeutischer Unternehmer	Gilead Sciences GmbH	**Beschlussdatum**	15.02.2024
Anwendungsgebiet	Mammakarzinom		

Sacituzumab govitecan (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, mind. 3 Vortherapien)			
Wirkstoff	Sacituzumab govitecan	**Handelsname**	Trodelvy
Pharmazeutischer Unternehmer	Gilead Sciences GmbH	**Beschlussdatum**	15.02.2024
Anwendungsgebiet	Mammakarzinom		

Sacituzumab govitecan (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, mind. 3 Vortherapien)			
Wirkstoff	Sacituzumab govitecan	**Handelsname**	Trodelvy
Pharmazeutischer Unternehmer	Gilead Sciences GmbH	**Beschlussdatum**	15.02.2024
Anwendungsgebiet	Mammakarzinom		

Sacituzumab govitecan (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, mind. 3 Vortherapien)			
Wirkstoff	Sacituzumab govitecan	**Handelsname**	Trodelvy
Pharmazeutischer Unternehmer	Gilead Sciences GmbH	**Beschlussdatum**	15.02.2024
Anwendungsgebiet	Mammakarzinom		

Sacituzumab govitecan (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, mind. 3 Vortherapien)			
Wirkstoff	Sacituzumab govitecan	**Handelsname**	Trodelvy
Pharmazeutischer Unternehmer	Gilead Sciences GmbH	**Beschlussdatum**	15.02.2024
Anwendungsgebiet	Mammakarzinom		

Sacituzumab govitecan (Neues Anwendungsgebiet: Mammakarzinom, HR+, HER2-, mind. 3 Vortherapien)			
Wirkstoff	Sacituzumab govitecan	**Handelsname**	Trodelvy
Pharmazeutischer Unternehmer	Gilead Sciences GmbH	**Beschlussdatum**	15.02.2024
Anwendungsgebiet	Mammakarzinom		

Kapitel 5.2.6: HER2-negatives Mammakarzinom im fortgeschrittenen oder metastasierten Stadium bei Vorliegen einer Keimbahn- BRCA1/2-Mutation

Verknüpfte Empfehlungen:

Empfehlung 5.46:

HER2-negative Patientinnen mit fortgeschrittenem oder metastasiertem Mammakarzinom mit *BRCA1/2*-Keimbahn-Mutation und Vorbehandlung mit einem Anthrazyklin und einem Taxan im (neo)adjuvanten oder metastasierten Setting, es sei denn, sie waren ungeeignet für diese Behandlungen, sollten mit Olaparib oder mit Talazoparib behandelt werden.

Literaturreferenzen: [235], [252], [253], [254], [255], [256], [237]

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Talazoparib (Mammakarzinom, BRCA1/2-Mutation, HER2-)			
Wirkstoff	Talazoparib	**Handelsname**	Talzenna
Pharmazeutischer Unternehmer	Pfizer Pharma GmbH	**Beschlussdatum**	20.11.2020
Anwendungsgebiet	Mammakarzinom		

Talazoparib (Mammakarzinom, BRCA1/2-Mutation, HER2-)			
Wirkstoff	Talazoparib	**Handelsname**	Talzenna
Pharmazeutischer Unternehmer	Pfizer Pharma GmbH	**Beschlussdatum**	20.11.2020

Talazoparib (Mammakarzinom, BRCA1/2-Mutation, HER2-)	
Anwendungsgebiet	Mammakarzinom

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung des neuen Arzneimittels Talzenna mit dem Wirkstoff Talazoparib. Talzenna wird als Monotherapie für die Behandlung von erwachsenen Patienten mit BRCA1/2-Mutationen in der Keimbahn angewendet, die ein HER2-negatives, lokal fortgeschrittenes oder metastasiertes Mammakarzinom aufweisen. Die Patienten sollten zuvor mit einem Anthrazyklin und/oder einem Taxan im (neo)adjuvanten, lokal fortgeschrittenen oder metastasierten Setting behandelt worden sein, es sei denn, sie waren für diese Behandlungen nicht geeignet. Patienten mit Hormonrezeptor (HR)-positivem Brustkrebs sollten außerdem bereits eine endokrin-basierte Therapie erhalten haben oder für diese als nicht geeignet eingestuft sein.
Die zweckmäßige Vergleichstherapie wurde wie folgt vom G-BA bestimmt:

- Capecitabin *oder*
- Eribulin *oder*
- Vinorelbin *oder*
- eine Anthrazyklin- oder Taxan-haltige Therapie (Nur für Patienten, die noch keine Anthrazyklin- und Taxan-haltige Therapie erhalten haben oder für die eine erneute Anthrazyklin- oder Taxan-haltige Therapie infrage kommt.)

Für die Bewertung des Zusatznutzens von Talazoparib liegen aus der offenen, randomisierten, kontrollierten Studie EMBRACA Ergebnisse im Vergleich zu Capecitabin, Vinorelbin oder Eribulin zur Mortalität (Gesamtüberleben), Morbidität, Lebensqualität und zu Nebenwirkungen vor.
In der Endpunktkategorie Mortalität zeigte sich für den Endpunkt Gesamtüberleben kein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen.
Die Ergebnisse zur Morbidität (Symptomatik) und gesundheitsbezogenen Lebensqualität zeigen positive Effekte durch eine Behandlung mit Talazoparib, die insgesamt als eine deutliche Verbesserung bewertet werden.
Bei den Nebenwirkungen ist hinsichtlich der schweren unerwünschten Ereignisse (CTCAE-Grad 3 oder 4) ein Vorteil von Talazoparib festzustellen. Kein Unterschied zeigten sich für die schwerwiegenden UE und Abbruch wegen UE. Bei den spezifischen UE überwiegen die positiven Effekte von Talazoparib. In der Kategorie Nebenwirkungen wird insgesamt ein Vorteil von Talazoparib abgeleitet.
Aufgrund des offenen Studiendesigns und des hohen Anteils der zurückgezogenen Einwilligungserklärungen im Chemotherapiearm ist in der Kategorie Morbidität, Lebensqualität und Nebenwirkungen überwiegend von einem hohen Verzerrungspotenzial auszugehen. Bezüglich der Aussagesicherheit kann daher nur ein Anhaltspunkt für einen Zusatznutzen abgeleitet werden.

In der Gesamtbetrachtung wird ein Anhaltspunkt für einen beträchtlichen Zusatznutzen für Talazoparib gegenüber Capecitabin, Vinorelbin oder Eribulin festgestellt.

Talazoparib (Mammakarzinom, BRCA1/2-Mutation, HER2-)			
Wirkstoff	Talazoparib	**Handelsname**	Talzenna
Pharmazeutischer Unternehmer	Pfizer Pharma GmbH	**Beschlussdatum**	20.11.2020
Anwendungsgebiet	Mammakarzinom		

Talazoparib (Mammakarzinom, BRCA1/2-Mutation, HER2-)			
Wirkstoff	Talazoparib	**Handelsname**	Talzenna
Pharmazeutischer Unternehmer	Pfizer Pharma GmbH	**Beschlussdatum**	20.11.2020
Anwendungsgebiet	Mammakarzinom		

Verknüpfte Empfehlungen:

Empfehlung 5.46:

HER2-negative Patientinnen mit fortgeschrittenem oder metastasiertem Mammakarzinom mit *BRCA1/2*-Keimbahn-Mutation und Vorbehandlung mit einem Anthrazyklin und einem Taxan im (neo)adjuvanten oder metastasierten Setting, es sei denn, sie waren ungeeignet für diese Behandlungen, sollten mit Olaparib oder mit Talazoparib behandelt werden.

Literaturreferenzen: [235], [252], [253], [254], [255], [256], [237]

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Olaparib (neues Anwendungsgebiet: Mammakarzinom, BRCA1/2-Mutationen, HER2-)			
Wirkstoff	Olaparib	**Handelsname**	Lynparza
Pharmazeutischer Unternehmer	AstraZeneca GmbH	**Beschlussdatum**	16.01.2020
Anwendungsgebiet	Mammakarzinom		

Olaparib (neues Anwendungsgebiet: Mammakarzinom, BRCA1/2-Mutationen, HER2-)			
Wirkstoff	Olaparib	**Handelsname**	Lynparza
Pharmazeutischer Unternehmer	AstraZeneca GmbH	**Beschlussdatum**	16.01.2020
Anwendungsgebiet	Mammakarzinom		

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung eines neuen Anwendungsgebietes für den Wirkstoff Olaparib. Das hier bewertete Anwendungsgebiet lautet: „Lynparza wird als Monotherapie für die Behandlung von erwachsenen Patienten mit BRCA1/2-Mutationen in der Keimbahn angewendet, die ein HER2-negatives, lokal fortgeschrittenes oder metastasiertes Mammakarzinom haben. Die Patienten sollten zuvor mit einem Anthrazyklin und einem Taxan im (neo)adjuvanten oder metastasierten Setting behandelt worden sein, es sei denn, die Patienten waren für diese Behandlungen nicht geeignet. Patienten mit Hormonrezeptor (HR)-positivem Mammakarzinom sollten außerdem eine Krankheitsprogression während oder nach einer vorherigen endokrinen Therapie aufweisen oder für eine endokrine Therapie nicht geeignet sein."
Die zweckmäßige Vergleichstherapie wurde wie folgt vom G-BA bestimmt:
Capecitabin oder Vinorelbin oder Eribulin oder ggf. eine Anthrazyklin- oder Taxan-haltige Therapie
Der pharmazeutische Unternehmer legt die Ergebnisse aus der offenen, randomisierten, kontrollierten Studie OlympiAD vor, in der Olaparib mit einer Chemotherapie nach Wahl des Arztes unter Verwendung von Capecitabin oder Vinorelbin oder Eribulin verglichen wird. In OlympiAD wurden Patienten mit HER2-negativem, metastasierten Brustkrebs mit BRCA1/2-Mutation in der Keimbahn eingeschlossen, die außer bei Vorliegen einer Kontraindikation in der (neo-)adjuvanten oder metastasierten Situation mit einem Anthrazyklin und Taxan vorbehandelt worden waren.
In der Endpunktkategorie Mortalität zeigte sich für den Endpunkt Gesamtüberleben kein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen.
Für die Endpunkte der Kategorien Morbidität (Symptomatik) und gesundheitsbezogene Lebensqualität lagen keine verwertbaren Daten vor.
Bei den Nebenwirkungen waren hinsichtlich der Endpunkte schwere unerwünschte Ereignisse (CTCAE-Grad 3 oder 4) sowie Abbruchs wegen UE Vorteile von Olaparib im Vergleich zu Capecitabin, Vinorelbin oder Eribulin festzustellen. Kein Unterschied zeigte sich für den Endpunkt schwerwiegende UE. Bei den spezifischen UE überwogen positive Effekte von Olaparib. In der Kategorie Nebenwirkungen war somit insgesamt ein Vorteil von Olaparib gegenüber Capecitabin, Vinorelbin oder Eribulin festzustellen.
In der Gesamtbetrachtung stellt der G-BA basierend auf den Vorteilen in der Endpunktkategorie Nebenwirkungen einen geringen Zusatznutzen für Olaparib gegenüber Capecitabin, Vinorelbin oder Eribulin fest.
Vor dem Hintergrund, dass aufgrund des offenen Studiendesigns der OlympiAD in der Kategorie Nebenwirkungen überwiegend von einem hohen Verzerrungspotenzial auszugehen ist und keine verwertbaren Daten zu den Endpunktkategorien Morbidität und gesundheitsbezogene Lebensqualität vorliegen, kann bezüglich der Aussagesicherheit nur ein Anhaltspunkt für einen Zusatznutzen abgeleitet werden.

Olaparib (neues Anwendungsgebiet: Mammakarzinom, BRCA1/2-Mutationen, HER2-)			
Wirkstoff	Olaparib	**Handelsname**	Lynparza
Pharmazeutischer Unternehmer	AstraZeneca GmbH	**Beschlussdatum**	16.01.2020

Olaparib (neues Anwendungsgebiet: Mammakarzinom, BRCA1/2-Mutationen, HER2-)	
Anwendungsgebiet	Mammakarzinom

Olaparib (neues Anwendungsgebiet: Mammakarzinom, BRCA1/2-Mutationen, HER2-)			
Wirkstoff	Olaparib	**Handelsname**	Lynparza
Pharmazeutischer Unternehmer	AstraZeneca GmbH	**Beschlussdatum**	16.01.2020
Anwendungsgebiet	Mammakarzinom		

Kapitel 5.2.7: Triple negatives Mammakarzinom im fortgeschrittenen oder metastasierten Stadium

Verknüpfte Empfehlungen:

Empfehlung 5.47:

Patientinnen mit triple-negativem fortgeschrittenem oder metastasiertem Mammakarzinom mit positivem PD-L1 Status sollen mit Pembrolizumab + Chemotherapie (Paclitaxel, nab-Paclitaxel oder Carboplatin/Gemcitabine) bei Combined positive score ≥ 10 behandelt werden. Alternativ kann mit Atezolizumab + nab-Paclitaxel bei IC ≥ 1% als Erstlinientherapie behandelt werden.

Literaturreferenzen: [235], [257], [258], [259], [260], [261], [262], [237]

Evidenzkurzprofil zu Atezolizumab als Erstlinientherapie beim triple negativen Mammakarzinom im fortgeschrittenen oder metastasierten Stadium I	
Population	Patientinnen mit triple-negativem fortgeschrittenen oder metastasierten Mammakarzinom mit positivem PD-L1 Status (IC ≥ 1)
Intervention	Atezolizumab als Erstlinientherapie
Evidenzgrundlage	Studie IMpassion130 (NCT02425891): Atezolizumab vs. nab-Paclitaxel (Quelle: Nutzenbewertungsverfahren zuAtezolizumab (2020))
GRADE	
⊕⊕⊕⊕	OS: Vorteil gegenüber Kontrollintervention
⊕⊕⊕⊕	PFS: Vorteil gegenüber Kontrollintervention

Evidenzkurzprofil zu Atezolizumab als Erstlinientherapie beim triple negativen Mammakarzinom im fortgeschrittenen oder metastasierten Stadium I	
⊕⊕⊕⊖	Patientenberichtete Symptomatik: Nachteil (Schmerzen), ansonsten keine Unterschiede
⊕⊕⊕⊖	QoL: keine Unterschiede
⊕⊕⊕⊖	Gesamt-SUE, Gesamt-UE CTCAE Grad ≥ 3, Therapieabbruch aufgrund von UE: Nachteil (Therapieabbruch), ansonsten keine Unterschiede
⊕⊕⊕⊖-⊕⊕⊖⊖	Spezifische UE: Nachteile bzw. kein Unterschied
Quelle: Das Kurzprofil fasst die Ergebnisse der umfassenderen Evidenzaufarbeitungen zu medikamentösen Therapien beim metastasierten Mammakarzinom zusammen.	

Verknüpfte Empfehlungen:

Empfehlung 5.47:

Patientinnen mit triple-negativem fortgeschrittenem oder metastasiertem Mammakarzinom mit positivem PD-L1 Status sollen mit Pembrolizumab + Chemotherapie (Paclitaxel, nab-Paclitaxel oder Carboplatin/Gemcitabine) bei Combined positive score ≥ 10 behandelt werden. Alternativ kann mit Atezolizumab + nab-Paclitaxel bei IC ≥ 1% als Erstlinientherapie behandelt werden.

Literaturreferenzen: [235], [257], [258], [259], [260], [261], [262], [237]

Evidenzkurzprofil zu Pembrolizumab als Erstlinientherapie beim triple negativen Mammakarzinom im fortgeschrittenen oder metastasierten Stadium	
Population	Patientinnen mit triple-negativen fortgeschrittenen oder metastasierten Mammakarzinom mit positivem PD-L1 Status (CPS ≥ 10)
Intervention	Pembrolizumab als Erstlinientherapie
Evidenzgrundlage	Studie KEYNOTE 355 (NCT02819518): Pembrolizumab + Chemotherapie vs. Chemotherapie (Quelle: Nutzenbewertungsverfahren zuPembrolizumab (2022))
GRADE	
⊕⊕⊕⊕	OS: Vorteil gegenüber Kontrollintervention
⊕⊕⊕⊕	PFS: Vorteil gegenüber Kontrollintervention
⊕⊕⊕⊖	Patientenberichtete Symptomatik: Vorteil (Symptome in der Brustregion) und Nachteil (Diarrhö), ansonsten keine Unterschiede

Evidenzkurzprofil zu Pembrolizumab als Erstlinientherapie beim triple negativen Mammakarzinom im fortgeschrittenen oder metastasierten Stadium	
⊕⊕⊕⊖	QoL: keine Unterschiede
⊕⊕⊕⊖	Gesamt-SUE, Gesamt-UE CTCAE Grad ≥ 3, Therapieabbruch aufgrund von UE: keine Unterschiede
⊕⊕⊕⊖-⊕⊕⊖⊖	Spezifische UE: Nachteil bzw. kein Unterschied
Quelle: Das Kurzprofil fasst die Ergebnisse der umfassenderen Evidenzaufarbeitungen zu medikamentösen Therapien beim metastasierten Mammakarzinom zusammen.	

Verknüpfte Empfehlungen:

Empfehlung 5.48:

Patientinnen mit triple-negativem fortgeschrittenem oder metastasiertem Mammakarzinom nach Vorbehandlung mit zwei oder mehr systemische Therapien, darunter mindestens 1 gegen die fortgeschrittene Erkrankung, sollten mit Sacituzumab Govitecan behandelt werden.

Literaturreferenzen: [235], [263], [264], [237]

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Sacituzumab Govitecan (Mammakarzinom, triple-negativ, mind. 2 Vortherapien)			
Wirkstoff	Sacituzumab Govitecan	**Handelsname**	Trodelvy
Pharmazeutischer Unternehmer	Gilead Sciences GmbH	**Beschlussdatum**	19.05.2022
Anwendungsgebiet	Mammakarzinom		

Sacituzumab Govitecan (Mammakarzinom, triple-negativ, mind. 2 Vortherapien)			
Wirkstoff	Sacituzumab Govitecan	**Handelsname**	Trodelvy
Pharmazeutischer Unternehmer	Gilead Sciences GmbH	**Beschlussdatum**	19.05.2022
Anwendungsgebiet	Mammakarzinom		

Sacituzumab Govitecan (Mammakarzinom, triple-negativ, mind. 2 Vortherapien)			
Wirkstoff	Sacituzumab Govitecan	**Handelsname**	Trodelvy
Pharmazeutischer Unternehmer	Gilead Sciences GmbH	**Beschlussdatum**	19.05.2022
Anwendungsgebiet	Mammakarzinom		

Sacituzumab Govitecan (Mammakarzinom, triple-negativ, mind. 2 Vortherapien)			
Wirkstoff	Sacituzumab Govitecan	**Handelsname**	Trodelvy
Pharmazeutischer Unternehmer	Gilead Sciences GmbH	**Beschlussdatum**	19.05.2022
Anwendungsgebiet	Mammakarzinom		

Sacituzumab Govitecan (Mammakarzinom, triple-negativ, mind. 2 Vortherapien)			
Wirkstoff	Sacituzumab Govitecan	**Handelsname**	Trodelvy
Pharmazeutischer Unternehmer	Gilead Sciences GmbH	**Beschlussdatum**	19.05.2022
Anwendungsgebiet	Mammakarzinom		

Kapitel 6: Behandlung, Betreuung und Begleitung

Kapitel 6.1: Nachsorge und Langzeitbetreuung

Kapitel 6.1.1: Untersuchungen zum lokoregionalen/intramammären Rezidiv beziehungsweise kontralateralen Mammakarzinom

Verknüpfte Empfehlungen:

Empfehlung 6.15:

Die bildgebende Diagnostik zur Detektion von lokal- und lokoregionären Rezidiven und kontralateralen Karzinomen sollte die jährliche Mammographie umfassen.

Literaturreferenzen: [265], [91]

Source: Moschetti, I., M. Cinquini, M. Lambertini, A. Levaggi, and A. Liberati. "Follow-up Strategies for Women Treated for Early Breast Cancer." Cochrane Database of Systematic Reviews, no. 5 (2016). https: //doi.org/10.1002/14651858.CD001768.pub3. http: //dx.doi.org/10.1002/14651858.CD001768.pub3.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: assess the effectiveness of different policies of follow-up for distant metastases on mortality, morbidity and quality of life in women treated for stage I, II or III breast cancer	**Design**: Systematic Review and Meta-Analysis **Search date**: until 4 July 2014 **Searched databases**: Cochrane Breast Cancer Group's Specialised	**Intervention** 1) Non-intensive follow-up (routine clinical visits plus yearly mammogram)	**Primary Outcome**: **Overall survival** (as estimated from the date of randomisation to the date of last contact or death from any cause)	**Primary Outcome**: **Overall survival** *Non-intensive follow-up vs intensive follow-up* HR 0.98, 95% CI 0.84-1.15; I^2=28%	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 2 critical flaws (items 7, 15)

Source: Moschetti, I., M. Cinquini, M. Lambertini, A. Levaggi, and A. Liberati. "Follow-up Strategies for Women Treated for Early Breast Cancer." Cochrane Database of Systematic Reviews, no. 5 (2016). https: //doi.org/10.1002/14651858.CD001768.pub3. http: //dx.doi.org/10.1002/14651858.CD001768.pub3.					
	Register, MEDLINE, Embase, CENTRAL, the World Health Organization (WHO) International Clinical Trials Registry Platform and ClinicalTrials.gov **Included study designs**: Multicentre RCTs **Number of included studies**: 5 (qualitative synthesis) Of those: 4 included in Meta-Analysis **Number of included patients**: 4023 women **Mean/median age**: N.A. **Median FU-time:** Varied from 16-120 months **Inclusion criteria**: RCTs;	2) Decentralised follow-up (delivered by general practitioner) 3) Conventionally scheduled follow-up **Control** 1) Intensive follow-up (i.e. with radiological/ laboratory tests added to routine visits) 2) Centralized follow-up **(i.e.** surveillance offered by a specialist at a multidisciplinary breast clinic) 3) surveillance on demand	**Health-related quality of life (HRQoL)**, (assessed using EORTC QLQ-C30, SF-36 and the "hospital anxiety and depression scale [HADS]") **Secondary Outcome**: **Disease-free survival** (expression of the time to detect a recurrence). It is used in this context to compare the power of different follow-up strategies to detect recurrence earlier, possibly in an asymptomatic stage **Occurrence of metastases** detected in an asymptomatic status	(2 studies, 2563 participants; FU: median 71 months) No significant differences in subgroup analysis: age, tumor size, nodal status, at 5 years *Decentralised follow-up vs centralised follow-up* HR 1.07, 95% CI 0.64-1.78; I^2 n.a. (1 study, 968 participants; FU: median 42 months) **Quality of life** No relative effect *Non-intensive follow-up vs intensive follow-up* no significant difference was found between the two follow-up strategies (1 study)	**Additional concerns about quality**: studies were initiated in the late 1980s and therefore results must be interpreted with caution (knowledge, technology and treatment for breast cancer have improved) **Quality of included studies**: Random sequence generation: 3 studies not adequate Allocation concealment: 1 study not adequate Blinding of outcome assessment: not adequate in 3 studies Incomplete outcome data: not adequate in 2 studies Selective reporting: bias possible in all studies No other bias.

Source: Moschetti, I., M. Cinquini, M. Lambertini, A. Levaggi, and A. Liberati. "Follow-up Strategies for Women Treated for Early Breast Cancer." Cochrane Database of Systematic Reviews, no. 5 (2016). https: //doi.org/10.1002/14651858.CD001768.pub3. http: //dx.doi.org/10.1002/14651858.CD001768.pub3.					
	Women who have had primary surgical treatment for breast cancer (clinical stage I, II or III), with no evidence of recurrence **Exclusion**: n.a.			*Decentralised follow-up vs centralised follow-up* no statistically significant differences were detected between groups over time for any of the scores (1 study) **Secondary Outcome**: **Disease-free survival** *Non-intensive follow-up vs intensive follow-up* HR 0.84, 95% CI 0.71-1.00; I^2=52% (2 studies, 2563 participants; FU: median 71 months) *Decentralised follow-up vs centralised follow-up* HR 1.06, 95% CI 0.76-1.47;	**Quality of evidence:** GRADE *Non-intensive follow-up vs intensive follow-up* Overall Surival: high Disease-free survival: low Quality of life: high *Decentralised follow-up vs centralised follow-up* Overall survival: moderate Disease-free survival: moderate Quality of life: high **Sources of funding:** no specific funding

Source: Moschetti, I., M. Cinquini, M. Lambertini, A. Levaggi, and A. Liberati. "Follow-up Strategies for Women Treated for Early Breast Cancer." Cochrane Database of Systematic Reviews, no. 5 (2016). https: //doi.org/10.1002/14651858.CD001768.pub3. http: //dx.doi.org/10.1002/14651858.CD001768.pub3.					
				(2 studies, 1264 participants; FU: median 42 months) **Occurrence of metastases detected in an asymptomatic status** *Non-intensive follow-up vs intensive follow-up* GIVIO trial: 31% of cases of metastases in the intensive group and 21% in the clinical group were detected in an asymptomatic phase RR 0.68, 95% CI 0.44-1.05; I^2 n.a. *Decentralised follow-up vs centralised follow-up and* *Regular follow-up vs surveillance on demand* No information on this outcome	

Source: Moschetti, I., M. Cinquini, M. Lambertini, A. Levaggi, and A. Liberati. "Follow-up Strategies for Women Treated for Early Breast Cancer." Cochrane Database of Systematic Reviews, no. 5 (2016). https: //doi.org/10.1002/14651858.CD001768.pub3. http: //dx.doi.org/10.1002/14651858.CD001768.pub3.

Abbreviations:

RCT = Randomised Controlled Trial

HADS = Hospital Anxiety and Depression Scale

HR = Hazard Ratio

95% CI = 95% Confidence Interval

FU = Follow Up

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 6.18:

Durch die ergänzende qualitätsgesicherte Ultraschalluntersuchung in der Nachsorge erhöht sich die Wiedereinbestellungs- und die Biopsierate. Patientinnen berichteten am häufigsten (82%) über psychisch positive Aspekte durch erhöhte Aufmerksamkeit und damit verbundenen Sicherheit, selten (<6%) psychische Belastungen durch Verunsicherung und Angst. Sie sollte bei nicht ausreichend beurteilbarer Mammographie durchgeführt werden.

Literaturreferenzen: [266], [267]

Source	Design and participants	Intervention	Outcomes	Results	Quality and comment, source of funding
AUTHOR: Wojcinskietal. JOURNAL: Ultrasoundin Medicine & Biology YEAR: 2011	Prospective, single-institutional Before- After study N=735eligiblepatients were recruited between 10/2004- 01/2006; N=490 asymptomatic subgroup received US Inclusion criteria: History of unilateral BC, interval of ≥6 months since last BC treatment (except endocrine) Exclusion criteria: Previously diagnosed recurrence, brain	Routine follow-up: Physical examination and mammogram accordingto AGO Breast Commission guidelines; symptomatic patients received additional US Study follow-up: After routine follow-up asymptomatic patients received US on the same day US was performed by DEGUM level I certified gynaecologist with linear probe (and 6-13MHz) or	Frequencyof occult BC recurrence, psychosocial aspects	Routine follow-up in n=735: *Physical exam or mammogram:* Of n=245 patients with abnormal findings n=66 biopsies were taken; n=27 malignant (3.7%) Studyfollow-up: *US:* Of n=490 asymptomatic patients n=21 (2.9%) additional biopsies were taken, N=6malignant(0.8%)	Noblindingof examiner Findings were histopathological assured *Sourceoffunding:* n.a. Due to methodological constraints wepropose a Level of evidence of **2c** instead of 2b

Source	Design and participants	Intervention	Outcomes	Results	Quality and comment, source of funding
	metastases, psychological disorder, ongoing cancertherapy	long linear probe (and 5-10MHz) ACR BI-RADS-US criteria were adopted for mammogram			

Verknüpfte Empfehlungen:

Empfehlung 6.18:

Durch die ergänzende qualitätsgesicherte Ultraschalluntersuchung in der Nachsorge erhöht sich die Wiedereinbestellungs- und die Biopsierate. Patientinnen berichteten am häufigsten (82%) über psychisch positive Aspekte durch erhöhte Aufmerksamkeit und damit verbundenen Sicherheit, selten (<6%) psychische Belastungen durch Verunsicherung und Angst. Sie sollte bei nicht ausreichend beurteilbarer Mammographie durchgeführt werden.

Literaturreferenzen: [266], [267]

Source	Design and participants	Intervention	Outcomes	Results	Quality and comment, source of funding
AUTHOR: Riebe et al. JOURNAL: Ultraschall in Med YEAR: 2007	Retrospective single-institution cross-sectional study with n=27 patients, who underwent breast- conserving therapy and radiation Inclusioncriteria: At least one diagnostic technique raised suspicion for recurrent disease	Palpation, mammography and US alone or in combination;Bi-RADSwas used forclassification of mammograms; US fulfilled requirements of DEGUM device list	Sensitivity, specificity, PPV, NPV,efficiency*	N=11truemalignancies *Palpation/mammogram:* Sensitivity: 81.8%;(9/11) specificity: 6.2% (1/16); PPV: 37.5;NPV: 33.3%,efficiency: 37% *Palpation/mammogram/ US:* Sensitivity: 100% (11/11); PPV: 41%; Efficiency: 41%	Findings were histopathological assured US examiners were not blinded to mammogram and palpation results Small sample size *Source of funding:* n.a. Duetomethodological constraintswe propose to downgrade **level of evidence** from 2b to **3a**

Kapitel 6.2: Rehabilitation

Verknüpfte Empfehlungen:

Empfehlung 6.27:

Eine Physiotherapie zur Mobilisation des Schultergelenks soll in den ersten beiden Wochen postoperativ beginnen.

Empfehlung 6.28:

Bei Lymphödemen sollte eine komplexe Entstauungstherapie (KPE) bestehend aus Hautpflege, manueller Lymphdrainage, Bewegungstherapie und Kompressionsbehandlung durchgeführt werden.

Literaturreferenzen: [268], [269]

Source: Redemski, T., D. G. Hamilton, S. Schuler, R. Liang, and Z. A. Michaleff. "Rehabilitation for Women Undergoing Breast Cancer Surgery: A Systematic Review and Meta-Analysis of the Effectiveness of Early, Unrestricted Exercise Programs on Upper Limb Function." [In eng]. Clinical breast cancer 22, no. 7 (2022): 650-65. https: //doi.org/10.1016/j.clbc.2022.06.001. https: //pubmed.ncbi.nlm.nih.gov/35902321/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: To evaluate the effectiveness of early range of movement (ROM) exercises (Early ROM) compared to delayed ROM exercises (Delayed ROM) or usual care (UC) in reducing common complications in	**Design**: Systematic review and Meta-Analysis **Search date**: until 15th of February 2021 **Searched databases**: Cochrane Central Register of Controlled Trials, PubMed, EMBASE, CINAHL, PEDro	**Intervention**: Early, unrestricted exercise program for the upper limb, defined as full ROM exercises commenced within the first 3 postoperative days. **Control**: Delayed or restricted exercise program (ie, period of	Shoulder range, wound outcomes and lymphedema incidence	**1) Flexion ROM** ***Early ROM vs Delayed ROM*** *MD=mean difference* Postoperative MD 7.8, 95% CI -13.7 to 29.4, I^2=97% (4 studies) Short-term	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 1 critical flaw (item 15) **Overall quality of evidence**: low **Additional concerns about quality**:

Source: Redemski, T., D. G. Hamilton, S. Schuler, R. Liang, and Z. A. Michaleff. "Rehabilitation for Women Undergoing Breast Cancer Surgery: A Systematic Review and Meta-Analysis of the Effectiveness of Early, Unrestricted Exercise Programs on Upper Limb Function." [In eng]. Clinical breast cancer 22, no. 7 (2022): 650-65. https: //doi.org/10.1016/j.clbc.2022.06.001. https: //pubmed.ncbi.nlm.nih.gov/35902321/.					
women following breast cancer surgery.	**Included study designs**: RCTs **Number of included studies**: n=20 **Number of included patients**: n=2,442 **Mean (SD)**: 56.24 (4.7) **Inclusion criteria**: Women who had undergone breast cancer surgery involving the following surgical techniques: mastectomy, BCS, SLNB, ALND, and reconstruction **Exclusion**: Trials including participants with melanoma	immobilization or restricted movement that was progressed to full ROM exercise program after day 3), no program, or usual care.		MD 9.8, 95% CI -17.3 to 37.0, I^2=95% (4 studies) Intermediate-term MD 24.5, 95% CI 15.8 to 33.2, I^2=n.a. (1 study) Long-term MD 6.5, 95% CI -104.1 to 117.2, I^2=98%, (2 studies) **Flexion ROM** ***Early ROM vs Usual care*** Postoperative MD 8.6, 95% CI -26.4 to 43.5, I^2=88% (3 studies) Short-term MD 16.1, 95% CI 9,9 to 22.3, I^2=n.a. (1 study) **2) Abduction ROM** ***Early ROM vs Delayed ROM*** Postoperative	Heterogeneity of included studies limited the number of studies eligible for meta-analysis; variability of definition and measurement of outcomes **Quality of included studies**: quality of evidence: low to very low (GRADE); Concealed allocation, blinding, intention to treat (unmet criteria within most trials) **Sources of funding:** No funding received

Source: Redemski, T., D. G. Hamilton, S. Schuler, R. Liang, and Z. A. Michaleff. "Rehabilitation for Women Undergoing Breast Cancer Surgery: A Systematic Review and Meta-Analysis of the Effectiveness of Early, Unrestricted Exercise Programs on Upper Limb Function." [In eng]. Clinical breast cancer 22, no. 7 (2022): 650-65. https: //doi.org/10.1016/j.clbc.2022.06.001. https: //pubmed.ncbi.nlm.nih.gov/35902321/.

				MD 6.0, 95% CI -7.5 to 19.5, I^2=74%, (4 studies) <u>Short-term</u> MD 8.5, 95% CI -31.0 to 48, I^2=95%, (4 studies) <u>Intermediate-term</u> MD 7.6, 95% CI -42.6 to 57.7, I^2=96%, (3 studies) <u>Long-term</u> MD -0.2, 95% CI – 22.7 to 22.3, I^2=93%, (4 studies) **Abduction ROM** ***Early ROM vs Usual care*** <u>Post-operative</u> MD 4.8, 95% CI -50.6 to 60.2, I^2=91%, (3 studies) <u>Short-term</u> MD 17.6, 95% CI 9.8 to 25.4, I^2=n.a., (1 study)	

Source: Redemski, T., D. G. Hamilton, S. Schuler, R. Liang, and Z. A. Michaleff. "Rehabilitation for Women Undergoing Breast Cancer Surgery: A Systematic Review and Meta-Analysis of the Effectiveness of Early, Unrestricted Exercise Programs on Upper Limb Function." [In eng]. Clinical breast cancer 22, no. 7 (2022): 650-65. https: //doi.org/10.1016/j.clbc.2022.06.001. https: //pubmed.ncbi.nlm.nih.gov/35902321/.

				3) Total drainage volume (TDV, ml) ***Early Rom vs delayed ROM*** Post-operative MD 131.0, 95% CI -9.1 to 271.1, I^2=62%, (8 studies) **Early Rom vs Usual care** Post-operative MD 47.9, 95% CI 23.5 to 72.2, I^2=0%, (2 studies) **4) Total drainage time (TDT, days)** ***Early ROM vs delayed ROM*** Post-operative MD 1.2, 95% CI 0.7 to 1.7, I^2=0%, (6 studies) ***Early Rom vs Usual care*** Post-operative	

Source: Redemski, T., D. G. Hamilton, S. Schuler, R. Liang, and Z. A. Michaleff. "Rehabilitation for Women Undergoing Breast Cancer Surgery: A Systematic Review and Meta-Analysis of the Effectiveness of Early, Unrestricted Exercise Programs on Upper Limb Function." [In eng]. Clinical breast cancer 22, no. 7 (2022): 650-65. https: //doi.org/10.1016/j.clbc.2022.06.001. https: //pubmed.ncbi.nlm.nih.gov/35902321/.

				MD -0.6, 95% CI -2.3 to 1.1, I^2=n.a., (1 study) **5) Hematoma incidence** ***Early ROM vs delayed ROM*** Post-operative RR 1.6, 95% CI 1.1 to 2.3, I^2=0%, (4 studies) **6) Lymphoedema incidence** ***Early ROM vs delayed ROM*** Post-operative RR 2.8, 95% CI 0.0 to 196.6, I^2=48%, (3 studies) Short-term RR 3.7, 95% CI 1.3 to 10.9, I^2=n.a. (2 studies, no events in 1 study) Intermediate-term	

Source: Redemski, T., D. G. Hamilton, S. Schuler, R. Liang, and Z. A. Michaleff. "Rehabilitation for Women Undergoing Breast Cancer Surgery: A Systematic Review and Meta-Analysis of the Effectiveness of Early, Unrestricted Exercise Programs on Upper Limb Function." [In eng]. Clinical breast cancer 22, no. 7 (2022): 650-65. https: //doi.org/10.1016/j.clbc.2022.06.001. https: //pubmed.ncbi.nlm.nih.gov/35902321/.

				RR 0.9, 95% CI 0.7 to 1.1, I^2=0%, (2 studies) <u>Long-term</u> RR 1.6, 95% CI 0.3 to 7.9, I^2=18%, (3 studies) **Lymphoedema incidence** ***Early ROM vs Usual care*** <u>Short-term</u> RR 0.7, 95% CI 0.2 to 2.1, I^2=n.a., (1 study) <u>Long-term</u> RR 1.3, 95% CI 0.1 to 20.4, I^2=0%, (2 studies)	

Abbreviations:

ROM = Range of Movement

UC = Usual Care

BCS = Breast-Conserving Surgery

SLNB = Sentinel Lymph Node Biopsy, Sentinel Lymph Node Dissection

Source: Redemski, T., D. G. Hamilton, S. Schuler, R. Liang, and Z. A. Michaleff. "Rehabilitation for Women Undergoing Breast Cancer Surgery: A Systematic Review and Meta-Analysis of the Effectiveness of Early, Unrestricted Exercise Programs on Upper Limb Function." [In eng]. Clinical breast cancer 22, no. 7 (2022): 650-65. https: //doi.org/10.1016/j.clbc.2022.06.001. https: //pubmed.ncbi.nlm.nih.gov/35902321/.

ALND = Axillary Lymph Node Dissection

RCT = Randomized Controlled Trial

MD = Mean Difference

RR = Risk Ratio

Verknüpfte Empfehlungen:

Empfehlung 6.27:

Eine Physiotherapie zur Mobilisation des Schultergelenks soll in den ersten beiden Wochen postoperativ beginnen.

Empfehlung 6.28:

Bei Lymphödemen sollte eine komplexe Entstauungstherapie (KPE) bestehend aus Hautpflege, manueller Lymphdrainage, Bewegungstherapie und Kompressionsbehandlung durchgeführt werden.

Literaturreferenzen: [268], [269]

Evidenztabelle zu Empfehlung 6.48 und 6.49

Source: Ribeiro, I. L., R. F. C. Moreira, A. V. Ferrari, F. Alburquerque-Sendín, P. R. Camargo, and T. F. Salvini. "Effectiveness of Early Rehabilitation on Range of Motion, Muscle Strength and Arm Function after Breast Cancer Surgery: A Systematic Review of Randomized Controlled Trials." [In eng]. Clinical rehabilitation 33, no. 12 (2019): 1876-86. https: //pubmed.ncbi.nlm.nih.gov/31480855/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Summarize evidence regarding the effectiveness of early rehabilitation in the immediate postoperative period of breast cancer surgery for arm function, range of motion and strength.	**Design**: Systematic review **Search date**: up to 06/2019 **Searched databases**: PubMed, MEDLINE, Embase, Bireme, CINAHL and LILACS	**Intervention** The exercise protocols started at the first week following the surgery and consisted of upper limb active exercises, passive and active	At 3 and 6 months: **Effectiveness of ROM exercising in improving** - ROM shoulder flexion - ROM shoulder abduction - ROM shoulder external rotation Upper limb function	At 3 months: **Effectiveness of ROM exercising in improving** ROM shoulder flexion Intervention: 49.7% Comparison: 50.3% (2 studies no treatment effect, 2 studies positive-	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 1 critical flaws (item 7) **Overall quality of evidence**: low **Quality of included studies**: 13 of 15

Source: Ribeiro, I. L., R. F. C. Moreira, A. V. Ferrari, F. Alburquerque-Sendín, P. R. Camargo, and T. F. Salvini. "Effectiveness of Early Rehabilitation on Range of Motion, Muscle Strength and Arm Function after Breast Cancer Surgery: A Systematic Review of Randomized Controlled Trials." [In eng]. Clinical rehabilitation 33, no. 12 (2019): 1876-86. https: //pubmed.ncbi.nlm.nih.gov/31480855/.					
	Included study designs: RCTs **Number of included studies**: n=15 **Number of included patients**: n=1,710 **Mean/median age**: n.a. **Inclusion criteria**: women who had undergone breast cancer surgery and received early rehabilitation, in the immediate postoperative period. The rehabilitation program had to commence within the first eight weeks after surgery.	stretching, shoulder range of motion and strengthening exercises combined with scar massage protocols were carried out from 10 to 19 days in three studies, between one and two months in four studies, between three and six months in five studies and two studies did not report protocol duration **Control:** not specified	**Effectiveness of muscle strengthening exercises in improving** Upper limb function **Effectiveness of ROM and strengthening exercises in improving** ROM shoulder flexion -ROM shoulder abduction -ROM shoulder external rotation	and 1 study negative treatment effect) <u>ROM shoulder abduction</u> Intervention: 55.2% Comparison: 44.8% (1 study without treatment effect, 3 studies with positive - and 1 study negative treatment effect) <u>ROM shoulder external rotation</u> Intervention: 51.9% Comparison: 48.1% (2 studies without - and 2 studies with positive treatment effect) <u>Upper limb function</u> Intervention: 49.0% Comparison: 51.0%	included studies high methodological quality; Only 5 studies reported blinding assessors **Sources of funding:** Research Support Foundation of São Paulo State (FAPESP) (Process: 2011/22122-5 and 2015/50303-5)

Source: Ribeiro, I. L., R. F. C. Moreira, A. V. Ferrari, F. Alburquerque-Sendín, P. R. Camargo, and T. F. Salvini. "Effectiveness of Early Rehabilitation on Range of Motion, Muscle Strength and Arm Function after Breast Cancer Surgery: A Systematic Review of Randomized Controlled Trials." [In eng]. Clinical rehabilitation 33, no. 12 (2019): 1876-86. https: //pubmed.ncbi.nlm.nih.gov/31480855/.					
				(1 study without – and 3 studies with positive treatment effect) **Effectiveness of muscle strengthening exercises in improving** <u>Upper limb function</u> Intervention: 48.8% Comparison: 51.2% (1 study without - and 3 studies with positive treatment effect) **Effectiveness of ROM and strengthening exercises in improving** <u>ROM shoulder flexion</u> Intervention: 50.9% Comparison: 49.1% (1 study without – and 2 studies with positive treatment effect)	

Source: Ribeiro, I. L., R. F. C. Moreira, A. V. Ferrari, F. Alburquerque-Sendín, P. R. Camargo, and T. F. Salvini. "Effectiveness of Early Rehabilitation on Range of Motion, Muscle Strength and Arm Function after Breast Cancer Surgery: A Systematic Review of Randomized Controlled Trials." [In eng]. Clinical rehabilitation 33, no. 12 (2019): 1876-86. https: //pubmed.ncbi.nlm.nih.gov/31480855/.					
				ROM shoulder abduction Intervention: 50.9% Comparison: 49.1% (3 studies with positive treatment effect) ROM shoulder external rotation Intervention: 50.9% Comparison: 49.1% (1 study without - and, 2 studies with positive treatment effect) At 6 months **Effectiveness of ROM exercising in improving** ROM shoulder flexion Intervention: 47.5% Comparison: 48.3% (3 studies without treatment effect, 2 studies with positive -	

Source: Ribeiro, I. L., R. F. C. Moreira, A. V. Ferrari, F. Alburquerque-Sendín, P. R. Camargo, and T. F. Salvini. "Effectiveness of Early Rehabilitation on Range of Motion, Muscle Strength and Arm Function after Breast Cancer Surgery: A Systematic Review of Randomized Controlled Trials." [In eng]. Clinical rehabilitation 33, no. 12 (2019): 1876-86. https: //pubmed.ncbi.nlm.nih.gov/31480855/.

				and 1 study negative treatment effect) <u>ROM shoulder abduction</u> Intervention: 47.5% Comparison: 48.3% (2 studies without treatment effect, 3 studies with positive – and 1 study negative treatment effect) <u>ROM shoulder external rotation</u> Intervention: 46.9% Comparison: 47.7% (2 studies without treatment effect, 2 studies with positive - and 1 study with negative treatment effect) <u>Upper limb function</u> Intervention: 46.7%	

Source: Ribeiro, I. L., R. F. C. Moreira, A. V. Ferrari, F. Alburquerque-Sendín, P. R. Camargo, and T. F. Salvini. "Effectiveness of Early Rehabilitation on Range of Motion, Muscle Strength and Arm Function after Breast Cancer Surgery: A Systematic Review of Randomized Controlled Trials." [In eng]. Clinical rehabilitation 33, no. 12 (2019): 1876-86. https: //pubmed.ncbi.nlm.nih.gov/31480855/.					
				Comparison: 53.3% (1 study without treatment effect, 2 studies with positive – and 1 study with negative treatment effect) **Effectiveness of muscle strengthening exercises in improving** <u>ROM shoulder flexion</u> Intervention: 48.4% Comparison: 51.6% (1 study without - and 1 study with positive treatment effect) <u>ROM shoulder abduction</u> Intervention: 48.4% Comparison: 51.6% (2 studies with positive treatment effect)	

Source: Ribeiro, I. L., R. F. C. Moreira, A. V. Ferrari, F. Alburquerque-Sendín, P. R. Camargo, and T. F. Salvini. "Effectiveness of Early Rehabilitation on Range of Motion, Muscle Strength and Arm Function after Breast Cancer Surgery: A Systematic Review of Randomized Controlled Trials." [In eng]. Clinical rehabilitation 33, no. 12 (2019): 1876-86. https: //pubmed.ncbi.nlm.nih.gov/31480855/.

				<u>ROM shoulder external rotation</u> Intervention: 48.4% Comparison: 51.6% (1 study without – and 1 study with positive treatment effect) <u>Upper limb function</u> Intervention: 50.5% Comparison: 49.5% (1 study without - and 1 study with positive treatment effect) **Effectiveness of ROM and strengthening exercises in improving** <u>ROM shoulder flexion</u> Intervention: 47.5% Comparison: 48.3% (3 studies without treatment effect, 2 study	

Source: Ribeiro, I. L., R. F. C. Moreira, A. V. Ferrari, F. Alburquerque-Sendín, P. R. Camargo, and T. F. Salvini. "Effectiveness of Early Rehabilitation on Range of Motion, Muscle Strength and Arm Function after Breast Cancer Surgery: A Systematic Review of Randomized Controlled Trials." [In eng]. Clinical rehabilitation 33, no. 12 (2019): 1876-86. https: //pubmed.ncbi.nlm.nih.gov/31480855/.

				with positive – and 1 study with <u>ROM shoulder abduction</u> Intervention: 47.5% Comparison: 48.3% (2 studies without treatment effect, 3 studies with positive and 1 study with negative treatment effect) <u>ROM shoulder external rotation</u> Intervention: 49.6% Comparison: 50.4% (2 studies without treatment effect, 2 studies with positive – and 1 study with negative treatment effect) <u>Upper limb function</u> Intervention: 51.5%	

Source: Ribeiro, I. L., R. F. C. Moreira, A. V. Ferrari, F. Alburquerque-Sendín, P. R. Camargo, and T. F. Salvini. "Effectiveness of Early Rehabilitation on Range of Motion, Muscle Strength and Arm Function after Breast Cancer Surgery: A Systematic Review of Randomized Controlled Trials." [In eng]. Clinical rehabilitation 33, no. 12 (2019): 1876-86. https: //pubmed.ncbi.nlm.nih.gov/31480855/.					
				Comparison: 54.2% (1 study without treatment effect, 1 study with positive – and 1 study with negative treatment effect)	
Abbreviations: RCT = Randomized Controlled Trial ROM = Range of Motion					

Kapitel 7: Spezielle Situationen bei Mammakarzinom

Kapitel 7.1: Fertilitätserhalt, Schwangerschaft nach Mammakarzinom, Mammakarzinom in Schwangerschaft und Stillzeit

Kapitel 7.1.1: Fertilitätserhalt

Verknüpfte Empfehlungen:

Empfehlung 7.2:

Die GnRH-Analoga-Gabe vor Beginn der Chemotherapie kann bei allen Frauen mit Wunsch zum Erhalt der Ovarfunktion/Fertilität erwogen werden.

Literaturreferenzen: [270], [271], [272], [273]

Source M, Lambertini, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, Boni L, et al. "Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients with Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 36, no. 19 (2018-7-1 2018): 1981-90. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29718793/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Investigation of the role of temporary ovarian suppression with gonadotropin-releasing hormone agonists (GnRHa) during chemotherapy as a	**Design**: Systematic review and individual patient-level meta-analysis **Search date**: until August 31, 2017	**Intervention** gonadotropin-releasing hormone agonists (GnRHa) during (neo)adjuvant chemotherapy	**Primary Outcome**: Rate of chemotherapy-induced premature ovarian insufficiency (POI) Post-treatment pregnancy rate	**Primary Outcome**: **Rate of chemotherapy-induced premature ovarian insufficiency (POI)**	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 3 critical flaws (items 9, 13, 15)

Source M, Lambertini, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, Boni L, et al. "Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients with Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 36, no. 19 (2018-7-1 2018): 1981-90. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29718793/.					
strategy to preserve ovarian function and fertility in premenopausal patients with early breast cancer.	**Searched databases**: PubMed, Embase, and the Cochrane Library **Included study designs**: RCTs **Number of included studies**: 13 eligible Of those: individual patient-level data available for **5 trials**: PROMISE-GIM6 [PRevention Of Menopause Induced by chemotherapy: A Study in Early breast cancer patients—Gruppo Italiano Mammella 6], POEMS [Prevention Of Early Menopause Study]/SWOG S0230,	type of GnRHA used: Triptorelin (2 trials), Goserelin (3 trials) **Control** (neo)adjuvant chemotherapy alone	**Secondary Outcome**: Safety (toxicity and survival outcomes): amenorrhea rates 1 and 2 years after chemotherapy GnRHa-related adverse events (hot flashes, sweating, mood changes, vaginal dryness, headache) Disease-free survival (DFS) Overall survival (OS) Prespecified subgroup analyses investigated the efficacy and safety of temporary ovarian suppression with GnRHa during chemotherapy according to age of the patients, estrogen receptor status,	data available in 722 (82.7%) patients; GnRHa group: n=51 (14.1%) of 363 patients Control group: n=111 (30.9%) of 359; OR 0.37, 95% CI 0.25 - 0.57, I^2=0% Effect of GnRHa on reducing the risk of POI was homogeneous among subgroups Age distribution, y ≤ 40: OR 0.28, 95% CI 0.16 - 0.49 ≥41: OR 0.52, 95% CI 0.29 - 0.92 Estrogen receptor status Positive:	**Additional concerns about quality**: By review authors: Possible, to obtain only individual patient data from 5 (of 13) RCTs à 55.2% (873 of 1,581) of eligible population; Similar results to previous Meta-Analysis (Lambertini 2015) except for 1-year amenorrhea; Lack of data on the extend of ovarian function preservation (e.g. biomarkers like anti-Müllerian hormone) Missing data: baseline characteristic and end point data **Quality of included studies**: n.a.

Source M, Lambertini, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, Boni L, et al. "Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients with Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 36, no. 19 (2018-7-1 2018): 1981-90. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29718793/.					
	Anglo Celtic Group OPTION, GBG [German Breast Group]-37 ZORO [ZOladex Rescue of Ovarian function], Moffitt-led trial **Number of included patients**: 5 trials with individual patient-level data: 873 patients GnRHa group: 436 Control group: 437 (The remaining 8 studies: 708 patients – data not available for this analysis) **Median age** at diagnosis: 38 years (IQR, 34-42)		type and duration of chemotherapy administered, and tumor stage	OR 0.46. 95% CI 0.27 - 0.79 Negative: OR 0.31, 95% CI 0.17 - 0.56 <u>Type of chemotherapy</u> Anthracyline only: OR 0.51, 95% CI 0.30 - 0.87 Anthracycline + taxane: OR 0.26, 95% CI 0.14 - 0.48 **Post-treatment pregnancy rate** Data available in 3 trials Information on post-treatment pregnancies in 726 (83.2%) of 873 patients <u>GnRHa group:</u> 37 (10.3%) of 359 women had at	**Level of Evidence:** Oxford 2011 Level 2 **Sources of funding:** Pfizer, Roche, Celgene, Amgen, Novartis (Inst)

Source M, Lambertini, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, Boni L, et al. "Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients with Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 36, no. 19 (2018-7-1 2018): 1981-90. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29718793/.

	Estrogen receptor positive: 350 patients (40.1%) Premenopausal patients with early breast cancer **Inclusion criteria**: RCT evaluating the efficacy of adding GnRHa to chemotherapy as a strategy to reduce the occurrence of chemotherapy-induced POI in premenopausal women with early breast cancer receiving (neo)adjuvant chemotherapy **Exclusion**: NR			least 1 post-treatment pregnancy <u>Control group:</u> 20 (5.5%) of 367; IRR, 1.82, 95% CI 1.05 - 3.14, p=0.30, I^2=0%; p=0.852 All pregnancies in patients ≤ 40y at time of diagnosis **Secondary Outcome**: **5 year DFS** <u>GnRHa group:</u> 79.5% (95% CI, 74.7% to 83.5%) <u>control group:</u> 80.0% (95% CI, 75.2% - 83.9%) (adjusted HR, 1.01; 95% CI, 0.72 - 1.42; P = .999;	

Source M, Lambertini, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, Boni L, et al. "Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients with Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 36, no. 19 (2018-7-1 2018): 1981-90. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29718793/.					
				Subgroup analysis according to estrogen receptor status no significant interaction: $P_{interaction}$ = .867; <u>estrogen receptor–positive:</u> adj. HR 1.17 (95% CI, 0.62 - 2.20); <u>estrogen receptor–negative:</u> adj. HR 0.95 (95% CI, 0.64 - 1.42) **5 year OS** GnRHa group: 90.2% (95% CI, 86.4% - 92.9%); control group: 86.3% (95% CI, 82.0% - 89.7%) adj. HR, 0.67; 95% CI, 0.42 - 1.06;	

Source M, Lambertini, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, Boni L, et al. "Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients with Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 36, no. 19 (2018-7-1 2018): 1981-90. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29718793/.					
				P = .083; I^2 = 51.1%; P = .105 Subgroup analysis according to estrogen receptor status no significant interaction: $P_{interaction}$ = .762; <u>estrogen receptor–positive:</u> Adj. HR 0.79 (95% CI, 0.24 - 2.59) <u>estrogen receptor–negative:</u> Adj. HR 0.65 (95% CI, 0.39 - 1.07) **Amenorrhea rates** **1-year amenorrhea data** available in 760 (87.1%) of 873 patients <u>GnRHa group:</u>	

Source M, Lambertini, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, Boni L, et al. "Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients with Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 36, no. 19 (2018-7-1 2018): 1981-90. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29718793/.					
				142 (36.8%) of 386 patients developed 1-year amenorrhea <u>control group:</u> 151 (40.4%) of 374 Adj. OR, 0.92; 95% CI, 0.66 to 1.28; P = .623 **2-year amenorrhea data** available in 424 (48.6%) of 873 patients; this end point was not collected in the PROMISEGIM6 study and in patients who developed DFS and/or OS events between 1 and 2 years <u>GnRHa group:</u>	

Source M, Lambertini, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, Boni L, et al. "Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients with Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 36, no. 19 (2018-7-1 2018): 1981-90. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29718793/.					
				39 (18.2%) of 214 patients developed 2-year amenorrhea, <u>control group:</u> 63 (30.0%) of 210 Adj. OR, 0.51; 95% CI, 0.31 to 0.85; P = .009	

Abbreviations:

GnRHa = Gonadotropin-releasing Hormone Agonists

POI = Premature Ovarian Insufficiency

DFS = Disease-free survival

OS = Overall survival

OR = Odds Ratio

HR = Hazard Ratio

IRR = Incidence Rate Ratio

95% CI = 95% Confidence Interval

RCT = Randomised Controlled Trial

y = years

Source M, Lambertini, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, Boni L, et al. "Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients with Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 36, no. 19 (2018-7-1 2018): 1981-90. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29718793/.

n.a. = not Available, not Applicable

NR = not Reported

Verknüpfte Empfehlungen:

Empfehlung 7.2:

Die GnRH-Analoga-Gabe vor Beginn der Chemotherapie kann bei allen Frauen mit Wunsch zum Erhalt der Ovarfunktion/Fertilität erwogen werden.

Literaturreferenzen: [270], [271], [272], [273]

Source: ZY, Li, Dong YL, Cao XZ, Ren SS, and Zhang Z. "Gonadotropin-Releasing Hormone Agonists for Ovarian Protection During Breast Cancer Chemotherapy: A Systematic Review and Meta-Analysis." [In eng]. Menopause (New York, N.Y.) 29, no. 9 (2022-9-1 2022): 1093-100. https: //doi.org/doi: 10.1097/GME.0000000000002019. https: //pubmed.ncbi.nlm.nih.gov/35917530/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: to assess the effects of GnRHa on ovarian function in women with breast cancer	**Design**: Systematic review and meta-analysis **Search date**: 31/01/2022 **Searched databases**: PubMed, Embase, Cochrane library **Included study designs**: RCT **Number of included studies**: 10 **Number of included patients**: 1,219 GnRHa group: 603	**Intervention** GnRHa during chemotherapy that included cyclophosphamide (GnRHa group) **Control** chemotherapy including cyclophosphamide alone	Ovarian function Resumed menstruation Spontaneous pregnancy	**Primary Outcome**: **Ovarian function** GnRHa group: 474 of 603 patients (78.6%); Control group: 344 of 616 patients (55.8%) OR, 3.04, 95% CI 1.87 - 4.94; p<0.001; I^2=60% **Resumed menstruation** 260 of 337 patients (77.2%):	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: low; 1 critical flaw (item 7) **Additional concerns about quality / limitations** Only 6 studies reported pregnancy data; 10 of 11 trials were open label; Limited follow-up time of RCTs (no information on

Source: ZY, Li, Dong YL, Cao XZ, Ren SS, and Zhang Z. "Gonadotropin-Releasing Hormone Agonists for Ovarian Protection During Breast Cancer Chemotherapy: A Systematic Review and Meta-Analysis." [In eng]. Menopause (New York, N.Y.) 29, no. 9 (2022-9-1 2022): 1093-100. https: //doi.org/doi: 10.1097/GME.0000000000002019. https: //pubmed.ncbi.nlm.nih.gov/35917530/.					
	Control: 616 **Mean/median age**: n.a. **Inclusion criteria**: RCTs that compared the effects of GnRHa during chemotherapy that included cyclophosphamide (GnRHa group) with chemotherapy including cyclophosphamide alone (control group) (1) contained at least two treatment groups (GnRHa plus chemotherapy and chemotherapy alone), (2) participants were adult (18 years and older) breast cancer patients,			GnRHa group: 142 of 167 participants (85.0%) Control group: 118 of 170 participants (69.4%) OR, 2.51; 95% CI, 1.07 - 5.89; P = 0.03; I^2=53% **Spontaneous pregnancy** 56 of the 652 participants (9.4%) reported in 6 studies became pregnant naturally; GnRHa group: 34 of 317 (10.7) Control group: 22 of 335 (6.6%) OR, 1.72; 95% CI, 0.99 - 2.99; P = 0.06; I^2 = 0%, P = 0.65	long-term impact of GnRHa on recovery of menses and fertility) Menses are not a reliable measure for ovarian function and fertility **Quality of included studies**: Cochrane Risk of Bias Tool: moderate risk of study design bias none of the 11 studies specified that all trial personnel and participants were blinded throughout each study's course **Level of Evidence** Oxford 2011 Level 2

Source: ZY, Li, Dong YL, Cao XZ, Ren SS, and Zhang Z. "Gonadotropin-Releasing Hormone Agonists for Ovarian Protection During Breast Cancer Chemotherapy: A Systematic Review and Meta-Analysis." [In eng]. Menopause (New York, N.Y.) 29, no. 9 (2022-9-1 2022): 1093-100. https: //doi.org/doi: 10.1097/GME.0000000000002019. https: //pubmed.ncbi.nlm.nih.gov/35917530/.					
	(3) GnRHa was administered concurrently with chemotherapy, and (4) cyclophosphamide was included in both the experimental and control groups **Exclusion**: (1) studies with incomplete or missing information, (2) reviews and case reports, (3) metastatic breast cancer, and (4) inflammatory breast cancer			hormone receptor-negative participants, 39 of 378 (10.3%) became pregnant naturally; GnRHa group: 25 of 185 (13.5%) Control group: 14 of 193 (7.3%) OR, 2.06; 95% CI, 1.03-4.11; P=0.04; I^2=0%, P = 0.89	(downgraded due to indirectness, heterogeneity) **Sources of funding:** none reported
Abbreviations: GnRHa = Gonadotropin-releasing Hormone Agonists RCT = Randomised Controlled Trial OR = Odds Ratio					

Source: ZY, Li, Dong YL, Cao XZ, Ren SS, and Zhang Z. "Gonadotropin-Releasing Hormone Agonists for Ovarian Protection During Breast Cancer Chemotherapy: A Systematic Review and Meta-Analysis." [In eng]. Menopause (New York, N.Y.) 29, no. 9 (2022-9-1 2022): 1093-100. https: //doi.org/doi: 10.1097/GME.0000000000002019. https: //pubmed.ncbi.nlm.nih.gov/35917530/.

95% CI = 95% Confidence Interval

n.a. = not Available, not Applicable

Kapitel 7.1.2: Schwangerschaft nach Mammakarzinom

Verknüpfte Empfehlungen:

Empfehlung 7.4:

Von einer Schwangerschaft soll nach einer Mammakarzinomerkrankung nicht abgeraten werden. Dies gilt unabhängig vom Hormonrezeptorstatus.

Empfehlung 7.5:

Der Zeitpunkt der eintretenden Schwangerschaft nach einer Mammakarzinomerkrankung korreliert nicht mit einer schlechteren Prognose.

Literaturreferenzen: [274], [275]

Source: M, Lambertini, Blondeaux E, Bruzzone M, Perachino M, Anderson RA, de Azambuja E, Poorvu PD, et al. "Pregnancy after Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 39, no. 29 (2021-10-10 2021): 3293-305. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34197218/.

Aim	Design and participants	Exposure and Control	Outcomes	Results	Quality and comment
Aim: To assess the likelihood of pregnancy in women with prior history of BC, their reproductive outcomes, and maternal safety	**Design**: Systematic Review and Meta-Analysis **Search date**: until Oct 31, 2020 **Searched databases**: Medline, Web of Science, Cochrane Database **Included study designs**: retrospective or prospective case-control	**Exposure** women with breast cancer who became pregnant any time after diagnosis **Control** healthy women from the general population breast cancer patients diagnosed at	**1) Likelihood of pregnancy** (comparison between the proportion of patients who had a pregnancy after prior history of BC versus the proportion of healthy women from the general population who had a pregnancy and the proportion of survivors	**1) Likelihood of pregnancy** 7 records included: Of 3,393,632 women included in these studies, 3,289,113 were from the general population, 57,739 had malignancies other than BC, and	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 4 critical flaws (items 2, 7, 9, 13) **Additional concerns about quality / limitations**

Source: M, Lambertini, Blondeaux E, Bruzzone M, Perachino M, Anderson RA, de Azambuja E, Poorvu PD, et al. "Pregnancy after Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 39, no. 29 (2021-10-10 2021): 3293-305. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34197218/.					
	or cohort studies and clinical trials reporting on pregnancy after BC **Number of included studies**: 39 **Number of included patients**: Among the 8,263,980 women included in these studies, 8,093,401 were from the general population, 57,739 had malignancies other than BC, and 112,840 had breast tumors Among the 112,840 patients with BC, 7,505 had a pregnancy after diagnosis **Mean/median age**: NR **Inclusion criteria**:	reproductive age but without subsequent pregnancy after diagnosis (comparator group for survival analysis)	who had a pregnancy after prior history of other malignancies) **2) Reproductive outcomes** in patients with prior history of BC versus those in healthy women from the general population, in terms of pregnancy completion, induced abortion, spontaneous abortion, low birth weight, preterm birth, intrauterine fetal death, small for gestational age, pre-eclampsia, congenital abnormalities, elective delivery, emergency caesarean section, and postpartum bleeding **3) Maternal safety** by comparing survival outcomes between	46,780 had breast tumors BC survivors had a 60% reduced likelihood of having a subsequent pregnancy (RR, 0.40; 95% CI, 0.32 to 0.49) **2) Reproductive Outcomes** 9 records included: 4,817,692 women with a pregnancy were included, of whom 4,814,452 from the general population and 3,240 had previous BC No difference was observed between patients with BC and the general population in terms of completed pregnancies:	Limited data for several reproductive outcomes; lack of data (patient characteristics, tumor size, anticancer therapies); High heterogeneity in some analyses (inclusion of studies with diefferent design, sample size, inclusion criteria, period of conduction, and controlling factors) **Quality of included studies**: most studies were retrospective observational **Sources of funding:** Supported in part by the Italian Ministry of Health—5x1000 funds 2017 (no grant number) and the Italian Association for Cancer

Source: M, Lambertini, Blondeaux E, Bruzzone M, Perachino M, Anderson RA, de Azambuja E, Poorvu PD, et al. "Pregnancy after Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 39, no. 29 (2021-10-10 2021): 3293-305. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34197218/.					
	studies with available information on one or more of the three outcomes of interest (likelihood of pregnancy after BC, reproductive outcomes, and/or maternal safety); and availability or possibility to estimate data on relative risk (RR), odds ratio (OR), and hazard ratio (HR), according to the analyzed outcome, with their 95% CIs **Exclusion**: (1) case reports and case series including less than 10 patients; (2) studies reporting on		BC patients with or without a subsequent pregnancy, in terms of **disease-free survival (DFS)** and **overall survival (OS)**	(OR, 1.21; 95% CI, 0.48 to 3.03), spontaneous abortions: (OR, 1.04; 95% CI, 0.86 to 1.26) induced abortions: (OR, 1.40; 95% CI, 0.71 to 2.76) developing pre-eclampsia: (OR, 1.03; 95% CI, 0.27 to 3.98) and postpartum bleeding: (OR, 0.88; 95% CI, 0.57 to 1.37) increased risk of caesarean section was observed in patients with BC (OR, 1.14; 95% CI, 1.04 to 1.25)	Research (AIRC; MFAG 2020 ID 24698) **Level of Evidence** Oxford 2011 Level 3

Source: M, Lambertini, Blondeaux E, Bruzzone M, Perachino M, Anderson RA, de Azambuja E, Poorvu PD, et al. "Pregnancy after Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 39, no. 29 (2021-10-10 2021): 3293-305. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34197218/.					
	pregnancy-associated BC (ie, BC diagnosed during pregnancy or within 5 years after pregnancy) with no data on pregnancy following BC diagnosis; and (3) ongoing studies with the results not presented nor published at the time of the literature search			Offspring of patients with BC was at increased risk of low birth weight (OR, 1.50; 95% CI, 1.31 to 1.73), preterm birth (OR, 1.45; 95% CI, 1.11 to 1.88) and small for gestational age (OR, 1.16; 95% CI, 1.01 to 1.33) compared with the general population No significantly increased risk of congenital abnormalities was observed for the offspring of BC survivors (OR, 1.63; 95% CI, 0.89 to 2.98) <u>Subgroup analysis</u> As compared with offspring of women from the general population, the increased risk of low	

Source: M, Lambertini, Blondeaux E, Bruzzone M, Perachino M, Anderson RA, de Azambuja E, Poorvu PD, et al. "Pregnancy after Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 39, no. 29 (2021-10-10 2021): 3293-305. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34197218/.					
				birth weight and small for gestational age appeared to be restricted to BC patients with previous exposure to chemotherapy **Maternal Safety** **DFS** (patients with or without pregnancy after BC) 11 studies: Among them: 4 studies: relapse-free survival, 1 study distant recurrence-free survival, 1 study distant DFS better DFS in those with post-treatment pregnancy: (HR, 0.66; 95% CI, 0.49 to 0.89) no effect of pregnancy after BC was observed in	

Source: M, Lambertini, Blondeaux E, Bruzzone M, Perachino M, Anderson RA, de Azambuja E, Poorvu PD, et al. "Pregnancy after Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 39, no. 29 (2021-10-10 2021): 3293-305. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34197218/.

				patients with hormone receptor–positive (HR, 1.10; 95% CI, 0.73 to 1.66) or hormone receptor–negative (HR, 0.72; 95% CI, 0.55 to 0.95) disease The lack of detrimental effect of pregnancy after BC was also observed irrespective of pregnancy outcome and timing of pregnancy after BC) **OS** Reported in 21 studies compared to patients with BC without subsequent pregnancy, those with a post-treatment pregnancy showed	

Source: M, Lambertini, Blondeaux E, Bruzzone M, Perachino M, Anderson RA, de Azambuja E, Poorvu PD, et al. "Pregnancy after Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 39, no. 29 (2021-10-10 2021): 3293-305. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34197218/.					
				better OS (HR, 0.56; 95% CI, 0.45 to 0.68) subgroup analysis: lack of detrimental effect of pregnancy after BC was observed irrespective of nodal status, previous treatment, pregnancy outcome and timing of pregnancy after BC; no effect of pregnancy after BC was observed in BRCA-mutated patients (HR, 0.85; 95% CI, 0.51 to 1.43)	
Abbreviations: BC = Breast Cancer DFS = Disease-Free Survival OS = Overall survival HR = Hazard Ratio					

Source: M, Lambertini, Blondeaux E, Bruzzone M, Perachino M, Anderson RA, de Azambuja E, Poorvu PD, et al. "Pregnancy after Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 39, no. 29 (2021-10-10 2021): 3293-305. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/34197218/.

OR = Odds Ratio

RR = Relative Risk

95% CI = 95% Confidence Interval

NR = not Reported

Verknüpfte Empfehlungen:

Empfehlung 7.4:

Von einer Schwangerschaft soll nach einer Mammakarzinomerkrankung nicht abgeraten werden. Dies gilt unabhängig vom Hormonrezeptorstatus.

Empfehlung 7.5:

Der Zeitpunkt der eintretenden Schwangerschaft nach einer Mammakarzinomerkrankung korreliert nicht mit einer schlechteren Prognose.

Literaturreferenzen: [274], [275]

Source: V, D'Ambrosio, Vena F, Di Mascio D, Faralli I, Musacchio L, Boccherini C, Brunelli R, et al. "Obstetrical Outcomes in Women with History of Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Breast cancer research and treatment 178, no. 3 (2019-12 2019): 485-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31451975/.

Aim	Design and participants	Exposure	Outcomes	Results	Quality and comment
Aim: to evaluate the strength of association between history of BC and obstetrical outcomes	**Design**: Systematic Review and Meta-Analysis **Search date**: up to 04/2019 **Searched databases**: PubMed, Embase, Medline, Cinahl, clinicaltrials.gov **Included study designs**: retrospective cohort studies	Pregnant women with a history of BC Comparison: Pregnant women without a history of BC	**Obstetrical complications** Preterm birth (PTB) < 37 weeks at delivery low birth weight (LBW): birth weight < 2500 g; Cesarean section Intrauterine fetal death (IUFD): fetal demise after 20 weeks of pregnancy	**Preterm birth** Higher risk in BC patients: OR, 1.68, 95% CI 1.43 – 1.99, I^2=12% **Low-birth weight** Higher risk in BC patients: OR, 1.88, 95% CI 1.55 – 2.27, I^2=0%	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 3 critical flaws (items 11, 13, 15) **Additional concerns about quality / limitations** small number of included studies, their retrospective,

Source: V, D'Ambrosio, Vena F, Di Mascio D, Faralli I, Musacchio L, Boccherini C, Brunelli R, et al. "Obstetrical Outcomes in Women with History of Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Breast cancer research and treatment 178, no. 3 (2019-12 2019): 485-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31451975/.					
	Number of included studies: 4 published between 2006 and 2017; study sizes: 165 to 4,031,349 **Number of included patients**: 1,466 cases of BC survivors; 6,912,485 controls **Mean/median age**: Maternal age: Study group: 34.3 (range 34-34.6); Control: 28.4 (range 27-30) Median interval between BC diagnosis and first pregnancy: 2.21 years Min: 1.5 y Max: 3.08 y		Fetal anomalies: minor and major malformations, including chromosomal anomalies	**Cesarean section** Higher risk in BC patients: OR, 1.78, 95% CI 1.39 – 2.27, I^2=89% **Intrauterine fetal death** OR, 1.25, 95% CI 0.36 – 4.35, I^2=0% **Fetal anomalies** Higher risk in BC patients: OR, 1.45, 95% CI 1.01 – 2.09, I^2=56%	non-randomized design, differences between the included populations, and dissimilar approach for the BC management overall sample sizes might be unbalanced, with 0.02% in the study group and 99.98% in the control group **Quality of included studies**: Assessed with Newcastle-Ottawa Scale **Level of Evidence:** Oxford 2011: Level 3 **Sources of funding:** no specific funding

Source: V, D'Ambrosio, Vena F, Di Mascio D, Faralli I, Musacchio L, Boccherini C, Brunelli R, et al. "Obstetrical Outcomes in Women with History of Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Breast cancer research and treatment 178, no. 3 (2019-12 2019): 485-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31451975/.

	Inclusion criteria: Prospective / retrospective cohorts reporting and describing the prevalence of obstetrical outcomes in pregnant women with BC history **Exclusion**: personal communications, case reports, reviews, conference abstracts, and case series with < 3 cases				

Abbreviations:

BC = Breast Cancer

PTB = Preterm birth

LBW = Low birth weight

IUFD = Intrauterine Fetal Death

Source: V, D'Ambrosio, Vena F, Di Mascio D, Faralli I, Musacchio L, Boccherini C, Brunelli R, et al. "Obstetrical Outcomes in Women with History of Breast Cancer: A Systematic Review and Meta-Analysis." [In eng]. Breast cancer research and treatment 178, no. 3 (2019-12 2019): 485-92. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/31451975/.

OR = Odds Ratio

95% CI = 95% Confidence Interval

y = years

Verknüpfte Empfehlungen:

Empfehlung 7.8:

Reproduktionsmedizinische Verfahren können nach einer Mammakarzinomerkrankung zum Erreichen einer Schwangerschaft eingesetzt werden.

Empfehlung 7.9:

Die Patientin soll darüber aufgeklärt werden, dass die Erfolgsaussichten für eine intakte Schwangerschaft bzw. ein Kind bei autologer Eizellverwendung bei Mammakarzinompatientinnen geringer sind als bei Nicht-Karzinompatientinnen.

Literaturreferenzen: [276], [277]

Source: RJ, Rodgers, Reid GD, Koch J, Deans R, Ledger WL, Friedlander M, Gilchrist RB, Walters KA, and Abbott JA. "The Safety and Efficacy of Controlled Ovarian Hyperstimulation for Fertility Preservation in Women with Early Breast Cancer: A Systematic Review." [In eng]. Human reproduction (Oxford, England) 32, no. 5 (2017-5-1 2017): 1033-45. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/28333356/.

Aims	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: safety and efficacy of controlled ovarian hyperstimulation (COH) for fertility preservation in women with early breast cancer	**Design**: Systematic review **Search date**: up to 04/2016 **Searched databases**: Medline, Embase, Cochrane library **Included study designs**:	**Intervention** Controlled ovarian hyperstimulation Letrozole: 882 Tamoxifen: 102 Anastrozole co-administration: 7 **Control** No COH	**Primary Outcome**: Breast cancer mortality / Recurrence **Secondary Outcome**: Peak oestradiol concentration (pg/ml) Oocyte yield Treatment complications	**Primary Outcome**: **Breast cancer mortality /** **Recurrence** Data from 4 studies, encompassing 464 women 1) prospective non-randomized study	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 6 critical flaws (items 2, 4, 7, 9, 13, 15) **Additional concerns about quality / limitations**

Source: RJ, Rodgers, Reid GD, Koch J, Deans R, Ledger WL, Friedlander M, Gilchrist RB, Walters KA, and Abbott JA. "The Safety and Efficacy of Controlled Ovarian Hyperstimulation for Fertility Preservation in Women with Early Breast Cancer: A Systematic Review." [In eng]. Human reproduction (Oxford, England) 32, no. 5 (2017-5-1 2017): 1033-45. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/28333356/.					
	Prospective (n=8) and retrospective studies (n=7) **Number of included studies**: 15 **Number of included patients**: 1,516 COH: 991 Control: 525 **Mean/median age**: n.a. **Study population:** premenopausal women diagnosed with Stage I–IIIB breast cancer who underwent COH in the immediate post-operative period, prior to the administration of chemotherapy **Inclusion criteria**: All COH protocols included; studies			COH with letrozole co-administration: N= 120 women with Stage I–III FU: 5.0y (SD 2.1) Control: N=217 women with similar disease who declined fertility preservation Treatment FU: 6.9y (SD 3.6) <u>breast cancer relapse-free survival:</u> HR 0.77, 95% CI 0.28–2.13; P = 0.61 <u>recurrence:</u> COH group: 6/120 (5%) recurrence Control group: 12/217 (5.5%) P=0.86	Only observational data; small patient numbers; relatively short follow-up Safety of COH is based on a limited number of observational studies **Quality of included studies**: **Level of Evidence:** Oxford 2011 Level 3 (downgraded: Low quality review; observational data) **Sources of funding:** none

Source: RJ, Rodgers, Reid GD, Koch J, Deans R, Ledger WL, Friedlander M, Gilchrist RB, Walters KA, and Abbott JA. "The Safety and Efficacy of Controlled Ovarian Hyperstimulation for Fertility Preservation in Women with Early Breast Cancer: A Systematic Review." [In eng]. Human reproduction (Oxford, England) 32, no. 5 (2017-5-1 2017): 1033-45. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/28333356/.

	reported data on primary and secondary outcome **Exclusion**: NR			*COH prior to surgery* COH group: 1/14 (7.0%) Control group: 5/106 (4.0%) P=0.47 <u>2) prospective observational study</u> N=29 women with Stage 0–IIIB breast cancer COH using tamoxifen only (12 women, 13 cycles; median follow-up of 418 days (SD 109)) tamoxifen plus FSH (7 women, 9 cycles; median follow-up of 609 days (SD 89)); letrozole plus FSH (11 women, 11 cycles; median follow-up of 272 days (SD 31); control:	

Source: RJ, Rodgers, Reid GD, Koch J, Deans R, Ledger WL, Friedlander M, Gilchrist RB, Walters KA, and Abbott JA. "The Safety and Efficacy of Controlled Ovarian Hyperstimulation for Fertility Preservation in Women with Early Breast Cancer: A Systematic Review." [In eng]. Human reproduction (Oxford, England) 32, no. 5 (2017-5-1 2017): 1033-45. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/28333356/.					
				31 women not undergoing fertility preservation treatment (median follow-up of 660 days (SD 71)) recurrence rate after COH COH group: 3/29 (10.3%) women Control group: 3/31 (9.7%) women HR, 1.5; 95% CI, 0.29–7.4, The duration of follow-up was significantly shorter in the letrozole-IVF group (P < 0.001) as the letrozole protocol was added to the study after its commencement 3) Prospective observational study (national cancer registry)	

Source: RJ, Rodgers, Reid GD, Koch J, Deans R, Ledger WL, Friedlander M, Gilchrist RB, Walters KA, and Abbott JA. "The Safety and Efficacy of Controlled Ovarian Hyperstimulation for Fertility Preservation in Women with Early Breast Cancer: A Systematic Review." [In eng]. Human reproduction (Oxford, England) 32, no. 5 (2017-5-1 2017): 1033-45. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/28333356/.					
				COH plus tamoxifen 43 women with ER+ breast cancer COH without tamoxifen 27 women with an oestrogen receptor negative (ER−) breast cancer Follow-up: 3–10 years cancer recurrence FSH plus tamoxifen versus tamoxifen alone groups: 2/33 (6.1%) versus 2/13 (15.4%) Mortality: 2/33 (6.1%) versus 1/13 (7.7%) 4) Retrospective study Recurrence	

Source: RJ, Rodgers, Reid GD, Koch J, Deans R, Ledger WL, Friedlander M, Gilchrist RB, Walters KA, and Abbott JA. "The Safety and Efficacy of Controlled Ovarian Hyperstimulation for Fertility Preservation in Women with Early Breast Cancer: A Systematic Review." [In eng]. Human reproduction (Oxford, England) 32, no. 5 (2017-5-1 2017): 1033-45. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/28333356/.					
				2 of 24 (8.3%) women with breast cancer who underwent COH for fertility preservation during the follow-up period of 20–52 months (no control group, BC stage at diagnosis not reported) **Secondary Outcome**: 1) Co-administration of an AI: Peak oestradiol concentration (pg/ml) Reduction, when letrozole is administred (5 studies) 2 studies: compared the GnRH agonist and hCG triggers in women undergoing COH with letrozole co-administration:	

Source: RJ, Rodgers, Reid GD, Koch J, Deans R, Ledger WL, Friedlander M, Gilchrist RB, Walters KA, and Abbott JA. "The Safety and Efficacy of Controlled Ovarian Hyperstimulation for Fertility Preservation in Women with Early Breast Cancer: A Systematic Review." [In eng]. Human reproduction (Oxford, England) 32, no. 5 (2017-5-1 2017): 1033-45. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/28333356/.					
				No difference found in peak oestradiol concentrations <u>Impact on oocyte yield</u> 2 studies encompassing 122 women: no change in the oocyte yield; 2 studies: small but significant decrease in oocyte yield <u>2) Tamoxifen during COH</u> 4 studies Peak oestradiol concentrations were significantly higher in women who were administered tamoxifen versus women undergoing natural cycle IVF	
Abbreviations: COH = Controlled Ovarian Hyperstimulation					

Source: RJ, Rodgers, Reid GD, Koch J, Deans R, Ledger WL, Friedlander M, Gilchrist RB, Walters KA, and Abbott JA. "The Safety and Efficacy of Controlled Ovarian Hyperstimulation for Fertility Preservation in Women with Early Breast Cancer: A Systematic Review." [In eng]. Human reproduction (Oxford, England) 32, no. 5 (2017-5-1 2017): 1033-45. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/28333356/.

FU = Follow-Up

HR = Hazard Ratio

SD = Standard Deviation

n.a. = not Available, not Applicable

NR = not Reported

Kapitel 7.1.3: Mammakarzinom während der Schwangerschaft

Verknüpfte Empfehlungen:

Empfehlung 7.13:

Eine Anti-HER2-Therapie soll in der Schwangerschaft nicht verabreicht werden.

Literaturreferenzen: [278], [279]

Source: LY, Xia, Hu QL, and Zhou Q. "Use of Trastuzumab in Treating Breast Cancer During Pregnancy: A Systematic Review and Meta-Analysis." [In eng]. BMC women's health 21, no. 1 (2021-4-21 2021): 169. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33882925/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: to evaluate fetal safety in pregnant, breast cancer patients on trastuzumab therapy	**Design**: Systematic review and Meta-Analysis **Search date**: up to 18/02/2020 **Searched databases**: Medline (PubMed) and Embase **Included study designs**: Case reports, small sample reviews **Number of included studies**: 22 (included in Meta-Analysis)	**Intervention** trastuzumab 2 pregnant women and 3 fetuses: combination of trastuzumab + endocrine therapy (1 case: tamoxifen; 1 case tamoxifen + goserelin) 6 pregnant women and 6 fetuses: combination of trastuzumab and chemotherapy 14 of 20 patients (70%)that reported gestational week patients	Pregnancy, fetal and newborn complications, follow-up results of neonatal health	**1) Pregnancy:** **Gestational weeks of delivery** ranged from 27 to 39 weeks, with an average of 34.3 weeks **Cesarean section** 13 patients (61.9%) **Spontaneous labor** 8 patients (38.1%) (no information in 1 patient) **Complications during pregnancy:**	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 6 critical flaws (items 2, 7, 9, 11, 13, 15) **Additional concerns about quality**: Case studies (no prospective studies have been conducted)

Source: LY, Xia, Hu QL, and Zhou Q. "Use of Trastuzumab in Treating Breast Cancer During Pregnancy: A Systematic Review and Meta-Analysis." [In eng]. BMC women's health 21, no. 1 (2021-4-21 2021): 169. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33882925/.					
	Number of included patients: 22 pregnant women and 23 fetuses **Mean age of pregnant patients**: 31.8 Range: 27 – 38 years **Hormone-receptor status:** reported by 20 patients 15/20 (75%): hormone-receptor negative 5/20 (25%) hormone-receptor positive **Inclusion criteria**: (1) breast cancer patients were exposed to trastuzumab during pregnancy, (2) studies including at least one of the main outcomes **Exclusion**: (1) spontaneous abortion,	chose to continue using trastuzumab after pregnancy confirmation average duration use of trastuzumab: 17 weeks; average total dose: 2791 mg gestational age of exposure to trastuzumab: 0-34 weeks **Control:** n.a.		Occurred in 77.2% of patients Amniotic fluid reduction: 15/22 (68.2%) **Decreased ejection fraction:** 2/22 (9.1%) **2) Fetal and newborn complications** **Newborn** Average apgar score: 7.9 Average birth weight: 2310 Healthy newborns: 9/23 (39.1%) Compliactions: 14/23 (60.9%) **Most common neonatal complications:** Respiratory related problems (transient tachypnoea and respiratory distress syndrome)	Only few reports on use of trastuzumab during pregnancy available Only 2 patients used trastuzumab in early pregnancy **Quality of included studies**: **Level of Evidence:** Oxford 2011 Level 4 **Sources of funding:** n.a.

Source: LY, Xia, Hu QL, and Zhou Q. "Use of Trastuzumab in Treating Breast Cancer During Pregnancy: A Systematic Review and Meta-Analysis." [In eng]. BMC women's health 21, no. 1 (2021-4-21 2021): 169. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33882925/.					
	(2) voluntary termination of pregnancy			**Trastuzumab only exposed in early pregnancy:** Fewer pregnancy and fetus related complications (compared to other periods) p=0.043 No significant difference in the incidence of neonatal complications (p=0.178) **Complications and patient age** Patients with gestational age greater than 30 years were more likely to have neonatal complications after trastuzumab during pregnancy (OR = 7.778, 95%CI 1.2–50.424, P = 0.04) **Complications and influencing factors**	

Source: LY, Xia, Hu QL, and Zhou Q. "Use of Trastuzumab in Treating Breast Cancer During Pregnancy: A Systematic Review and Meta-Analysis." [In eng]. BMC women's health 21, no. 1 (2021-4-21 2021): 169. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33882925/.					
				Pregnancy and fetal complications, neonatal complications and child deaths were not statistically different in terms of tumor stage, trastuzumab schedule, exposed time, total dose of trastuzumab, combined endocrine therapy and combined chemotherapy **3) Follow-up** 4/23 (17.4%) of the children died after an average FU of 25.3 months (all of them suffer serious complications after birth)	
Abbreviations: 95% CI = 95% Confidence Interval n.a. = not Available, not Applicable					

Verknüpfte Empfehlungen:

Empfehlung 7.13:

Eine Anti-HER2-Therapie soll in der Schwangerschaft nicht verabreicht werden.

Literaturreferenzen: [278], [279]

Source: A, Andrikopoulou, Apostolidou K, Chatzinikolaou S, Bletsa G, Zografos E, Dimopoulos MA, and Zagouri F. "Trastuzumab Administration During Pregnancy: An Update." [In eng]. BMC cancer 21, no. 1 (2021-4-26 2021): 463. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33902516/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: effect of trastuzumab on fetal and maternal outcome	**Design**: Systematic Review **Search date**: up to 01/09/2020 **Searched databases**: MEDLINE, ClinicalTrials.gov **Included study designs**: Case studies **Number of included studies**: 28 **Number of included patients**: 30 patients and 32 fetuses (exposed to	**Intervention** Trastuzumab during pregnancy As **monotherapy** regimen (14 cases); **Combination** with: pertuzumab (1 study); vinorelbine (2 studies); paclitaxel (2 studies); docetaxel and carboplatin (2 studies); tamoxifen (3 studies);	**Fetal outcomes**: Oligohydramnios or anhydramnios; Cesarean section; Gestational age at delivery; Birth weight at delivery; Completely healthy neonate; **Maternal outcomes**: cardiotoxicity; decreased ejection fraction	Adverse events **1) Fetal outcomes** **Complications with Oligohydramnios or anhydramnios** in 58.1% 17 of 24 pregnancies (70.8%) trastuzumab was administered during the second or/and third trimester 1 of the 6 cases (16.7%) of trastuzumab exposure exclusively during first trimester à trend pointing to a	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review; critically low; 4 critical flaws (items 2, 7, 9, 13) **Additional concerns about quality**: Case studies **Quality of included studies**: n.a. **Level of Evidence:** Oxford 2011: Level 4 (downgraded due to low

Source: A, Andrikopoulou, Apostolidou K, Chatzinikolaou S, Bletsa G, Zografos E, Dimopoulos MA, and Zagouri F. "Trastuzumab Administration During Pregnancy: An Update." [In eng]. BMC cancer 21, no. 1 (2021-4-26 2021): 463. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33902516/.					
	trastuzumab during pregnancy) **Mean/median age**: Mean age of patients at pregnancy 31.1 years (SD: 3.96; median: 31.5; range 23–38) mean age at breast cancer diagnosis was 29.9 years (SD: 4.21; median: 30.0; range: 22–38) **Inclusion criteria**: All studies that examined the efficacy and safety of trastuzumab during pregnancy administration of trastuzumab at some point during pregnancy even if treatment commenced	tamoxifen and lapatinib (1 study); docetaxel and cyclophosphamide (1 study); doxorubicin and cyclophosphamide and paclitaxel (1 study); concurrently with brain RT (1 study) in more than half of the cases administered in metastatic setting The mean duration of trastuzumab administration during gestation was 15.7 weeks (SD: 10.8; median: 17.5; range: 1–32) 23.3% of patients		positive association between the duration of trastuzumab treatment and the development of oligohydramnios or anhydramnios: OR 1.05, 95% CI: 0.96–1.14, increment: 1 week, P = 0.316 **Cesarean section:** in 67.9% of cases; 9 pregnancies: vaginal delivery **Gestational age at delivery:** Mean: 34.6 weeks (SD: 3.26) Median: 35.4 (range: 27-39) **Birth weight at delivery** Mean: 2371g (SD: 771.2)	quality review and low quality studies) **Sources of funding:** no specific funding

Source: A, Andrikopoulou, Apostolidou K, Chatzinikolaou S, Bletsa G, Zografos E, Dimopoulos MA, and Zagouri F. "Trastuzumab Administration During Pregnancy: An Update." [In eng]. BMC cancer 21, no. 1 (2021-4-26 2021): 463. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33902516/.

	prior to pregnancy initiation prospective, retrospective studies, case reports **Exclusion**: all cases where therapeutic or spontaneous abortion occurred articles assessing trastuzumab administration before or after the gestation period	were exposed to trastuzumab during all trimesters of pregnancy 20.0% of patients with breast cancer were exposed to trastuzumab exclusively during the first trimester **Control** -		Median: 2490 (range: 1015-3820) **Completely healthy neonate:** In 13 cases (43.3%) **Theremaining cases**: renal agenesis/hypoplasia (2 cases), mild transient tachypnoea (three cases), respiratory distress syndrome (six cases), respiratory failure (two cases), renal failure (three cases), transient respiratory failure and elevated creatinine (one case), severe pulmonary hypoplasia (one case), capillary leak syndrome	

Source: A, Andrikopoulou, Apostolidou K, Chatzinikolaou S, Bletsa G, Zografos E, Dimopoulos MA, and Zagouri F. "Trastuzumab Administration During Pregnancy: An Update." [In eng]. BMC cancer 21, no. 1 (2021-4-26 2021): 463. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33902516/.

				and necrotizing enterocolitis (one case), pulmonary hypertension and persistence of arterial canal (one case), prematurity-related disorders (two cases), conductive hearing loss and mild hypertonia/hyperreflexia (one case), bacterial sepsis (one case), cardiorespiratory arrest (one case) 41.7% (10 out of 24) of fetuses exposed to trastuzumab during the second and/or third trimester were born completely healthy and 75.0% of fetuses (3 cases) exposed	

Source: A, Andrikopoulou, Apostolidou K, Chatzinikolaou S, Bletsa G, Zografos E, Dimopoulos MA, and Zagouri F. "Trastuzumab Administration During Pregnancy: An Update." [In eng]. BMC cancer 21, no. 1 (2021-4-26 2021): 463. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33902516/.					
				exclusively in the first trimester à trend pointing to a negative association between the duration of trastuzumab administration and the delivery of a completely healthy neonate did not reach statistical significance OR = 0.921, 95% CI: 0.85–1.00, P = 0.061 **2) Maternal outcomes** all patients with breast cancer were alive at a median follow-up of 47.0 months (ranging between 9 and 100 months), while only two patients relapsed during follow-up according to existing data;	

Source: A, Andrikopoulou, Apostolidou K, Chatzinikolaou S, Bletsa G, Zografos E, Dimopoulos MA, and Zagouri F. "Trastuzumab Administration During Pregnancy: An Update." [In eng]. BMC cancer 21, no. 1 (2021-4-26 2021): 463. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33902516/.					
				three cases (10%) of cardiotoxicity and decreased ejection fraction during pregnancy	

Abbreviations:

RT = Radiation Therapy

SD = Standard Deviation

OR = Odds Ratio

95% CI = 95% Confidence Interval

n.a. = not Available, not Applicable

Verknüpfte Empfehlungen:

Empfehlung 7.14:

Eine endokrine Therapie soll in der Schwangerschaft nicht verabreicht werden.

Literaturreferenzen: [280]

Source: TN, Schuurman, Witteveen PO, van der Wall E, Passier JLM, Huitema ADR, Amant F, and Lok CAR. "Tamoxifen and Pregnancy: An Absolute Contraindication?" [In eng]. Breast cancer research and treatment 175, no. 1 (2019-5 2019): 17-25. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30707336/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: effect of tamoxifen exposure during pregnancy	**Design**: Systematic Review **Search date**: up to 04/10/2018 **Searched databases**: PubMed, database of the Netherlands Pharmacovigilance Centre Lareb, database of the International Network on Cancer, Infertility and Pregnancy **Included study designs**: case reports and reviews of case reports	**Intervention** Tamoxifen **Control** -	Safety of tamoxifen congenital abnormalities fetal defects	total number of 238 pregnancies during tamoxifen therapy Of the 142 live births documented, 13 infants had a congenital malformation (1: 11) including the pregnancies without live birth but with documented fetal outcome, a total of 21 out of 167 pregnancies were complicated by **fetal defects** (1: 8) 71 of the reported 238 pregnancies were not	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 3 critical flaws (items 2, 7, 9) **Additional concerns about quality**: General low quality of evidence (based on case reports and other retrospective data); reporting bias due to the fact that adverse outcomes are much more likely to be documented

Source: TN, Schuurman, Witteveen PO, van der Wall E, Passier JLM, Huitema ADR, Amant F, and Lok CAR. "Tamoxifen and Pregnancy: An Absolute Contraindication?" [In eng]. Breast cancer research and treatment 175, no. 1 (2019-5 2019): 17-25. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30707336/.					
	Number of included studies: 14 **Number of included patients**: 238 pregnancies **Mean/median age**: n.a. **Inclusion criteria**: English / Dutch language study reporting on the research question of this review **Exclusion**: studies not meeting the research question animal studies			included in this evaluation, since 56 pregnancies had an unknown outcome, 12 spontaneous abortions occurred without known cause, and 2 induced abortions and 1 ectopic pregnancy were reported total incidence of **congenital anomalies** cannot be assessed adequately based on these findings number of reports on tamoxifen therapy after the first trimester was very limited, but one article was found showing three known congenital abnormalities out of 15 pregnancies overall miscarriage rate: 6.7%	no causal relationships; additional risk factors; lack of long-term follow-up of the exposed infants; **Quality of included studies**: Low quality studies **Level of Evidence:** Oxford 2011 Level 4 (downgraded due to low quality review and low study quality) **Sources of funding:** n.a.

Source: TN, Schuurman, Witteveen PO, van der Wall E, Passier JLM, Huitema ADR, Amant F, and Lok CAR. "Tamoxifen and Pregnancy: An Absolute Contraindication?" [In eng]. Breast cancer research and treatment 175, no. 1 (2019-5 2019): 17-25. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/30707336/.

Abbreviations:

n.a. = not Available, not Applicable

Kapitel 7.2: Transgender und Brustkrebs

Verknüpfte Empfehlungen:

Empfehlung 7.48:

Bei Transgender-Männern soll vor der Mastektomie eine altersentsprechende Früherkennung und die histologische Untersuchung des entfernten Brustgewebes durchgeführt werden.

Literaturreferenzen: [281], [282], [283]

Source: AC, Fledderus, Gout HA, Ogilvie AC, and van Loenen DKG. Breast Malignancy in Female-to-Male Transsexuals: Systematic Review, Case Report, and Recommendations for Screening. (2020-10 2020). https: //pubmed.ncbi.nlm.nih.gov/32679529/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Authors aimed to provide an insight into the reported number of Female-to Male (FtM) transsexuals developing breast cancer after testosterone therapy by systematically reviewing the literature and evaluating the evidence regarding associations between testosterone	**Design**: Systematic Review **Search date**: Search was performed 06/2020 **Searched databases**: PubMed/Medline, Ovid/Embase **Included study designs**: Case reports, Cohort studies **Number of included studies**: 22		**Incidence**	**Incidence**: The incidence of breast cancer cases described in the FtM transsexuals cohort studies is shown to be significantly lower than the breast cancer incidence in natal women. The lower incidence of breast cancer found in the studies can	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 3 critical flaws (items 2, 7, 13) **Overall quality of evidence**: critically low **Additional concerns about quality**: Due to the low level of

Source: AC, Fledderus, Gout HA, Ogilvie AC, and van Loenen DKG. Breast Malignancy in Female-to-Male Transsexuals: Systematic Review, Case Report, and Recommendations for Screening. (2020-10 2020). https: //pubmed.ncbi.nlm.nih.gov/32679529/.					
therapy and breast cancer	**Number of included patients**: n.a. **Mean**: 42 years **Median age**: 41 year **Inclusion criteria**: All articles evaluating breast cancer in FtM transsexuals after testosterone therapy were deemed eligible. ***Exclusion**: /*			be attributed to the performed mastectomies. Breast cancer screening of FtM transsexuals prior to mastectomy and histological examination of the mammalian tissue after mastectomy could be considered. When breast tumors are discovered before mastectomy, tumors can be removed more precisely. In consultation with every individual FtM transsexual, physicians can decide if screening before and after mastectomy is necessary.	evidence (case reports) and high risk of bias of the included cohort studies, it is not possible to conclude a correlation between hormone therapy and the development of breast cancer. All cohort studies and case reports did not report screening for cancer in advance of testosterone therapy, which complicates the evaluation of its potential causal relationship with cancer. Confounders were poorly described and none was appropriately corrected for in the analysis. **Quality of included studies:** JBI tools used.

Source: AC, Fledderus, Gout HA, Ogilvie AC, and van Loenen DKG. Breast Malignancy in Female-to-Male Transsexuals: Systematic Review, Case Report, and Recommendations for Screening. (2020-10 2020). https: //pubmed.ncbi.nlm.nih.gov/32679529/.					
					Case Reports do not match the AMSTAR 2 criteria. Due to the small study population we propose to downgrade the **level of evidence** from 3a to **3b** **Sources of funding:** There was no funding for this study.
Abbreviations: FtM = Female-to Male n.a. = not Available, not Applicable					

Verknüpfte Empfehlungen:

Empfehlung 7.48:

Bei Transgender-Männern soll vor der Mastektomie eine altersentsprechende Früherkennung und die histologische Untersuchung des entfernten Brustgewebes durchgeführt werden.

Literaturreferenzen: [281], [282], [283]

Source: R, Joint, Chen ZE, and Cameron S. "Breast and Reproductive Cancers in the Transgender Population: A Systematic Review." [In eng]. BJOG: an international journal of obstetrics and gynaecology 125, no. 12 (2018-11 2018): 1505-12. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29706033/.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: To assess breast and reproductive cancer prevalence in the transgender population. To elucidate any associations between gender-affirming hormones and risk of these cancers.	**Design**: Systematic Review **Search date**: Search was performed 02/2017 **Searched databases**: MEDLINE, Embase, PsycINFO, The Cochrane Library, Web of Science **Included study designs**: Case-control, Cohort, Case report, **Number of included studies**: 43		**Incidence**	**Incidence**: Evidence relating to breast cancers in the trans population is limited and insufficient to estimate cancer prevalence. Asmall number of studies and consisting of incidence rates and histopathological findings does not suggest that there is an increased risk of breast cancers associated with the use of	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 1 critical flaw (items 2) **Overall quality of evidence**: low **Additional concerns about quality**: The review was limited by a lack of clinical and epidemiological data for prevalence estimation or for further analysis investigating an

Source: R, Joint, Chen ZE, and Cameron S. "Breast and Reproductive Cancers in the Transgender Population: A Systematic Review." [In eng]. BJOG: an international journal of obstetrics and gynaecology 125, no. 12 (2018-11 2018): 1505-12. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29706033/.					
	Number of included patients: n.a. **Mean/median age**: n.a. **Inclusion criteria**: Peer-reviewed and possesses primary data relating specifically to the population of interest Population: persons that identify as transgender Exposures (investigation, experience or discussion of): a) A positive diagnosis by a medical professional of one or more of: breast cancer, cervical cancer, uterine cancer, ovarian cancer, (neo)vaginal cancer, prostate cancer, and testicular cancer b) Treatment for one or more of the above mentioned cancers Comparator (where available): persons that			gender-affirming hormones.	association between gender-affirming hormones andbreast/reproductive cancer. A unique limitation was the varying language used to describe the trans population. Articles were often excluded because they lacked data relating specifically to trans people. The results of some studies were presented withoutdistinction between trans and cis people, as all participants were represented by the LGBT acronym. ***Quality of included studies:*** GRADE

Source: R, Joint, Chen ZE, and Cameron S. "Breast and Reproductive Cancers in the Transgender Population: A Systematic Review." [In eng]. BJOG: an international journal of obstetrics and gynaecology 125, no. 12 (2018-11 2018): 1505-12. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29706033/.					
	identify as non-transgender or cisgender Outcomes: a) Rates of breast cancer, cervical cancer, uterine cancer, ovarian cancer, (neo)vaginal cancer, prostate cancer, or testicular cancer b) Treatment regimen for one or more of: breast, cervical cancer, uterine cancer, ovarian cancer, (neo)vaginal cancer, prostate cancer, and testicular cancer Study design: randomised control trials, case-control studies, cohort studies, crosssectional studies, and case reports **Exclusion***:* Does not make clear the natal sex and gender identity of participants				The overall evidence quality was very low to low. **Planned included studies**: / Due to the small study population we propose to downgrade the **level of evidence** from 3a to **3b** **Sources of funding:** No funding was received.

Source: R, Joint, Chen ZE, and Cameron S. "Breast and Reproductive Cancers in the Transgender Population: A Systematic Review." [In eng]. BJOG: an international journal of obstetrics and gynaecology 125, no. 12 (2018-11 2018): 1505-12. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29706033/.					
	Study design: secondary studies, opinions, editorials, and conference abstracts Purely addresses screening of breast or reproductive cancers				

Abbreviations:

n.a. = not Available, not Applicable

LGBT = Lesbian, Gay, Bisexual, and Transgender

Verknüpfte Empfehlungen:

Empfehlung 7.48:

Bei Transgender-Männern soll vor der Mastektomie eine altersentsprechende Früherkennung und die histologische Untersuchung des entfernten Brustgewebes durchgeführt werden.

Literaturreferenzen: [281], [282], [283]

Source: Stone JP, Hartley RL, Temple-Oberle C. Breast cancer in transgender patients: A systematic review. Part 2: Female to Male. Eur J Surg Oncol. 2018 Oct;44(10): 1463-1468. doi: 10.1016/j.ejso.2018.06.021. Epub 2018 Jul 5. PMID: 30037639.

Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: The aim is to perform a systematic review of the literature and document all reported cases of FtM breast cancer as well as provide research recommendations	**Design**: Systematic Review **Search date**: from inception to 01. April 2018 **Searched databases**: MEDLINE, ProQuest, PubMed, Cochrane Database of Systematic Reviews, Google Scholar **Included study designs**: Case Report, Cross-sectional, Case series, Retrospective Cohort		**Incidence**	**Incidence**: The predominant screening recommendations for transgender men are conservative, recommending screening as per natal females with mammograms every two years between the ages of 50 and 69, regardless of CSH. While FtM patients appear to have a decreased risk of breast cancer than natal females after top	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 3 critical flaws (items 2, 7,13) **Overall quality of evidence**: critically low **Additional concerns about quality**: However, because transgender recognition and transgender literature are relatively new, this may reflect a latent period, where the disease has

Source: Stone JP, Hartley RL, Temple-Oberle C. Breast cancer in transgender patients: A systematic review. Part 2: Female to Male. Eur J Surg Oncol. 2018 Oct;44(10): 1463-1468. doi: 10.1016/j.ejso.2018.06.021. Epub 2018 Jul 5. PMID: 30037639.					
	Number of included studies: 8 **Number of included patients**: n.a. **Mean/median age**: n.a. **Inclusion criteria**: Both MtF and FtM studies were included in level one and two screening to encompass all possible cases. **Exclusion***:* Articles were excluded, if they have no transgender patients, no confirmed breast cancer events in transgender patients or no breast cancer screening in transgender patients were excluded.			surgery, there is limited research to determine at which risk threshold is it acceptable to withhold breast cancer screening in this population.	been initiated but the presence of symptoms not yet manifested. **Quality of included studies:** Overall, study quality was low. Level of evidence (Oxford 2011: 3) **Sources of funding:** The authors have no financial disclosures.
Abbreviations:					

Source: Stone JP, Hartley RL, Temple-Oberle C. Breast cancer in transgender patients: A systematic review. Part 2: Female to Male. Eur J Surg Oncol. 2018 Oct;44(10): 1463-1468. doi: 10.1016/j.ejso.2018.06.021. Epub 2018 Jul 5. PMID: 30037639.

FtM = Female-to-Male

MtF = Male-to-Female

CSH = Cross-Sex Hormone

n.a. = not Available, not Applicable

Kapitel 7.3: Brustrekonstruktion

Verknüpfte Empfehlungen:

Empfehlung 7.50:

Die Patientin soll darüber aufgeklärt werden, dass die Rekonstruktion der Brust, unabhängig von der gewählten Methode, mit erhöhten operativen Komplikationsrisiken im Vergleich zur alleinigen Mastektomie einhergeht.

Literaturreferenzen: [284], [285], [286], [287], [288], [289], [290], [291], [292], [293], [294], [295]

Grigor, EJM, Stein, MJ, Arnaout, A, Ghaedi, B, Cormier, N, Ramsay, T, et.al. The effect of immediate breast reconstruction on adjuvant therapy delay, locoregional recurrence, and disease-free survival.. Breast J, 2021. 27 (12)(12): p. 857-862., https: //pubmed.ncbi.nlm.nih.gov/34651372/.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Any type of MO (total mastectomy, skin-sparing mastectomy, or nipple-sparing mastectomy) and MIBR (mastectomy and direct-to-implant [MIBRi1], mastectomy and 2-stage reconstruction [MIBRi2], and mastectomy and autologous flap reconstruction [MIBRf]) **Exclusion criteria** (for analysis):	**Interventions** A: reconstruction · N = 277 Subgroups: · Mastectomy with 1-stage direct to implant IBR: N = 140 · Mastectomy with 2-stage tissue expander to implant IBR: N = 96 B: No reconstruction (mastectomy only) · N = 443	**Any complications** · Reconstruction: 109/277 · No reconstruction: 201/443 **Major complications** · Reconstruction: 58/277 · No reconstruction: 30/443 Minor complications · Reconstruction: 76/277 · No reconstruction: 193/443	**General information** Follow-up: mean 3.30 (±1.44) Funding: NR CoI: The authors have no conflict of interest to disclose. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective study Confounding: yes

Grigor, EJM, Stein, MJ, Arnaout, A, Ghaedi, B, Cormier, N, Ramsay, T, et.al. The effect of immediate breast reconstruction on adjuvant therapy delay, locoregional recurrence, and disease-free survival.. Breast J, 2021. 27 (12)(12): p. 857-862., https: //pubmed.ncbi.nlm.nih.gov/34651372/.				
	Risk-reduction mastectomy Mammoplasty Partial mastectomy Distant metastatic disease De novo stage IV cancer Recurrent breast cancer **Enrolment period:** 01.01.2013 - 31.05.2019 **Follow-up** (mean, sd): Mastectomy with 1-stage direct to implant IBR: 3.40 (1.75) Mastectomy with 2-stage tissue expander to implant IBR: 3.48 (1.60) Mastectomy with autologous flap IBR: 2.14 (1.05) No reconstruction: 3.33 (1.28) **Descriptive statistics** Age (mean, sd)	Analysis Frequencies, multivariable regression analysis No matching No adjustment		Rate of participation/Exclusions reported (selection bias into the study): yes Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status: no Drop-out rate & reasons reported: no Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (àIf not, Knowledge of exposure status likely to influence the outcome?: no (retrospective) Main cofounders taken into account: no Confidence intervals reported: no

Grigor, EJM, Stein, MJ, Arnaout, A, Ghaedi, B, Cormier, N, Ramsay, T, et.al. The effect of immediate breast reconstruction on adjuvant therapy delay, locoregional recurrence, and disease-free survival.. Breast J, 2021. 27 (12)(12): p. 857-862., https: //pubmed.ncbi.nlm.nih.gov/34651372/.				
	· Masetctomy with 1-stage direct to implant IBR: 50.3 (11.3) · Mastectomy with 2-stage tissue expander to implant IBR: 48.6 (10.2) · Mastectomy with autologous flap IBR: 51.9 (7.46) · No reconstruction: 66.2 (13.8) BMI (mean, sd) · Mastectomy with 1-stage direct to implant IBR: 24.6 (4.45) · Mastectomy with 2-stage tissue expander to implant IBR: 24.6 (5.53) · Mastectomy with autologous flap IBR: 26.4 (3.90) · No reconstruction: 26.3 (5.30) Stadium (TNM)			Selective reporting (comparison with protocol): unclear **Other limitations or comments:** retrospective design

Grigor, EJM, Stein, MJ, Arnaout, A, Ghaedi, B, Cormier, N, Ramsay, T, et.al. The effect of immediate breast reconstruction on adjuvant therapy delay, locoregional recurrence, and disease-free survival.. Breast J, 2021. 27 (12)(12): p. 857-862., https: //pubmed.ncbi.nlm.nih.gov/34651372/.				
	· Mastectomy with 1-stage direct to implant IBR: Tis: 22 (15.7);T1: 16 (11.4) ;T1b: 30 (21.4) ;T1c: 35 (25.0);T2: 6 (4.28);T3: 0 (0);T4: 21 (15.0);Not reported: 9 (7.14) · Mastectomy with 2-stage tissue expander to implant IBR: Tis: 7 (7.29);T1: 15 (15.6) ;T1b: 18 (18.8) ;T1c: 32 (33.3);T2: 13 (13.5);T3: 2 (2.08);T4: 8 (8.33);Not reported: 9 (7.14) · Mastectomy with autologous flap: Tis: 6 (14.6);T1: 4 (9.76);T1b: 9 (22.0);T1c: 3 (7.32);T2: 2 (4.88);T3: 0 (0);T4: 14 (34.1); Not reported: 3 (7.32) · No reconstruction: Tis: 54 (7.44) ;T1: 60 (8.26) ;T1b: 165 (22.7);T1c: 260 (35.9);T2: 81 (11.2) ;T3: 6 (0.826);T4: 77 (10.6);Not reported: 17 (2.36) Chemotherapy (% yes) (previous)			

Grigor, EJM, Stein, MJ, Arnaout, A, Ghaedi, B, Cormier, N, Ramsay, T, et.al. The effect of immediate breast reconstruction on adjuvant therapy delay, locoregional recurrence, and disease-free survival.. Breast J, 2021. 27 (12)(12): p. 857-862., https: //pubmed.ncbi.nlm.nih.gov/34651372/.				
	· NR Reconstruction type (flap type) · 1-stage direct to implant IBR: 140/720 · 2-stage tissue expander to implant IBR: 96/720 Autologous flap IBR: 41/720			

Verknüpfte Empfehlungen:

Empfehlung 7.50:

Die Patientin soll darüber aufgeklärt werden, dass die Rekonstruktion der Brust, unabhängig von der gewählten Methode, mit erhöhten operativen Komplikationsrisiken im Vergleich zur alleinigen Mastektomie einhergeht.

Literaturreferenzen: [284], [285], [286], [287], [288], [289], [290], [291], [292], [293], [294], [295]

Ho, D, Chan, E, Izwan, S, Ng, J, Teng, R, Swindon, D, et.al. Uptake of breast reconstruction following mastectomy: a Gold Coast experience.. ANZ J Surg, 2022. 92 (11)(11): p. 3011-3016., https: //pubmed.ncbi.nlm.nih.gov/35426189/.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): All women above 18 years-old Women who had unilateral mastectomy with subsequent development of new contralateral breast cancer **Exclusion criteria** (for analysis): Male Under 18 years of age Underwent palliative mastectomy	**Interventions** A: Reconstruction · N = 311 B: No reconstruction (mastectomy only) · N = 618 **Analysis** Frequencies No matching No adjustment	**General complications requiring return to theatre within follow-up period** · Reconstruction: 39/311 · No reconstruction: 44/618	**General information** Follow-up: median 36-months (range: 2 to 74 months) Funding: NR CoI: None declared. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: Retrospective observational study Confounding: yes

Ho, D, Chan, E, Izwan, S, Ng, J, Teng, R, Swindon, D, et.al. Uptake of breast reconstruction following mastectomy: a Gold Coast experience.. ANZ J Surg, 2022. 92 (11)(11): p. 3011-3016., https: //pubmed.ncbi.nlm.nih.gov/35426189/.				
	Women who had prophylactic mastectomies Those who had previous oncologic surgery prior to the study date or outside of the hospital service **Enrolment period:** 01.01.2016 – 31.12.2021 **Follow-up:** median 36-months, range: 2 - 74 months **Descriptive statistics** Age (median, range) · Reconstruction: 48 (23-83) · No reconstruction: 64 (30-92) BMI (mean) · Reconstruction: 26.0 · No reconstruction: 28.6S Stadium (TNM) · NR Chemotherapy (% yes) (previous)			Rate of participation/Exclusions reported (selection bias into the study): no Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status: no Drop-out rate & reasons reported: no Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: no (retrospective) Main cofounders taken into account: no Confidence intervals reported: no

Ho, D, Chan, E, Izwan, S, Ng, J, Teng, R, Swindon, D, et.al. Uptake of breast reconstruction following mastectomy: a Gold Coast experience.. ANZ J Surg, 2022. 92 (11)(11): p. 3011-3016., https: //pubmed.ncbi.nlm.nih.gov/35426189/.				
	· NR Reconstruction type (flap type) (%) · Immediate: 278/311 (89.4%) · Autologous: 17% · Implant: 80% · Deep inferior epigastric perforator (DIEP) flap: 74.2%) · Transverse rectus abdominis musculocutaneous (TRAM) flap: 3.2% · Latissimus dorsi flap: 16.1%) · Mixed autologous reconstruction, including DIEP and TRAM flaps: 6.5% · Mixed (implant and autologous): 3.2% · Delayed implant BR: 19 (6.1%) · Delayed autologous BR: 9 (2.9%)			Selective reporting (comparison with protocol): yes **Other limitations or comments:** retrospective design mean 3.30 (±1.44)

Verknüpfte Empfehlungen:

Empfehlung 7.50:

Die Patientin soll darüber aufgeklärt werden, dass die Rekonstruktion der Brust, unabhängig von der gewählten Methode, mit erhöhten operativen Komplikationsrisiken im Vergleich zur alleinigen Mastektomie einhergeht.

Literaturreferenzen: [284], [285], [286], [287], [288], [289], [290], [291], [292], [293], [294], [295]

Nickel, KB, Myckatyn, TM, Lee, CN, Fraser, VJ, Olsen, MA, Individualized Risk Prediction Tool for Serious Wound Complications After Mastectomy With and Without Immediate Reconstruction.. Ann Surg Oncol, 2022. 29 (12)(12): p. 7751-7764., https: //pubmed.ncbi.nlm.nih.gov/35831524/.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): All mastectomy operations among women aged ≥ 21 years **Exclusion criteria** (for analysis): NR **Enrolment period:** 01.07.2010 – 31.12.2015 **Follow-up:** 180 days **Descriptive statistics** Age (median, IQR) · Overall: 53 years (45–63) BMI (median, range)	**Interventions** A: Reconstruction (implant and/or flap) · N = 1410 Subgroups: · Implant reconsruction: N = 1271 · Flap reconstruction: N = 139 B: No reconstruction (mastectomy only) · N = 749 **Analysis**	**Any serious wound complications** · Reconstruction (implant and/or flap): 237/1410 · Implant reconstruction: 199/1271 · Flap reconstruction: 38/139 · No reconstruction: 30/749	**General information** Follow-up: 180 days Funding: NR CoI: Margaret A. Olsen reports consultant work and grant funding from Pfizer for work outside the submitted manuscript. Victoria J. Fraser reports that her spouse is the Chief Clinical Officer at Cigna Corporation. Terence M. Myckatyn reports advisory board membership, investigator-initiated grant, and device development royalties for RTI Surgical. He reports

Nickel, KB, Myckatyn, TM, Lee, CN, Fraser, VJ, Olsen, MA, Individualized Risk Prediction Tool for Serious Wound Complications After Mastectomy With and Without Immediate Reconstruction.. Ann Surg Oncol, 2022. 29 (12)(12): p. 7751-7764., https: //pubmed.ncbi.nlm.nih.gov/35831524/.				
	· NR Stadium (TNM) · NR Chemotherapy (% yes) (previous) · NR Reconstruction type (flap type) (%) · Subpectoral implant reconstruction: 1271/2159 (58.9%) - Of those with a tissue expander: 1080/1271 (85%) · Flap reconstruction: 108/2159 (5.0%) · Flap plus implant reconstruction: 31/2159 (1.4%)	Frequencies, multivariable analysis No matching No adjustment		former investigator-initiated grants and advisory board work with Allergan, and an unencumbered research award from Sientra. Clara N. Lee was supported by a grant from the Agency for Healthcare Research and Quality (R18 HS026699-01A1). The remaining authors have no conflicts of interest. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: yes Rate of participation/Exclusions reported (selection bias into the study): no Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no

Nickel, KB, Myckatyn, TM, Lee, CN, Fraser, VJ, Olsen, MA, Individualized Risk Prediction Tool for Serious Wound Complications After Mastectomy With and Without Immediate Reconstruction.. Ann Surg Oncol, 2022. 29 (12)(12): p. 7751-7764., https: //pubmed.ncbi.nlm.nih.gov/35831524/.				
				· Possibly affected by knowledge of outcome status: no Drop-out rate & reasons reported: no Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: no (retrospective) Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): yes **Other limitations or comments:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.50:

Die Patientin soll darüber aufgeklärt werden, dass die Rekonstruktion der Brust, unabhängig von der gewählten Methode, mit erhöhten operativen Komplikationsrisiken im Vergleich zur alleinigen Mastektomie einhergeht.

Literaturreferenzen: [284], [285], [286], [287], [288], [289], [290], [291], [292], [293], [294], [295]

O'Connell, RL, Rattay, T, Dave, RV, Trickey, A, Skillman, J, Barnes, NLP, et.al. The impact of immediate breast reconstruction on the time to delivery of adjuvant therapy: the iBRA-2 study.. Br J Cancer, 2019. 120 (9)(9): p. 883-895., https: //pubmed.ncbi.nlm.nih.gov/30923359/.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Consecutive women aged 18 or over Undergoing mastectomy with or without IBR using any technique for invasive or preinvasive (ductal carcinoma in situ, DCIS) breast cancer with curative intent at participating centres **Exclusion criteria** (for analysis): Patients undergoing risk-reducing surgery (without a	**Interventions** A: Reconstruction · N = 1126 procedures Subgroups: · Implant reconstruction: N = 773 · Pedicled flap reconstruction: N = 106 · Free flap reconstruction: N = 247 B: No reconstruction (mastectomy only) · N = 1606 procedures	**Any complications** · Implant reconstruction: 223/667 · Pedicled flap reconstruction: 42/105 · Free flap reconstruction: 94/228 · No reconstruction: 570/1517 **Major complications** · Implant reconstruction: 100/675 · Pedicled flap reconstruction: 7/105	**General information** Follow-up: NR Funding: NR CoI: The authors declare no competing interests. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: Prospective multicentre cohort study Confounding: yes

O'Connell, RL, Rattay, T, Dave, RV, Trickey, A, Skillman, J, Barnes, NLP, et.al. The impact of immediate breast reconstruction on the time to delivery of adjuvant therapy: the iBRA-2 study.. Br J Cancer, 2019. 120 (9)(9): p. 883-895., https: //pubmed.ncbi.nlm.nih.gov/30923359/.				
	therapeutic mastectomy for breast cancer) Partial mastectomy including wide local excision with volume replacement (latissimus dorsi miniflaps; lateral intercostal perforator (LICAP) or thoracodorsal artery perforator (TDAP) flaps) Displacement techniques (therapeutic mammaplasty), Those with distant metastatic disease **Enrolment period:** 01.07.2016 – 31.12.2016 **Follow-up:** NR **Descriptive statistics** Age (median, IQR) · Implant reconstruction: 50 (43-57), range: 23-82 · Pedicled flap reconstruction: 52 (47-60), range: 25-74	**Analysis** Frequencies, univariable and multivariable logistic regression analysis No matching Adjusted for age, BMI, smoking and ASA grade	· Free flap reconstruction: 38/228 · No reconstruction: 76/1532	Rate of participation/Exclusions reported (selection bias into the study): no Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status: no Drop-out rate & reasons reported: no Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: no (possible) Main cofounders taken into account: Confidence intervals reported: no

O'Connell, RL, Rattay, T, Dave, RV, Trickey, A, Skillman, J, Barnes, NLP, et.al. The impact of immediate breast reconstruction on the time to delivery of adjuvant therapy: the iBRA-2 study.. Br J Cancer, 2019. 120 (9)(9): p. 883-895., https: //pubmed.ncbi.nlm.nih.gov/30923359/.				
	· Free-flap reconstruction: 50 (44.5-56), range: 21-72 · No reconstruction: 65 (54-75), range: 26-96 BMI (median, IQR) · Implant reconstruction: 24.4 (21.9-27.6), range: 16.0-61.4 · Pedicled flap reconstruction: 26.6 (23.3-30.6), range: 18.5-39.2 · Free-flap reconstruction: 27.4 (24.2-30.19), range15.6-31.1 · No reconstruction: 27.3 (23.7-32.2), range: 13.4-80.7 Stadium (TNM) · Implant-based reconstruction: Tis: 163/707 (71.7%), T1a: 71/707 (10.0%), T1b: 63/707 (8.9%), T1c: 156/707 (22.1%), T2: 185/707 (26.2%), T3: 55/707 (7.8%), Not reported: 14/707 (2.0%) · Pedicled flap: Tis: 26/105 (24.8%), T1a: 9/105 (8.6%),			Selective reporting (comparison with protocol): unclear **Other limitations or comments:** NR

O'Connell, RL, Rattay, T, Dave, RV, Trickey, A, Skillman, J, Barnes, NLP, et.al. The impact of immediate breast reconstruction on the time to delivery of adjuvant therapy: the iBRA-2 study.. Br J Cancer, 2019. 120 (9)(9): p. 883-895., https: //pubmed.ncbi.nlm.nih.gov/30923359/.				
	T1b: 13/105 (12.4%), T1c: 17/105 (16.2%), T2: 28/105 (26.7%), T3: 9/105 (8.6%), Not reported: 3/105 (2.9%) · Free-flap: Tis: 58/231 (25.1%), T1a: 19/231 (8.2%), T1b: 14/231 (6.1%), T1c: 46/231 (19.9%), T2: 63/231 (27.3%), T3: 18/231 (7.8%), Not reported: 13/231 (5.6%) · No reconstruction: Tis: 141/1564 (9.0%), T1a: 88/1564 (5.6%), T1b: 89/1564 (5.7%), T1c: 359/1564 (23.0%), T2: 672/1564 (43.0%), T3: 190/1564 (12.2%), Not reoprted: 25/1564 (1.6%) Chemotherapy (% yes) (previous) · NR Reconstruction type (flap type) (%) · Implant: 675/2540 (26.6%) (157 subpectoral expanders;			

O'Connell, RL, Rattay, T, Dave, RV, Trickey, A, Skillman, J, Barnes, NLP, et.al. The impact of immediate breast reconstruction on the time to delivery of adjuvant therapy: the iBRA-2 study.. Br J Cancer, 2019. 120 (9)(9): p. 883-895., https: //pubmed.ncbi.nlm.nih.gov/30923359/.				
	410 subpectoral reconstructions with · Biological or synthetic mesh; 105 dermal-sling procedures and 98 prepectoral reconstructions) · Pedicled flap: 105/2540 (4.1%) (62 autologous LD, 39 LD with implant, 2 pedicled TRAM and 2 other) · Free-flap: 228/2540 (8.9%) (19 DIEPs, 16 free TRAMs, 4 SIEA, 7 TUG flaps and 1 other)			

Verknüpfte Empfehlungen:

Empfehlung 7.50:

Die Patientin soll darüber aufgeklärt werden, dass die Rekonstruktion der Brust, unabhängig von der gewählten Methode, mit erhöhten operativen Komplikationsrisiken im Vergleich zur alleinigen Mastektomie einhergeht.

Literaturreferenzen: [284], [285], [286], [287], [288], [289], [290], [291], [292], [293], [294], [295]

Delenne S, Philip CA, Guimont I, Bienstman J, Mojallal AA, Cortet M. Mastectomies for breast cancer: Comparison between peri-operative morbidity after simple mastectomy or after immediate breast reconstruction in a unicentric serie of 210 patients. J Gynecol Obstet Hum Reprod. 2024 Jan;53(1): 102695. doi: 10.1016/j.jogoh.2023.102695. Epub 2023 Nov 22. PMID: 37995939.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective, descriptive and unicentric study	**Inclusion criteria** (for analysis): Patients who received a mastectomy for their breast cancer between 2016 and 2020 Patients who automatically received a bilateral mastectomy for a bilateral breast cancer **Exclusion criteria** (for analysis): Male patients Prophylactic mastectomies History of breast surgery	**Interventions** A: Reconstruction · N = 32 B: No reconstruction (mastectomy only) · N = 153 **Analysis** Frequencies, secondary univariate analysis No matching No adjustment	**Post-operative complications** Grade II · Reconstruction: 12/32 · No reconstruction: 39/153 Grade IIIa · Reconstruction: 6/32 · No reconstruction: 72/153 Grade IIIb · Reconstruction: 4/32 · No reconstruction: 21/153 IVA complications	**General information** Follow-up: NR Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. CoI: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Delenne S, Philip CA, Guimont I, Bienstman J, Mojallal AA, Cortet M. Mastectomies for breast cancer: Comparison between peri-operative morbidity after simple mastectomy or after immediate breast reconstruction in a unicentric serie of 210 patients. J Gynecol Obstet Hum Reprod. 2024 Jan;53(1): 102695. doi: 10.1016/j.jogoh.2023.102695. Epub 2023 Nov 22. PMID: 37995939.				
	Mastectomies for non-breast cancer or recurrence of breast cancer after autologous reconstruction **Enrolment period:** 2016 - 2020 **Follow-up:** NR **Descriptive statistics** Age (n (%)) · Reconstruction: below or equal to 70: 28/32 (88%); above 70: 4/32 (12%) · No reconstruction: below or equal to 70: 101/153 (66%); above 70: 52/153 (34%) BMI (n (%)) · Reconstruction: below or equal to 25: 23/32 (72%); above 25: 9/32 (28%) · No reconstruction: below or equal to 25: 100/153 (65%); above 25: 53/153 (35%)		· Reconstruction: 0/32 · No reconstruction: 0/153 <u>IVB complications</u> · Reconstruction: 0/32 No reconstruction: 0/153	**Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective, descriptive and unicentric study Confounding: yes Rate of participation/Exclusions reported (selection bias into the study): yes Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status: no Drop-out rate & reasons reported: no Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (àIf not, Knowledge

Delenne S, Philip CA, Guimont I, Bienstman J, Mojallal AA, Cortet M. Mastectomies for breast cancer: Comparison between peri-operative morbidity after simple mastectomy or after immediate breast reconstruction in a unicentric serie of 210 patients. J Gynecol Obstet Hum Reprod. 2024 Jan;53(1): 102695. doi: 10.1016/j.jogoh.2023.102695. Epub 2023 Nov 22. PMID: 37995939.				
	Stadium (TNM) · Reconstruction: · No reconstruction: Chemotherapy (% yes) (previous) · Reconstruction: 5/32 (16%) · No reconstruction: 105/153 (69%) Reconstruction type (flap type) (%) Immediate breast reconstruction only			of exposure status likely to influence the outcome?: no (retrospective) Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): yes **Other limitations or comments:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.50:

Die Patientin soll darüber aufgeklärt werden, dass die Rekonstruktion der Brust, unabhängig von der gewählten Methode, mit erhöhten operativen Komplikationsrisiken im Vergleich zur alleinigen Mastektomie einhergeht.

Literaturreferenzen: [284], [285], [286], [287], [288], [289], [290], [291], [292], [293], [294], [295]

Taqi K, Pao JS, Chen L, Ma C, Zhang M, McKevitt E, Bazzarelli A, Dingee C, Warburton R. Immediate breast reconstruction in locally advanced breast cancer: is it safe? Breast Cancer Res Treat. 2021 Nov;190(2): 175-182. doi: 10.1007/s10549-021-06366-6. Epub 2021 Aug 31. PMID: 34467443.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective study	**Inclusion criteria** (for analysis): Patients with clinically locally advanced breast cancer on presentation who underwent mastectomy Patients who were treated with neoadjuvant therapy (NAT) or upfront surgery **Exclusion criteria** (for analysis): Patients with inflammatory breast cancer or who had mastectomy for recurrent	**Interventions** A: Reconstruction · N = 112 B: No reconstruction (mastectomy only) · N = 155 **Analysis** Frequencies No matching No adjustment	**Reoperation** · Reconstruction: 9/112 · No reconstruction: 2/155 · p = 0.559	**General information** Follow-up (median, sd): 50.7 (23.4 months), range: 0–107 Funding: The authors received no funding for the project. CoI: The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective study

Taqi K, Pao JS, Chen L, Ma C, Zhang M, McKevitt E, Bazzarelli A, Dingee C, Warburton R. Immediate breast reconstruction in locally advanced breast cancer: is it safe? Breast Cancer Res Treat. 2021 Nov;190(2): 175-182. doi: 10.1007/s10549-021-06366-6. Epub 2021 Aug 31. PMID: 34467443.				
	breast cancer or with palliative intent **Enrolment period:** 01.01.2012 – 31.12.2017 **Follow-up:** median: 50.7 ± 23.4 months (0–107) **Descriptive statistics** Age (mean, sd) · Reconstruction: 48.82 (10.08) · No reconstruction: 61.42 (13.50) BMI (median, range) · NR Stadium (TNM) · Reconstruction: T1N2: 2/112 (1.8%); T2N1: 36/112 (32.1%); T2N2: 8/112 (7.1%); T2N3: 3/112 (2.7%); T3N0: 15/112 (13.4%); T3N1: 33/112 (29.5%); T3N2: 8/112 (7.1%); T3N3: 2/112 (1.8%); T4N0: 2/112 (1.8%); T4N1: 2/112 (1.8%); T4N2: 1/112 (0.9%)			Confounding: yes Rate of participation/Exclusions reported (selection bias into the study): no Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status: no Drop-out rate & reasons reported: no Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: no (retrospective) Main cofounders taken into account: no

Taqi K, Pao JS, Chen L, Ma C, Zhang M, McKevitt E, Bazzarelli A, Dingee C, Warburton R. Immediate breast reconstruction in locally advanced breast cancer: is it safe? Breast Cancer Res Treat. 2021 Nov;190(2): 175-182. doi: 10.1007/s10549-021-06366-6. Epub 2021 Aug 31. PMID: 34467443.				
	· No Reconstruction: T1N2: 3/155 (1.9%); T2N1: 69/155 (44.5%=; T2N2: 7/155 (4.5%); T2N3: 3/155 (1.9%); T3N0: 13/155 (8.4%); T3N1: 27/155 (17.5%); T3N2: 4/155 (2.6%); T3N3: 4/155 (2.6%); T4N0: 6/155 (3.9%); T4N1: 16/155 (10.3%); T4N2: 3/155 (1.9%) Chemotherapy (% yes) (previous) · NR Reconstruction type (flap type) (%) · Tissue expander: 53/112 (47.3%) · Implant with bioprosthesis: 36/112 (32.1%) · TRAM flap: 16/112 (14.3%) · DIEP flap: 7/112 (6.3%)			Confidence intervals reported: no Selective reporting (comparison with protocol): yes **Other limitations or comments:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.50:

Die Patientin soll darüber aufgeklärt werden, dass die Rekonstruktion der Brust, unabhängig von der gewählten Methode, mit erhöhten operativen Komplikationsrisiken im Vergleich zur alleinigen Mastektomie einhergeht.

Literaturreferenzen: [284], [285], [286], [287], [288], [289], [290], [291], [292], [293], [294], [295]

Afshar-Bakshloo M, Albers S, Richter C, Berninger O, Blohmer JU, Roehle R, Speiser D, Karsten MM. How breast cancer therapies impact body image - real-world data from a prospective cohort study collecting patient-reported outcomes. BMC Cancer. 2023 Jul 28;23(1): 705. doi: 10.1186/s12885-023-11172-y. PMID: 37507687; PMCID: PMC10375629.

Study type	Population	Interventions	Main results	Methodological evaluation
Prospective cohort study	**Inclusion criteria** (for analysis): First clinic visit at Charité breast center between 11/17/2016 and 10/31/2019 Written consent for PRO collection Received BCS, mastectomy without or with immediate breast reconstruction for invasive breast cancer or DCIS. **Exclusion criteria** (for analysis):	**Interventions** A: Reconstruction · N = 86 B: No reconstruction (mastectomy only) · N = 27 **Analysis** Frequencies, Linear mixed regression model No matching No adjustment	**Reoperation** · Reconstruction: 33/86 · No reconstruction: 3/27 · p = 0.022	**General information** Follow-up: median 370 days Funding: Open Access funding enabled and organized by Projekt DEAL. The study as part of the patient-reported outcome program at Charité breast center was funded by Charité – Universitätsmedizin Berlin. CoI: OB: Employee and stockholder at Takeda Pharma (financial interests). MMK: Speaker fee from Roche, Gilead, Astra Zeneca, Sysmex

Afshar-Bakshloo M, Albers S, Richter C, Berninger O, Blohmer JU, Roehle R, Speiser D, Karsten MM. How breast cancer therapies impact body image - real-world data from a prospective cohort study collecting patient-reported outcomes. BMC Cancer. 2023 Jul 28;23(1): 705. doi: 10.1186/s12885-023-11172-y. PMID: 37507687; PMCID: PMC10375629.				
	No consent No e-mail-address No therapeutic breast surgery cM1 at first clinic visit Palliative treatment (for reasons other than cM1) Missing information on postoperative therapeutic course No PRO-measurement from at least two time points **Enrolment period:** 17.11.2016 – 31.09.2019 **Follow-up** (overall population): Median: 370 days Maximum: 41.5 months **Descriptive statistics** Age (mean, sd) · Reconstruction: 47.05 (10.90)			(financial interests). MAB, SA, CR, JUB, RR, DS declare that they have no competing interests. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: prospective cohort study Confounding: yes Rate of participation/Exclusions reported (selection bias into the study): yes Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status: no Drop-out rate & reasons reported: no Outcome

Afshar-Bakshloo M, Albers S, Richter C, Berninger O, Blohmer JU, Roehle R, Speiser D, Karsten MM. How breast cancer therapies impact body image - real-world data from a prospective cohort study collecting patient-reported outcomes. BMC Cancer. 2023 Jul 28;23(1): 705. doi: 10.1186/s12885-023-11172-y. PMID: 37507687; PMCID: PMC10375629.				
	· No reconstruction: 65.19 (12.01) BMI (median (25%-, 75%-quartile)) · Reconstruction: 22.86 (20.66, 25.91) · No reconstruction: 25.47 (21.64, 27.78) Stadium (TNM) · NR Chemotherapy (% yes) (previous) · NR Reconstruction type (flap type) (%) · NR			· Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (If not, Knowledge of exposure status likely to influence the outcome?): possible Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): yes **Other limitations or comments:** real-world data

Verknüpfte Empfehlungen:

Empfehlung 7.50:

Die Patientin soll darüber aufgeklärt werden, dass die Rekonstruktion der Brust, unabhängig von der gewählten Methode, mit erhöhten operativen Komplikationsrisiken im Vergleich zur alleinigen Mastektomie einhergeht.

Literaturreferenzen: [284], [285], [286], [287], [288], [289], [290], [291], [292], [293], [294], [295]

Shen, Z, Sun, J, Yu, Y, Chiu, C, Zhang, Z, Zhang, Y, et.al. Oncological safety and complication risks of mastectomy with or without breast reconstruction: A Bayesian analysis.. J Plast Reconstr Aesthet Surg, 2021. 74 (2)(2): p. 290-299., https: //pubmed.ncbi.nlm.nih.gov/33093010/.

Source and Purpose	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: ""..surgeons and researchers remain uncertain about the oncological safety of breast reconstruction. 13 Which surgical choice offers the greatest balance of benefits and risks is still unclear. Therefore, a systematic review of the current literature with a Bayesian network meta-analysis was con- ducted to compare data on oncological safety and compli- cation risks	**Design**: Systematic review with Metaanalysis Study design Cohort studies, case control studies Search dates November 2019 Databases: Cochrane library PubMed/MEDLINE EMBASE	**Intervention** *A: IBR* B: DBR *C: No reconstruction (Mastectomy only)*	**Complications**	**Complications** *IBR vs. no reconstruction (A vs. C)* • 6 studies • Effect: OR: 0.78 (95%-CI: 0.43 – 1.44); I^2: 97.6%	Risk of bias assessment of studies: not assessed, reassessed for the current clinical guideline Overall confidence in results of SR (AMSTAR-2): moderate PICO elements: yes A priori design: partial yes Justification for design: no

Shen, Z, Sun, J, Yu, Y, Chiu, C, Zhang, Z, Zhang, Y, et.al. Oncological safety and complication risks of mastectomy with or without breast reconstruction: A Bayesian analysis.. J Plast Reconstr Aesthet Surg, 2021. 74 (2)(2): p. 290-299., https: //pubmed.ncbi.nlm.nih.gov/33093010/.					
among the MA, IBR, and DBR groups.	China National Knowledge Infrastructure Inclusion criteria prospective or retrospective studies that enrolled breast cancer patients with MA alone or breast re- construction (IBR and DBR) after MA comparisons of any two or three surgical options (MA, IBR, or DBR) report on at least one of the outcomes for oncological safety (disease- free survival (DFS), overall survival, local recurrence, and distant metastases) and complication risks (overall compli- cations, surgical site infection, and lymphedema) Exclusion criteria:				Literature search >= 2 databases, search strategy + other sources: · 3 databases · String for PubMed provided · No further resources searched Selection in duplicate: yes Data extraction in duplicate: yes List of excluded studies: no sufficient detail on studies: partial yes RoB assessed: no (NOS was used to assess the quality of the cohorts, but no results reported on each study included) Funding of incl. studies: no MA appropriate: yes

Shen, Z, Sun, J, Yu, Y, Chiu, C, Zhang, Z, Zhang, Y, et.al. Oncological safety and complication risks of mastectomy with or without breast reconstruction: A Bayesian analysis.. J Plast Reconstr Aesthet Surg, 2021. 74 (2)(2): p. 290-299., https: //pubmed.ncbi.nlm.nih.gov/33093010/.					
	studies enrolling participants with prophylactic MA or primary breast augmentation or the ones published be- fore 2000				RoB considered in MA: no RoB in interpretation: no Heterogeneity explained: no Publication bias investigated: yes Sources of CoI: The authors report no conflicts of interest. Sources of funding NR

Verknüpfte Empfehlungen:

Empfehlung 7.50:

Die Patientin soll darüber aufgeklärt werden, dass die Rekonstruktion der Brust, unabhängig von der gewählten Methode, mit erhöhten operativen Komplikationsrisiken im Vergleich zur alleinigen Mastektomie einhergeht.

Literaturreferenzen: [284], [285], [286], [287], [288], [289], [290], [291], [292], [293], [294], [295]

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nr of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no reconstruction (mastectomy alone)	Risk with any breast reconstruction			
Any complications	166 per 1.000	184 per 1.000 (116 to 280)	OR 1.13 (0.66 to 1.95)	14251 (8 non-randomised studies)	⊕◯◯◯ Very low[a,b,c]
Major complications	54 per 1.000	159 per 1.000 (120 to 196)	OR 3.33 (2.41 to 4.30)	3260 (2 non-randomised studies)	⊕⊕⊕◯ Moderate[a]
Reoperation	62 per 1.000	140 per 1.000 (88 to 217)	OR 2.47 (1.46 to 4.20)	1516 (4 non-randomised studies)	⊕⊕⊕◯ Moderate[a]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

siehe Meta-Analysen

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nr of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no reconstruction (mastectomy alone)	Risk with any breast reconstruction			

Explanations

a. Downgraded by two levels due to very serious risk of bias: Included studies were observational only, and the majority did not adjust at all for relevant baseline characteristics. Results are thus prone to confounding.

b. Downgraded by one level due to serious inconsistency (above 70%): Outcome definitions varied between studies. In addition, heterogeneity is high.

c. Downgraded by one level due to serious imprecision; the 95% confidence interval includes both effects.

Verknüpfte Empfehlungen:

Empfehlung 7.50:

Die Patientin soll darüber aufgeklärt werden, dass die Rekonstruktion der Brust, unabhängig von der gewählten Methode, mit erhöhten operativen Komplikationsrisiken im Vergleich zur alleinigen Mastektomie einhergeht.

Literaturreferenzen: [284], [285], [286], [287], [288], [289], [290], [291], [292], [293], [294], [295]

Author, year	Country	Study design	Patients (n)	Age, median (years)	Stage (I/II/III/IV)	Lymph node (+)	Estrogen receptor (+)	Chemotherapy	Radiotherapy	Follow up, median (years)	Quality Scores (NOS)
Browne 2017	Ireland	Prospective	BR: 2226 No BR: 4179	NR	NR	NR	NR:	NR	NR	1.5	Selection: 4 Comparability: 2 Exposure: 2
Eriksen 2011	Sweden	Retrospective (pre-post)	BR: 300 No BR: 300	BR: 46 No BR: 46	NR	BR: 36.70% No BR: 79.90%	BR: NR No BR: 68.6%	BR: NR No BR: 34.20%	BR: NR No BR: 24.80%	BR: NR No BR: 11.5	Selection: 3 Comparability: 2 Exposure: 3

Author, year	Country	Study design	Patients (n)	Age, median (years)	Stage (I/II/III/IV)	Lymph node (+)	Estrogen receptor (+)	Chemotherapy	Radiotherapy	Follow up, median (years)	Quality Scores (NOS)
Ryu 2017	Korea	Retrospective	BR: 580 No BR: 878	BR: 43.9 No BR: 47.3	BR: 348/196/36/0 No BR: 435/ 375/ 68/0	NR	BR: 79.10% No BR: 76%	BR: 50.50% No BR: 60%	BR: 13.50% No BR: 19.10%	BR: 3.44 No BR: 3.62	Selection: 3 Comparability: 2 Exposure: 2

Verknüpfte Empfehlungen:

Empfehlung 7.50:

Die Patientin soll darüber aufgeklärt werden, dass die Rekonstruktion der Brust, unabhängig von der gewählten Methode, mit erhöhten operativen Komplikationsrisiken im Vergleich zur alleinigen Mastektomie einhergeht.

Literaturreferenzen: [284], [285], [286], [287], [288], [289], [290], [291], [292], [293], [294], [295]

Simon P, Barrou J, Cohen M, Rua S, Lambaudie E, Houvenaeghel G. Types of Mastectomies and Immediate Reconstructions for Ipsilateral Breast Local Recurrences. Front Oncol. 2020 Dec 10;10: 567298. doi: 10.3389/fonc.2020.567298. PMID: 33363007; PMCID: PMC7758529.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective monocentric cohort study	**Inclusion criteria** (for analysis): Patients who required a total mastectomy Mastectomies performed for ILBLR after initial BCT **Exclusion criteria** (for analysis): Not reported. **Enrolment period:** January 2016 – April 2019 **Follow-up:** median: 198 months (95%-CI: 175-207)from initial breast cancer diagnosis	**Interventions** Immediate reconstruction · N = 68 No reconstruction (mastectomy only) · N = 139 **Analysis** Frequencies, Multivariate analyses using binary logistic regression No matching	**Reoperation** · Reconstruction: 8/68 · No reconstruction: 9/139 · p = 0.151	**General information** Follow-up: median 198 months (95%-CI: 175-207)from initial breast cancer diagnosis; 21 months (95%-CI: 21-25) from the date of mastectomy for recurrence Funding: NR CoI: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Simon P, Barrou J, Cohen M, Rua S, Lambaudie E, Houvenaeghel G. Types of Mastectomies and Immediate Reconstructions for Ipsilateral Breast Local Recurrences. Front Oncol. 2020 Dec 10;10: 567298. doi: 10.3389/fonc.2020.567298. PMID: 33363007; PMCID: PMC7758529.				
	median 21 months (95%-CI: 21-25) from the date of mastectomy for recurrence **Descriptive statistics** Age (n, (%)) · Reconstruction: ≤ 40: 2/68 (2.9%); 41-50: 12/68 (17.6%); 51-74: 47/68 (69.1%); ≥75: 7/68 (10.3%) · No reconstruction: ≤ 40: 0/139 (0.0%); 41-50: 12/139 (8.6%); 51-74: 88/139 (63.3%); ≥75: 39/139 (28.1%) BMI (n, (%))) · Reconstruction: <25: 51/68 (75.0%); 25.0-29.9: 14/68 (20.6%); ≥30: 3/68 (4.4%) · No reconstruction: <25: 74/139 (53.2%); 25.0-29.9: 35/139 (25.2%); ≥30: 30/139 (21.6%) Stadium (TNM) · NR	No adjustment		**Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective, monocentric, cohort study Confounding: yes Rate of participation/Exclusions reported (selection bias into the study): no Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status: no Drop-out rate & reasons reported: no Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (àIf not, Knowledge of exposure status likely to

Simon P, Barrou J, Cohen M, Rua S, Lambaudie E, Houvenaeghel G. Types of Mastectomies and Immediate Reconstructions for Ipsilateral Breast Local Recurrences. Front Oncol. 2020 Dec 10;10: 567298. doi: 10.3389/fonc.2020.567298. PMID: 33363007; PMCID: PMC7758529.				
	Chemotherapy (% yes) (previous) · Reconstruction: 12/68 (17.6%) · No reconstruction: 37/139 (26.6%) Reconstruction type (flap type) (%) · implant alone: 31/68 (45.6%) · LDF: 37/68 (54.4%)			influence the outcome?: no (retrospective) Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): yes **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.50:

Die Patientin soll darüber aufgeklärt werden, dass die Rekonstruktion der Brust, unabhängig von der gewählten Methode, mit erhöhten operativen Komplikationsrisiken im Vergleich zur alleinigen Mastektomie einhergeht.

Empfehlung 7.51:

Patientinnen sollten darüber aufgeklärt werden, dass die autologe Brustrekonstruktion der Implantat-basierten Brustrekonstruktion bezüglich der patientenberichteten Outcomeparameter (PROMs) Zufriedenheit mit der Rekonstruktion, Zufriedenheit mit der Brust und körperliches Wohlbefinden langfristig (>2 Jahre nach Brustrekonstruktion) überlegen zu sein scheint.

Empfehlung 7.54:

Das operative Verfahren der Implantat-basierten Brustrekonstruktion (einzeitig versus zweizeitig über Expander-Implantat-Sequenz) soll unter Berücksichtigung der onkologischen Situation, individueller Risikofaktoren und individueller Wünsche mit der Patientin besprochen werden.

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Empfehlung 7.59:

Die Patientin soll darüber aufgeklärt werden, dass die adjuvante Bestrahlung der autolog rekonstruierten Brust mit einem erhöhten Auftreten von Fettgewebsnekrosen und verminderten Werten der patientenberichteten Outcomeparameter (Zufriedenheit mit der rekonstruierten Brust, körperliche Gesundheit, seelische Gesundheit) assoziiert ist.

Literaturreferenzen: [284], [285], [286], [287], [288], [289], [290], [291], [292], [293], [294], [295]

Zu weiterführenden methodischen Informationen siehe den kompletten Evidenzbericht zur Brustrekonstruktion.

Verknüpfte Empfehlungen:

Empfehlung 7.51:

Patientinnen sollten darüber aufgeklärt werden, dass die autologe Brustrekonstruktion der Implantat-basierten Brustrekonstruktion bezüglich der patientenberichteten Outcomeparameter (PROMs) Zufriedenheit mit der Rekonstruktion, Zufriedenheit mit der Brust und körperliches Wohlbefinden langfristig (>2 Jahre nach Brustrekonstruktion) überlegen zu sein scheint.

Literaturreferenzen: [296], [297], [298], [299], [300], [301], [302], [303], [304], [305], [306], [307], [308]

Broyles, JM, Balk, EM, Adam, GP, Cao, W, Bhuma, MR, Mehta, S, et.al. Implant-based versus Autologous Reconstruction after Mastectomy for Breast Cancer: A Systematic Review and Meta-analysis.. Plast Reconstr Surg Glob Open, 2022. 10 (3)(3): p. e4180., https: //pubmed.ncbi.nlm.nih.gov/35291333/.

Source and Purpose	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: This "Given the preference sensitive nature of breast reconstruction, the evolving nature of the evidence, and the lack of an agreed-upon preferred surgical modality, we conducted a systematic review (SR) with meta-analysis to assess the benefits and surgical complications of IBR versus AR after mastectomy for breast cancer (or prophylaxis)."	**Design**: Systematic review with Metaanalysis **Search dates** From database inception through March 23, 2021 **Databases:** Medline (via PubMed) Embase Cochrane Central Register of Controlled Trials (CENTRAL) CINAHL	**Intervention vs. Comparator** A: Autologous B: Implant	1) BREAST-Q QoL 2) Mortality 3) Surgical complications 4) Reconstructive failure	**BREAST-Q QoL outcomes** Satisfaction with breasts 7 studies reportedthis outcome 3 studies (pooled data) Overall Mean difference: 8.08 (95% CI 6.11 to 10.05) in favor of autologous breast reconstruction Physical well-being	Risk of bias assessment of studies: 25 of the 38 NRCSs had a high risk of bias (mostly due to critical or serious risk of confounding and lack of blinding) and 13 had a moderate risk (mostly due to lack of blinding). RCTs had moderate risk of bias. Overall confidence in results of SR (AMSTAR-2): PICO elements: partially described

Broyles, JM, Balk, EM, Adam, GP, Cao, W, Bhuma, MR, Mehta, S, et.al. Implant-based versus Autologous Reconstruction after Mastectomy for Breast Cancer: A Systematic Review and Meta-analysis.. Plast Reconstr Surg Glob Open, 2022. 10 (3)(3): p. e4180., https: //pubmed.ncbi.nlm.nih.gov/35291333/.					
Sources of funding: The authors have no financial interest to declare in relation to the content of this article. This project was funded under Contract No. HHSA 75Q80120D00001 from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services.	ClinicalTrials.gov Inclusion criteria: NR **Exclusion criteria:** Does not address any Key Question (n=313) >=10% of patients underwent breast augmentation (n = 7) >=10% of patients underwent revision reconstruction (n=3) Does not address breast reconstruction (n = 17) Does not address mastectomy for breast cancer (n = 5) Does not report any outcome of interest (n=28) Protocol/methods only with no results (n = 20)			6 studies reported this outcome, no pooled data Overall Mean difference: NR “Results were inconsistent across studies.” General Quality of Life 3 studies reported this outcome, no pooled data Overall Mean difference: NR “For each instrument in each study, differences in general quality of life between IBR and AR were not statistically significant.” Psychosocial well-being 5 studies reported this outcome 3 studies (pooled data)	A priori design: no Justification for design: no Literature search >= 2 databases, search strategy + other sources: · 3 databases · String for PubMed provided · No further resources searched Selection in duplicate: yes w Data extraction in duplicate: · “All extracted data were confirmed by a second, independent researcher.” · List of excluded studies: no sufficient detail on studies: no RoB assessed: yes

Broyles, JM, Balk, EM, Adam, GP, Cao, W, Bhuma, MR, Mehta, S, et.al. Implant-based versus Autologous Reconstruction after Mastectomy for Breast Cancer: A Systematic Review and Meta-analysis.. Plast Reconstr Surg Glob Open, 2022. 10 (3)(3): p. e4180., https: //pubmed.ncbi.nlm.nih.gov/35291333/.					
	NRCS, N<30 participants per arm (n = 103) NRCS without adequate adjustment (n = 234) Single group studies, N<500 participants (n = 187) Single group studies, N> 500 participants, no surgical complications data (n=26) Case report or series of case reports (n = 7) Narrative review/commentary (n=55) Systematic review (n = 20) Copublication of included study with no new data (n=35) Unable to retrieve article (n = 20)			Overall Mean difference 3.14 (95% CI 1.26 to 5.02) Sexual well-being 4 studies reported this outcome 3 studies (pooled data) Overall Mean difference 5.83 (95% CI 3.44 to 8.23) in favor of autologous breast reconstruction **Mortality** 1 study reported this outcome Overall: adjusted OR 0.96, 95% CI 0.89–1.04 **Surgical complications** 3 studies reported this outcome No pooled data Reconstructive failure	Funding of incl. studies: no RoB considered in MA: no RoB in interpretation: yes Heterogeneity explained: no Publication bias investigated: no Sources of CoI: yes (see Sources of funding) Sources of funding The authors have no financial interest to declare in relation to the content of this article. This project was funded under Contract No. HHSA 75Q80120D00001 from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services.

Broyles, JM, Balk, EM, Adam, GP, Cao, W, Bhuma, MR, Mehta, S, et.al. Implant-based versus Autologous Reconstruction after Mastectomy for Breast Cancer: A Systematic Review and Meta-analysis.. Plast Reconstr Surg Glob Open, 2022. 10 (3)(3): p. e4180., https: //pubmed.ncbi.nlm.nih.gov/35291333/.					
	Duplicates (n = 70) Did not address any key question addressed in current review (n = 61) Single-group studies (n = 86)			4 studies reported this outcome No pooled data	

Verknüpfte Empfehlungen:

Empfehlung 7.51:

Patientinnen sollten darüber aufgeklärt werden, dass die autologe Brustrekonstruktion der Implantat-basierten Brustrekonstruktion bezüglich der patientenberichteten Outcomeparameter (PROMs) Zufriedenheit mit der Rekonstruktion, Zufriedenheit mit der Brust und körperliches Wohlbefinden langfristig (>2 Jahre nach Brustrekonstruktion) überlegen zu sein scheint.

Literaturreferenzen: [296], [297], [298], [299], [300], [301], [302], [303], [304], [305], [306], [307], [308]

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nr of participants (studies)	Certainty of the evidence (GRADE)
	Risk with implant-based reconstruction	Risk with autologous reconstruction			
Satisfaction with breast (NRSIs)	The mean satisfaction with breasts was 61	MD 8.51 higher (6.08 higher to 10.94 higher)	-	2051 (10 non-randomised studies)	⨁⨁◯◯ Low[a]
Satisfaction with outcome (NRSIs)	The mean satisfaction with outcome was 70	MD 9.14 higher (6.99 higher to 11.3 higher)	-	1474 (6 non-randomised studies)	⨁⨁◯◯ Low[a]
Physical well-being (NRSIs)	The mean physical well-being was 68	MD 3.49 higher (1.22 higher to 5.76 higher)	-	2024 (9 non-randomised studies)	⨁⨁◯◯ Low[a]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

siehe Meta-Analysen

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nr of participants (studies)	Certainty of the evidence (GRADE)
	Risk with implant-based reconstruction	Risk with autologous reconstruction			

Explanations

a. Downgraded by two levels due to very serious risk of bias: Included studies were observational only, and the majority did not adjust at all for relevant baseline characteristics. Results are thus prone to confounding.

Verknüpfte Empfehlungen:

Empfehlung 7.51:

Patientinnen sollten darüber aufgeklärt werden, dass die autologe Brustrekonstruktion der Implantat-basierten Brustrekonstruktion bezüglich der patientenberichteten Outcomeparameter (PROMs) Zufriedenheit mit der Rekonstruktion, Zufriedenheit mit der Brust und körperliches Wohlbefinden langfristig (>2 Jahre nach Brustrekonstruktion) überlegen zu sein scheint.

Literaturreferenzen: [296], [297], [298], [299], [300], [301], [302], [303], [304], [305], [306], [307], [308]

Cai L, Momeni A. The Impact of Reconstructive Modality and Postoperative Complications on Decision Regret and Patient-Reported Outcomes following Breast Reconstruction. Aesthetic Plast Surg. 2022 Apr;46(2): 655-660. doi: 10.1007/s00266-021-02660-2. Epub 2021 Nov 29. PMID: 34845512.

Study type	Population	Interventions	Main results	Methodological evaluation
Prospective cohort study	**Inclusion criteria** (for analysis): Adult female patients older than 18 years Previously undergone either autologous breast reconstruction or implant-based breast reconstruction by the senior author At least 1 year of postoperative follow-up **Exclusion criteria** (for analysis): NR	**Interventions** Autologous breast reconstruction · N = 38 Implant-based breast reconstruction N = 25 **Analysis** NR No matching No adjustment	**Loss of implant/flap** · Autologous: 1/69 · Implant-based: 0/40 **QoL-Outcomes: Breast –Q (mean, sd)** Satisfaction with breasts · Autologous: 84.7 (18.6) · Implant-based: 77.0 (19.1)	**General information** Follow-up: NR Funding: None. CoI: None. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: prospective cohort study Populations comparable (confounding): no

Cai L, Momeni A. The Impact of Reconstructive Modality and Postoperative Complications on Decision Regret and Patient-Reported Outcomes following Breast Reconstruction. Aesthetic Plast Surg. 2022 Apr;46(2): 655-660. doi: 10.1007/s00266-021-02660-2. Epub 2021 Nov 29. PMID: 34845512.				
	Enrolment period: NR **Follow-up:** NR **Descriptive statistics** Age (mean, sd) · Overall population: 51(9.8) BMI (mean, sd) · Overall population: 27.5 (6.3) Stadium: · NR Neoadjuvant chemotherapy (% yes) · NR Adjuvant chemotherapy (% yes) · NR Reconstruction type · NR Smoke · NR			Rate of participation/ Exclusions reported (selection bias into the study): no Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: no Outcome: yes Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results Main cofounders taken into account: no. Confidence intervals reported: no

Cai L, Momeni A. The Impact of Reconstructive Modality and Postoperative Complications on Decision Regret and Patient-Reported Outcomes following Breast Reconstruction. Aesthetic Plast Surg. 2022 Apr;46(2): 655-660. doi: 10.1007/s00266-021-02660-2. Epub 2021 Nov 29. PMID: 34845512.				
				Selective reporting (comparison with protocol): no

Verknüpfte Empfehlungen:

Empfehlung 7.51:

Patientinnen sollten darüber aufgeklärt werden, dass die autologe Brustrekonstruktion der Implantat-basierten Brustrekonstruktion bezüglich der patientenberichteten Outcomeparameter (PROMs) Zufriedenheit mit der Rekonstruktion, Zufriedenheit mit der Brust und körperliches Wohlbefinden langfristig (>2 Jahre nach Brustrekonstruktion) überlegen zu sein scheint.

Literaturreferenzen: [296], [297], [298], [299], [300], [301], [302], [303], [304], [305], [306], [307], [308]

Gao P, Bai P, Kong X, Fang Y, Gao J, Wang J. Patient-Reported Outcomes and Complications Following Breast Reconstruction: A Comparison Between Biological Matrix-Assisted Direct-to-Implant and Latissimus Dorsi Flap. Front Oncol. 2022 Jan 27;12: 766076. doi: 10.3389/fonc.2022.766076. PMID: 35155227; PMCID: PMC8828647.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): All women aged 18 years and older First-time breast reconstruction with LDF or one-stage implant for cancer treatment at the National Cancer Center of China **Exclusion criteria** (for analysis): Contraindications with porcine	**Interventions** Autologous breast reconstruction · N = 56 Implant-based breast reconstruction · N = 79 **Analysis** Chi-square test No matching No adjustment	**Loss of implant/flap** · Autologous: 0/56 · Implant-based: 5/79 **Minor complications** · Autologous: 6/56 · Implant-based: 5/79 **Major complications** · Autologous: 5/56 · Implant-based: 5/79 **QoL-Outcomes: Breast –Q (mean, sd)**	**General information** Follow-up: 66.97 vs. 17.55 Funding: This work was supported by the Natural Science Foundation of China (No. 81872160, No. 82072940), the China National Key R&D (or Research and Development) Program (No. 2020AAA0105000 and No. 2020AAA0105004), the Beijing Municipal Natural Science Foundation (Key Project) (No. 7191009), the Beijing Municipal Natural Science Foundation

Gao P, Bai P, Kong X, Fang Y, Gao J, Wang J. Patient-Reported Outcomes and Complications Following Breast Reconstruction: A Comparison Between Biological Matrix-Assisted Direct-to-Implant and Latissimus Dorsi Flap. Front Oncol. 2022 Jan 27;12: 766076. doi: 10.3389/fonc.2022.766076. PMID: 35155227; PMCID: PMC8828647.				
	Enrolment period: August 2010 - April 2019 **Follow-up (mean, sd):** Autologous: 66.97 (26.64) Implant-based: 17.55 (4.83) **Descriptive statistics** Age (mean, sd) · Autologous: 39.52 (8.39) · Implant-based: 41.14 (7.03) BMI (mean, sd) · Autologous: 24.08 (5.28) · Implant-based: 21.73 (2.20) Stadium: · NR Neoadjuvant chemotherapy (% yes) · Autologous: 12/56 (21.4%) · Implant-based: 9/79 (11.4%) Adjuvant chemotherapy (% yes) · Autologous: 46/56 (82.1%)		<u>Satisfaction with breasts</u> · Autologous: 61.6 (15.99) · Implant-based: 60.27 (17.71) <u>Physical well-being</u> · Autologous: 36.0 (20.30) · Implant-based: 39.60 (17.39)	(No. 7204293), the Special Research Fund for Central Universities, Peking Union Medical College (No. 3332019053), the Beijing Hope Run Special Fund of Cancer Foundation of China (No. LC2019B03, No. LC2019L07, No. LC2020L01), the Golden Bridge Project Seed Fund of Beijing Association for Science and Technology (No. ZZ20004), the 2021 Chaoyang District Social Development Science and Technology Plan Project (Medical and Health Field) (No. CYSF2115), the Chinese Young Breast Experts Research project (No. CYBER-2021-005), the XianSheng Clinical Research Special Fund of China International Medical Foundation (No. Z-2014-06-2103), and the Beijing Xisike Clinical Oncology Research Foundation (No. Y-Young2021-0017).

Gao P, Bai P, Kong X, Fang Y, Gao J, Wang J. Patient-Reported Outcomes and Complications Following Breast Reconstruction: A Comparison Between Biological Matrix-Assisted Direct-to-Implant and Latissimus Dorsi Flap. Front Oncol. 2022 Jan 27;12: 766076. doi: 10.3389/fonc.2022.766076. PMID: 35155227; PMCID: PMC8828647.				
	· Implant-based: 46/79 (58.2%) Reconstruction type · Autologous: LDF (Latissimus Dorsi Flap) · Implant-based: SIS matrix-assisted DTI (Direct to Implant) Smoke · Autologous: 0/56 (0%) Implant-based: 0/79 (0%)			CoI: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Populations comparable (confounding): yes Rate of participation/ Exclusions reported (selection bias into the study): no Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no

Gao P, Bai P, Kong X, Fang Y, Gao J, Wang J. Patient-Reported Outcomes and Complications Following Breast Reconstruction: A Comparison Between Biological Matrix-Assisted Direct-to-Implant and Latissimus Dorsi Flap. Front Oncol. 2022 Jan 27;12: 766076. doi: 10.3389/fonc.2022.766076. PMID: 35155227; PMCID: PMC8828647.				
				Drop-out rate & reasons reported: no Outcome: yes · Outcome measure is well-defined, valid and reliable · No blind outcome assessment, however, this is unlikely to affect the results Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): no

Verknüpfte Empfehlungen:

Empfehlung 7.51:

Patientinnen sollten darüber aufgeklärt werden, dass die autologe Brustrekonstruktion der Implantat-basierten Brustrekonstruktion bezüglich der patientenberichteten Outcomeparameter (PROMs) Zufriedenheit mit der Rekonstruktion, Zufriedenheit mit der Brust und körperliches Wohlbefinden langfristig (>2 Jahre nach Brustrekonstruktion) überlegen zu sein scheint.

Literaturreferenzen: [296], [297], [298], [299], [300], [301], [302], [303], [304], [305], [306], [307], [308]

Miseré RM, van Kuijk SM, Claassens EL, Heuts EM, Piatkowski AA, van der Hulst RR. Breast-related and body-related quality of life following autologous breast reconstruction is superior to implant-based breast reconstruction - A long-term follow-up study. Breast. 2021 Oct;59: 176-182. doi: 10.1016/j.breast.2021.07.003. Epub 2021 Jul 7. PMID: 34271290; PMCID: PMC8287213.

Study type	Population	Interventions	Main results	Methodological evaluation
Multicenter, cross-sectional survey	**Inclusion criteria** (for analysis): Women who underwent immediate or delayed IBR or ABR **Exclusion criteria** (for analysis): Bilateral reconstruction with unilateral IBR and contralateral ABR or a mixed timing Tertiary breast reconstruction (after failed reconstruction or unsatisfactory results)	**Interventions** Autologous breast reconstruction · N = 224 Implant-based breast reconstruction · N = 112 **Analysis** Multivariable linear regression analysis No matching	**QoL-outcomes: Breast-Q (mean, sd)** Satisfaction with breasts · Autologous: 68.3 (19.4) · Implant-based: 55.5 (18.4) · Adjusted mean difference: 14.10 (95% CI: 8.3- 21.0) Satisfaction with overall outcome · Autologous: 70.9 (21.6) · Implant-based: 60 (20.8)	**General information** Follow-up: Mean 46.7 months (SD 14.8) Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. CoI: None. **Risk of bias considerations** (adapted from SIGN cohort study checklist)

Miseré RM, van Kuijk SM, Claassens EL, Heuts EM, Piatkowski AA, van der Hulst RR. Breast-related and body-related quality of life following autologous breast reconstruction is superior to implant-based breast reconstruction - A long-term follow-up study. Breast. 2021 Oct;59: 176-182. doi: 10.1016/j.breast.2021.07.003. Epub 2021 Jul 7. PMID: 34271290; PMCID: PMC8287213.				
	Breast reconstruction by autologous fat transfer (AFT) Currently no breast reconstruction after previously failed reconstruction Currently distant metastases **Enrolment period:** November - December 2020 **Follow-up (mean, sd):** 46.7 months (14.8) **Descriptive statistics** Age (mean, sd) · Autologous: 55.0 (8.9) · Implant-based: 56.4 (11.3) BMI (mean, sd) · Autologous: 26.3 (4.2) · Implant-based: 24.2 (3.9) Stadium (overall population) T:	Adjusted for age, BMI, cup size preoperatively, smoking, educational level, tumor classification (T stage, N stage), radiotherapy, hormone therapy, reconstruction type, reconstruction timing, follow-up duration after reconstruction	· Adjusted mean difference: 14.90 (95% CI: 8.0- 21.9) <u>Physical well-being</u> · Autologous: 68.7 (17.2) · Implant-based: 64.2 (17.6) · Adjusted mean difference: 6.20 (95% CI: 0.8- 11.7)	Study type: multicenter, cross-sectional survey Populations comparable (confounding): yes Rate of participation/ Exclusions reported (selection bias into the study): no Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: no Outcome: yes · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results

Miseré RM, van Kuijk SM, Claassens EL, Heuts EM, Piatkowski AA, van der Hulst RR. Breast-related and body-related quality of life following autologous breast reconstruction is superior to implant-based breast reconstruction - A long-term follow-up study. Breast. 2021 Oct;59: 176-182. doi: 10.1016/j.breast.2021.07.003. Epub 2021 Jul 7. PMID: 34271290; PMCID: PMC8287213.				
	· Autologous: T1: 82/224 (36.6%), T2: 63/224 (28.1%), T3: 8/224 (3.6%) · Implant-based: T1: 43/112 (38.4%), T2: 28/112 (25.0%), T3: 5/112 (4.5%) N: · Autologous: N0: 92/224 (41.1%), N1: 51/224 (22.8%), N2: 8/224 (3.6%), N3: 4/224 (1.8%) · Implant-based: N0: 63/112 (56.3%), N1: 12/112 (10.7%), N2: 1/112 (0.9%), N3: 0/112 (0%) M: · Autologous: M0: 168/224 · Implant-based: M0: 81/112 Neoadjuvant chemotherapy (% yes) · NR Adjuvant chemotherapy (% yes)			Main cofounders taken into account: adjusted for some main characteristics Confidence intervals reported: yes Selective reporting (comparison with protocol): no

Miseré RM, van Kuijk SM, Claassens EL, Heuts EM, Piatkowski AA, van der Hulst RR. Breast-related and body-related quality of life following autologous breast reconstruction is superior to implant-based breast reconstruction - A long-term follow-up study. Breast. 2021 Oct;59: 176-182. doi: 10.1016/j.breast.2021.07.003. Epub 2021 Jul 7. PMID: 34271290; PMCID: PMC8287213.				
	· Autologous: 126/224 (56.3%) · Implant-based: 54/112 (48.2%) Reconstruction type · Autologous: NR · Implant-based: NR Smoke · Autologous: 10/224 (4.5%) Implant-based: 21/112 (18.8%)			

Verknüpfte Empfehlungen:

Empfehlung 7.51:

Patientinnen sollten darüber aufgeklärt werden, dass die autologe Brustrekonstruktion der Implantat-basierten Brustrekonstruktion bezüglich der patientenberichteten Outcomeparameter (PROMs) Zufriedenheit mit der Rekonstruktion, Zufriedenheit mit der Brust und körperliches Wohlbefinden langfristig (>2 Jahre nach Brustrekonstruktion) überlegen zu sein scheint.

Literaturreferenzen: [296], [297], [298], [299], [300], [301], [302], [303], [304], [305], [306], [307], [308]

Nelson JA, Shamsunder MG, Myers PL, Polanco TO, Coriddi MR, McCarthy CM, Matros E, Dayan JH, Disa JJ, Mehrara BJ, Pusic AL, Allen RJ Jr. Matched Preliminary Analysis of Patient-Reported Outcomes following Autologous and Implant-Based Breast Reconstruction. Ann Surg Oncol. 2022 Aug;29(8): 5266-5275. doi: 10.1245/s10434-022-11504-5. Epub 2022 Apr 3. PMID: 35366702; PMCID: PMC9253052.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Women who underwent immediate ABR or IBR for therapeutic or prophylactic indications ABR procedures employed a deep inferior epigastric artery perforator flap, a superficial inferior epigastric artery flap, a muscle-sparing transverse rectus abdominis myocutaneous flap, or a free	**Interventions** Autologous breast reconstruction · Year 1: N = 97 · Year 2: N = 70 Implant-based breast reconstruction · Year 1: N = 134 · Year 2: N = 116 **Analysis** Linear regression	**QoL-outcomes: Breast –Q (mean, sd)** Satisfaction with breasts (year 1) · Autologous: 69.4 (20.3) · Implant-based: 67 (16.8) Satisfaction with breasts (year 2) · Autologous: 69.7 (20.5) · Implant-based: 68.1 (16.3)	**General information** Follow-up: NR Funding: Dr. Pusic is a code developer of the BREAST-Q questionnaire, which is owned by Memorial Sloan Kettering Cancer Center. She receives a portion of the licensing fees (royalty payments) when the questionnaire is used in industry-sponsored clinical trials. Dr. Dayan is a paid consultant for Stryker Corp. All other authors had no

Nelson JA, Shamsunder MG, Myers PL, Polanco TO, Coriddi MR, McCarthy CM, Matros E, Dayan JH, Disa JJ, Mehrara BJ, Pusic AL, Allen RJ Jr. Matched Preliminary Analysis of Patient-Reported Outcomes following Autologous and Implant-Based Breast Reconstruction. Ann Surg Oncol. 2022 Aug;29(8): 5266-5275. doi: 10.1245/s10434-022-11504-5. Epub 2022 Apr 3. PMID: 35366702; PMCID: PMC9253052.				
	transverse rectus abdominis myocutaneous flap IBR procedures were two stage, with submuscular placement of the tissue expander **Exclusion criteria** (for analysis): Patients who underwent a nonabdominal free flap procedure, delayed reconstruction, or radiotherapy as part of oncologic treatment **Enrolment period:** January 2007- June 2017 **Follow-up:** NR **Descriptive statistics** Age (mean, sd) · Autologous: 49.6 (8.0) · Implant-based: 49.5 (10.0) BMI (mean, sd) · Autologous: 29.3 (4.8)	No matching No adjustment	Satisfaction with breasts (longest follow-up) · Autologous: 69.3 (19.9) · Implant-based: 66.5 (16.6) Physical well-being (year 1) · Autologous: 74.8 (15.9) · Implant-based: 75.3 (15.5) Physical well-being (year 2) · Autologous: 77.0 (14.2) · Implant-based: 77.6 (16.0) Physical well-being (longest follow-up) · Autologous: 75.2 (15.3) · Implant-based: 76.2 (16.3)	competing interests. Dr. Mehrara is an Advisor to PureTech Corp; investigator initiated grant Regeneron corp. This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748. CoI: NR. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Populations comparable (confounding): yes Rate of participation/ Exclusions reported (selection bias into the study): no Intervention · Assessment reliable: yes · Assessed more than once: no

Nelson JA, Shamsunder MG, Myers PL, Polanco TO, Coriddi MR, McCarthy CM, Matros E, Dayan JH, Disa JJ, Mehrara BJ, Pusic AL, Allen RJ Jr. Matched Preliminary Analysis of Patient-Reported Outcomes following Autologous and Implant-Based Breast Reconstruction. Ann Surg Oncol. 2022 Aug;29(8): 5266-5275. doi: 10.1245/s10434-022-11504-5. Epub 2022 Apr 3. PMID: 35366702; PMCID: PMC9253052.				
	· Implant-based: 25.1 (5.1) Stadium: · NR Neoadjuvant chemotherapy (% yes) · Autologous: 0/159 (0%) · Implant-based: 11/2175 (5.8%) Adjuvant chemotherapy (% yes) · Autologous: 1/159 (0.6%) · Implant-based: 728/2175 (33.5%) Reconstruction type · Autologous: NR · Implant-based: NR Smoke · Autologous: Never smoker: 99/159 (62.3%), Previous smoker: 56/159 (35.2%),			· Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: no Outcome: yes · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results Main cofounders taken into account: no. Confidence intervals reported: no Selective reporting (comparison with protocol): no

Nelson JA, Shamsunder MG, Myers PL, Polanco TO, Coriddi MR, McCarthy CM, Matros E, Dayan JH, Disa JJ, Mehrara BJ, Pusic AL, Allen RJ Jr. Matched Preliminary Analysis of Patient-Reported Outcomes following Autologous and Implant-Based Breast Reconstruction. Ann Surg Oncol. 2022 Aug;29(8): 5266-5275. doi: 10.1245/s10434-022-11504-5. Epub 2022 Apr 3. PMID: 35366702; PMCID: PMC9253052.				
	Current smoker: 4/159 (2.5%), Unknown: 0/159 (0%) Implant-based: Never smoker: 1396/2175 (64.2%), Previous smoker: 584/2175 (26.9%), Current smoker: 119/2175 (5.5%), Unknown: 487/2175 (22.4%)			

Verknüpfte Empfehlungen:

Empfehlung 7.51:

Patientinnen sollten darüber aufgeklärt werden, dass die autologe Brustrekonstruktion der Implantat-basierten Brustrekonstruktion bezüglich der patientenberichteten Outcomeparameter (PROMs) Zufriedenheit mit der Rekonstruktion, Zufriedenheit mit der Brust und körperliches Wohlbefinden langfristig (>2 Jahre nach Brustrekonstruktion) überlegen zu sein scheint.

Literaturreferenzen: [296], [297], [298], [299], [300], [301], [302], [303], [304], [305], [306], [307], [308]

Persichetti P, Barone M, Salzillo R, Cogliandro A, Brunetti B, Ciarrocchi S, Alessandri Bonetti M, Tenna S, Sorotos M, Santanelli Di Pompeo F. Impact on Patient's Appearance Perception of Autologous and Implant Based Breast Reconstruction Following Mastectomy Using BREAST-Q. Aesthetic Plast Surg. 2022 Jun;46(3): 1153-1163. doi: 10.1007/s00266-022-02776-z. Epub 2022 Feb 28. PMID: 35229192; PMCID: PMC9411234.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Patients who underwent to breast reconstruction for cancer Follow-up of at least 2 years Fluent in the Italian language Signed the study consent Patients having undergone prophylactic mastectomy due to genetic indication from	**Interventions** Autologous breast reconstruction · N = 133 Implant-based breast reconstruction · N = 192 **Analysis** Linear regression No matching No adjustment	**QoL-outcomes: Breast-Q (mean, sd)** Satisfaction with breasts · Autologous: 62.7 (16.2) · Implant-based: 52.9 (12.1) Satisfaction with overall outcome · Autologous: 77.7 (18.8) · Implant-based: 66.5 (17.2) Physical well-being · Autologous: 73.3 (16.6)	**General information** Follow-up: NR Funding: No intramural or extramural funding supported any aspect of this work. CoI: The authors do not have any commercial associations that might pose or create a conflict of interest with information presented in this communication.

Persichetti P, Barone M, Salzillo R, Cogliandro A, Brunetti B, Ciarrocchi S, Alessandri Bonetti M, Tenna S, Sorotos M, Santanelli Di Pompeo F. Impact on Patient's Appearance Perception of Autologous and Implant Based Breast Reconstruction Following Mastectomy Using BREAST-Q. Aesthetic Plast Surg. 2022 Jun;46(3): 1153-1163. doi: 10.1007/s00266-022-02776-z. Epub 2022 Feb 28. PMID: 35229192; PMCID: PMC9411234.				
	deleterious BRCA1/2 or CDH1 mutations **Exclusion criteria** (for analysis): If they underwent delayed procedures Follow-up of less than 2 years Postoperative complications that compromised reconstruction Legally incompetent Women who did not sign the consent form to participate to this study **Enrolment period:** January 2014 - January 2020 **Follow-up:** NR **Descriptive statistics** Age (mean, sd) · Autologous: 51.3 (9.5) · Implant-based: 51.9 (10.7)		· Implant-based: 65.2 (9.5)	**Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Populations comparable (confounding): yes Rate of participation/ Exclusions reported (selection bias into the study): no Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: no Outcome: yes · Outcome measure is well-defined, valid and reliable;

Persichetti P, Barone M, Salzillo R, Cogliandro A, Brunetti B, Ciarrocchi S, Alessandri Bonetti M, Tenna S, Sorotos M, Santanelli Di Pompeo F. Impact on Patient's Appearance Perception of Autologous and Implant Based Breast Reconstruction Following Mastectomy Using BREAST-Q. Aesthetic Plast Surg. 2022 Jun;46(3): 1153-1163. doi: 10.1007/s00266-022-02776-z. Epub 2022 Feb 28. PMID: 35229192; PMCID: PMC9411234.				
	BMI (mean, sd) · Autologous: 25.2 (4.0) · Implant-based: 26.2 (2.9) Stadium: · NR Neoadjuvant chemotherapy (% yes) · Autologous: 32/133 (24.1%) · Implant-based: 57/192 (50.0%) Adjuvant chemotherapy (% yes) · Autologous: 8/133 (6.0%) · Implant-based: 25/192 (13.0%) Reconstruction type · Autologous: (DIEP) deep inferior epigastric perforator · Implant-based: IBR (implant-based Breast Reconstruction) Smoke			· No blind outcome assessment, however, this is unlikely to affect the results Main cofounders taken into account: no. Confidence intervals reported: no Selective reporting (comparison with protocol): no

Persichetti P, Barone M, Salzillo R, Cogliandro A, Brunetti B, Ciarrocchi S, Alessandri Bonetti M, Tenna S, Sorotos M, Santanelli Di Pompeo F. Impact on Patient's Appearance Perception of Autologous and Implant Based Breast Reconstruction Following Mastectomy Using BREAST-Q. Aesthetic Plast Surg. 2022 Jun;46(3): 1153-1163. doi: 10.1007/s00266-022-02776-z. Epub 2022 Feb 28. PMID: 35229192; PMCID: PMC9411234.				
	· Autologous: Never smoker: 62/133 (46.6%), Previous smoker: 34/133 (25.6%), Current smoker: 37/133 (27.8%) Implant-based: Never smoker: 96/192 (50.0%), Previous smoker: 42/192 (21.9%), Current smoker: 54/192 (28.1%)			

Verknüpfte Empfehlungen:

Empfehlung 7.51:

Patientinnen sollten darüber aufgeklärt werden, dass die autologe Brustrekonstruktion der Implantat-basierten Brustrekonstruktion bezüglich der patientenberichteten Outcomeparameter (PROMs) Zufriedenheit mit der Rekonstruktion, Zufriedenheit mit der Brust und körperliches Wohlbefinden langfristig (>2 Jahre nach Brustrekonstruktion) überlegen zu sein scheint.

Literaturreferenzen: [296], [297], [298], [299], [300], [301], [302], [303], [304], [305], [306], [307], [308]

Sadok N, Krabbe-Timmerman IS, Buisman NH, van Aalst VC, de Bock GH, Werker PMN. Short-Term Quality of Life after Autologous Compared with Alloplastic Breast Reconstruction: A Prospective Study. Plast Reconstr Surg. 2023 Oct 1;152(4S): 55S-68S. doi: 10.1097/PRS.0000000000010496. Epub 2023 Sep 28. PMID: 37036311; PMCID: PMC10521783.

Study type	Population	Interventions	Main results	Methodological evaluation
Prospective multicenter cohort study	**Inclusion criteria** (for analysis): Prospective multicenter cohort study in women undergoing autologous or alloplastic BR Aged 18 years and older **Exclusion criteria** (for analysis): NR **Enrolment period:** 2012 - 2019 **Follow-up:** NR **Descriptive statistics**	**Interventions** Autologous breast reconstruction · N = 63 Implant-based breast reconstruction · N = 75 **Analysis** Generalized linear regression No matching No adjusted data reported	**Flap loss** · Autologous: 1/63 · Implant-based: 0/75 **Any complications** · Autologous: 39/63 · Implant-based: 38/75 **QoL-ooutcomes: Breast-Q (mean, sd)** Satisfaction with breasts (6 months post-operative) · Autologous: 68 (17)	**General information** Follow-up: NR Funding: Prof. Werker is SERB member for Fidia Ltd., Milan, Italy CoI: All the other authors have no financial interest to declare in relation to the content of this article. **Risk of bias considerations** (adapted from SIGN cohort study checklist)

Sadok N, Krabbe-Timmerman IS, Buisman NH, van Aalst VC, de Bock GH, Werker PMN. Short-Term Quality of Life after Autologous Compared with Alloplastic Breast Reconstruction: A Prospective Study. Plast Reconstr Surg. 2023 Oct 1;152(4S): 55S-68S. doi: 10.1097/PRS.0000000000010496. Epub 2023 Sep 28. PMID: 37036311; PMCID: PMC10521783.				
	Age (mean, sd) · Autologous: 49 (9) · Implant-based: 47 (11) BMI (median, IQR) · Autologous: 27 (25 - 39) · Implant-based: 25 (22 - 30) Stadium: · NR Neoadjuvant chemotherapy (% yes) · Autologous: 6/63 (5%) · Implant-based: 8/75 (6%) Adjuvant chemotherapy (% yes) · Autologous: 2/63 (1%) · Implant-based: 14/75 (10%) Reconstruction type · Autologous: The autologous technique was a deep inferior		· Implant-based: 57 (19) Satisfaction with overall outcome (6 months post-operative) · Autologous: 74 (23) · Implant-based: 71 (19) Physical well-being (6 months post-operative) · Autologous: 74 (18) · Implant-based: 73 (13)	Study type: prospective multicenter cohort study Populations comparable (confounding): yes Rate of participation/ Exclusions reported (selection bias into the study): yes Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: no Outcome: yes · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results

Sadok N, Krabbe-Timmerman IS, Buisman NH, van Aalst VC, de Bock GH, Werker PMN. Short-Term Quality of Life after Autologous Compared with Alloplastic Breast Reconstruction: A Prospective Study. Plast Reconstr Surg. 2023 Oct 1;152(4S): 55S-68S. doi: 10.1097/PRS.0000000000010496. Epub 2023 Sep 28. PMID: 37036311; PMCID: PMC10521783.				
	epigastric perforator (DIEP) flap BR · Implant-based: direct implant (one stage), tissue expander followed by implant (two stages), or tissue expander/implant combined with a latissimus dorsi flap) Smoke · Autologous: 1/63 (1%) · Implant-based: 16/75 (11%)			Main cofounders taken into account: no. Confidence intervals reported: no Selective reporting (comparison with protocol): no

Verknüpfte Empfehlungen:

Empfehlung 7.51:

Patientinnen sollten darüber aufgeklärt werden, dass die autologe Brustrekonstruktion der Implantat-basierten Brustrekonstruktion bezüglich der patientenberichteten Outcomeparameter (PROMs) Zufriedenheit mit der Rekonstruktion, Zufriedenheit mit der Brust und körperliches Wohlbefinden langfristig (>2 Jahre nach Brustrekonstruktion) überlegen zu sein scheint.

Literaturreferenzen: [296], [297], [298], [299], [300], [301], [302], [303], [304], [305], [306], [307], [308]

von Glinski M, Holler N, Kümmel S, Reinisch M, Wallner C, Wagner JM, Dadras M, Sogorski A, Lehnhardt M, Behr B. Autologous vs. implant-based breast reconstruction after skin- and nipple-sparing mastectomy-A deeper insight considering surgical and patient-reported outcomes. Front Surg. 2022 Sep 5;9: 903734. doi: 10.3389/fsurg.2022.903734. PMID: 36132203; PMCID: PMC9483019.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): History of ABR or IBR after skin/nipple-sparing mastectomy Follow-up after reconstruction of at least one year Free of cancer or metastases Conversant in German **Exclusion criteria** (for analysis):	**Interventions** Autologous breast reconstruction · N = 36 Implant-based breast reconstruction · N = 72 **Analysis** Fisher exact test + Mann-Whitney tests No matching	**Reoperation** · Autologous: 7/36 · Implant-based: 13/72 **Minor complications** · Autologous: 8/36 · Implant-based: 8/72 **Major complications** · Autologous: 3/36 · Implant-based: 22/72	**General information** Follow-up: 34.9 vs. 27.1 months Funding: We acknowledge support from the Open Access Publication Funds of the Ruhr-Universität Bochum. CoI: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

von Glinski M, Holler N, Kümmel S, Reinisch M, Wallner C, Wagner JM, Dadras M, Sogorski A, Lehnhardt M, Behr B. Autologous vs. implant-based breast reconstruction after skin- and nipple-sparing mastectomy-A deeper insight considering surgical and patient-reported outcomes. Front Surg. 2022 Sep 5;9: 903734. doi: 10.3389/fsurg.2022.903734. PMID: 36132203; PMCID: PMC9483019.				
	Patients with an ABR after IBR and vice versa Any patient undergoing reconstruction with a pedicled flap or a mixed approach (bilateral reconstruction with unilateral flap and unilateral implant or additional use of a pedicled flap) **Enrolment period: J**anuary 2014 - May 2020 **Follow-up (mean, sd):** Autologous: 34.9 months (20.5) Implant-based: 27.1 months (9.3) **Descriptive statistics** Age (mean, sd) · Autologous: 46.6 (7.3), range: 32 - 69) · Implant-based: 48.9 (9.9), range: 28 - 70)	No adjustment	**QoL-outcomes: Breast-Q (mean, sd)** <u>Satisfaction with breasts</u> · Autologous: 67.7 (15.6) · Implant-based: 59.9 (17.9) <u>Satisfaction with overall outcome</u> · Autologous: 78.4 (19.0) · Implant-based: 73.2 (20.2) <u>Physical well-being</u> · Autologous: 71.4 (15.90) · Implant-based: 67.6 (13.90)	**Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Populations comparable (confounding): yes Rate of participation/ Exclusions reported (selection bias into the study): no Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: no Outcome: yes · Outcome measure is well-defined, valid and reliable;

von Glinski M, Holler N, Kümmel S, Reinisch M, Wallner C, Wagner JM, Dadras M, Sogorski A, Lehnhardt M, Behr B. Autologous vs. implant-based breast reconstruction after skin- and nipple-sparing mastectomy-A deeper insight considering surgical and patient-reported outcomes. Front Surg. 2022 Sep 5;9: 903734. doi: 10.3389/fsurg.2022.903734. PMID: 36132203; PMCID: PMC9483019.				
	BMI (mean, sd) · Autologous: 26.9 (5.4) · Implant-based: 24.3 (4.3) Stadium: · NR Neoadjuvant chemotherapy (% yes) · Autologous: 16/36 (44.4%) · B Implant-based 13/72 (18.1%) Adjuvant chemotherapy (% yes) · NR Reconstruction type · Autologous: DIEP, TRAM, and the superficial inferior epigastric artery (SIEA) flap · Implant-based: NR Smoke (Currently smoking) · Autologous: 6/36 (16.7%)			· No blind outcome assessment, however, this is unlikely to affect the results Main cofounders taken into account: no. Confidence intervals reported: no Selective reporting (comparison with protocol): no

von Glinski M, Holler N, Kümmel S, Reinisch M, Wallner C, Wagner JM, Dadras M, Sogorski A, Lehnhardt M, Behr B. Autologous vs. implant-based breast reconstruction after skin- and nipple-sparing mastectomy-A deeper insight considering surgical and patient-reported outcomes. Front Surg. 2022 Sep 5;9: 903734. doi: 10.3389/fsurg.2022.903734. PMID: 36132203; PMCID: PMC9483019.				
	Implant-based: 9/72 (12.5%)			

Verknüpfte Empfehlungen:

Empfehlung 7.51:

Patientinnen sollten darüber aufgeklärt werden, dass die autologe Brustrekonstruktion der Implantat-basierten Brustrekonstruktion bezüglich der patientenberichteten Outcomeparameter (PROMs) Zufriedenheit mit der Rekonstruktion, Zufriedenheit mit der Brust und körperliches Wohlbefinden langfristig (>2 Jahre nach Brustrekonstruktion) überlegen zu sein scheint.

Literaturreferenzen: [296], [297], [298], [299], [300], [301], [302], [303], [304], [305], [306], [307], [308]

Tallroth L, Mobargha N, Velander P, Becker M, Klasson S. Expander prosthesis and DIEP flaps in delayed breast reconstruction: Sensibility, patient-reported outcome, and complications in a five-year randomised follow-up study. J Plast Surg Hand Surg. 2023 Sep 22;58: 101-109. doi: 10.2340/jphs.v58.13477. PMID: 37747180.

Study type	Population	Interventions	Main results	Methodological evaluation
Randomized controlled study	**Inclusion criteria** (for analysis): Patients with prior unilateral mastectomy, but no RT **Exclusion criteria** (for analysis): Insufficient abdominal donor tissue for a DIEP flap reconstruction Earlier abdominal liposuction Previous abdominoplasty Pronounced scars on the chest	**Interventions** Autologous breast reconstruction · N = 44 Implant-based breast reconstruction · N = 29 **Analysis** Fisher exact test + Mann-Whitney tests No matching No adjustment	**Overall complications (within the first 30 postoperative days)** · Autologous: 16/44 · Implant-based: 2/29 **QoL-outcomes: Breast-Q (mean, sd)** Satisfaction with breasts · Autologous: 72.1 (17.7) · Implant-based: 63.4 (11.8) Satisfaction with overall outcome	**General information** Study duration: April 2012 – January 2018 Median Follow up/ data cutoff: NR ITT: Yes Randomisation: Yes Blinding: No Funding: None. COI: None Other limitations: None.

Tallroth L, Mobargha N, Velander P, Becker M, Klasson S. Expander prosthesis and DIEP flaps in delayed breast reconstruction: Sensibility, patient-reported outcome, and complications in a five-year randomised follow-up study. J Plast Surg Hand Surg. 2023 Sep 22;58: 101-109. doi: 10.2340/jphs.v58.13477. PMID: 37747180.				
	Shoulder disability Warfarin treatment for atrial fibrillation. **Enrolment period:** April 2012 - January 2018 **Follow-up:** NR **Descriptive statistics** Age (mean, sd) · Autologous: 52.3 (10), range: 34 - 70 · Implant-based: 55.8 (8.9), range: 36 - 70) BMI (mean, sd) · Autologous: 26.1 (2.7), range: 20.5 - 33.0) · Implant-based: 25.1 (3.1), range: 19.0 - 30.8) Stadium: · NR Neoadjuvant chemotherapy (% yes)		· Autologous: 82.3 (21.4) · Implant-based: 79.4 (14.2) <u>Physical well-being</u> · Autologous: 79.6 (21.1) · Implant-based: 72.0 (21.5)	**Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: RCT Random sequence generation: Unclear Allocation concealment: Unclear Blinding of participants: High Blinding of study personnel: High Blinding of outcome assessors (objective outcomes): Low Blinding of outcome assessors (subjective outcomes): Unclear Incomplete outcome data: Low Selective outcome reporting: Low Other bias: Low Overall: Moderate

Tallroth L, Mobargha N, Velander P, Becker M, Klasson S. Expander prosthesis and DIEP flaps in delayed breast reconstruction: Sensibility, patient-reported outcome, and complications in a five-year randomised follow-up study. J Plast Surg Hand Surg. 2023 Sep 22;58: 101-109. doi: 10.2340/jphs.v58.13477. PMID: 37747180.				
	· NR Adjuvant chemotherapy (% yes) · Autologous: 25/44 (57%) · Implant-based: 13/29 (45%) Reconstruction type · Autologous: (DIEP) deep inferior epigastric perforator expander prosthesis (EP) · Implant-based: expander prosthesis (EP) Smoke · Autologous: Never smokers: 29/44 (66%); Former smoker: 11/44 (25%), Stopped before surgery: 4/44 (9%) · Implant-based: Never smoker: 16/29 (55%); Former smoker: 11/29 (38%); Stopped before surgery. 2/29 (7%)			

Verknüpfte Empfehlungen:

Empfehlung 7.51:

Patientinnen sollten darüber aufgeklärt werden, dass die autologe Brustrekonstruktion der Implantat-basierten Brustrekonstruktion bezüglich der patientenberichteten Outcomeparameter (PROMs) Zufriedenheit mit der Rekonstruktion, Zufriedenheit mit der Brust und körperliches Wohlbefinden langfristig (>2 Jahre nach Brustrekonstruktion) überlegen zu sein scheint.

Literaturreferenzen: [296], [297], [298], [299], [300], [301], [302], [303], [304], [305], [306], [307], [308]

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
Brito 2020	• Women 18 years or older	• Patients with second	retrospective cohort study	January 2014 and May 2018	48.8	25	NR	NR	34	pedicled TRAM or LD-flap	NR	NR

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	rwhoundenrwentimmediateordel	aryreconstruction,immediate										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	ayedprimaryBRfollowingmastectomy	reconstructionononebreast, a										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	• ctomy with implant-based or aut	ndcontralateral delayed recon										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	ologous reconstruction (pedic	struction, orhybrid implantan										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	• ledTRAMorLD-flap) at least 12m	dautologous reconstruction(o										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	onths after reconstruction	ther than LD)										
Eltahir	• Wom	• age	prospective	2006 and 2010	51 vs. 44	26 vs. 23	NR	23 vs. 12	7 vs. 4	Diep, TMG,	implant, LD+	NR

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
2015	enwithsuccessfulautologousso	• youunger18yearslegallyincomp	multicenter cohort study							TRAM, DIEP + SIEA	implant, SIEA + Implant	

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	rimplantbreastreconstructi	• etentwomenpresenceofmetasta										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	• ongoodunderstandingofDutchl	• sisorseverereillnessreconstru										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	• anguage signed informed consse	• ctionfailurewomenwhodidnotg										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	nt	ive informed consent										
Kouwenberg 2020	• Patients	• Patients	retrospective cohort study	2008 - 2018	59.58 vs. 60.05	NR	NR	47.6 vs. 43.9	NR	NR	NR	NR

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	who had been surgically treated	who had developed distant metas										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	for non-metastatic breast cancer	tassessing curative treatment										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	rinthepast10years(2008to201	orwhowerenotproficientinDut										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	8).	ch										
McCarthy 2014	• age ≥ 21 years • history of mast	• a history of irradiation • del	retrospective cohort study	2003–2008	52 vs. 50	30.2 vs. 23.92	29 vs. 85	NR	0 vs. 8	immediate postmastectomy autogenous tissue flap reconstruction	immediate postmastectomy two-stage tissue expander/implant reconstruction	NR

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	ectomy alone, immediate post mastectomy reconstru	ayed post mastectomy reconstru										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	stectomy two-stage tissue expa	• ction combined autogenous tiss										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	nder/implantrekonstruktion,	ue/implantbrearekonstruct										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	orimmediate postmastectomy au	• iondocumented local recurrenc										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	togenous tissue flap reconstru	• eof breast cancer and/or histor										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	• ction of complete dmastect	y of complex regional pain syndr										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	omyorreconstructionatleastl	ome										

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	yearbutnomorethan5yearspri											

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	• oral etoricad and complete aque											

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	stionnaire book let written int											

Study	Inclusion criteria	Exclusion criteria	Study design	Enrolment period	Age	BMI kg/m2	Previous chemotherapy	Adjuvant chemotherapy	Smoking status	Type of autologous BR	Type of implant BR	Length of follow-up
	heEnglishlanguage											

Verknüpfte Empfehlungen:

Empfehlung 7.54:

Das operative Verfahren der Implantat-basierten Brustrekonstruktion (einzeitig versus zweizeitig über Expander-Implantat-Sequenz) soll unter Berücksichtigung der onkologischen Situation, individueller Risikofaktoren und individueller Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [309], [310], [311], [312], [313], [314], [315], [316], [317], [318], [319], [320], [321], [322], [323], [324], [325], [326], [327], [328], [329], [330], [331], [332], [333]

van der Wielen, A, Negenborn, V, Burchell, GL, Remmelzwaal, S, Lapid, O, Driessen, C, Less is more? One-stage versus two-stage implant-based breast reconstruction: A systematic review and meta-analysis of comparative studies. J Plast Reconstr Aesthet Surg, 2023. 86 (): p. 109-127., https: //pubmed.ncbi.nlm.nih.gov/37716248/.

Source and Purpose	Design and participants	Intervention	Outcomes & results	Quality and comment
Aim: "This systematic review examines whether there is a difference in reported outcomes and complications between one- and two-staged implant-based breast reconstruction implant-based breast reconstruction in women undergoing breast reconstruction after mastectomy." **Sources of funding**: This systematic review and meta-analysis was not sponsored by external parties.	**Design**: Systematic review with Metaanalysis **Search date**: Searched from Inception to 27.09.2022 **Searched databases**: PubMed, Embase, The Cochrane Library, Web of Science **Included study designs**: cohort studies **Number of included studies and patients**:	**Intervention** A: Direct-to-implant (DTI, one-stage) **Comparator** B: Tissue expander (TE, two-stage)	**Overall complications** **Reoperations** **Satisfaction with breasts (BREAST-Q)** **Satisfaction with outcome (BREAST-Q)** Analysed as incidences, therefore, relevant outcomes were re-extracted and analysed for this guideline (OR), see meta-analyses.	**Risk of bias assessment of studies:** mostly fair rating, see table from van der Wielen 2023 below; although confounding may not have been assessed as strictly as we would have done with ROBINS-I or similar tools **Overall confidence in results of SR (AMSTAR-2):** PICO elements: yes A priori design: not explicitly stated, no PROSPERO or protocol link provided. Justification for design: no

van der Wielen, A, Negenborn, V, Burchell, GL, Remmelzwaal, S, Lapid, O, Driessen, C, Less is more? One-stage versus two-stage implant-based breast reconstruction: A systematic review and meta-analysis of comparative studies. J Plast Reconstr Aesthet Surg, 2023. 86 (): p. 109-127., https: //pubmed.ncbi.nlm.nih.gov/37716248/.				
	33 studies published up to September 2022, including 20,614 breasts that received implant-based reconstruction DTI: 5,201 TE: 15,413 * studies that were used for the re-analysis **Mean/median age**: mean ages was between 40 and 55 years old **Inclusion criteria**: Mastectomy Primary or secondary reconstruction **Exclusion criteria:** Reviews, case reports & series, and articles with insufficient outcome reporting N < 20 Non-English publication			Literature search >= 2 databases, search strategy + other sources: · 4 databases · String for all provided · Reference lists · No further resources searched w Selection in duplicate: yes Data extraction in duplicate: · Probably yes List of excluded studies: no Sufficient detail on studies: yes, table 1 and 2 RoB assessed: yes, Study Quality Assessment Tools of the National Heart, Lung, and Blood Institute Funding of incl. studies: no MA appropriate: partly; proportions pooled, different from what we need regarding

van der Wielen, A, Negenborn, V, Burchell, GL, Remmelzwaal, S, Lapid, O, Driessen, C, Less is more? One-stage versus two-stage implant-based breast reconstruction: A systematic review and meta-analysis of comparative studies. J Plast Reconstr Aesthet Surg, 2023. 86 (): p. 109-127., https: //pubmed.ncbi.nlm.nih.gov/37716248/.				
				our PICO, therefore re-analysed. RoB considered in MA: NA (not the analysis we need) RoB in interpretation: NA (not the analysis we need) w Heterogeneity explained: no Publication bias investigated: discussed, but not presented Sources of CoI: The authors have no conflict of interest to disclose.

Verknüpfte Empfehlungen:

Empfehlung 7.54:

Das operative Verfahren der Implantat-basierten Brustrekonstruktion (einzeitig versus zweizeitig über Expander-Implantat-Sequenz) soll unter Berücksichtigung der onkologischen Situation, individueller Risikofaktoren und individueller Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [309], [310], [311], [312], [313], [314], [315], [316], [317], [318], [319], [320], [321], [322], [323], [324], [325], [326], [327], [328], [329], [330], [331], [332], [333]

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nr of participants (studies)	Certainty of the evidence (GRADE)
	Risk with tissue expander breast reconstruction	Risk with direct-to-implant breast reconstruction			
Overall complication (RCT)	141 per 1 000	396 per 1 000 (246 to 574)	OR 3.42 (2.28 to 5.12)	183 (1 RCT)	⊕⊕◯◯ Low[a,b]
Overall complication (NRSIs)	100 per 1 000	113 per 1 000 (91 to 137	OR 1.14 (0.90 to 1.43)	14839 (16 non-randomised studies)	⊕◯◯◯ Very low[c,d]
Reoperation (RCT)	120 per 1 000	283 per 1 000 (154 to 462)	OR 2.91 (1.34 to 6.34)	183 (1 RCT)	⊕⊕◯◯ Low[a,b]
Reoperation (NRSI)	90 per 1 000	129 per 1 000 (81 to 199)	OR 1.49 (0.89 to 2.50)	14166 (9 non-randomised studies)	⊕◯◯◯ Very low[c,e]

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nr of participants (studies)	Certainty of the evidence (GRADE)
	Risk with tissue expander breast reconstruction	Risk with direct-to-implant breast reconstruction			
Satisfaction with breast (NRSIs)	The mean NRSI: Satisfaction with breast was 60	MD 1.51 higher (1.32 lower to 4.34 higher)	-	1370 (10 non-randomised studies)	⊕⊕◯◯ Low[c]
Satisfaction with breast (RCT)	The mean RCT: Satisfaction with breast was 79.3	MD 1.3 lower (6.68 lower to 4.08 higher)	-	92 (1 RCT)	⊕⊕⊕◯ Moderate[a]
Satisfaction with outcome (NRSIs)	The mean NRSI: Satisfaction with outcome was 75	MD 0.37 lower (2.13 lower to 1.39 higher)	-	1109 (7 non-randomised studies)	⊕⊕◯◯ Low[c]
Satisfaction with outcome (RCT)	The mean RCT: Satisfaction with outcome was 67.8	MD 5 higher (2.28 lower to 12.28 higher)	-	91 (1 RCT)	⊕⊕◯◯ Low[a,b]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

siehe Meta-Analysen

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nr of participants (studies)	Certainty of the evidence (GRADE)
	Risk with tissue expander breast reconstruction	Risk with direct-to-implant breast reconstruction			

Explanations

a. Downgraded by one level due to serious risk of bias (unclear allocation concealment, per protocol analysis, unclear reporting bias)

b. Downgraded by one level due to serious imprecision; large confidence intervals and small sample size.

c. Downgraded by two levels due to very serious risk of bias: Included studies were observational only, and the majority did not adjust at all for relevant baseline characteristics. Results are thus prone to confounding / bias by indication.

d. Downgraded by one level due to serious imprecision; the 95% confidence interval includes both favorable and unfavorable effect of DTI reconstruction.

e. Downgraded by one level due to serious inconsistency; the heteorgeneity across studies is high.

Verknüpfte Empfehlungen:

Empfehlung 7.54:

Das operative Verfahren der Implantat-basierten Brustrekonstruktion (einzeitig versus zweizeitig über Expander-Implantat-Sequenz) soll unter Berücksichtigung der onkologischen Situation, individueller Risikofaktoren und individueller Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [309], [310], [311], [312], [313], [314], [315], [316], [317], [318], [319], [320], [321], [322], [323], [324], [325], [326], [327], [328], [329], [330], [331], [332], [333]

Study	Study design	Level of evidence	Number of patients	Number of breast	One-stage- (n. patients)	One-stage+ (n. patients)	Two-stage- (n. patients)	Two-stage+ (n. patients)	Follow-up (months)	Mean age		Mean BMI		Smoke		RxT		CxT		Mean FIV (mL)	
										DTI	TE	DTI	TE	DTI	TE	DTI	TE	DTI	TE	DTI	TE
Aliotta et al. 2021	Retrospective cohort	III	150	NA	0	50	50	50	17.2 + 14.8	56.6 + 12.4*	50.9 + 10.9 / 48.4 I 10.9*	25.3 + 5.9*	27.7 + 6.3/ 25.3 + 5.5*	4*	4/8*	NA	NA	NA	NA	NA	NA

Study	Study design	Level of evidence	Number of patients	Number of breast	One-stage- (n. patients)	One-stage+ (n. patients)	Two-stage- (n. patients)	Two-stage+ (n. patients)	Follow-up (months)	Mean age		Mean BMI		Smoke		RxT		CxT		Mean FIV (mL)	
Azouz et al. 2017	Retrospective cohort	III	119	196	69	0	50	0	14.7	NA	NA	27.6 I 6.2	26.2 # 4.8	15	17	8	5	38	29	NA	NA
Bennet et al. 2018	Prospective cohort	III	1637	2655	112	0	1525	0	24	48.2 I 12.1	48.4 + 10.3	25.1 + 6.2	25.7 + 5.3	NA	40	23	398	13	518	NA	NA
Caputo	Retrospective	III	192	NA	0	96	96	0	NA	53.4 I 8.9*	53.6 I 9.5	NA	NA	NA	NA	0	0	2*	2	NA	NA

Study	Study design	Level of evidence	Number of patients	Number of breast	One-stage- (n. patients)	One-stage+ (n. patients)	Two-stage- (n. patients)	Two-stage+ (n. patients)	Follow-up (months)	Mean age		Mean BMI		Smoke		RxT		CxT		Mean FIV (mL)	
et al. 2021	cohort																				
Casella et al. 2019	Retrospective cohort	III	407	709	210	0	197	0	38	56.1 + NA	55.5 + NA	24.1 + NA	24.9 + NA	36	24	78	53	NA	NA	NA	NA
Damen et al. 2011	Prospective cohort	III	207	335	151	0	56	0	65	42.4 + NA	39.2 + NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Study	Study design	Level of evidence	Number of patients	Number of breast	One-stage- (n. patients)	One-stage+ (n. patients)	Two-stage- (n. patients)	Two-stage+ (n. patients)	Follow-up (months)	Mean age		Mean BMI		Smoke		RxT		CxT		Mean FIV (mL)	
Davila et al. 2013	Prospective cohort	III	10561	13789	1528	0	9033	0	1	50.8 + 10.6	50.9 + 10.5	26.5 + 6.7	26.9 + 6.3	201	1276	7	28	53	380	NA	NA
Dikmans et al. 2016	RCT	I	121	183	0	59	62	0	24	43.5 + 11.7 *	47.3 + 12.1	23.4 + 2.9"	22.9 + 2.5	12*	8	5*	6	22*	21	393.4 + 93.7 *	408.0 +- 123.8
Dimovska	Prospective	III	223	223	187	0	36	0	NA	44.4 I 8.1	43.8 + 7.7	22.0 I 2.9	20.7 + 3.1	NA	NA	37	9	132	28	226.7 +	256.1 +- 71.5

Study	Study design	Level of evidence	Number of patients	Number of breast	One-stage- (n. patients)	One-stage+ (n. patients)	Two-stage- (n. patients)	Two-stage+ (n. patients)	Follow-up (months)	Mean age		Mean BMI		Smoke		RxT		CxT		Mean FIV (mL)	
et al. 2021	cohort																			67.8*	
Gao et al. 2021	Retrospective cohort	III	124	125	0	79	45	0	NA	41.1 + 7.0*	38.6 + 7.3	21.7 + 2.2*	22.0 + 2.2	0*	0	0*	2	55*	41	231.58 + 53.27*	266.64 +- 38.64
Han et al. 2018	Retrospective cohort	III	290	298	NA	0	NA	0	13.5	42 + NA	44 + NA	NA	NA	8	2	40	23	112	40	NA	NA

Study	Study design	Level of evidence	Number of patients	Number of breast	One-stage- (n. patients)	One-stage+ (n. patients)	Two-stage- (n. patients)	Two-stage+ (n. patients)	Follow-up (months)	Mean age		Mean BMI		Smoke		RxT		CxT		Mean FIV (mL)	
Hangge et al. 2019	Retrospective cohort	III	339	577	193	0	146	0	22.9	50.9 + 11.0	51.5 + 11.3	25.0 + 5.0	25.4 + 5.1	3	10	NA	NA	46	34	NA	NA
Hillberg et al. 2018	Prospective cohort	III	52	75	0	31	21	0	12	40.8 + 12.2*	49.5 + 10.9	22.1 + 2.2*	21.8 + 2.5	4*	3	6*	4	NA	NA	353.8 + 88.3*	379-7 +- 85-8
Hwang	Retrospective	III	62	75	0	27	0	35	17.0 + 7.8	52.7 + 7.1*	49.0 + 8.7*	23.9 + 2.5*	22.4 + 3.0*	1*	2*	1*	0*	NA	NA	NA	NA

Study	Study design	Level of evidence	Number of patients	Number of breast	One-stage- (n. patients)	One-stage+ (n. patients)	Two-stage- (n. patients)	Two-stage+ (n. patients)	Follow-up (months)	Mean age		Mean BMI		Smoke		RxT		CxT		Mean FIV (mL)	
et al. 2022	cohort																				
Innocenti et al. 2021	Retrospective cohort	III	81	92	0	29	52	0	NA	48.5 + 10.0 *	50.1 + 9.3	NA	NA	NA	NA	4*	9	19*	33	NA	NA
Innocenti et al.	Retrospective cohort	III	72	78	0	32	40	0	NA	48.9 # NA*	50.3 + NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Study	Study design	Level of evidence	Number of patients	Number of breast	One-stage- (n. patients)	One-stage+ (n. patients)	Two-stage- (n. patients)	Two-stage+ (n. patients)	Follow-up (months)	Mean age		Mean BMI		Smoke		RxT		CxT		Mean FIV (mL)	
2022																					
Meshulam-Derazon et al. 2018	Retrospective cohort	III	59	90	0	39	20	0	24.6 + 12,7	42.8 # 10.3 *	53.1 + 10.24	NA	NA	3*	2	4*	5	NA	NA	375 + 105 *	370 +- 100
Negenborn et al.	RCT	I	121	183	0	59	62	0	24	43.5 # 11.6 *	47.4 + 12.2	23.4 + 2.9*	22.9 + 2.5	12"	8	5*	6	22*	21	393.4 I 93.7 *	408.0+- 123.8

Study	Study design	Level of evidence	Number of patients	Number of breast	One-stage- (n. patients)	One-stage+ (n. patients)	Two-stage- (n. patients)	Two-stage+ (n. patients)	Follow-up (months)	Mean age		Mean BMI		Smoke		RxT		CxT		Mean FIV (mL)	
2018																					
Negenborn et al. 2019	RCT	III	121	183	0	59	62	0	24	43.5 # 11.6 *	47.4 + 12.2	23.4 + 2.9*	22.9 + 2.5	12"	8	5*	6	22*	21	393.4 I 93.7 *	408.0+- 123.8
Riggio et al. 2022	Retrospective cohort	III	120	NA	66	0	54	0	NA	45.6 # 8.4	46.28 # 6.5	21.5 + 2.7	21.9 + 2.7	NA	NA	5	9	39	32	351.2 + 94.3	462-8 +- 116.6

Study	Study design	Level of evidence	Number of patients	Number of breast	One-stage- (n. patients)	One-stage+ (n. patients)	Two-stage- (n. patients)	Two-stage+ (n. patients)	Follow-up (months)	Mean age		Mean BMI		Smoke		RxT		CxT		Mean FIV (mL)	
Roostaeian et al. 2012	Retrospective cohort	III	85	149	35	0	50	0	14	45 + NA	47 + NA	22 + NA	22.6 + NA	1	3	6	8	6	16	397 + 93	386 +- 128
Sgarzani et al. 2021	Retrospective cohort	IV	54	NA	0	28	26	0	NA	46 I NA*	48 + NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Susarla	Retrospective	III	346	582	NA	0	NA	0	NA	47.2 + 10.3	47.6 + 10.2	24.6 + 5.0	25.4 + 4.9	16	33	38	112	NA	NA	NA	NA

Study	Study design	Level of evidence	Number of patients	Number of breast	One-stage- (n. patients)	One-stage+ (n. patients)	Two-stage- (n. patients)	Two-stage+ (n. patients)	Follow-up (months)	Mean age		Mean BMI		Smoke		RxT		CxT		Mean FIV (mL)	
et al. 2015	cohort																				
Theunissen et al. 2021	Retrospective cohort	III	383	NA	56	0	327	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Du, F, Liu, R, Zhang, H, Xiao, Y, Long, X, Post-mastectomy adjuvant radiotherapy for direct-to-implant and two-stage implant-based breast reconstruction: A meta-analysis.. J Plast Reconstr Aesthet Surg, 2022. 75 (9)(9): p. 3030-3040., https: //pubmed.ncbi.nlm.nih.gov/35961927/.

Source and Purpose	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: "This meta-analysis aims to evaluate the outcomes of DTI and TEI procedures followed by PMRT." **Sources of funding**: National High Level Hospital Clinical Research Funding (2022-PUMCH-A-209), the National Key R&D Program of China (2020YFE0201600) and the CAMS Innovation Fund for Medical Sciences	**Design**: Systematic review with Metaanalysis **Search date**: w 01.01.1995 to 31.12.2021 **Searched databases**: - PubMed, Embase, The Cochrane Library ((radiation therapy) OR (radiotherapy)) AND ((post*) OR (adjuvant) OR (after)) AND ((implant) OR (expander)) AND (breast)	**Intervention/ Comparator** A: PMRT B: no PMRT	1) Capsular contracture (Baker grade 3-4) 2) Overall complications	Capsular contracture (Baker grade 3-4) Overall pooled results (DTI + TEI): 10 studies PMRT: 158/929 No PMRT: 126/3817 Risk ratio 4.48 (95% CI 3.60 to 5.58) in favor of no PMRT DTI only pooled results 5 studies	Risk of bias assessment of studies: not assessed, reassessed for the current clinical guideline Overall confidence in results of SR (AMSTAR-2): PICO elements: yes A priori design: partial yes, review question and search strategy Justification for design: no

Du, F, Liu, R, Zhang, H, Xiao, Y, Long, X, Post-mastectomy adjuvant radiotherapy for direct-to-implant and two-stage implant-based breast reconstruction: A meta-analysis.. J Plast Reconstr Aesthet Surg, 2022. 75 (9)(9): p. 3030-3040., https: //pubmed.ncbi.nlm.nih.gov/35961927/.					
(No. 2020-I2M- C&T-A-004).	**Included study designs**: w Cohort studies, case control studies **Number of included studies**: n=22 **Number of included patients**: 15,345 pts **Mean/median age**: 44.9 - 52 **Inclusion criteria** immediate breast reconstruction surgery TE or DTI **Exclusion criteria:** reviews, case reports, and articles with insufficient full text breast-conserving therapy patients without a history of breast cancer			PMRT: 55/355 No PMRT: 95/1666 Risk ratio 3.60 (95% CI 2.62 to 4.96) Overall complications Definition: the sum of any recorded complications except capsular contracture of all reconstruction procedures, including seroma, delayed wound healing, implant loss, wound breakdown, revision surgery, reconstruction failure, etc. Overall pooled results (DTI + TEI): 12 studies PMRT: 406/1797 No PMRT: 1247/11045	Literature search >= 2 databases, search strategy + other sources: · 3 databases · String for PubMed provided · No further resources searched Selection in duplicate: probably. Data extraction in duplicate: · Data are collected by one author from each report and independently confirmed by another author. List of excluded studies: no sufficient detail on studies: partial yes, table 1 provided but not with all necessary information

Du, F, Liu, R, Zhang, H, Xiao, Y, Long, X, Post-mastectomy adjuvant radiotherapy for direct-to-implant and two-stage implant-based breast reconstruction: A meta-analysis.. J Plast Reconstr Aesthet Surg, 2022. 75 (9)(9): p. 3030-3040., https: //pubmed.ncbi.nlm.nih.gov/35961927/.					
				Risk ratio 1.67 95% CI 1.52 to 1.85) in favor of no PMRT DTI only pooled results 4 studies PMRT: 88/276 No PMRT: 194/696 Risk ratio 1.11 (95% CI 0.90 to 1.37)	RoB assessed: no Funding of incl. studies: no MA appropriate: partly; overall complications with varying definitions RoB considered in MA: NA, no RoB assessment RoB in interpretation: NA, no RoB assessment Heterogeneity explained: no Publication bias investigated: discussed, but not presented Sources of CoI: The authors have no conflict of interest to disclose.

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nr of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no radiotherapy	Risk with Radiotherapy			
Major complications	60 per 1 000	128 per 1 000 (80 to 199)	OR 2.32 (1.37 to 3.93)	9770 (9 non-randomised studies)	⊕⊕◯◯ Low[a,b,d]
Capsular contracture	97 per 1 000	421 per 1 000 (323 to 526)	OR 6.79 (4.46 to 10.33)	16178 (26 non-randomised studies)	⊕⊕⊕⊕ High[a,e]
Implant loss (absolute failure)	31 per 1 000	70 per 1 000 (51 to 96)	OR 2.32 (1.65 to 3.25)	13900 (19 non-randomised studies)	⊕⊕⊕◯ Moderate[a,d]
Implant loss (any reason / patient wish)	101 per 1 000	215 per 1 000 (169 to 270)	OR 2.44 (1.81 to 3.29)	18921 (26 non-randomised studies)	⊕⊕◯◯ Low[a,d,f]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nr of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no radiotherapy	Risk with Radiotherapy			

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

siehe Meta-Analysen

Explanations

a. Downgraded by two levels due to very serious risk of bias: Included studies were observational only, and the majority did not adjust at all for relevant baseline characteristics. Results are thus prone to confounding / bias by indication - those receiving radiotherapy were probably at higher stage or higher likelihood of disease progression.

b. Downgraded by one level due to serious inconsistency: Outcome definitions varied between studies. In addition, heterogeneity is high.

d. Upgraded by one level due to large effect (OR > 2).

e. Upgraded by two levels due to very large effect (OR > 5).

f. Downgraded by one level due to serious inconsistency: Heterogeneity is high.

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Author, Year	Country	Enrolment period	N PMRT	N control	Age (mean, range) PMRT/ control	BMI (kg/m², mean, range) PMRT/ control	Follow-up (months, mean, range) PMRT/ control	Reconstruction Type	Outcomes reported
Allué-Cabañuz 2019	Spain	2000 to 2016	71	100	48.4.9.0 (26-87) a	NA	NA	DTI	necrosis, infection, seroma, hematoma, reintervention, capsular contracture III/IV
Apte 2020	UK	February 2012 to July 2017	29	62	50.66 (30-77) *	NA	36 (2-77)	DTI	seroma, delayed wound healing, implant loss,

Author, Year	Country	Enrolment period	N PMRT	N control	Age (mean, range) PMRT/ control	BMI (kg/m², mean, range) PMRT/ control	Follow-up (months, mean, range) PMRT/ control	Reconstruction Type	Outcomes reported
									wound breakdown, revision surgery, capsular contracture
Cordeiro 2015	USA	2003 to 2012	304	1468	46.3 + 8.9;46.1: + 10.6b	25.3+5.0; 26.3+5.6b	40.3(1.6-113): 30.1 (0.5-118) b	TEI	TE removal, implant removal
Hamann 2019	Germany	2008 to 2012	26	52	50.2/52.8	NA	17.0 (3.9-61.0)/16.6 (2.7-50.0) a	TEI	Capsular contracture III/IV
Hille-Betz 2015	Germany	2009 -2013	4	57	46*	NA	19.6 (0.4-47.1)*	DTI or TEI	seroma, skin flap necrosis, capsular contracture
Korwar 2014	UK	2006 - 2011	45	47	49.5/52.1[a]	27.3/27.2	23/18 a	DTI or TEI	early implant loss, late

Author, Year	Country	Enrolment period	N PMRT	N control	Age (mean, range) PMRT/ control	BMI (kg/m², mean, range) PMRT/ control	Follow-up (months, mean, range) PMRT/ control	Reconstruction Type	Outcomes reported
									implant loss, delayed implant, necrosis, hematoma, seroma, infection, fat necrosis, capsular contracture
Loreti 2020	Italy	2013 to 2018	312*	312	49.3*	NA	36 (12-36)*	DTI	Capsular contracture III-IV
Masia 2020	Spain	November 2012 to June 2018	159	1243	52.4*	23.9*	22.7*	DTI or TEI	seroma, dehiscence, hematoma, necrosis, infection, extrusion, RBA, fever,

Author, Year	Country	Enrolment period	N PMRT	N control	Age (mean, range) PMRT/ control	BMI (kg/m², mean, range) PMRT/ control	Follow-up (months, mean, range) PMRT/ control	Reconstruction Type	Outcomes reported
									implant rotation, rippling, implant loss, capsular contracture
Naoum 2020	UK	1997 -2017	407	568	49.7/52.4˚(DTI); 46.5/49.1˚(TEI)	NA	52/50 (DTI); 75/73 (TEI);	DTI, TEI	infection, necrosis, fat necrosis, seroma hematoma, capsular contracture
Nava 2011	Italy	NR	109	50	49	NA	50 (median)	TEI	Baker grade III, IV
Riggio 2019	Italy	December 2011 to June 2014	4 38	57 DTI 163 TEI	46(23-74) (DTI); 48(27-75) *(TEI); (median)	20.6 (16.6-27.8) *(DTI); 23.0 (16.0-	26 (median)	DTI, TEI	necrosis, infection, inflammation and seroma,

Author, Year	Country	Enrolment period	N PMRT	N control	Age (mean, range) PMRT/ control	BMI (kg/m², mean, range) PMRT/ control	Follow-up (months, mean, range) PMRT/ control	Reconstruction Type	Outcomes reported
						37.6) *(TEI); (median)			implant damage, exposure, rupture or severe lateral displacement.
Salzberg 2016	USA	December of 2001 to May of 2014	52	763	47	24.4 (4.8; range 16 to 54)	56.4	DTI	capsular contracture
Seth 2015	USA	February 1999 to January 2008	208 248	879	48.6*	25.3*	360*	TEI	Exposure, infection, pain/tightness, hematoma, seroma, flap necrosis, ECF (explanation or conversion to flap)

Author, Year	Country	Enrolment period	N PMRT	N control	Age (mean, range) PMRT/ control	BMI (kg/m², mean, range) PMRT/ control	Follow-up (months, mean, range) PMRT/ control	Reconstruction Type	Outcomes reported
Sinnott 2018	USA	January 2010 to December 2017	21	87	52.7/52.4	30.0/28.9	20.6/18.7	DTI or TEI	Infection, seroma, hematoma, dehiscence, necrosis, capsular contracture, rippling, implant loss
Spear 2012	USA	August of 2004 to June of 2010	56	355	44.9/46.2	25.8/24.3	15.2 (6.0-80.5)	TEI	Capsular contracture III/IV
Tejera Hernandez 2019	Spain	2010 to 2016	23	41	NA	NA	43.9/54.9	TEI	General complications, capsular contracture

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Hannah Coudé Adam, Axel Frisell, Yihang Liu, Helena Sackey, Ira Oikonomou, Ann-Charlot Docherty Skogh, Jan Frisell, Jana de Boniface, Effect of radiotherapy on expanders and permanent implants in immediate breast reconstruction: long-term surgical and patient-reported outcomes in a large multicentre cohort, British Journal of Surgery, Volume 108, Issue 12, December 2021, Pages 1474–1482, https: //doi.org/10.1093/bjs/znab333

Study type	Population	Interventions	Main results	Methodological evaluation
Prospective cohort study	**Inclusion criteria** (for analysis): Prospectively registered consecutive patients with breast cancer who underwent mastectomy and implant-based IBR **Exclusion criteria** (for analysis): NR **Enrolment period:** 1 January 2007 to 31 December 2011	**Interventions** RT after implant · N = 304 No RT after implant · N = 386 RT before implant · N = 64 · not considered in analysis **Analysis**	**Implant loss (implant removal due to any reason)** · HR 3.41 (95% CI 2.24 to 5.23) in favour of no PMRT · RT: 73/299 · No RT: 24/388 **Reoperation** · RT: 63/303 · No RT: 34/384 **Minor complications** · RT: 86/303	**General information** Follow-up: Median follow-up 120 (range 1–171) months Funding: JdB is supported by grants from the Swedish Cancer Society and Stockholm County Council together with the Karolinska Institutet (ALF grant). This study was supported by the Percy Falk Foundation. CoI: The authors declare no conflict of interest.

Hannah Coudé Adam, Axel Frisell, Yihang Liu, Helena Sackey, Ira Oikonomou, Ann-Charlot Docherty Skogh, Jan Frisell, Jana de Boniface, Effect of radiotherapy on expanders and permanent implants in immediate breast reconstruction: long-term surgical and patient-reported outcomes in a large multicentre cohort, British Journal of Surgery, Volume 108, Issue 12, December 2021, Pages 1474–1482, https: //doi.org/10.1093/bjs/znab333				
	Follow-up: Median follow-up 120 (range 1–171) months **Descriptive statistics** Age (median, range) · RT: 46 (21-74) years · No RT: 50 (24-77) years BMI (mean, sd) · RT: 24.3 (.8) · No RT: 23.8 (3.6) Stadium: · NR Adjuvant chemotherapy (% yes) · RT: 22.7% · No RT: 1.8% Neoadjuvant chemotherapy (% yes) · RT: 57.8% · No RT: 35.7% Reconstruction type	Univariable and multivariable Cox proportional hazards regression No matching Adjusted for age, year of reconstruction for outcome implant removal only	· No RT: 110/384 **Major complications** · RT: 15/303 · No RT: 21/384 **QoL-outcomes: Breast -Q** Satisfaction with breasts: · Post-score (2020): 52.64 Satisfaction with overall outcome: · Post-score (2020): 66.66 Psychosocial well-being · Post-score (2020): 69.81 Sexual well-being · Post-score (2020): 49.21 Physical well-being · Post-score (2020): 76.24	**Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: prospective cohort study Confounding: High risk (Baseline characteristics are not well-balanced across groups, i.e., tumor size, pre- and postoperative chemotherapy; only adjustment for one outcome) Selection bias into the study: Unclear, no comparison between groups. The response rate was 72.2%. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no

Hannah Coudé Adam, Axel Frisell, Yihang Liu, Helena Sackey, Ira Oikonomou, Ann-Charlot Docherty Skogh, Jan Frisell, Jana de Boniface, Effect of radiotherapy on expanders and permanent implants in immediate breast reconstruction: long-term surgical and patient-reported outcomes in a large multicentre cohort, British Journal of Surgery, Volume 108, Issue 12, December 2021, Pages 1474–1482, https: //doi.org/10.1093/bjs/znab333				
	· All direct to implant Mesh/ADM (%) · No mesh used Implant position · All subpectoral			Drop-out rate & reasons reported: · Similar across groups: “"A responder analysis showed no differences in demographics and tumour characteristics between responders and non-responders, except for a higher proportion of smokers (12.3 versus 19.3 per cent; P=0.045) and of women with breast cancer recurrence (5.6 versus 12.7 per cent; P=0.006) among non-responders." Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results Main cofounders taken into account: no. Confidence intervals reported: partly.

Hannah Coudé Adam, Axel Frisell, Yihang Liu, Helena Sackey, Ira Oikonomou, Ann-Charlot Docherty Skogh, Jan Frisell, Jana de Boniface, Effect of radiotherapy on expanders and permanent implants in immediate breast reconstruction: long-term surgical and patient-reported outcomes in a large multicentre cohort, British Journal of Surgery, Volume 108, Issue 12, December 2021, Pages 1474–1482, https: //doi.org/10.1093/bjs/znab333				
				Selective reporting (comparison with protocol): not protocol provided, not assessable. **Other limitations:** NR

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Bernini M, Meattini I, Saieva C, Becherini C, Salvestrini V, Visani L, Stocchi G, Bellini C, Lorenzetti V, Sordi S, Nori J, De Benedetto D, Desideri I, Bianchi S, Livi L, Orzalesi L. Pre-pectoral breast reconstruction: early and long-term safety evaluation of 146 unselected cases of the early pre-pectoral era of a single-institution, including cases with previous breast irradiation and post-mastectomy radiation therapy. Breast Cancer. 2022 Mar;29(2): 302-313. doi: 10.1007/s12282-021-01314-0. Epub 2021 Nov 14. PMID: 34775540.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Therapeutic or prophylactic pre-pectoral IBBR **Exclusion criteria** (for analysis): NR **Enrolment period:** October 2012 - May 2016 **Follow-up:** 4 years median follow up time (mean 3.9 years; range 3–5.5)	**Interventions** RT after implant · N = 37 No RT after implant · N = 108 (may have received pre-operative RT) **Analysis** Frequencies No matching No adjustment	**Implant loss (explantation rate due to any reason)** · RT: 3/33 · No RT: 4/83 **Overall complications** (acute toxicities: BR failure and surgical complications such as skin-nipple necrosis, seroma, wound dehiscence, surgical site infection, hematoma, and atopic versus graft reaction) · RT: 5/37	**General information** Follow-up: 4.0 year median follow up time (mean 3.9 years; range 3–5.5) Funding: None. CoI: All authors have no conflict of interest to declare. **Risk of bias considerations** (adapted from SIGN cohort study checklist)

Bernini M, Meattini I, Saieva C, Becherini C, Salvestrini V, Visani L, Stocchi G, Bellini C, Lorenzetti V, Sordi S, Nori J, De Benedetto D, Desideri I, Bianchi S, Livi L, Orzalesi L. Pre-pectoral breast reconstruction: early and long-term safety evaluation of 146 unselected cases of the early pre-pectoral era of a single-institution, including cases with previous breast irradiation and post-mastectomy radiation therapy. Breast Cancer. 2022 Mar;29(2): 302-313. doi: 10.1007/s12282-021-01314-0. Epub 2021 Nov 14. PMID: 34775540.				
	Descriptive statistics (reported for overall population) Age · >55 years: 21% BMI: · >25: 21.9% Stadium: · NR Adjuvant chemotherapy: · 11% Neoadjuvant chemotherapy: · 29.7% Reconstruction type (%) · Tissue expander: 43.8% · DTI: 56.2% Mesh/ADM: · all		· No RT: 14/83 **Mortality** · RT: 2/33 · No RT: 1/83 **Local recurrence** · RT: 2/33 · No RT: 3/83 **Metastatic disease** · RT: 8/33 · No RT: 6/83	Study type: retrospective cohort study Confounding: High risk (no adjustment or matching of baseline characteristics, no comparison between RT arms provided) Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: · Not reported. Outcome

Bernini M, Meattini I, Saieva C, Becherini C, Salvestrini V, Visani L, Stocchi G, Bellini C, Lorenzetti V, Sordi S, Nori J, De Benedetto D, Desideri I, Bianchi S, Livi L, Orzalesi L. Pre-pectoral breast reconstruction: early and long-term safety evaluation of 146 unselected cases of the early pre-pectoral era of a single-institution, including cases with previous breast irradiation and post-mastectomy radiation therapy. Breast Cancer. 2022 Mar;29(2): 302-313. doi: 10.1007/s12282-021-01314-0. Epub 2021 Nov 14. PMID: 34775540.				
	Implant position: · all prepectoral			· Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results Main cofounders taken into account: no. Confidence intervals reported: no. Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Cagli B, Morelli Coppola M, Augelli F, Segreto F, Tenna S, Cogliandro A, Persichetti P. Postmastectomy Radiation Therapy in the Setting of Two-Stage Retropectoral Implant-Based Breast Reconstruction: Should It be Delivered Before or After Implant Exchange? A Retrospective Analysis on 183 Patients. Aesthetic Plast Surg. 2022 Dec;46(6): 2643-2654. doi: 10.1007/s00266-022-03001-7. Epub 2022 Jul 19. PMID: 35854008.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Diagnosis of ductal or lobular breast cancer or ductal carcinoma in situ; Modified radical mastectomy (MRM) or skin/nipple-sparing mastectomy (S/NSM); Immediate reconstruction with submuscular TE; No previous breast surgery (either cosmetic either	**Interventions** RT after implant, on tissue expander or final implant (subgroup timing reported) · N = 105 No RT after implant · N = 78 **Analysis** Univariable logistic regression analysis of various patient-related and treatment-related factors for the outcomes	**Complications** Minor complications: · RT to TE/I: 13/105 · No RT: 7/78 Major complications: · RT to TE/I: 19/105 · No RT: 13/78 **Seroma** · RT to TE/I: 3/105 · No RT: 1/78	**General information** Follow-up: mean follow-up · TE-PMRT: 4.58 years · PI-PMRT: 7 years · no-PMRT: 5.75 years Funding: No intramural or extramural funding supported this study. CoI: The authors declare that they have no conflict of interest.

Cagli B, Morelli Coppola M, Augelli F, Segreto F, Tenna S, Cogliandro A, Persichetti P. Postmastectomy Radiation Therapy in the Setting of Two-Stage Retropectoral Implant-Based Breast Reconstruction: Should It be Delivered Before or After Implant Exchange? A Retrospective Analysis on 183 Patients. Aesthetic Plast Surg. 2022 Dec;46(6): 2643-2654. doi: 10.1007/s00266-022-03001-7. Epub 2022 Jul 19. PMID: 35854008.				
	oncological), nor radiation therapy **Exclusion criteria** (for analysis): Previous breast-conserving surgery followed by RT, Previous breast augmentation, Diagnosis of breast sarcoma, prophylactic mastectomy, Immediate autologous reconstruction (ABR), Direct-to-implant (DTI) and prepectoral implants, Delayed reconstruction **Enrolment period:** between 2010 and 2019 **Follow-up:** between 4.6 and 7 years mean FU depending on the group **Descriptive statistics** Age (mean, SD, years)	implant failure and capsular contracture No matching No adjustment	**Necrosis** · RT to TE/I: 3/105 · No RT: 8/78 **Implant failure** · RT to TE/I: 27/105 · No RT: 3/78 **Infections** · RT to TE/I: 9/105 · No RT: 3/78 **Capsular contracture** · RT to TE/I: 60/105 · No RT: 3/78 **Implant loss** · RT to TE/I: 8/105 · No RT: 2/78 **Reoperation** · RT to TE/I: 11/105 · No RT: 7/78	**Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: Moderate risk (baseline characteristics are comparable, however, no adjustment in analysis, remaining unobserved confounding possible) Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No (prospective data collection) Drop-out rate & reasons reported:

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	· TE-PMRT: 49.4 (9.8) · PI-PMRT: 51.08 (12.1) · No RT: 50.3 (10.6) BMI (median, range) · TE-PMRT: 25.9 (5.3) · PI-PMRT: 25.3 (4.06) · No RT: 23.5 (3.7) Stadium · TE-PMRT: G1: 1.8%, G2: 34.5%, G3: 32.7%, Gx: 31% · PI-PMRT: G1: 6.1%, G2: 40%, G3: 30.6%, Gx: 24.5% · No RT: G1: 9%, G2: 43.6%, G3: 38.5%, Gx: 9% Adjuvant chemotherapy (% yes) · TE-PMRT: 58.2% · PI-PMRT: 70% · No RT: 53.9%		**Wound complications** · RT to TE/I: 4/105 · No RT: 6/78	· Low risk: no drop-outs Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: oly for two outcomes. Confidence intervals reported: no (for two outcomes: yes) Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Cagli B, Morelli Coppola M, Augelli F, Segreto F, Tenna S, Cogliandro A, Persichetti P. Postmastectomy Radiation Therapy in the Setting of Two-Stage Retropectoral Implant-Based Breast Reconstruction: Should It be Delivered Before or After Implant Exchange? A Retrospective Analysis on 183 Patients. Aesthetic Plast Surg. 2022 Dec;46(6): 2643-2654. doi: 10.1007/s00266-022-03001-7. Epub 2022 Jul 19. PMID: 35854008.				
	Neoadjuvant chemotherapy (% yes) · TE-PMRT: 38.2% · PI-PMRT: 42% · No RT: 7.5% Reconstruction type: · Tissue expander and later implant Mesh/ADM: · No mesh used Implant position: · Retropectoral			

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Conte B, Shermoen C, Lubarsky M, Fiser CK, Liu SN, Kesmodel SB, Goel N, Cerbon D, Wang L. Post-Mastectomy Implant Complications in the Hispanic Breast Cancer Patient Population. Anticancer Res. 2023 Nov;43(11): 4953-4959. doi: 10.21873/anticanres.16693. PMID: 37909997.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Female at birth 18 years or older and underwent mastectomy with immediate IBR **Exclusion criteria** (for analysis): Patients who did not present to their follow-up visits Patients who underwent autologous tissue reconstruction using a deep inferior epigastric perforator	**Interventions** RT after implant-based reconstruction · N = 73 No RT after implant · N = 244 **Analysis** Frequencies, for overall complications multivariable analysis No matching	**Overall complications** · RT: 45/72 · No RT: 130/395 **Capsular contracture** · RT to TE/I: 26/72 · No RT: 63/395 **Implant loss** · RT to TE/I: 26/72 · No RT: 80/395	**General information** Follow-up: NR Funding: NR CoI: The Authors have no conflicts to interest to declare in relation to this study. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: Moderate risk for overall complications, high risk

Conte B, Shermoen C, Lubarsky M, Fiser CK, Liu SN, Kesmodel SB, Goel N, Cerbon D, Wang L. Post-Mastectomy Implant Complications in the Hispanic Breast Cancer Patient Population. Anticancer Res. 2023 Nov;43(11): 4953-4959. doi: 10.21873/anticanres.16693. PMID: 37909997.				
	(DIEP) flap technique were included in demographic data but excluded from the statistical analysis of complications following IBR **Enrolment period:** 1 January 2017 - 31 December 2019 **Follow-up:** NR **Descriptive statistics** (reported for complete cohort) Age: · median 51 (range 19 to 83) years BMI: · median 26.5 (range 16.64 to 48.90) Stadium: · I: 21% · II: 20% · III: 9% · IV: 1%	adjusted for age, ethnicity, race, mastectomy type, DTI vs expander reconstruction, use of dermal matrix, neoadjuvant chemotherapy, BMI, smoking, diabetes, autoimmune disease, previous cosmetic breast surgery		for capsular contracture, implant loss Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No Drop-out rate & reasons reported: · moderate risk: 34 out of 351 patients were excluded due to lack of follow-up Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as

Conte B, Shermoen C, Lubarsky M, Fiser CK, Liu SN, Kesmodel SB, Goel N, Cerbon D, Wang L. Post-Mastectomy Implant Complications in the Hispanic Breast Cancer Patient Population. Anticancer Res. 2023 Nov;43(11): 4953-4959. doi: 10.21873/anticanres.16693. PMID: 37909997.				
	· Prophylactic: 47% · Unknown: 2% Adjuvant chemotherapy: · NR Neoadjuvant chemotherapy: · NR Reconstruction type · DTI: 35% · Tissue expander: 60% Mesh/ADM (%) · Dermal matrix: 75% · No dermal matrix: 25% Implant position: · NR			the outcomes are standard clinical characteristics Main cofounders taken into account: only for overall complications Confidence intervals reported: no (for overall complications yes) Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

de Boniface J, Coudé Adam H, Frisell A, Oikonomou I, Ansarei D, Ljung Konstantinidou A, Liu Y, Abo Alniaj B, Wallmon P, Halle M, Johansson ALV, Sackey H. Long-term outcomes of implant-based immediate breast reconstruction with and without radiotherapy: a population-based study. Br J Surg. 2022 Oct 14;109(11): 1107-1115. doi: 10.1093/bjs/znac283. PMID: 35949111; PMCID: PMC10364787.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Primary or recurrent breast cancer Patients with bilateral disease were registered as two cases if both sides fulfilled the inclusion criteria; otherwise, only the eligible side was registered. **Exclusion criteria** (for analysis): Risk-reducing mastectomies	**Interventions** RT after implant · N = 749 No RT after implant · N = 856 **Analysis** Univariable and multivariable logistic regression analyses for implant loss, frequencies for reoperation No matching	**Reoperation** · RT: 549/749 · No RT: 536/856 **Implant loss (due to complication or patient wish)** · RT: 132/631 · No RT: 56/636 · HR: 2.44, 95% CI 1.7 to 3.52	**General information** Follow-up, median · PMRT: 72 (range 1-190) · no PMRT: 71 (range 1-198) Funding: Swedish Breast Cancer Association (Bröstcancerförbundet). · J.d.B. is supported by a Junior Clinical Investigator Award from the Swedish Cancer Society (CAN 2017/1036). A.L.V.J. is supported by a Research Starting Grant from

de Boniface J, Coudé Adam H, Frisell A, Oikonomou I, Ansarei D, Ljung Konstantinidou A, Liu Y, Abo Alniaj B, Wallmon P, Halle M, Johansson ALV, Sackey H. Long-term outcomes of implant-based immediate breast reconstruction with and without radiotherapy: a population-based study. Br J Surg. 2022 Oct 14;109(11): 1107-1115. doi: 10.1093/bjs/znac283. PMID: 35949111; PMCID: PMC10364787.				
	Enrolment period: 1 January 2005 to 31 December 2015 **Follow-up:** median 72 months **Descriptive statistics** Age (median, range) · PMRT: 47 (range 21-78) · No PMRT: 50 (range 21-79) BMI (median, range): · NR Stadium · PMRT: T1: 38.6%, T2: 43.7%, T3: 16.9%, Missing: 0.7% · no PMRT: T1: 66.6%, T2: 32.0%, T3: 0.9%, Missing: 0.5% Neoadjuvant chemotherapy (% yes) · PMRT: 25.8% · No PMRT: 3.6% Adjuvant chemotherapy	Implant loss adjusted for low risk: adjusted for ADM, hospital, lymph node dissection, nipple-sparing mastectomy, specimen weight, type of implant, ipsilateral revisional surgery, neoadjuvant chemotherapy, endocrine therapy, smoking, diabetes, antihypertensive meds, immunosuppressive meds, BMI, Age		the Swedish Research Council (2021-01657). The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. CoI: The authors declare no conflict of interest. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: low risk for implant loss (overall), high risk for reoperation (no adjustment) Selection bias into the study: Unclear, no information provided.

de Boniface J, Coudé Adam H, Frisell A, Oikonomou I, Ansarei D, Ljung Konstantinidou A, Liu Y, Abo Alniaj B, Wallmon P, Halle M, Johansson ALV, Sackey H. Long-term outcomes of implant-based immediate breast reconstruction with and without radiotherapy: a population-based study. Br J Surg. 2022 Oct 14;109(11): 1107-1115. doi: 10.1093/bjs/znac283. PMID: 35949111; PMCID: PMC10364787.				
	· PMRT: 82.8% · No PMRT: 48.2% Reconstruction type (%) · Permanent: PMRT: 17.4%, No PMRT: 24.9% · Permanent expander: PMRT: 51.1%, No PMRT: 46.1% · Temp. expander PMRT: 30.4%, No PMRT: 27.3% Mesh/ADM (%) · PMRT: 3.7% · No PMRT: 4.1% Implant position (sub, prepectoral?) · Complete muscle coverage: PMRT: 94.7%, No PMRT: 94.7% · Partly submuscular PMRT: 5.3%, No PMRT: 5.3% · Prepectoral PMRT: 0, No PMRT: 0			Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No Drop-out rate & reasons reported: · High risk: not reported Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: yes, for implant loss, no for reoperation Confidence intervals reported: partly

de Boniface J, Coudé Adam H, Frisell A, Oikonomou I, Ansarei D, Ljung Konstantinidou A, Liu Y, Abo Alniaj B, Wallmon P, Halle M, Johansson ALV, Sackey H. Long-term outcomes of implant-based immediate breast reconstruction with and without radiotherapy: a population-based study. Br J Surg. 2022 Oct 14;109(11): 1107-1115. doi: 10.1093/bjs/znac283. PMID: 35949111; PMCID: PMC10364787.				
				Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Jeon HB, Lee M, Roh TS, Jeong J, Ahn SG, Bae SJ, Lee N, Kim YS. Complications Including Capsular Contracture in Direct-to-Implant Breast Reconstruction With Textured Anatomical Versus Smooth Round Implants: A Single Center Retrospective Analysis. J Breast Cancer. 2023 Feb;26(1): 25-34. doi: 10.4048/jbc.2023.26.e7. PMID: 36852965; PMCID: PMC9981986.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Diagnosed with primary breast cancer, who had undergone mastectomy with DTI breast reconstruction **Exclusion criteria** (for analysis): Previous breast surgery, Refusal to sign the consent form, Previous radiotherapy,	**Interventions** RT after implant · N = 64 No RT after implant · N = 176 **Analysis** Multivariable logistic regression No matching Adjusted for age, body mass index, pathologic tumor stage, mastectomy, axillary surgery,	**Overall complications** · OR 1.906, 95% CI 1.032 to 3.521 **Capsular contracture** · OR 3.261, 95% CI 1.576 to 1.155 in favour of no RT	**General information** Follow-up: approximately 20 months Funding: Faculty Research Grant from Yonsei University College of Medicine (6-2018-0062, Kim YS). CoI: The authors declare that they have no competing interests. **Risk of bias considerations** (adapted from SIGN cohort study checklist)

Jeon HB, Lee M, Roh TS, Jeong J, Ahn SG, Bae SJ, Lee N, Kim YS. Complications Including Capsular Contracture in Direct-to-Implant Breast Reconstruction With Textured Anatomical Versus Smooth Round Implants: A Single Center Retrospective Analysis. J Breast Cancer. 2023 Feb;26(1): 25-34. doi: 10.4048/jbc.2023.26.e7. PMID: 36852965; PMCID: PMC9981986.				
	Follow-up period < 6 months, Missing data for the pertinent variables **Enrolment period:** August 2011 to June 2021 **Follow-up:** · approximately 20 months **Descriptive statistics** (reported for overall population) Age · mean 47 years, SD 7.9 BMI · mean 22.5, SD 3 Stadium: · 0: 30% · 1: 33.5% · 2: 29.5% · 3: 6.4% · 4: 0.3%	implant-based breast reconstruction (size, surface, insertion plane), positive lymph nodes, dissected lymph nodes, neo-adjuvant and adjuvant chemotherapy, Herceptin, hormone, radiotherapy, diabetes mellitus, hypertension, smoking, drainage duration, follow-up duration.		Study type: retrospective cohort study Confounding: Low risk, adjusted for relevant confounders Selection bias into the study: Unclear, patients with missing data were excluded Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No Drop-out rate & reasons reported: · High risk: not reported Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is

Jeon HB, Lee M, Roh TS, Jeong J, Ahn SG, Bae SJ, Lee N, Kim YS. Complications Including Capsular Contracture in Direct-to-Implant Breast Reconstruction With Textured Anatomical Versus Smooth Round Implants: A Single Center Retrospective Analysis. J Breast Cancer. 2023 Feb;26(1): 25-34. doi: 10.4048/jbc.2023.26.e7. PMID: 36852965; PMCID: PMC9981986.				
	Neoadjuvant chemotherapy: · 45% Adjuvant chemotherapy · 60% Reconstruction type · all DTI Mesh/ADM · 100% ADM Implant position · mostly sub-pectoral			unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: yes Confidence intervals reported: yes Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Kooijman MML, Hage JJ, Scholten AN, Vrancken Peeters MTFD, Woerdeman LAE. Short-Term Surgical Complications of Skin-Sparing Mastectomy and Direct-to-Implant Immediate Breast Reconstruction in Women Concurrently Treated with Adjuvant Radiotherapy for Breast Cancer. Arch Plast Surg. 2022 May 27;49(3): 332-338. doi: 10.1055/s-0042-1748648. PMID: 35832162; PMCID: PMC9142242.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Therapeutically operated for carcinoma or ductal carcinoma in situ (DCIS) **Exclusion criteria** (for analysis): Prophylactic procedures Two-staged tissue expander/implant, RT before mastectomy	**Interventions** RT after implant · N = 273 No RT after implant N = 739 **Analysis** Frequencies No matching No adjustment	**Implant loss** · RT: 16/273 · No RT: 45/739 **Reoperation (surgical reintervention)** · RT: 56/273 · No RT: 182/739 **Hematoma** · RT: 14/273	**General information** Follow-up: 16 weeks Funding: NR CoI: None declared. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: high risk: no adjustment despite considerable differences in

Kooijman MML, Hage JJ, Scholten AN, Vrancken Peeters MTFD, Woerdeman LAE. Short-Term Surgical Complications of Skin-Sparing Mastectomy and Direct-to-Implant Immediate Breast Reconstruction in Women Concurrently Treated with Adjuvant Radiotherapy for Breast Cancer. Arch Plast Surg. 2022 May 27;49(3): 332-338. doi: 10.1055/s-0042-1748648. PMID: 35832162; PMCID: PMC9142242.				
	Enrolment period: 1 January 2013 to 31 December 2018 **Follow-up:** 16 weeks **Descriptive statistics** Age (mean, sd) · PMRT: 44.1 (11.57), range 25-72 · No PMRT: 48.4 (10.91), range 19-76 BMI (mean, sd) · PMRT: 24.0 (3.72), range: 16.7–43.4 · No PMRT: 23.5 (3.90), range: 16.5–40.4 Stadium · NR Neoadjuvant chemotherapy · PMRT: 77.5% · No PMRT: 29.7% Adjuvant chemotherapy		· No RT: 27/739 **Seroma** · RT: 0/273 · No RT: 3/739 **Necrosis** · RT: 28/273 · No RT: 123 /739 **Infections** · RT: 14/273 · No RT: 29/739	baseline characteristics, such as previous and adjuvant chemotherapy, carcinoma, etc. Selection bias into the study: low risk: prospective data collection, reasons for exclusions provided Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No Drop-out rate & reasons reported: · Low risk: no drop-outs Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as

Kooijman MML, Hage JJ, Scholten AN, Vrancken Peeters MTFD, Woerdeman LAE. Short-Term Surgical Complications of Skin-Sparing Mastectomy and Direct-to-Implant Immediate Breast Reconstruction in Women Concurrently Treated with Adjuvant Radiotherapy for Breast Cancer. Arch Plast Surg. 2022 May 27;49(3): 332-338. doi: 10.1055/s-0042-1748648. PMID: 35832162; PMCID: PMC9142242.				
	· PMRT: 8.4% · No PMRT: 22.6% Reconstruction type · all DTI Mesh/ADM · 100% ADM (alloderm) Implant position · all sub-pectoral			the outcomes are standard clinical characteristics Main cofounders taken into account: No Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Lee KT, Kim J, Jeon BJ, Pyon JK, Bang SI, Mun GH. Longitudinal analysis of long-term outcomes of abdominal flap-based microsurgical reconstruction and two-stage prosthetic reconstruction. Sci Rep. 2023 Mar 11;13(1): 4062. doi: 10.1038/s41598-023-31218-2. PMID: 36906629; PMCID: PMC10008543.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Patients who had undergone DIEP flap surgery (DIEP flap group) or two-stage TE/I for breast reconstruction (TE/I group) **Exclusion criteria** (for analysis): Other reconstruction modalities, such as latissimus dorsi myocutaneous or direct-to-implant flaps, which were rarely adopted in our	**Interventions** RT after implant · N = 223 No RT after implant · N = 939 **Analysis** Frequencies, Multivariable Cox regression analysis No matching Adjusted for age, BMI, diabetes, hypertension, smoking status, type of mastectomy, weight of	**Major complications** · RT: 42/223 · No RT: 70/939 · HR 2.612, 95% CI 1.78 to 3.832	**General information** Follow-up: 24 months Funding: NR CoI: The authors declare no competing interests. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: moderate: multivariable model, PICO of publication DIEP vs. TE, so no

Lee KT, Kim J, Jeon BJ, Pyon JK, Bang SI, Mun GH. Longitudinal analysis of long-term outcomes of abdominal flap-based microsurgical reconstruction and two-stage prosthetic reconstruction. Sci Rep. 2023 Mar 11;13(1): 4062. doi: 10.1038/s41598-023-31218-2. PMID: 36906629; PMCID: PMC10008543.				
	institution during the study period Those who did not complete both stages during the follow-up period owing to causes unrelated to complications; Those who underwent the second stage of exchange-to-implant in another clinic; Those who had planned conversion to autologous tissue reconstruction following tissue expander insertion; Those who had been lost to follow-up within 2 years postoperatively. **Enrolment period:** 2012 to 2017 **Follow-up:** Minimum 24 months **Descriptive statistics** (reported for overall population) Age	the mastectomy specimen, neoadjuvant chemotherapy, adjuvant chemotherapy, and adjuvant radiotherapy		baseline table 1 for our question. Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No Drop-out rate & reasons reported: · High risk: not reported Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics

Lee KT, Kim J, Jeon BJ, Pyon JK, Bang SI, Mun GH. Longitudinal analysis of long-term outcomes of abdominal flap-based microsurgical reconstruction and two-stage prosthetic reconstruction. Sci Rep. 2023 Mar 11;13(1): 4062. doi: 10.1038/s41598-023-31218-2. PMID: 36906629; PMCID: PMC10008543.				
	· mean 44.1 years (range: 18–66 years) BMI · mean 22.5 kg/m2 (range: 15.1–39.8) Stadium · NR Neoadjuvant chemotherapy · 8% Adjuvant chemotherapy · 36% Reconstruction type · all tissue expander and later implant Mesh/ADM · 100% NR Implant position · NR			Main cofounders taken into account: yes Confidence intervals reported: yes Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Martins LL, Barbosa RF, Guerreiro FC, Andresen C, Pereira MJ, Pinho CJ, Rebelo MA, Ribeiro MM. A Two-Year Retrospective Analysis of the Clinical Outcomes of Immediate Submuscular Breast Reconstructions With Native® Acellular Dermal Matrix. Cureus. 2023 Jul 4;15(7): e41343. doi: 10.7759/cureus.41343. PMID: 37546031; PMCID: PMC10399605.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Female gender, Those aged above 18 years, Direct-to-implant submuscular breast reconstruction with an ADM sling with Native® biological matrix **Exclusion criteria** (for analysis): Other types of breast reconstruction,	**Interventions** RT after implant · N = 21 No RT after implant · N = 105 **Analysis** Frequencies, RR reported No matching Unclear adjustment	**Capsular contracture** · RT: 11/21 · No RT: 2/105	**General information** Follow-up: mean 24 (SD 15) Funding: NR CoI: The authors have declared that no competing interests exist. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study

Martins LL, Barbosa RF, Guerreiro FC, Andresen C, Pereira MJ, Pinho CJ, Rebelo MA, Ribeiro MM. A Two-Year Retrospective Analysis of the Clinical Outcomes of Immediate Submuscular Breast Reconstructions With Native® Acellular Dermal Matrix. Cureus. 2023 Jul 4;15(7): e41343. doi: 10.7759/cureus.41343. PMID: 37546031; PMCID: PMC10399605.				
	Submuscular reconstruction with tissue expanders Less than one month of follow-up. Patients with advanced disease at the initial diagnosis, as it represents a contraindication for immediate reconstruction **Enrolment period:** October 2016 to March 2020 **Follow-up:** w mean 24 (sd 15) **Descriptive statistics** (reported for overall population) Age (mean, sd) · 45.9 (9.1) BMI (mean, sd) · 23.4 (3.3) Stadium · NR Neoadjuvant chemotherapy			Confounding: moderate risk: multivariable model, main PICO does not correspond, unclear which covariates stayed in the model Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No Drop-out rate & reasons reported: · High risk: not reported Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is

Martins LL, Barbosa RF, Guerreiro FC, Andresen C, Pereira MJ, Pinho CJ, Rebelo MA, Ribeiro MM. A Two-Year Retrospective Analysis of the Clinical Outcomes of Immediate Submuscular Breast Reconstructions With Native® Acellular Dermal Matrix. Cureus. 2023 Jul 4;15(7): e41343. doi: 10.7759/cureus.41343. PMID: 37546031; PMCID: PMC10399605.				
	· 14% Adjuvant chemotherapy · 37% Reconstruction type · all DTI Mesh/ADM · ADM Native biological matrix Implant position · all sub-pectoral			unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: no Confidence intervals reported: yes Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Naoum GE, Ioakeim MI, Shui AM, Salama L, Colwell A, Ho AY, Taghian AG. Radiation Modality (Proton/Photon), Timing, and Complication Rates in Patients With Breast Cancer Receiving 2-Stages Expander/Implant Reconstruction. Pract Radiat Oncol. 2022 Nov-Dec;12(6): 475-486. doi: 10.1016/j.prro.2022.05.017. Epub 2022 Jun 27. PMID: 35989216; PMCID: PMC9637758.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Primary tumor treated with mastectomy and immediate two stages (TE/I) reconstruction **Exclusion criteria** (for analysis): Bilateral breast cancer, Inflammatory breast cancer, Local failure cases treated with mastectomy and reconstruction,	**Interventions** RT after implant · N = 309 No RT after implant · N = 352 **Analysis** Logistic regression for RT on tissue expander and final implant separately reported, otherwise frequencies	**Infections** · RT: 64/309 · No RT: 45/352 · For RT on tissue expander: OR 2.17 (95% CI 1.35-3.47) · For RT on final implant: OR 1.38 (95% CI 0.69-2.76) **Capsular contracture** · RT: 47/309 · No RT: 17/352	**General information** Follow-up, median, range · RTE: 84.3 (46.6, 115.7) · RTI: 45.5 (30.7, 68.5) · no PMRT: 101.5 (58.8, 136.4) Funding: NR CoI: Alphonse Taghian has the following Grants No. R01CA139118 (A.G.T.) and P50CA08393 (A.G.T.) from the National Cancer Institute, the Adele McKinnon Research Fund

Naoum GE, Ioakeim MI, Shui AM, Salama L, Colwell A, Ho AY, Taghian AG. Radiation Modality (Proton/Photon), Timing, and Complication Rates in Patients With Breast Cancer Receiving 2-Stages Expander/Implant Reconstruction. Pract Radiat Oncol. 2022 Nov-Dec;12(6): 475-486. doi: 10.1016/j.prro.2022.05.017. Epub 2022 Jun 27. PMID: 35989216; PMCID: PMC9637758.				
	Patients who received radiation after lumpectomy and electively underwent mastectomy with reconstruction Patients who underwent direct-to-implant immediate reconstruction. **Enrolment period:** 2000 to 2019 **Follow-up:** · RTE: 84.3 (46.6, 115.7) · RTI: 45.5 (30.7, 68.5) · No PMRT: 101.5 (58.8, 136.4) **Descriptive statistics** Age (median, IQR) · RTE: 46.3 (40.5, 51.8) · RTI: 44.1 (38.9, 49.9) · no PMRT: 48.2 (42.5, 54.2) BMI (median, IQR) · RTE: 24.4 (21.6, 28.5)	No matching Adjusted for expander/implant coverage, smoking, and BMI, and compared RTI and RTE to no PMRT	· For RT on tissue expander: OR 3.4 (95% CI 1.77 to 6.54) · For RT on final implant: OR 5.22 (95% CI 2.4 to 11.4) **Implant loss ("overall failure": removal of implant for any complications regardless replacement)** · RT: 115/309 · No RT: 77/352 · For RT on tissue expander: OR 2.72 (95% CI 1.82 to 4.05) · For RT on final implant: OR 1.76 (95% CI 1.0 to 3.1) **Implant loss ("absolute failure": expander or implant total loss)** · RT: 28/309 · No RT: 13/352 · For RT on tissue expander: OR 2.55 (95% CI 1.18-5.52)	for Breast Cancer-Related Lymphedema (A.G.T.), the Olayan-Xefos Family Fund for Breast Cancer Research (A.G.T.), and the Heinz Family Foundation (A.G.T.). **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: moderate risk: multivariable model, but not all relevant covariates considered Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No

Naoum GE, Ioakeim MI, Shui AM, Salama L, Colwell A, Ho AY, Taghian AG. Radiation Modality (Proton/Photon), Timing, and Complication Rates in Patients With Breast Cancer Receiving 2-Stages Expander/Implant Reconstruction. Pract Radiat Oncol. 2022 Nov-Dec;12(6): 475-486. doi: 10.1016/j.prro.2022.05.017. Epub 2022 Jun 27. PMID: 35989216; PMCID: PMC9637758.				
	· RTI: 24.9 (21.8, 27.8) · No PMRT: 23.6 (21.3, 26.7) Stadium · T0: RTE: 6.4%, RTI: 4.5%, no PMRT: 18.2% · T1: RTE: 34.5%, RTI: 34.8%, no PMRT: 65.6% · T2: RTE: 45%, RTI: 47.2%, no PMRT: 15.6% · T3: RTE: 13.2%, RTI: 13.5%, no PMRT: 0.6% · T4: RTE: 0.9%, RTI: 0%, no PMRT: 0% Neoadjuvant chemotherapy (% yes) · RTE: 28.6% · RTI: 21.3% · no PMRT: 4.3% Adjuvant chemotherapy (%yes) · RTE: 63.6%		· For RT on final implant: 2.93 (95% CI 1.13-7.6)	Drop-out rate & reasons reported: · High risk: not reported Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: partly Confidence intervals reported: no (for subgroups TE versus implant RT yes) Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Naoum GE, Ioakeim MI, Shui AM, Salama L, Colwell A, Ho AY, Taghian AG. Radiation Modality (Proton/Photon), Timing, and Complication Rates in Patients With Breast Cancer Receiving 2-Stages Expander/Implant Reconstruction. Pract Radiat Oncol. 2022 Nov-Dec;12(6): 475-486. doi: 10.1016/j.prro.2022.05.017. Epub 2022 Jun 27. PMID: 35989216; PMCID: PMC9637758.				
	· RTI: 68.5% · no PMRT: 35.9% Reconstruction type (%) · tissue-expander and implant replacing Mesh/ADM (%) · Alloderm: RTE: 40.1%, RTI: 41%, no PMRT: 23.9% · other mesh: RTE: 6.9%, RTI: 15.7%, no PMRT: 7.8% Implant position · all subpectoral			

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Nelson JA, Cordeiro PG, Polanco T, Shamsunder MG, Patel A, Allen RJ Jr, Matros E, Disa JJ, Cuaron JJ, Morrow M, Mehrara BJ, Pusic AL, McCarthy CM. Association of Radiation Timing with Long-Term Satisfaction and Health-Related Quality of Life in Prosthetic Breast Reconstruction. Plast Reconstr Surg. 2022 Jul 1;150(1): 32e-41e. doi: 10.1097/PRS.0000000000009180. Epub 2022 May 2. PMID: 35499580; PMCID: PMC9453854.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Implant-based reconstruction **Exclusion criteria** (for analysis): Patients <18 years Autologous breast reconstruction, Without BREAST-Q data at ≥1 year following reconstruction **Enrolment period:** January 2010 and June 2017	**Interventions** RT after implant · TE: N = 290 · TI: N = 228 No RT after implant · N = 2175 **Analysis** Frequencies, mean, sd No matching	**Implant loss (implant removal)** · RT: 24/518 · No RT: 44/2175 **Implant exchange** · RT: 112/518 · No RT: 578/2175 **Capsular contracture (Grade 3-4)** · RT: 154/518 · No RT: 161/2175	**General information** Follow-up: 3 years of follow up Funding: This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748 CoI: Andrea Pusic is a codeveloper of the BREAST-Q, which is owned by Memorial Sloan Kettering Cancer Center. She receives a portion of the licensing fees (royalty payments) when the BREAST-Q is used in industry-sponsored

Nelson JA, Cordeiro PG, Polanco T, Shamsunder MG, Patel A, Allen RJ Jr, Matros E, Disa JJ, Cuaron JJ, Morrow M, Mehrara BJ, Pusic AL, McCarthy CM. Association of Radiation Timing with Long-Term Satisfaction and Health-Related Quality of Life in Prosthetic Breast Reconstruction. Plast Reconstr Surg. 2022 Jul 1;150(1): 32e-41e. doi: 10.1097/PRS.0000000000009180. Epub 2022 May 2. PMID: 35499580; PMCID: PMC9453854.				
	Follow-up: 3 years **Descriptive statistics** Age (mean, SD) · RTE: 48.6 (10.0) · RTI: 47.3 (9.8) · No RT: 49.5 (10.0) BMI (mean, SD) · RTE: 26.2 (5.3) · RTI: 25.5 (5.1) · No RT: 25.11 (5.1) w Stadium · NR Neoadjuvant chemotherapy (% yes) · RTE: 34.1% · RTI: 4.4% · No RT: 5.8% Adjuvant chemotherapy (% yes) · RTE: 36.6%	No adjustment	**Wound complication (wound dehiscence)** · RT: 4/518 · No RT: 10/2175 **QoL-outcomes: Breast-Q (mean, sd)** <u>Satisfaction with breasts (year 1):</u> · RT-TE: 56.5 (18.2) · RT-I: 56.8 (18.1) · No RT: 66.5 (18.1) <u>Satisfaction with breasts (year 2):</u> · RT-TE: 57.2 (20.3) · RT-I: 56.4 (17.4) · No RT: 66.3 (17.4) <u>Satisfaction with breasts (year 3):</u> · RT-TE: 57.6 (16.7) · RT-I: 56.7 (17.8)	clinical trials. Joseph Dayan is a consultant for Stryker. Babak Mehrara is a consultant for PureTech Corporation. The remaining authors declare no conflicts of interest. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: High risk: no adjustment Selection bias into the study: low risk: prospective data collection Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No

Nelson JA, Cordeiro PG, Polanco T, Shamsunder MG, Patel A, Allen RJ Jr, Matros E, Disa JJ, Cuaron JJ, Morrow M, Mehrara BJ, Pusic AL, McCarthy CM. Association of Radiation Timing with Long-Term Satisfaction and Health-Related Quality of Life in Prosthetic Breast Reconstruction. Plast Reconstr Surg. 2022 Jul 1;150(1): 32e-41e. doi: 10.1097/PRS.0000000000009180. Epub 2022 May 2. PMID: 35499580; PMCID: PMC9453854.				
	· RTI: 80.7% · No RT: 33.5% Reconstruction type · Tissue expander and implant replacement Mesh/ADM · NR Implant position · NR		· No RT: 65.5 (18.7) <u>Physical well-being (year 1):</u> · RT-TE: 67.7 (16.9) · RT-I: 65.7 (16.1) · No RT: 75.5 (15.3) <u>Physical well-being (year 2):</u> · RT-TE: 69.0 (19.4) · RT-I: 67.7 (16.3) · No RT: 77.1 (15.2) <u>Physical well-being (year 3):</u> · RT-TE: 69.9 (17.6) · RT-I: 70.4 (13.8) · No RT: 77.2 (15.9)	Drop-out rate & reasons reported: · Unclear: not reported per group Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Ostapenko E, Nixdorf L, Devyatko Y, Exner R, Wimmer K, Fitzal F. The Impact of Adjuvant Radiotherapy on Immediate Prepectoral Implant-Based Breast Reconstruction. Aesthetic Plast Surg. 2024 Jul;48(13): 2432-2438. doi: 10.1007/s00266-023-03661-z. Epub 2023 Sep 22. PMID: 37737875.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Histologically proven BC, Age > 18 years, Female sex, NSM following prepectoral IBBR **Exclusion criteria** (for analysis): Other IBBR techniques, Other mastectomy techniques, Lost to follow-up	**Interventions** RT after implant · N = 28 No RT after implant · N = 70 **Analysis** Frequencies, means, SD No matching No adjustment	**Overall complications** · RT: 9/28 · No RT: 16/70 **Hematoma** · RT: 0/28 · No RT: 16/70 **Necrosis** · RT: 2/28 · No RT: 2/70 **Seroma** · RT: 1/28	**General information** Follow-up (mean,sd): · PMRT: 31.44± 12.37 · no PMRT: 30.91 ± 13.21 Funding: The authors received no financial support for the research, authorship and publication of this article. CoI: Dr. F.F. has received personal honoraries and educational grants from Pfizer, Novartis, Roche, Astra Zeneca, Springer, Medtronic and Bondimed. The remaining

Ostapenko E, Nixdorf L, Devyatko Y, Exner R, Wimmer K, Fitzal F. The Impact of Adjuvant Radiotherapy on Immediate Prepectoral Implant-Based Breast Reconstruction. Aesthetic Plast Surg. 2024 Jul;48(13): 2432-2438. doi: 10.1007/s00266-023-03661-z. Epub 2023 Sep 22. PMID: 37737875.				
	Enrolment period: March 2017 to November 2021 **Follow-up (mean, sd):** · PMRT: 31.44 (12.37) · No PMRT: 30.91 (13.21) **Descriptive statistics** Age (mean, SD) · PMRT: 44.65 ± 11.58 · No PMRT: 46.51 ± 12.45 BMI (median, range) · NR Stadium · PMRT: pTis: 10.7%, pT1: 39.3%, pT2: 32.1%, pT3: 17.9%, No tumor: 0% · No PMRT: pTis: 18.6%, pT1: 64.3%, pT2: 8.6%, pT3: 0%, No tumor: 8.5% Neoadjuvant chemotherapy (% yes) · PMRT: 82.1%		· No RT: 2/70 **Infections** · RT: 2/28 · No RT: 3/70 **Implant loss** · RT: 3/28 · No RT: 1/70 **Capsular contracture** · RT: 5/28 · No RT: 3/70 **Local recurrence** · RT: 2/28 · No RT: 3/70 **QoL-outcomes: Breast-Q (mean, sd)** <u>Satisfaction with overall outcome:</u> · RT: 72.53 (21.43) · No RT: 77.28 (21.31) <u>Psychosocial well-being:</u>	authors have no financial interests to declare in relation to the content of this article. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: high risk: no adjustment, although relevant baseline characteristics differ between groups ("patients in the RT group compared to non-RT differed significantly in the rate of axillary lymph node dissection (17.1% vs. 50%; p=0.001), neoadjuvant (p\.0001) and adjuvant chemotherapy (p\.0001), final tumor stage, and lymph node stage." Selection bias into the study: Unclear, no information provided. Intervention

Ostapenko E, Nixdorf L, Devyatko Y, Exner R, Wimmer K, Fitzal F. The Impact of Adjuvant Radiotherapy on Immediate Prepectoral Implant-Based Breast Reconstruction. Aesthetic Plast Surg. 2024 Jul;48(13): 2432-2438. doi: 10.1007/s00266-023-03661-z. Epub 2023 Sep 22. PMID: 37737875.				
	· No PMRT: 25.7% Adjuvant chemotherapy (% yes) · PMRT: 67.9% · No PMRT: 18.6% Reconstruction type (%) · Single-Stage: PMRT: 85.71%, no PMRT: 84.3% · Two Stage: PMRT: 14.3%, no PMRT: 15.7% Mesh/ADM: NR Implant position · all prepectoral		· RT: 78.73 (17.39) · No RT: 79.22 (15.56) <u>Sexual well-being:</u> · RT: 61.38 (22.72) · No RT: 70.26 (22.78) <u>Physical well-being:</u> · RT: 57.94 (30.08) · No RT: 58.89 (25.21)	· Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No Drop-out rate & reasons reported: · High risk: not reported. Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol provided, not assessable.

Ostapenko E, Nixdorf L, Devyatko Y, Exner R, Wimmer K, Fitzal F. The Impact of Adjuvant Radiotherapy on Immediate Prepectoral Implant-Based Breast Reconstruction. Aesthetic Plast Surg. 2024 Jul;48(13): 2432-2438. doi: 10.1007/s00266-023-03661-z. Epub 2023 Sep 22. PMID: 37737875.				
				Other limitations: retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Polotto S, Pedrazzi G, Bergamini M, D'Abbiero N, Cattelani L. ADM-Assisted Direct-to-Implant Prepectoral Breast Reconstruction in Postmastectomy Radiation Therapy Setting: Long-Term Results. Clin Breast Cancer. 2023 Oct;23(7): 704-711. doi: 10.1016/j.clbc.2023.06.011. Epub 2023 Jul 1. PMID: 37479666.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Oncologic or risk-reducing nipple or skin-sparing mastectomy Direct-to-implant ADM-assisted PPBR Age ≥18 and ≤85 years, TNM stage Not active smokers in the last 3 preoperative weeks,	**Interventions** RT after implant · N = 84 No RT after implant · N = 401 **Analysis** Frequencies, nonparametric tests (Mann-Whitney's U-test, Kruskal-Wallis test) No matching	**Overall complications** · RT: 18/84 · No RT: 45/401 **Hematoma** · RT: 0/84 · No RT: 1/401 **Seroma** · RT: 6/84 · No RT: 15/401 **Infections** · RT: 1/84	**General information** Follow-up (median, range): · PMRT: 28.5 (range 10.6 to 73.2) · no PMRT: 30.4 (range 8.3 to 84) Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Polotto S, Pedrazzi G, Bergamini M, D'Abbiero N, Cattelani L. ADM-Assisted Direct-to-Implant Prepectoral Breast Reconstruction in Postmastectomy Radiation Therapy Setting: Long-Term Results. Clin Breast Cancer. 2023 Oct;23(7): 704-711. doi: 10.1016/j.clbc.2023.06.011. Epub 2023 Jul 1. PMID: 37479666.				
	≤1 significant comorbidity (ie, diabetes, obesity, connective tissue disease) **Exclusion criteria** (for analysis): Undergone previous breast, mantle field or total body radiation therapy Patients with <6 months of FU 2-stage PPBR or other typology of reconstruction planned **Enrolment period:** January 2015 to December 2020 **Follow-up (median):** · PMRT: 28.5 (range 10.6 to 73.2) · No PMRT: 30.4 (range 8.3 to 84) **Descriptive statistics** Age (median, range) · PMRT: 54.0 (11.0) · No PMRT: 55.1 (11.5)	No adjustment	· No RT: 8/401 **Capsular contracture** · RT: 7/84 · No RT: 1/401 **Necrosis** · RT: 0/84 · No RT: 6/401 **Wound complications (dehiscence)** · RT: 0/84 · No RT: 0/401 **Implant loss** · RT: 4/84 · No RT: 14/401	CoI: The authors have stated that they have no conflicts of interest. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: High risk: no adjustment Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No Drop-out rate & reasons reported: · High risk: not reported

Polotto S, Pedrazzi G, Bergamini M, D'Abbiero N, Cattelani L. ADM-Assisted Direct-to-Implant Prepectoral Breast Reconstruction in Postmastectomy Radiation Therapy Setting: Long-Term Results. Clin Breast Cancer. 2023 Oct;23(7): 704-711. doi: 10.1016/j.clbc.2023.06.011. Epub 2023 Jul 1. PMID: 37479666.				
	BMI (median, range) · PMRT: 23.3 (3.4) · No PMRT: 23.1 (3.4) Stadium · NR Neoadjuvant chemotherapy (% yes) · PMRT: 33.3% · No PMRT: 14.9% Adjuvant chemotherapy (% yes) · PMRT: 70.2% · No PMRT: 27.3% Reconstruction type (%) · all direct-to-implant Mesh/ADM · 100% with mesh Implant position · all prepectoral			Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Safran T, Al-Badarin F, Al-Halabi B, Viezel-Mathieu A, Dionisopoulos T. Aesthetic Limitations in Direct-to-Implant Prepectoral Breast Reconstruction. Plast Reconstr Surg. 2022 Jul 1;150(1): 22e-31e. doi: 10.1097/PRS.0000000000009189. Epub 2022 May 2. PMID: 35499675.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Unilateral or bilateral direct-to-implant prepectoral breast reconstruction following mastectomy **Exclusion criteria** (for analysis): Patient preference, Previously failed implantbased reconstruction, Delayed reconstruction,	**Interventions** RT after implant · N = 81 No RT after implant · N = 253 **Analysis** Multivariable logistic regression analysis No matching Adjusted for Age, BMI, diabetes, smoker, skin-sparing	**Capsular contracture** · OR 7.195 · p = 0.007	**General information** Follow-up: 30.5 months Funding: No funding was received for this work. CoI: Dr. Dionisopoulos received travel support from Allergan/Lifecell for educational conferences. The remaining authors have no financial interests to declare. **Risk of bias considerations** (adapted from SIGN cohort study checklist)

Safran T, Al-Badarin F, Al-Halabi B, Viezel-Mathieu A, Dionisopoulos T. Aesthetic Limitations in Direct-to-Implant Prepectoral Breast Reconstruction. Plast Reconstr Surg. 2022 Jul 1;150(1): 22e-31e. doi: 10.1097/PRS.0000000000009189. Epub 2022 May 2. PMID: 35499675.				
	Autologous-based reconstruction **Enrolment period:** June 2016 to June 2019 **Follow-up:** 30.5 months **Descriptive statistics** (reported for overall population) Age · mean 48.4 years (range, 19 to 83 years) BMI · mean 25.89 kg/m2 (range, 18.2 to 53.9 kg/m2) Stadium · NR Neoadjuvant chemotherapy · 35.1% Adjuvant chemotherapy · NR Reconstruction type	mastectomy, midlateral, wise pattern, implant size, ADM, days drain inserted, pocket infection, seroma, hematoma, minor complications		Study type: retrospective cohort study Confounding: high risk: adjustment for other complications as well, which may be on the causal pathway instead of confounder Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No Drop-out rate & reasons reported: · High risk: not reported Outcome · Outcome measure is well-defined, valid and reliable;

Safran T, Al-Badarin F, Al-Halabi B, Viezel-Mathieu A, Dionisopoulos T. Aesthetic Limitations in Direct-to-Implant Prepectoral Breast Reconstruction. Plast Reconstr Surg. 2022 Jul 1;150(1): 22e-31e. doi: 10.1097/PRS.0000000000009189. Epub 2022 May 2. PMID: 35499675.				
	· all DTI Mesh/ADM · 74.9% with mesh Implant position · all pre-pectoral			· No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: only for overall complications Confidence intervals reported: p-value used for calculation of CI Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Saksornchai K, Ganoksil P, Rongkavilit S, Suwajo P. Impact of radiation on immediate breast reconstruction: a retrospective single institution cohort study. Gland Surg. 2023 Aug 30;12(8): 1050-1059. doi: 10.21037/gs-23-61. Epub 2023 Aug 23. PMID: 37701294; PMCID: PMC10493629.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Women aged >18 years Mastectomy and immediate breast reconstruction using a one-stage, direct-to-implant (DTI) approach, autologous-based reconstruction, or a combination of both techniques **Exclusion criteria** (for analysis): Palliative surgery,	**Interventions** RT after implant · N = 38 No RT after implant · N = 48 **Analysis** Frequencies No matching No adjustment	**Overall complications** · RT: 23/42 · No RT: 19/52 **Capsular contracture (grade 3-4)** · RT: 16/38 · No RT: 7/48 **Extrusion** · RT: 1/42 · No RT: 0/48	**General information** Follow-up, mean, SD · PMRT: 53.42±36.96 · no PMRT: 54.17±34.98 Funding: This research was supported by grants for the Development of New Faculty Staff and the Ratchadaphiseksomphot Endowment Fund. CoI: The authors have no conflicts of interest to declare.

Saksornchai K, Ganoksil P, Rongkavilit S, Suwajo P. Impact of radiation on immediate breast reconstruction: a retrospective single institution cohort study. Gland Surg. 2023 Aug 30;12(8): 1050-1059. doi: 10.21037/gs-23-61. Epub 2023 Aug 23. PMID: 37701294; PMCID: PMC10493629.				
	Cosmetic surgery (transgender patients), Reconstruction with a pedicled omental flap **Enrolment period:** January 2008 to December 2018 **Follow-up:** · PMRT: 53.42, SD 36.96 · No PMRT: 54.17, SD 34.98 **Descriptive statistics** Age (mean, SD) · PMRT: 44.81 (8.96) · no PMRT: 45.27 (7.41) BMI (mean, SD) · PMRT: 22.31 (3.56) · no PMRT: 22.02 (3.24) Stadium: · 0: PMRT: 1.5%, no PMRT: 16.7 · I: PMRT: 17.6%, no PMRT: 37.9			**Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: High risk, no adjustment Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No Drop-out rate & reasons reported: · High risk: not reported Outcome · Outcome measure is well-defined, valid and reliable;

Saksornchai K, Ganoksil P, Rongkavilit S, Suwajo P. Impact of radiation on immediate breast reconstruction: a retrospective single institution cohort study. Gland Surg. 2023 Aug 30;12(8): 1050-1059. doi: 10.21037/gs-23-61. Epub 2023 Aug 23. PMID: 37701294; PMCID: PMC10493629.				
	· II: PMRT: 38.2%, no PMRT: 31.8% · III: PMRT: 32.4%, no PMRT: 3% · IV: PMRT: 1.5%, no PMRT: 0% · NA: PMRT: 8.8%, no PMRT: 10.6% Neoadjuvant chemotherapy · NR Adjuvant chemotherapy (% yes) · PMRT: 79.4% · No PMRT: 51.5% Reconstruction type (%): · Implant: PMRT: 61.8%, no PMRT: 78.8% · Autologous: PMRT: 38.2%, no PMRT: 21.2% · Combined approach: PMRT: 25%, no PMRT: 33% Mesh/ADM · NR			· No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Saksornchai K, Ganoksil P, Rongkavilit S, Suwajo P. Impact of radiation on immediate breast reconstruction: a retrospective single institution cohort study. Gland Surg. 2023 Aug 30;12(8): 1050-1059. doi: 10.21037/gs-23-61. Epub 2023 Aug 23. PMID: 37701294; PMCID: PMC10493629.				
	Implant position: · Prepectoral: PMRT: 19%, no PMRT: 30.8% · Subpectoral: PMRT: 81%, no PMRT: 69.2%			

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Sewart E, Turner NL, Conroy EJ, Cutress RI, Skillman J, Whisker L, Thrush S, Barnes N, Holcombe C, Potter S; iBRA Steering Group and the Breast Reconstruction Research Collaborative. The Impact of Radiotherapy on Patient-reported Outcomes of Immediate Implant-based Breast Reconstruction With and Without Mesh. Ann Surg. 2022 May 1;275(5): 992-1001. doi: 10.1097/SLA.0000000000004245. Epub 2020 Jul 9. PMID: 32657919.

Study type	Population	Interventions	Main results	Methodological evaluation
Prospective cohort study	**Inclusion criteria** (for analysis): IBBR using any technique Subpectoral reconstructions with and without mesh, and pre-pectoral techniques Patients undergoing neoadjuvant chemotherapy or endocrine therapy before IBBR were eligible for inclusion. **Exclusion criteria** (for analysis):	**Interventions** RT after implant · N = 214 No RT after implant · N = 514 **Analysis** Frequencies, means, sd No matching No adjustment	**Infections (at 3 months)** · RT: 62/214 · No RT: 115/516 **Implant loss (at 3 months)** · RT: 13/214 · No RT: 26/516 **Reoperation (at 3 months)** · RT: 35/214 · No RT: 84/516	**General information** Follow-up: 18 months Funding: NR CoI: NR **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: High risk, no adjustment

Sewart E, Turner NL, Conroy EJ, Cutress RI, Skillman J, Whisker L, Thrush S, Barnes N, Holcombe C, Potter S; iBRA Steering Group and the Breast Reconstruction Research Collaborative. The Impact of Radiotherapy on Patient-reported Outcomes of Immediate Implant-based Breast Reconstruction With and Without Mesh. Ann Surg. 2022 May 1;275(5): 992-1001. doi: 10.1097/SLA.0000000000004245. Epub 2020 Jul 9. PMID: 32657919.				
	Delayed reconstruction Implant in combination with an autologous flap **Enrolment period:** 1 February 2014 to 30 June 2016 **Follow-up:** 18 months **Descriptive statistics** Age (median, IQR, range) · PMRT: 50 (44–58; 28–80) · No PMRT: 52 (47–60.5; 16–83) BMI (median, IQR, range) · PMRT: 24.9 (22.9–28.4; 16.4–41) · No PMRT: 24.5 (22.3–28; 16.8–42.6) Stadium · NR Neoadjuvant chemotherapy (% yes)		**Hospitalisation (readmission at 3 months)** · RT: 38/214 · No RT: 77/516 **QoL-outcomes: Breast-Q** (median, IWR, range; not used in analysis), 18 months post-score <u>Satisfaction with breasts:</u> · RT: 49 (41–62; 0–100) · No RT: 61 (49–73; 0–100) <u>Satisfaction with overall outcome:</u> · RT: 67 (51–75; 0–100) · No RT: 75 (61–86; 0–100) <u>Psychosocial well-being:</u> · RT: 61.5 (48–79; 0–100) · No RT: 67 (52–86; 0–100) <u>Sexual well-being:</u> · RT: 41 (26–57; 0–100)	Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No Drop-out rate & reasons reported: · High risk: not reported Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics

Sewart E, Turner NL, Conroy EJ, Cutress RI, Skillman J, Whisker L, Thrush S, Barnes N, Holcombe C, Potter S; iBRA Steering Group and the Breast Reconstruction Research Collaborative. The Impact of Radiotherapy on Patient-reported Outcomes of Immediate Implant-based Breast Reconstruction With and Without Mesh. Ann Surg. 2022 May 1;275(5): 992-1001. doi: 10.1097/SLA.0000000000004245. Epub 2020 Jul 9. PMID: 32657919.				
	· PMRT: 22% · No PMRT: 6% Adjuvant chemotherapy (% yes) · PMRT: 77% · No PMRT: 7% Reconstruction type (%) · Single-stage reconstruction: PMRT: 77%, no PMRT: 80% · Two-stage reconstruction: PMRT: 23%, no PMRT: 20% · Different approach per breast: PMRT: 1%, no PMRT: 1% Mesh/ADM (%) · Biological mesh: PMRT: 52%, no PMRT: 58% Implant position · mostly sub-pectoral		· No RT: 45 (33–60; 0–100) <u>Physical well-being:</u> · RT: 68 (60–81; 13–100) · No RT: 77 (66–85; 18–100)	Main cofounders taken into account: only for overall complications Confidence intervals reported: no (for overall complications yes) Selective reporting (comparison with protocol): study was registered and planned satisfaction with care, complications and health-related quality of life (BREAST-Q) **Other limitations:** NR

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Stuart SR, Munhoz AM, Chaves CLG, Montag E, Cordeiro TCS, Fuzisaki TT, Marta GN, Carvalho HA. Complications after breast reconstruction with alloplastic material in breast cancer patients submitted or not to post mastectomy radiotherapy. Rep Pract Oncol Radiother. 2021 Sep 30;26(5): 730-739. doi: 10.5603/RPOR.a2021.0087. PMID: 34760307; PMCID: PMC8575365.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Immediate breast reconstruction after mastectomy Alloplastic Staged breast reconstruction **Exclusion criteria** (for analysis): Not reported. **Enrolment period:** 2009-2013 **Follow-up:** Minimum 24 months	**Interventions** RT after implant · N = 167 No RT after implant · N = 84 **Analysis** Frequencies No matching No adjustment	**Overall complications (early)** · RT: 40/167 · No RT: 26/84 **Seroma** · RT: 45/167 · No RT: 14/84 **Hematoma** · RT: 0/167 · No RT: 2/84 **Infections (local infection)**	**General information** Follow-up: minimum follow-up of 24 months Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. CoI: None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript. S.R.S., C.L.G.C., E.M., T.C.S.C., T.T.F., G.N.M., H.A.C. — none

Stuart SR, Munhoz AM, Chaves CLG, Montag E, Cordeiro TCS, Fuzisaki TT, Marta GN, Carvalho HA. Complications after breast reconstruction with alloplastic material in breast cancer patients submitted or not to post mastectomy radiotherapy. Rep Pract Oncol Radiother. 2021 Sep 30;26(5): 730-739. doi: 10.5603/RPOR.a2021.0087. PMID: 34760307; PMCID: PMC8575365.				
	Descriptive statistics Age (mean, range) · PMRT: 48.6 (25–74) · No PMRT: 51.6 (32–78) BMI (median, range) · PMRT: 27.7 (17.9–41.1) · No PMRT: 26.5 (16.2–43.2) Stadium · In situ: PMRT: 7.8%, no PMRT: 16.7% · I–IIB: PMRT: 48.5%, no PMRT: 72.6% · III: PMRT: 44.3%, no PMRT: 10.7% Neoadjuvant chemotherapy (% yes) · PMRT: 46.7% · No PMRT: 14.3% Adjuvant chemotherapy (% yes)		· RT: 9/167 · No RT: 9/84 **Necrosis (partial necrosis)** · RT: 8/167 · No RT: 4/84 **Wound complications (total dehiscence, >1/3)** · RT: 1/167 · No RT: 0/84 **Reoperation (second surgical intervention)** · RT: 25/167 · No RT: 11/84 **Implant loss** · RT: 16/167 · No RT: 9/84 **Extrusion** · RT: 1/167 · No RT: 0/84	declared; A.M.M is a Member of the Medical Advisory Board, Establishment Labs. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: high risk: no adjustment, although baseline characteristics differ, i.e., stage, chemotherapy, etc. Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No

Stuart SR, Munhoz AM, Chaves CLG, Montag E, Cordeiro TCS, Fuzisaki TT, Marta GN, Carvalho HA. Complications after breast reconstruction with alloplastic material in breast cancer patients submitted or not to post mastectomy radiotherapy. Rep Pract Oncol Radiother. 2021 Sep 30;26(5): 730-739. doi: 10.5603/RPOR.a2021.0087. PMID: 34760307; PMCID: PMC8575365.				
	· PMRT: 40.7% · No PMRT: 46.4% Reconstruction type · Tissue expander with later implant placement Mesh/ADM (%) · None Implant position · all sub-pectoral		**Capsular contracture (severe)** · RT: 6/167 · No RT: 2/84	Drop-out rate & reasons reported: · High risk: not reported Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: only for overall complications Confidence intervals reported: no (for overall complications yes) Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Sun L, Zhu W, Zhang J, Zhong B, Li S, Li H, Gan L. The risk factors and the relationship between radiation dose and complications and prosthetic reconstruction failure in patients with post-mastectomy breast implant reconstruction: a retrospective cohort study. Gland Surg. 2022 Nov;11(11): 1817-1831. doi: 10.21037/gs-22-633. PMID: 36518801; PMCID: PMC9742054.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Women with breast ductal carcinoma in situ (DCIS) or clinical stage I–III invasive breast cancer Mastectomy and breast reconstruction with or without PMRT **Exclusion criteria** (for analysis): Loss to follow-up or deceased	**Interventions** RT after implant · N = 59 No RT after implant N = 221 **Analysis** Univariable and multivariate logistic regression analyses for reconstruction failure and overall complications	**Overall complications** · RT: 30/59 · No RT: 73/221 · OR 2.0 (95% CI 1.065 to 3.754) **Necrosis** · RT: 2/59 · No RT: 3/221 **Bleeding** · RT: 4/59	**General information** Follow-up: · PMRT: 37.2 · No PMRT: 51.3 Funding: None. CoI: The authors have no conflicts of interest to declare. **Risk of bias considerations** (adapted from SIGN cohort study checklist)

Sun L, Zhu W, Zhang J, Zhong B, Li S, Li H, Gan L. The risk factors and the relationship between radiation dose and complications and prosthetic reconstruction failure in patients with post-mastectomy breast implant reconstruction: a retrospective cohort study. Gland Surg. 2022 Nov;11(11): 1817-1831. doi: 10.21037/gs-22-633. PMID: 36518801; PMCID: PMC9742054.				
	Incomplete expander-implant replacement Implant removal for reasons unrelated to surgery Completed postoperative adjuvant RT in other medical institutions Presented with benign tumors. **Enrolment period:** January 2012 to June 2020 **Follow-up:** · PMRT: 37.2 months · No PMRT: 51.3 months **Descriptive statistics** Age (mean, SD) · PMRT: 36.71 (9.19) · no PMRT: 40.54 (8.03) BMI (mean, SD) · PMRT: 21.53 (2.45) · no PMRT: 21.51 (2.38)	No matching Multivariable analysis adjusted for age, BMI, personal history, history, adjuvant therapy, reconstruction type, and implant volume	· No RT: 9/221 **Wound complications (incision dehiscence)** · RT: 9/59 · No RT: 15/221 **Seroma** · RT: 2/59 · No RT: 5/221 **Hematoma** · RT: 0/59 · No RT: 1/221 **Infections** · RT: 13/59 · No RT: 21/221 **Reconstruction failure** · RT: 11/59 · No RT: 19/221 · OR: 2.44 (95% CI 1.01 to 5.91)	Study type: retrospective cohort study Confounding: high risk for most outcomes: no adjustment, although baseline characteristics differ, i.e., stage, chemotherapy, etc.; moderate risk for reconstruction failure and overall complications Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No Drop-out rate & reasons reported: · unclear: drop-out rate reported, but not per group

Sun L, Zhu W, Zhang J, Zhong B, Li S, Li H, Gan L. The risk factors and the relationship between radiation dose and complications and prosthetic reconstruction failure in patients with post-mastectomy breast implant reconstruction: a retrospective cohort study. Gland Surg. 2022 Nov;11(11): 1817-1831. doi: 10.21037/gs-22-633. PMID: 36518801; PMCID: PMC9742054.				
	Stadium · 0: PMRT: 0%, no PMRT: 45% · IA: PMRT: 1.7%, no PMRT: 31% · IB: PMRT: 3.4%, no PMRT: 0% · IIA: PMRT: 16.9%, no PMRT: 37.0% · IIB: PMRT: 25.4%, no PMRT: 9.7% · IIIA: PMRT: 45.8%, no PMRT: 1.4% · IIIB&C: PMRT: 6.8%, no PMRT: 0% Neoadjuvant chemotherapy (% yes) · PMRT: 39% · No PMRT: 12.5% Adjuvant chemotherapy (% yes) · PMRT: 100% · No PMRT: 76.9%			Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: only for overall complications and reconstruction failure Confidence intervals reported: no (for overall complications and reconstruction failure yes) Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Sun L, Zhu W, Zhang J, Zhong B, Li S, Li H, Gan L. The risk factors and the relationship between radiation dose and complications and prosthetic reconstruction failure in patients with post-mastectomy breast implant reconstruction: a retrospective cohort study. Gland Surg. 2022 Nov;11(11): 1817-1831. doi: 10.21037/gs-22-633. PMID: 36518801; PMCID: PMC9742054.				
	Reconstruction type (%) · 1-stage: PMRT: 25.4%, no PMRT: 61.5% · 2-stage: PMRT: 74.6%, no PMRT: 38.5% Mesh/ADM · no mesh used Implant position · all subpectoral			

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Yin Z, Wang H, Liu Y, Wang Y, Chang EI, Yin J. Single-Institution Algorithm for Prevention and Management of Complications in Direct-to-Implant Breast Reconstruction. Plast Reconstr Surg. 2022 Oct 1;150: 48S-60S. doi: 10.1097/PRS.0000000000009490. Epub 2022 Sep 28. PMID: 35943963.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Age 18 years or older and documentation of direct-to-implant breast reconstruction. **Exclusion criteria** (for analysis): Metastatic breast cancer, Two-stage expander-implant breast reconstruction, Bilateral breast reconstruction,	**Interventions** RT after implant · N = 130 No RT after implant · N = 897 **Analysis** Multivariable logistic regression analysis No matching	**Major complications (Surgical-site infection, wound dehiscence, and mastectomy flap necrosis requireing rehospitalisation or reoperation) at 3 months** · RT: 21/130 · No RT: 69/897 · OR 1.91 (95% CI 1.01 to 3.62)	**General information** Follow-up: NR Funding: This work was supported by a Tianjin the Belt and Road Technological Innovation and Cooperation Grant (no. 18PTZWHZ00050) to the Sino-Russian Joint Research Center for Oncoplastic Breast Surgery. CoI: NR **Risk of bias considerations** (adapted from SIGN cohort study checklist)

Yin Z, Wang H, Liu Y, Wang Y, Chang EI, Yin J. Single-Institution Algorithm for Prevention and Management of Complications in Direct-to-Implant Breast Reconstruction. Plast Reconstr Surg. 2022 Oct 1;150: 48S-60S. doi: 10.1097/PRS.0000000000009490. Epub 2022 Sep 28. PMID: 35943963.				
	Reconstruction after polyacrylamide hydrogel removal Implant removal because of locoregional cancer relapse or cosmetic complaints, Use of implant during revision surgery **Enrolment period:** 2014 to 2019 **Follow-up:** NR **Descriptive statistics** (reported for overall population) Age · >40 years: 52% BMI · >24kg/m²: 28% Stadium: · benign: 4% · 0: 16%	Adjusted for year of surgery and laterality, implant size, adjuvant targeted therapy		Study type: retrospective cohort study Confounding: moderate risk: adjustment for year, laterality, implant size, adjuvant targeted therapy Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No Drop-out rate & reasons reported: · High risk: not reported Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is

Yin Z, Wang H, Liu Y, Wang Y, Chang EI, Yin J. Single-Institution Algorithm for Prevention and Management of Complications in Direct-to-Implant Breast Reconstruction. Plast Reconstr Surg. 2022 Oct 1;150: 48S-60S. doi: 10.1097/PRS.0000000000009490. Epub 2022 Sep 28. PMID: 35943963.				
	· I: 36% · IIA: 36% · IIB: 11% · III: 4% Neoadjuvant chemotherapy · 3.5% Adjuvant chemotherapy · 13% Reconstruction type · all DTI · immediate: 92.4% · delayed: 7.6% Mesh/ADM · 20% with Mesh Implant position · pectoralis muscle			unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: yes Confidence intervals reported: yes Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrposective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Dave RV, Vucicevic A, Barrett E, Highton L, Johnson R, Kirwan CC, Harvey JR, Murphy J. Risk factors for complications and implant loss after prepectoral implant-based immediate breast reconstruction: medium-term outcomes in a prospective cohort. Br J Surg. 2021 May 27;108(5): 534-541. doi: 10.1002/bjs.11964. PMID: 34043774.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): PP-IBBR owing to mastectomy for cancer Prophylactic mastectomy for risk reduction Prepectoral correction of previous submuscular reconstruction, such as for implant displacement, animation deformity **Exclusion criteria** (for analysis): Not reported.	**Interventions** RT after implant-based reconstruction · N = 9 No RT after implant · N = 436 **Analysis** Frequencies, for overall complications and implant loss multivariable analysis No matching	**Minor complications** · RT: 2/9 · No RT: 47/436 **Major complications** · RT to TE/I: 4/9 · No RT: 23/436 · OR 7.11, 95% CI 1.6 to 31.61 **Overall complications** · RT to TE/I: 70/9 · No RT: 80/436 **Implant loss**	**General information** Follow-up: Median follow-up was 21 (range 2–71) months Funding: NR CoI: The authors declare no conflict of interest. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study

Dave RV, Vucicevic A, Barrett E, Highton L, Johnson R, Kirwan CC, Harvey JR, Murphy J. Risk factors for complications and implant loss after prepectoral implant-based immediate breast reconstruction: medium-term outcomes in a prospective cohort. Br J Surg. 2021 May 27;108(5): 534-541. doi: 10.1002/bjs.11964. PMID: 34043774.				
	Enrolment period: June 2013 to March 2019 **Follow-up:** Median follow-up 21 (range 2–71) months **Descriptive statistics** (reported for overall population) Age · mean age 44 (range 20–78) years BMI · >=30: 10.2% Stadium · NR Adjuvant chemotherapy · NR Neoadjuvant chemotherapy · 6,2% Reconstruction type · all DTI	No adjustment for frequencies, multivariable analysis adjusted for sentinel node biopsy, axillary clearance, Wise-pattern incision, and adjuvant radiotherapy	· RT to TE/I: 2/9 · No RT: 13/436 · OR 5.09, 95% CI 0.83 to 31.18	Confounding: High risk, no adjustment for baseline characteristics Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No Drop-out rate & reasons reported: · High risk: not reported Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics

Dave RV, Vucicevic A, Barrett E, Highton L, Johnson R, Kirwan CC, Harvey JR, Murphy J. Risk factors for complications and implant loss after prepectoral implant-based immediate breast reconstruction: medium-term outcomes in a prospective cohort. Br J Surg. 2021 May 27;108(5): 534-541. doi: 10.1002/bjs.11964. PMID: 34043774.				
	Mesh/ADM · 100% Implant position · 100% prepectoral Reconstruction type · all DTI · immediate: 92.4% · delayed: 7.6% Mesh/ADM · 20% with Mesh Implant position · pectoralis muscle			Main cofounders taken into account: No Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Lin AM, Lorenzi R, Van Der Hulst JE, Liao EC, Austen WG Jr, Webster A, Smith BL, Colwell AS. A Decade of Nipple-Sparing Mastectomy: Lessons Learned in 3035 Immediate Implant-Based Breast Reconstructions. Plast Reconstr Surg. 2024 Feb 1;153(2): 277-287. doi: 10.1097/PRS.0000000000010616. Epub 2023 May 2. PMID: 37141449.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Therapeutically operated for carcinoma or ductal carcinoma in situ (DCIS) **Exclusion criteria** (for analysis): Prophylactic procedures Two-staged tissue expander/implant, RT before mastectomy **Enrolment period:** 1 January 2013 to 31 December 2018	**Interventions** RT after implant · N = 360 No RT after implant · N = 2675 **Analysis** Multivariable logistic regression analysis No matching Adjusted for age, BMI, diabetes, smoking, preoperative RT,	**Major complications** · OR 1.457, 95% CI 0.986 to 2.153 **Necrosis** · OR 0.969, 95% CI 0.283 to 3.316	**General information** Follow-up: minimum 24 months Funding: NR CoI: Dr. Liao had consulting contracts with Abbvie/Allergan, the Musculoskeletal Transplant Foundation, and Integra, but he is explicitly not a speaker nor does he represent any industry entities. Dr. Austen is a founder of Cytrellis, Durvena, and AuraGen, which was acquired by Sientra, and owns stock in Sientra. Dr. Colwell will receive

Lin AM, Lorenzi R, Van Der Hulst JE, Liao EC, Austen WG Jr, Webster A, Smith BL, Colwell AS. A Decade of Nipple-Sparing Mastectomy: Lessons Learned in 3035 Immediate Implant-Based Breast Reconstructions. Plast Reconstr Surg. 2024 Feb 1;153(2): 277-287. doi: 10.1097/PRS.0000000000010616. Epub 2023 May 2. PMID: 37141449.				
	Follow-up: 16 weeks **Descriptive statistics** (reported for overall population) Age · mean age 47.7 years (range, 18 to 80 years) BMI · mean 24.3 kg/m2 (range, 15.4 to 43.7 kg/m2) Stadium · NR Neoadjuvant chemotherapy · 13% Adjuvant chemotherapy · 25% Reconstruction type · DTI: 2043 · TE: 992 Mesh/ADM	neoadjuvant chemotherapy, reconstruction type, pocket technique, incision type		royalties from Wolters Kluwer as the Plastic Surgery section editor for UpToDate. The remaining authors have no financial disclosures to report. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: Moderate risk: multivariable model, PICO does not correspond, unclear which covariates stayed in the model Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No

Lin AM, Lorenzi R, Van Der Hulst JE, Liao EC, Austen WG Jr, Webster A, Smith BL, Colwell AS. A Decade of Nipple-Sparing Mastectomy: Lessons Learned in 3035 Immediate Implant-Based Breast Reconstructions. Plast Reconstr Surg. 2024 Feb 1;153(2): 277-287. doi: 10.1097/PRS.0000000000010616. Epub 2023 May 2. PMID: 37141449.				
	· 100% ADM (alloderm) Implant position · all sub-pectoral			Drop-out rate & reasons reported: · High risk: not reported Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: partly Confidence intervals reported: yes Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Pires G, Marquez JL, Memmott S, Sudduth JD, Moss W, Eddington D, Hobson G, Tuncer F, Agarwal JP, Kwok AC. Early Complications after Prepectoral Tissue Expander Placement in Breast Reconstruction with and without Acellular Dermal Matrix. Plast Reconstr Surg. 2024 Jun 1;153(6): 1221-1229. doi: 10.1097/PRS.0000000000010801. Epub 2023 Jun 6. PMID: 37285211.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Consecutive patients undergoing mastectomy With concurrent prepectoral tissue expander placement **Exclusion criteria** (for analysis): Patients from May 2021 to July 2021 were excluded from the analyses to account for a 3-month learning curve in which surgeons adjusted their	**Interventions** RT after implant · N = 50 No RT after implant · N = 196 **Analysis** Logistic regression No matching Adjusted for age, body mass index, history of diabetes,	w Infections (any infection) · OR 0.7 (95% CI 0.28 to 1.76) **Implant loss (explantation, 2)** · OR 1.08 (95% CI 0.03 to 33.69) **Reoperation (return to operating room)** · OR 1.34 (95% CI 0..36 to 4.9)	**General information** Follow-up: at least 3 months Funding: University of Utah Population Health Research Foundation, with funding in part from the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through grant UL1TR002538 (formerly 5UL1TR001067-05, 8UL1TR000105, and UL1RR025764

Pires G, Marquez JL, Memmott S, Sudduth JD, Moss W, Eddington D, Hobson G, Tuncer F, Agarwal JP, Kwok AC. Early Complications after Prepectoral Tissue Expander Placement in Breast Reconstruction with and without Acellular Dermal Matrix. Plast Reconstr Surg. 2024 Jun 1;153(6): 1221-1229. doi: 10.1097/PRS.0000000000010801. Epub 2023 Jun 6. PMID: 37285211.				
	practices to include increasing the initial tissue expander fill volume, and increasing drain time to at least 14 days **Enrolment period:** August 2020 to January 2022 **Follow-up:** at least 3 months **Descriptive statistics** (reported for overall population) Age · median 47 years BMI · mean 26.3 Stadium · NR Neoadjuvant chemotherapy · 35% Adjuvant chemotherapy · 35%	tobacco use, neoadjuvant chemotherapy, and postoperative radiotherapy		CoI: The authors have no financial interest to disclose in relation to the content of this study. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: moderate risk: probably adjusted for the listed covariates Selection bias into the study: Unclear, no information provided. Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? No

Pires G, Marquez JL, Memmott S, Sudduth JD, Moss W, Eddington D, Hobson G, Tuncer F, Agarwal JP, Kwok AC. Early Complications after Prepectoral Tissue Expander Placement in Breast Reconstruction with and without Acellular Dermal Matrix. Plast Reconstr Surg. 2024 Jun 1;153(6): 1221-1229. doi: 10.1097/PRS.0000000000010801. Epub 2023 Jun 6. PMID: 37285211.				
	Reconstruction type · all tissue expander and implant replacing Mesh/ADM · 50% with mesh Implant position · all pre-pectoral			Drop-out rate & reasons reported: · High risk: not reported Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: partly Confidence intervals reported: yes Selective reporting (comparison with protocol): no protocol provided, not assessable. **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.55:

Die Patientin soll darüber aufgeklärt werden, dass die Bestrahlung bei Implantat-basierter Brustrekonstruktion mit einer erhöhten kurz- und langfristigen Komplikationsrate (postoperative Komplikationen, Kapselfibrose, Implantatversagen) verbunden ist.

Literaturreferenzen: [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373]

Emanuele Lisa AV, Salgarello M, Huscher A, Corsi F, Piovani D, Rubbino F, Andreoletti S, Papa G, Klinger F, Tinterri C, Testori A, Scorsetti M, Veronesi P, Leonardi MC, Rietjens M, Cortinovis U, Summo V, Rampino Cordaro E, Parodi PC, Persichetti P, Barone M, De Santis G, Murolo M, Riccio M, Aquinati A, Cavaliere F, Vaia N, Pagura G, Dalla Venezia E, Bassetto F, Vindigni V, Ciuffreda L, Bocchiotti MA, Sciarillo A, Renzi N, Meneghini G, Kraljic T, Loreti A, Fortunato L, Pino V, Vinci V, Klinger M. The Effect of Adjuvant Radiotherapy on One- and Two-Stage Prosthetic Breast Reconstruction and on Autologous Reconstruction: A Multicenter Italian Study among 18 Senonetwork Breast Centres. Breast J. 2023 May 9;2023: 6688466. doi: 10.1155/2023/6688466. PMID: 37205012; PMCID: PMC10188256.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective case-control study	**Inclusion criteria** (for analysis): Female patients Age over 18 years at the time of diagnosis Patients who had undergone mastectomy and immediate reconstruction with implant in one or two stages or with autologous flaps with or without adjuvant radiotherapy	**Interventions** RT after implant · N = 1088 No RT after implant · N = 1841 **Analysis** Frequencies No matching	Reconstruction failure · RT: 48/1088 · No RT: 20/1841 Implant loss · RT: 194/1088 · No RT: 115/1841 Reoperation · RT: 270/1088 · No RT: 81/1841	**General information** Follow-up: · DTI: PMRT: 2.8 years (IQR 2.0-4.0), no PMRT: 2.4 years (IQR 1.9-3.3) · TE: PMRT: 2.3 years (IQR 1.5-3.4), no PMRT: 2.4 years (1.6-3.2) Funding: Humanitas Clinical and Research Center

Emanuele Lisa AV, Salgarello M, Huscher A, Corsi F, Piovani D, Rubbino F, Andreoletti S, Papa G, Klinger F, Tinterri C, Testori A, Scorsetti M, Veronesi P, Leonardi MC, Rietjens M, Cortinovis U, Summo V, Rampino Cordaro E, Parodi PC, Persichetti P, Barone M, De Santis G, Murolo M, Riccio M, Aquinati A, Cavaliere F, Vaia N, Pagura G, Dalla Venezia E, Bassetto F, Vindigni V, Ciuffreda L, Bocchiotti MA, Sciarillo A, Renzi N, Meneghini G, Kraljic T, Loreti A, Fortunato L, Pino V, Vinci V, Klinger M. The Effect of Adjuvant Radiotherapy on One- and Two-Stage Prosthetic Breast Reconstruction and on Autologous Reconstruction: A Multicenter Italian Study among 18 Senonetwork Breast Centres. Breast J. 2023 May 9;2023: 6688466. doi: 10.1155/2023/6688466. PMID: 37205012; PMCID: PMC10188256.

	Exclusion criteria (for analysis): Patients with prior breast or chest wall irradiation Delayed reconstruction Patients lost to follow-up **Enrolment period:** 2001 to 2020 **Follow-up:** Between 2 and 3 years, see methodological evaluation **Descriptive statistics** Age · DTI: PMRT: median 49 (IQR 43-56), no PMRT: median 47 (IQR 41-53) · TE: PMRT: median 49 (IQR 43-57), no PMRT: median 50 (IQR 44-58) BMI (%)	No adjustment	**Overall complications** · RT: 662/1088 · No RT: 472/1841 **Minor complications** · RT: 209/1088 · No RT: 270/1841 **Major complications** · RT: 551/1088 · No RT: 229/1841 **Hematoma** · RT: 37/1088 · No RT: 60/1841 **Seroma** · RT: 133/1066 · No RT: 139/1841 **Necrosis** · RT: 61/1088	CoI: The authors declare that they have no conLicts of interest. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Confounding: high risk: no adjustment for relevant clinical characteristics such as receipt of chemotherapy or axillary dissection. Selection bias into the study: Unclear, patients lost to follow-up were excluded, unclear how many these were; case-control study Intervention · Assessment reliable: yes · Assessed more than once: no

Emanuele Lisa AV, Salgarello M, Huscher A, Corsi F, Piovani D, Rubbino F, Andreoletti S, Papa G, Klinger F, Tinterri C, Testori A, Scorsetti M, Veronesi P, Leonardi MC, Rietjens M, Cortinovis U, Summo V, Rampino Cordaro E, Parodi PC, Persichetti P, Barone M, De Santis G, Murolo M, Riccio M, Aquinati A, Cavaliere F, Vaia N, Pagura G, Dalla Venezia E, Bassetto F, Vindigni V, Ciuffreda L, Bocchiotti MA, Sciarillo A, Renzi N, Meneghini G, Kraljic T, Loreti A, Fortunato L, Pino V, Vinci V, Klinger M. The Effect of Adjuvant Radiotherapy on One- and Two-Stage Prosthetic Breast Reconstruction and on Autologous Reconstruction: A Multicenter Italian Study among 18 Senonetwork Breast Centres. Breast J. 2023 May 9;2023: 6688466. doi: 10.1155/2023/6688466. PMID: 37205012; PMCID: PMC10188256.				
	· DTI: PMRT: median 22.4 (IQR 20.6-24.2), no PMRT: median 22.0 (IQR 20.1-23.7) · TE: PMRT: 23.7 (IQR 21.0-26.6), no PMRT: 23.2 (IQR 21.1-25.8) Stadium: · NR Neoadjuvant chemotherapy: · DTI: PMRT: 32.1%, no PMRT: 20.2% · TE: PMRT: 25.1%, no PMRT: 10.3% Adjuvant chemotherapy: · DTI: PMRT: 57.4%, no PMRT: 26.4% · TE: PMRT: 53.3%, no PMRT: 35.3% Reconstruction type (%)		· No RT: 104 /1841 **Infections** · RT: 66/1088 · No RT: 176 /1841	· Possibly affected by knowledge of outcome status? Although this is a case-control study, it is unlikely that RT-status was manipulated after data acquisition. Drop-out rate & reasons reported: · High risk: not reported Outcome · Outcome measure is well-defined, valid and reliable; · No blind outcome assessment, however, this is unlikely to affect the results; as the outcomes are standard clinical characteristics Main cofounders taken into account: no Confidence intervals reported: no

Emanuele Lisa AV, Salgarello M, Huscher A, Corsi F, Piovani D, Rubbino F, Andreoletti S, Papa G, Klinger F, Tinterri C, Testori A, Scorsetti M, Veronesi P, Leonardi MC, Rietjens M, Cortinovis U, Summo V, Rampino Cordaro E, Parodi PC, Persichetti P, Barone M, De Santis G, Murolo M, Riccio M, Aquinati A, Cavaliere F, Vaia N, Pagura G, Dalla Venezia E, Bassetto F, Vindigni V, Ciuffreda L, Bocchiotti MA, Sciarillo A, Renzi N, Meneghini G, Kraljic T, Loreti A, Fortunato L, Pino V, Vinci V, Klinger M. The Effect of Adjuvant Radiotherapy on One- and Two-Stage Prosthetic Breast Reconstruction and on Autologous Reconstruction: A Multicenter Italian Study among 18 Senonetwork Breast Centres. Breast J. 2023 May 9;2023: 6688466. doi: 10.1155/2023/6688466. PMID: 37205012; PMCID: PMC10188256.				
	· DTI: 1227 pts, PMRT: 31.9%, no PMRT: 67.9% · TE: 1702 pts, PMRT: 40.9%, no PMRT: 59.1% Mesh/ADM · no mesh used Implant position · retropectoral			Selective reporting (comparison with protocol): protocol/trial registry entry available, no selective reporting **Other limitations:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [374], [375], [376], [377], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [390], [391], [392], [393], [394]

Bargon CA, Young-Afat DA, Ikinci M, Braakenburg A, Rakhorst HA, Mureau MAM, Verkooijen HM, Doeksen A. Breast cancer recurrence after immediate and delayed postmastectomy breast reconstruction-A systematic review and meta-analysis. Cancer. 2022 Oct 1;128(19): 3449-3469. doi: 10.1002/cncr.34393. Epub 2022 Jul 27. PMID: 35894936; PMCID: PMC9546326.

Source and Purpose	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: Therefore, with this SR/MA, we aim to investigate whether delayed PMBR leads to different (loco) regional recurrence, distant metastasis, and overall recurrence rates than immediate PMBR in patients with primary breast cancer. Because of differences in nature and indications of implant-based and autologous breast reconstructive techniques,5 this	**Design**: Systematic review with Metaanalysis **Search date**: Searched from inception until 19.11.2020 **Searched databases**: MEDLINE, Embase, Cochrane Library **Included study designs**: Retrospective and prospective studies **Number of included studies**: n=55	**Intervention** Immediate autologous PMBR delayed autologous PMBR Immediate implant-based PMBR Immediate implant-based PMBR	1) Local recurrence 2) Regional recurrence 3) Locoregional recurrence 4) Distant metastasis	**Local recurrence** 31 studies Immediate: 163/6249; Weighted average proportion: 0.03 (95% CI, 0.02–0.03) Delayed: 22/1037; Weighted average proportion: 0.02 (95% CI, 0.01–0.04) **Regional recurrence** 14 studies	**Risk of bias assessment of studies:** assessed using The Methological Index For Non-Randomized Studies (Minors) tool) „The quality of included studies ranged from 6 to 12 points for noncomparative studies, and from 10 to 20 points for comparative studies “ **Overall confidence in results of SR (AMSTAR-2):**

Bargon CA, Young-Afat DA, Ikinci M, Braakenburg A, Rakhorst HA, Mureau MAM, Verkooijen HM, Doeksen A. Breast cancer recurrence after immediate and delayed postmastectomy breast reconstruction-A systematic review and meta-analysis. Cancer. 2022 Oct 1;128(19): 3449-3469. doi: 10.1002/cncr.34393. Epub 2022 Jul 27. PMID: 35894936; PMCID: PMC9546326.					
question was evaluated separately for autologous and implant-based breast reconstruction.	**Number of included patients**: 14,452 pts **Mean/median age**: 33 - 35 **Inclusion criteria**: Original articles including patients >18 years old and reporting oncological outcomes (i.e., “local,” “regional,” “locoregional” or “total breast cancer recurrences,” and “distant metastasis”) after PMBR in patients with breast cancer prospective and retrospective observational studies Comparative studies with only one study arm meeting in- and exclusion criteria **Exclusion criteria:**			Immediate: 83/3454; Weighted average proportion: 0.02 (95% CI, 0.01–0.03) Delayed: 14/674; Weighted average proportion: 0.02 (95% CI, 0.01–0.03) **Locoregional recurrence** 16 studies Immediate: Average weighted proportion: 0.04 (95% CI, 0.03–0.06 Delayed: Average weighted proportion: 0.01 (95% CI, <0.01–0.03) **Distant metastasis** Immediate: 368/5476 Delayed: 125/1380	PICO elements: yes A priori design: yes Justification for design: no Literature search >= 2 databases, search strategy + other sources: yes Selection in duplicate: yes Data extraction in duplicate: yes List of excluded studies: no sufficient detail on studies: yes RoB assessed: no Funding of incl. studies: no MA appropriate: no RoB considered in MA: no RoB in interpretation: no

Bargon CA, Young-Afat DA, Ikinci M, Braakenburg A, Rakhorst HA, Mureau MAM, Verkooijen HM, Doeksen A. Breast cancer recurrence after immediate and delayed postmastectomy breast reconstruction-A systematic review and meta-analysis. Cancer. 2022 Oct 1;128(19): 3449-3469. doi: 10.1002/cncr.34393. Epub 2022 Jul 27. PMID: 35894936; PMCID: PMC9546326.					
	other publication types non-English or non-Dutch language articles studies published before 2000 studies including cohorts with <50 patients studies with mean follow-up <24 months or unknown follow-up studies including patients with PMBR after initial breast-conserving surgery or prophylactic mastectomy, studies including patients with distant metastasis at time of diagnosis or PMBR, and breast cancer recurrence before PMBR Nonavailable full-text articles				Heterogeneity explained: yes **Sources of funding:** Not reported.

Verknüpfte Empfehlungen:

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [374], [375], [376], [377], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [390], [391], [392], [393], [394]

Matar DY, Wu M, Haug V, Orgill DP, Panayi AC. Surgical complications in immediate and delayed breast reconstruction: A systematic review and meta-analysis. J Plast Reconstr Aesthet Surg. 2022 Nov;75(11): 4085-4095. doi: 10.1016/j.bjps.2022.08.029. Epub 2022 Aug 22. PMID: 36202732.

Source and Purpose	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: This review seeks to analyze and summarize the litera-ture to provide a better understanding of the surgical risks and complication rates associated with breast reconstruction in immediate versus delayed reconstructions following mastectomy.	**Design**: Systematic review with Metaanalysis **Search date**: Searched from inception until 01.05.2021 **Searched databases**: Pubbmed, Embase, Cochrane **Included study designs**: Prospective studies, case series **Number of included studies**: n=30	**Intervention** Immediate breast reconstruction delayed breast reconstruction	1) Surgical complications 2) Infection 3) Fat necrosis 4) Skin necrosis 5)Hematoma or seroma 6) Wound dehiscence 7) Reoperation rate	**Surgical complications** 29 studies Immediate: 7275 pts Delayed: 6477 pts OR 1.30, 95% CI 1.03, 1.65 p = 0.03 **Infection** 14 studies Immediate: 5558 Delayed: 4984 OR: 1.21 [0.82, 1.79]	**Risk of bias assessment of study:** assessment not available; reported level of evidence (LoE) of 4 as defined by the Oxford Centre for Evidence-Based Medicine **Overall confidence in results of SR (AMSTAR-2):** PICO elements: partial yes A priori design: partial yes

Matar DY, Wu M, Haug V, Orgill DP, Panayi AC. Surgical complications in immediate and delayed breast reconstruction: A systematic review and meta-analysis. J Plast Reconstr Aesthet Surg. 2022 Nov;75(11): 4085-4095. doi: 10.1016/j.bjps.2022.08.029. Epub 2022 Aug 22. PMID: 36202732.					
	Number of included patients: 14,034 pts **Mean/median age**: Not reported. **Inclusion criteria**: cohort studies, case series, randomized controlled trials, and case-control studies re- porting original data on breast reconstruction outcomes in immediate versus delayed reconstruction who underwent mastectomy for the treatment or prophylaxis of any type of breast cancer The following surgical interventions were considered: prosthetic implants, including tissue ex- pander, and autologous reconstruction, including abdominal advance flaps,			p = 0.34 **Fat necrosis** 13 studies Immediate: 3211 Delayed: 1982 OR: 1.31 [0.79, 2.17] p = 0.29 **Skin necrosis** 13 studies Immediate: 2549 Delayed: 1758 OR: 1.61 [0.81, 3.22] p = 0.18 **Hematoma or seroma** 12 studies Immediate: 2647 Delayed: 1734 OR: 2.01 [1.27, 3.17] p = 0.003	Justification for design: no Literature search >= 2 databases, search strategy + other sources: partial yes Selection in duplicate: yes Data extraction in duplicate: no List of excluded studies: no sufficient detail on studies: partial yes RoB assessed: no Funding of incl. studies: no MA appropriate: no RoB considered in MA: no RoB in interpretation: no Heterogeneity explained: no

Matar DY, Wu M, Haug V, Orgill DP, Panayi AC. Surgical complications in immediate and delayed breast reconstruction: A systematic review and meta-analysis. J Plast Reconstr Aesthet Surg. 2022 Nov;75(11): 4085-4095. doi: 10.1016/j.bjps.2022.08.029. Epub 2022 Aug 22. PMID: 36202732.					
	LDM flaps, pedicled, free and muscle- sparing TRAM flaps, SIEA flaps, GAP flaps, and DIEP flaps Only English language studies **Exclusion criteria:** Not reoprted.				Publication bias investigated: no Sources of CoI: yes **Sources of funding** This work was funded by The Gillian Reny Stepping Strong Center for Trauma Innovation./The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Verknüpfte Empfehlungen:

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [374], [375], [376], [377], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [390], [391], [392], [393], [394]

Marquez, J. L., Sudduth, J. D., Kuo, K., Patel, A. A., Eddington, D., Agarwal, J. P., & Kwok, A. C. (2023). A Comparison of Postoperative Outcomes Between Immediate, Delayed Immediate, and Delayed Autologous Free Flap Breast Reconstruction: Analysis of 2010-2020 NSQIP Data. Journal of reconstructive microsurgery, 39(8), 664–670. https: //doi.org/10.1055/a-2056-0909

Study type	Population	Interventions	Main results	Methodological evaluation
prospective cohort study	**Inclusion criteria** (for analysis): NR **Exclusion criteria** (for analysis): NR **Enrolment period:** 2010 – 2020 **Follow-up:** 30 days **Descriptive statistics** Age (median, IQR) · Immediate: 51.0 (44.2, 58.0) · Delayed-immediate: 49.0 (43.0, 56.0)	**Interventions** Immediate autologous reconstruction · N = 7,907 Delayed-immediate autologous reconstruction · N = 976 Delayed autologous breast reconstruction · N = 6713 **Analysis**	**Surgical site infection** · Immediate: 494/7907 · Delayed-immediate: 54/976 · Delayed: 408/6713 **Wound dehiscence** · Immediate: 147/7907 · Delayed-immediate: 17/976 · Delayed: 120/6713 **Return to operating room** · Immediate: 1045/7907 · Delayed-immediate: 88/976	**General information** Follow-up: 30 days Funding: None. CoI: None declared. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: prospective cohort study Confounding: adjusted for but still possible (moderate risk)

Marquez, J. L., Sudduth, J. D., Kuo, K., Patel, A. A., Eddington, D., Agarwal, J. P., & Kwok, A. C. (2023). A Comparison of Postoperative Outcomes Between Immediate, Delayed Immediate, and Delayed Autologous Free Flap Breast Reconstruction: Analysis of 2010-2020 NSQIP Data. Journal of reconstructive microsurgery, 39(8), 664–670. https: //doi.org/10.1055/a-2056-0909				
	· Delayed: 51.0 (44.0, 58.0) BMI (median, IQR) · Immediate: 29.0 (25.5, 32.9) · Delayed-immediate: 29.4 (26.3, 33.1) · Delayed: 29.2 (25.8, 33.0) Stadium · Immediate: NR · Delayed-immediate: NR · Delayed: NR Chemotherapy (% yes) · Immediate: NR · Delayed-immediate: NR · Delayed: NR Reconstruction type (flap type) (%) · Free flap breast reconstruction only	univariate analysis; single-step multinomial logistic regression No matching Adjusted for age, race, body mass index (BMI), diabetes, hypertension, ASA classification, and laterality of reconstruction)	· Delayed: 734/6713	Rate of participation/Exclusions reported (selection bias into the study): no Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: not reported Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (àIf not, Knowledge of exposure status likely to influence the outcome?:) no Main cofounders taken into account: yes Confidence intervals reported: no

Marquez, J. L., Sudduth, J. D., Kuo, K., Patel, A. A., Eddington, D., Agarwal, J. P., & Kwok, A. C. (2023). A Comparison of Postoperative Outcomes Between Immediate, Delayed Immediate, and Delayed Autologous Free Flap Breast Reconstruction: Analysis of 2010-2020 NSQIP Data. Journal of reconstructive microsurgery, 39(8), 664–670. https: //doi.org/10.1055/a-2056-0909				
				Selective reporting (comparison with protocol): no protocol found **Other limitations or comments:** Not applicable.

Verknüpfte Empfehlungen:

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [374], [375], [376], [377], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [390], [391], [392], [393], [394]

Ochoa, O., Garza, R., 3rd, Pisano, S., Chrysopoulo, M., Ledoux, P., Arishita, G., Ketchum, N., Michalek, J. E., & Nastala, C. (2022). Prospective Longitudinal Patient-Reported Satisfaction and Health-Related Quality of Life following DIEP Flap Breast Reconstruction: Effects of Reconstruction Timing. Plastic and reconstructive surgery, 149(5), 848e-857e. https: //doi.org/10.1097/PRS.0000000000009044

Study type	Population	Interventions	Main results	Methodological evaluation
Prospective study	**Inclusion criteria** (for analysis): NR **Exclusion criteria** (for analysis): Patients that did not complete all three required questionnaires were excluded from patient-reported outcomes analysis (non-responders) **Enrolment period:** July 2012 – August 2016 **Follow-up:** Unclear (1 month following completion of	**Interventions** Immediate autologous reconstruction · N = 57 Delayed autologous reconstruction · N = 16 **Analysis** Frequencies; linear mixed models for BREAST-Q No matching No adjustment	**Hematoma** · Immediate: 4/103 · Delayed: 0/27 **Mild infection** · Immediate: 11/103 · Delayed: 1/27 **Mild delayed wound healing** · Immediate: 11/103 · Delayed: 5/27 **Moderate delayed wound healing**	**General information** Follow-up: unclear Funding: The authors have no financial interest to declare in relation to the content of this article. CoI: NR **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: prospective study Confounding: high

Ochoa, O., Garza, R., 3rd, Pisano, S., Chrysopoulo, M., Ledoux, P., Arishita, G., Ketchum, N., Michalek, J. E., & Nastala, C. (2022). Prospective Longitudinal Patient-Reported Satisfaction and Health-Related Quality of Life following DIEP Flap Breast Reconstruction: Effects of Reconstruction Timing. Plastic and reconstructive surgery, 149(5), 848e-857e. https: //doi.org/10.1097/PRS.0000000000009044				
	planned breast revision, nipple reconstruction, and contralateral symmetry procedure, if applicable) **Descriptive statistics** Age (median, range) · Immediate: 52 (22-73) · Delayed: 47.5 (41-51) BMI (median, range) · Immediate: 28 (20-40) · Delayed: 28 (20-38) Stadium · NR Chemotherapy (% yes) · Immediate: 26.3% (15/57) · Delayed: 81.3% (13/16) Reconstruction type (flap type) (%) · Immediate: DIEP flap (only)		· Immediate: 2/103 · Delayed: 0/27 **Severe delayed wound healing** · Immediate: 1/103 · Delayed: 1/27 **Total delayed wound healing** · Immediate: 14/103 · Delayed: 6/27 **Fat necrosis** · Immediate: 8/103 · Delayed: 3/27 **Flap loss** · Immediate: 0/103 · Delayed: 1/27	Rate of participation/Exclusions reported (selection bias into the study): yes Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? possible Drop-out rate & reasons reported: yes · Similar across groups: unclear · If high: comparison of those lost with available: unclear Outcome · Outcome measure is well-defined, valid and reliable: unclear · Blind outcome assessment to exposure: (àIf not, Knowledge

Ochoa, O., Garza, R., 3rd, Pisano, S., Chrysopoulo, M., Ledoux, P., Arishita, G., Ketchum, N., Michalek, J. E., & Nastala, C. (2022). Prospective Longitudinal Patient-Reported Satisfaction and Health-Related Quality of Life following DIEP Flap Breast Reconstruction: Effects of Reconstruction Timing. Plastic and reconstructive surgery, 149(5), 848e-857e. https: //doi.org/10.1097/PRS.0000000000009044				
	· Delayed: DIEP flap (only)			of exposure status likely to influence the outcome?:) no Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): protocol not available **Other limitations or comments:** Not applicable.

Verknüpfte Empfehlungen:

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [374], [375], [376], [377], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [390], [391], [392], [393], [394]

Wu Young MY, Garza RM, Chang DW. "Immediate versus delayed autologous breast reconstruction in patients undergoing post-mastectomy radiation therapy: A paradigm shift". J Surg Oncol. 2022 Nov;126(6): 949-955. doi: 10.1002/jso.27005. Epub 2022 Jul 7. PMID: 35796741; PMCID: PMC9796673.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective study	**Inclusion criteria** (for analysis): Not reported. **Exclusion criteria** (for analysis): Not reported. **Enrolment period:** January 2015 – December 2019 **Follow-up:** NR **Descriptive statistics** Age (median) · Immediate: 51.6 years · Delayed: 51.5 years BMI (median)	**Interventions** Immediate autologous reconstruction · N = 36 Delayed autologous reconstruction · N = 89 **Analysis** frequencies No matching No adjustment	**Surgical site infection** · Immediate: 5/36 · Delayed: 11/89 **Partial flap necrosis** · Immediate: 0/36 · Delayed: 4/89 **Mastectomy flap necrosis** · Immediate: 5/36 · Delayed: 3/89 **Wound dehiscence** · Immediate: 11/36	**General information** Follow-up: NR Funding: NR CoI: The authors declare no conflict of interest. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective chart review Confounding: high

Wu Young MY, Garza RM, Chang DW. "Immediate versus delayed autologous breast reconstruction in patients undergoing post-mastectomy radiation therapy: A paradigm shift". J Surg Oncol. 2022 Nov;126(6): 949-955. doi: 10.1002/jso.27005. Epub 2022 Jul 7. PMID: 35796741; PMCID: PMC9796673.				
	· Immediate: 29.6 · Delayed: 29.8 Stadium · Immediate: 0: 0% (0/36); IA: 5.56% (2/36); IB: 0% (0/36); IIA: 22.2% (8/36; IIB: 44.4% (16/36); IIIA: 16.7% (6/36); IIIB: 5.6% (2/36); IIIC: 5.6% (2/36) · Delayed: 0: 2.2% (2/89); IA: 1.1% (1/89); IB: 0% (0/89); IIA: 13.5% (12/89); IIB: 18.0% (16/89); IIIA: 229.2% (26/89); IIIB: 5.6% (5/89); IIIC: 5.6% (5/89) Chemotherapy (% yes) · Immediate: 50.0% (18/36) · Delayed: 35.9% (28/89) Reconstruction type (flap type) (%) · Immediate: NR · Delayed: NR		· Delayed: 24/89 **Fat necrosis** · Immediate: 13/36 · Delayed: 28/89 **Patients requiring revision** · Immediate: 17/36 Delayed: 62/89	Rate of participation/Exclusions reported (selection bias into the study): not reported Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: not reported Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (àIf not, Knowledge of exposure status likely to influence the outcome?:) no (retrospective) Main cofounders taken into account: no Confidence intervals reported: no

Wu Young MY, Garza RM, Chang DW. "Immediate versus delayed autologous breast reconstruction in patients undergoing post-mastectomy radiation therapy: A paradigm shift". J Surg Oncol. 2022 Nov;126(6): 949-955. doi: 10.1002/jso.27005. Epub 2022 Jul 7. PMID: 35796741; PMCID: PMC9796673.				
				Selective reporting (comparison with protocol): no protocol found **Other limitations or comments:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [374], [375], [376], [377], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [390], [391], [392], [393], [394]

Shammas RL, Gordee A, Lee HJ, Sergesketter AR, Scales CD, Hollenbeck ST, Phillips BT. Complications, Costs, and Healthcare Resource Utilization After Staged, Delayed, and Immediate Free-Flap Breast Reconstruction: A Longitudinal, Claims-Based Analysis. Ann Surg Oncol. 2023 Apr;30(4): 2534-2549. doi: 10.1245/s10434-022-12896-0. Epub 2022 Dec 6. PMID: 36474094; PMCID: PMC9735033.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective study	**Inclusion criteria** (for analysis): Women ≥18 years Diagnosed with breast cancer Underwent a mastectomy with eventual free-flap breast reconstruction Continuous enrollment 12 months pre-mastectomy to 90 days post free-flap breast reconstruction **Exclusion criteria** (for analysis):	**Interventions** Immediate autologous reconstruction · N = 2310 Delayed autologous reconstruction · N = 388 C: Delayed-immediate autologous reconstruction · N = 612 **Analysis**	**Wound dehiscence** · Immediate: 266/2310 · Delayed: 52/388 · Delayed-immediate: 113/612 **Wound infection** · Immediate: 93/2310 · Delayed: 13/388 · Delayed-immediate: 64/612 **Hematoma** · Immediate: 132/2310 · Delayed: 36/388	**General information** Follow-up: 90 days Funding: CTSA Grant (UL1TR002553) from the National Center for Advancing Translational Sciences (NCATS) of the NIH and the NIH Roadmap for Medical Research CoI: No conflicts of interest pertaining to this manuscript are present or need to be disclosed

Shammas RL, Gordee A, Lee HJ, Sergesketter AR, Scales CD, Hollenbeck ST, Phillips BT. Complications, Costs, and Healthcare Resource Utilization After Staged, Delayed, and Immediate Free-Flap Breast Reconstruction: A Longitudinal, Claims-Based Analysis. Ann Surg Oncol. 2023 Apr;30(4): 2534-2549. doi: 10.1245/s10434-022-12896-0. Epub 2022 Dec 6. PMID: 36474094; PMCID: PMC9735033.				
	Displayed codes for a free-flap prior to their mastectomy No breast cancer diagnosis on the date of or in the year prior to mastectomy Distant metastasis breast implant procedure within 1 year of mastectomy to 90 days after the free-flap Tissue expander placed prior to mastectomy and not on the index surgery Free-flap performed within 2 weeks of the index mastectomy but not within the index admission Tissue expander placed after the index admission but before freeflap reconstruction Pedicled flap performed prior to their free-flap procedure **Enrolment period**	Means and standard deviation, frequencies, modified Poisson regression No matching Adjusted for age, NCI comorbidity index, urban/rural ZIP code, geographic region, employment status, laterality of mastectomy, lymph node surgery at the time of mastectomy, chemotherapy before or after mastectomy, radiation before or after mastectomy, and presence of other cancer diagnoses	· Delayed-immediate: 33/612 **Fat necrosis** · Immediate: 126/2310 · Delayed: 31/388 · Delayed-immediate: 53/612 **Hematoma requiring reoperation** · Immediate: 128/2310 · Delayed: 41/388 · Delayed-immediate: 45/612 **Wound infection requiring reoperation** · Immediate: 148/2310 · Delayed: 24/388 · Delayed-immediate: 57/612 **Wound complication requiring reoperation** · Immediate: 46/2310 · Delayed: 10/388	**Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective study Confounding: high Rate of participation/Exclusions reported (selection bias into the study): not reported Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: no Outcome · Outcome measure is well-defined, valid and reliable: unclear · Blind outcome assessment to exposure: (àlf not, Knowledge

Shammas RL, Gordee A, Lee HJ, Sergesketter AR, Scales CD, Hollenbeck ST, Phillips BT. Complications, Costs, and Healthcare Resource Utilization After Staged, Delayed, and Immediate Free-Flap Breast Reconstruction: A Longitudinal, Claims-Based Analysis. Ann Surg Oncol. 2023 Apr;30(4): 2534-2549. doi: 10.1245/s10434-022-12896-0. Epub 2022 Dec 6. PMID: 36474094; PMCID: PMC9735033.				
	January 2015 – December 2019 **Follow-up** NR **Descriptive statistics** Age (mean, sd) · Immediate: 51.3 (8.3); median: 52.0 ; Q1, Q3: 45.0, 58.0; range: 21.0 - 75.0 · Delayed: 49.6 (8.8); median: 50.0 ; Q1, Q3: 43.0, 57.0; range: 19.0 - 68.0 · Delayed-immediate: 49.4 (8.1); median: 49.0 ; Q1, Q3: 44.0, 56.0; range: 22.0 - 68.0 BMI (median, range) · NR Stadium · NR Chemotherapy (% yes) · Immediate: 184 (8.0%)		· Delayed-immediate: 32/612 **Any reoperations** · Immediate: 276/2310 · Delayed: 67/388 Delayed-immediate: 188/612	of exposure status likely to influence the outcome?:) no (retrospective) Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol found **Other limitations or comments:** retrospective design

Shammas RL, Gordee A, Lee HJ, Sergesketter AR, Scales CD, Hollenbeck ST, Phillips BT. Complications, Costs, and Healthcare Resource Utilization After Staged, Delayed, and Immediate Free-Flap Breast Reconstruction: A Longitudinal, Claims-Based Analysis. Ann Surg Oncol. 2023 Apr;30(4): 2534-2549. doi: 10.1245/s10434-022-12896-0. Epub 2022 Dec 6. PMID: 36474094; PMCID: PMC9735033.				
	· Delayed: 58 (14.9%) · Delayed-immediate: 84 (13.7%) Reconstruction type (flap type) (%) · Immediate: 37 (1.6%) · Delayed: 2 (0.5%) · Delayed-immediate: 2 (0.3%)			

Verknüpfte Empfehlungen:

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [374], [375], [376], [377], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [390], [391], [392], [393], [394]

Barnes LL, Patterson A, Lem M, Holland MC, Lentz R, Sbitany H, Piper ML. Immediate Versus Delayed-Immediate Autologous Breast Reconstruction After Nipple-Sparing Mastectomy. Ann Plast Surg. 2023 May 1;90(5): 432-436. doi: 10.1097/SAP.0000000000003539. PMID: 37146309.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective study	**Inclusion criteria** (for analysis): Not reported. **Exclusion criteria** (for analysis): No reconstruction at the time of NSM Completed implant-based breast reconstruction at the time of autologous reconstruction Patients who were noted to be planning for 2-stage implant-based breast reconstruction at the time of their NSM with tissue expander placement	**Interventions** Immediate autologous breast reconstruction · N = 59 (89 breasts) Delayed-immediate autologous breast reconstruction · N = 42 (62 breasts) **Analysis** Frequencies No matching No adjustment	**Hematoma** · Immediate: 4/89 · Delayed: 2/62 **Any infection** · Immediate: 4/89 · Delayed: 13/62 **Infection requiring PO antibiotics** · Immediate: 4/89 · Delayed: 13/62 **Infection requiring IV antibiotics**	**General information** Follow-up: NR Funding: Conflicts of interest and sources of funding: none declared. CoI: Conflicts of interest and sources of funding: none declared. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective chart review Confounding: high

Barnes LL, Patterson A, Lem M, Holland MC, Lentz R, Sbitany H, Piper ML. Immediate Versus Delayed-Immediate Autologous Breast Reconstruction After Nipple-Sparing Mastectomy. Ann Plast Surg. 2023 May 1;90(5): 432-436. doi: 10.1097/SAP.0000000000003539. PMID: 37146309.				
	Enrolment period: January 2004 – September 2021 **Follow-up:** NR **Descriptive statistics** Age (mean, sd) · Immediate: 47.71 (8.48) · Delayed: 47.23 (9.69) BMI (mean, sd) · Immediate: 27.24 (4.24) · Delayed: 28.26 (5.24) Stadium · NR Chemotherapy (% yes) · NR Reconstruction type (flap type) (%): Abdomen-based free flap breast reconstruction		· Immediate: 0/89 · Delayed: 7/62 **Fat necrosis** · Immediate: 8/89 · Delayed: 1/62 **Delayed wound healing** · Immediate: 16/89 · Delayed: 7/62 **Wound requiring reoperation** · Immediate: 8/89 · Delayed: 4/62 **Mastectomy skin flap necrosis** · Immediate: 18/89 · Delayed: 0/62 **Total flap loss** · Immediate: 1/89 · Delayed: 1/62 **Partial flap loss**	Rate of participation/Exclusions reported (selection bias into the study): no (retrospective) Exposure/Intervention · Assessment reliable: unclear · Assessed more than once: no · Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: not reported Outcome · Outcome measure is well-defined, valid and reliable: unclear · Blind outcome assessment to exposure: Unclear, probably no (àIf not, Knowledge of exposure status likely to influence the outcome?:) no Main cofounders taken into account: no

Barnes LL, Patterson A, Lem M, Holland MC, Lentz R, Sbitany H, Piper ML. Immediate Versus Delayed-Immediate Autologous Breast Reconstruction After Nipple-Sparing Mastectomy. Ann Plast Surg. 2023 May 1;90(5): 432-436. doi: 10.1097/SAP.0000000000003539. PMID: 37146309.				
			· Immediate: 1/89 · Delayed: 0/62 **Reoperation** · Immediate: 18/89 · Delayed: 10/62	Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol found **Other limitations or comments:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [374], [375], [376], [377], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [390], [391], [392], [393], [394]

Christopher AN, Morris MP, Broach RB, Serletti JM. A Comparative Analysis of Immediate and Delayed-immediate Breast Reconstruction after Postmastectomy Radiation Therapy. J Reconstr Microsurg. 2022 Jul;38(6): 499-505. doi: 10.1055/s-0041-1740123. Epub 2021 Dec 17. PMID: 34921369.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective study	**Inclusion criteria** (for analysis): ABR with superficial inferior epigastric artery (SIEA), deep inferior epigastric perforator (DIEP), or muscle-sparing transverse rectus abdominis myocutaneous (TRAM) flaps, where one or both of the lateral and medial segments of the rectus muscle are preserved. Flaps that were reconstructed in a delayed-immediate fashion only if they had DI-ABR with radiation therapy between mastectomy/TE placement and	**Interventions** Immediate autologous reconstruction · N = 66 B: Delayed-immediate autologous reconstruction · N = 66 **Analysis** Frequencies; median (SD); univariate analyses; Wilcoxon rank-sum test No matching No adjustment	**Hematoma** · Immediate: 4/66 · Delayed-immediate: 4/66 **Surgical site infection** · Immediate: 3/66 · Delayed-immediate: 1/66 **Delayed healing** · Immediate: 12/66 · Delayed-immediate: 4/66 **Fat necrosis** · Immediate: 16/66	**General information** Follow-up: 3.1 (2.2-8.5) vs. 2.0 (1.3-6.0) Funding: NR CoI: Non declared. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective review Confounding: high Rate of participation/Exclusions reported (selection bias into the study): not reported

Christopher AN, Morris MP, Broach RB, Serletti JM. A Comparative Analysis of Immediate and Delayed-immediate Breast Reconstruction after Postmastectomy Radiation Therapy. J Reconstr Microsurg. 2022 Jul;38(6): 499-505. doi: 10.1055/s-0041-1740123. Epub 2021 Dec 17. PMID: 34921369.				
	autologous reconstruction (DI-ABR cohort). **Exclusion criteria** (for analysis): Patients undergoing non-abdominally based flap procedures **Enrolment period:** 2005 – 2018 **Follow-up (median, IQR):** Immediate: 3.1 (2.2 - 8.5) Delayed-immediate: 2.0 (1.3 - 6.0) **Descriptive statistics** Age (median, IQR) · Immediate: 48.7 (43–56) · Delayed-immediate: 49.4 (40–53) BMI (median, IQR) · Immediate: 29.1 (26–33)		· Delayed-immediate: 6/66 **Skin necrosis** · Immediate: 12/66 · Delayed-immediate: 0/66 **Flap loss due to vascular compromise** · Immediate: 1/66 · Delayed-immediate: 0/66 **Readmission with reoperation** · Immediate: 2/66 Delayed-immediate: 1/66	Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: not reported Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?:) no (retrospective) Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol found

Christopher AN, Morris MP, Broach RB, Serletti JM. A Comparative Analysis of Immediate and Delayed-immediate Breast Reconstruction after Postmastectomy Radiation Therapy. J Reconstr Microsurg. 2022 Jul;38(6): 499-505. doi: 10.1055/s-0041-1740123. Epub 2021 Dec 17. PMID: 34921369.				
	· Delayed-immediate: 28.2 (25–32) Stadium · Immediate: NR · Delayed-immediate: NR Chemotherapy (% yes) · Immediate: 51.1% (34/66) · Delayed-immediate: 87.9% (58/66) Reconstruction type (flap type) (%) · Immediate: TRAM: 71.2% (47/66); DIEP: 24.2% (16/66); SIEA: 4.55% (3/66) Delayed-immediate: TRAM: 71.2% (47/66); DIEP: 24.2% (16/66); SIEA: 4.55% (3/66)			**Other limitations or comments:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [374], [375], [376], [377], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [390], [391], [392], [393], [394]

Pittelkow E, DeBrock W, Christopher L, Mercho R, Suh LJ, Fisher CS, Hartman B, Lester M, Hassanein AH. Advantages of the Delayed-Immediate Microsurgical Breast Reconstruction: Extending the Choice. J Reconstr Microsurg. 2022 Sep;38(7): 579-584. doi: 10.1055/s-0041-1742240. Epub 2022 Feb 8. PMID: 35135030.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective study	**Inclusion criteria** (for analysis): Patients were included if their preference was for DIEP flap **Exclusion criteria** (for analysis): No immediate reconstruction (DIEP or tissue expander) at the time of Latissimus flap or thigh-based free flap Final implant reconstruction and initially chose implant	**Interventions** Immediate autologous reconstruction · N = 36 Delayed-immediate autologous reconstruction · N = 11 **Analysis** Mean (SD) No matching No adjustment	**Hematoma** · Immediate: 0/36 · Delayed-immediate: 1/11 **Surgical site infection** · Immediate: 2/36 · Delayed-immediate: 0/11 **Breast skin flap necrosis** · Immediate: 3/36 · Delayed-immediate: 0/11 **Fat necrosis** · Immediate: 1/36	**General information** Follow-up: NR Funding: NR CoI: None declared. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective study Confounding: high Rate of participation/Exclusions reported (selection bias into the study): not reported Exposure/Intervention

Pittelkow E, DeBrock W, Christopher L, Mercho R, Suh LJ, Fisher CS, Hartman B, Lester M, Hassanein AH. Advantages of the Delayed-Immediate Microsurgical Breast Reconstruction: Extending the Choice. J Reconstr Microsurg. 2022 Sep;38(7): 579-584. doi: 10.1055/s-0041-1742240. Epub 2022 Feb 8. PMID: 35135030.				
	reconstruction during the preoperative evaluation. Initial tissue expander reconstruction, but the preoperative documentation was unclear about patients preference for implant or DIEP **Enrolment period:** 2017 - 2019 **Follow-up:** NR **Descriptive statistics** Age (median) · Immediate: 48.8 · Delayed-immediate: 50.7 BMI (median) · Immediate: 30.1 · Delayed-immediate: 31.3 Stadium · NR Chemotherapy (% yes) · NR		· Delayed-immediate: 1/11 **Flap loss** · Immediate: 0/36 · Delayed-immediate: 0/11	· Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: not reported Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (àIf not, Knowledge of exposure status likely to influence the outcome?:) no (retrospective) Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol found

Pittelkow E, DeBrock W, Christopher L, Mercho R, Suh LJ, Fisher CS, Hartman B, Lester M, Hassanein AH. Advantages of the Delayed-Immediate Microsurgical Breast Reconstruction: Extending the Choice. J Reconstr Microsurg. 2022 Sep;38(7): 579-584. doi: 10.1055/s-0041-1742240. Epub 2022 Feb 8. PMID: 35135030.				
	Reconstruction type (flap type) (%) · DIEP for both groups			**Other limitations or comments:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [374], [375], [376], [377], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [390], [391], [392], [393], [394]

Joosen MEM, Schop SJ, Reinhoudt LL, van Kuijk SMJ, Beugels J, de Bruïne AP, Goudkade D, Heuts EM, van der Hulst RRWJ, de Grzymala AAP. The difference in local, regional and distant breast cancer recurrence between the immediate and delayed DIEP flap procedure; a retrospective cohort study. Breast Cancer Res Treat. 2021 Jul;188(2): 389-398. doi: 10.1007/s10549-021-06199-3. Epub 2021 May 24. PMID: 34028673; PMCID: PMC8260410.

Study type	Population	Interventions	Main results	Methodological evaluation
Multicenter retrospective cohort study	**Inclusion criteria** (for analysis): Female Older than 18 years Diagnosis of breast cancer in the breast to be reconstructed **Exclusion criteria** (for analysis): Reconstructions after prophylactic mastectomy Women who had a metastasis at the time of mastectomy	**Interventions** Immediate autologous reconstruction · N = 326 Delayed autologous reconstruction · N = 536 **Analysis** Cox proportional hazards regression analysis, multivariable Cox regression No matching	**Local recurrence** · Immediate: 5/326 · Delayed: 9/536 · HR: 0.804 (95%-CI: 0.483–1.337); p = 0.001 **Regional recurrence** · Immediate: 12/326 · Delayed: 13/536 · HR: 0.306 (95%-CI: 0.214–0.436); p = 0.631 **Distant recurrence**	**General information** Follow-up: 46 months vs. 56 months Funding: NR CoI: The authors declare that they have no conflict of interest to disclose. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: multicenter retrospective cohort study Confounding: moderate

Joosen MEM, Schop SJ, Reinhoudt LL, van Kuijk SMJ, Beugels J, de Bruïne AP, Goudkade D, Heuts EM, van der Hulst RRWJ, de Grzymala AAP. The difference in local, regional and distant breast cancer recurrence between the immediate and delayed DIEP flap procedure; a retrospective cohort study. Breast Cancer Res Treat. 2021 Jul;188(2): 389-398. doi: 10.1007/s10549-021-06199-3. Epub 2021 May 24. PMID: 34028673; PMCID: PMC8260410.				
	Women who had a delayed reconstruction and experienced a recurrence after mastectomy, but before reconstructive surgery, were excluded as well **Enrolment period:** January 2010 - December 2018 **Follow-up:** · Immediate: 46 months (45) · Delayed: 56 months (56) **Descriptive statistics** Age (mean, sd) · Immediate: 52.79 (8.28) · Delayed: 50.92 (8.48) BMI (mean, sd) · Immediate: 52.79 (8.28) · Delayed: 50.92 (8.48) Stadium · Immediate: 0: 73.9% (241/326); Tis: 24.5% (80/326); 1: 40.5% (132/326); 2: 23.6%	Adjusted for immortal time bias, age at operation, histological tumor type, TN stage, y stage, Bloom Richardson grade, axillary treatment, chemotherapy, radiation therapy, endocrine therapy and immunotherapy	· Immediate: 7/251 · Delayed: 32/466 · HR: 1.351 (95%-CI: 0.960–1.903); p < 0.001	Rate of participation/Exclusions reported (selection bias into the study): yes Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: no Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (àIf not, Knowledge of exposure status likely to influence the outcome?:) no Main cofounders taken into account: yes (for local, regional & distant recurrence)

Joosen MEM, Schop SJ, Reinhoudt LL, van Kuijk SMJ, Beugels J, de Bruïne AP, Goudkade D, Heuts EM, van der Hulst RRWJ, de Grzymala AAP. The difference in local, regional and distant breast cancer recurrence between the immediate and delayed DIEP flap procedure; a retrospective cohort study. Breast Cancer Res Treat. 2021 Jul;188(2): 389-398. doi: 10.1007/s10549-021-06199-3. Epub 2021 May 24. PMID: 34028673; PMCID: PMC8260410.				
	(77/326); 3: 2.1% (7/326); 4: 0.3% (7/326); missing: 5.2% (17/326) · Delayed: 0: 5.2% (28/536); Tis: 9.3% (50/536); 1: 31.2% (167/536); 2: 34.1% (183/536); 3: 8.8% (47/536); 4: 2.1% (11/536); missing: 9.3% (50/536) Chemotherapy (% yes) · Immediate: 49.1% (160/326) · Delayed: 68.8% (369/536) Reconstruction type (flap type) (%) DIEP flap breast reconstruction only			Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol found **Other limitations or comments:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [374], [375], [376], [377], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [390], [391], [392], [393], [394]

Shammas RL, Cason RW, Sergesketter AR, Glener AD, Broadwater G, Hollins A, Le E, Marks C, Atia AN, Orr JP, Hollenbeck ST. A Comparison of Surgical Complications in Patients Undergoing Delayed versus Staged Tissue-Expander and Free-Flap Breast Reconstruction. Plast Reconstr Surg. 2021 Sep 1;148(3): 501-509. doi: 10.1097/PRS.0000000000008208. PMID: 34270511.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective study	**Inclusion criteria** (for analysis): Patients had undergone postmastectomy radiation therapy Patients had significant medical comorbidities Patients were uncertain about their reconstruction and/or had tenuous skin flaps at the time of mastectomy **Exclusion criteria** (for analysis):	**Interventions** Delayed autologous reconstruction · N = 140 Delayed-immediate autologous reconstruction · N = 54 **Analysis** Frequencies No matching No adjustment	**Surgical site infection** · Delayed: 9/140 · Delayed-immediate: 7/54 **Wound healing complications** · Delayed: 17/140 · Delayed-immediate: 4/54 **Hematoma** · Delayed: 1/140 · Delayed-immediate: 2/54 **Return to operation room** · Delayed: 6/140	**General information** Follow-up: NR Funding: None of the authors has a financial disclosure to report CoI: None of the authors has a financial disclosure to report. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective study Confounding: high

Shammas RL, Cason RW, Sergesketter AR, Glener AD, Broadwater G, Hollins A, Le E, Marks C, Atia AN, Orr JP, Hollenbeck ST. A Comparison of Surgical Complications in Patients Undergoing Delayed versus Staged Tissue-Expander and Free-Flap Breast Reconstruction. Plast Reconstr Surg. 2021 Sep 1;148(3): 501-509. doi: 10.1097/PRS.0000000000008208. PMID: 34270511.				
	Patients who did not undergo free-flap breast reconstruction Incomplete medical records Those who did not carry a cancer diagnosis Patients who did not have staged or delayed autologous breast reconstruction or who had both autologous and implant-based reconstruction **Enrolment period:** 2010 - 2018 **Follow-up (mean, sd):** Delayed: 4.9 (2.58) Delayed-immediate: 2.9 (1.91) **Descriptive statistics** Age (mean, sd) · Delayed: 48.6 (8.51); range: 30.5–69.1 · Delayed-immediate: 47.8 (8.46); range: 28.1–70.3		· Delayed-immediate: 4/54	Rate of participation/Exclusions reported (selection bias into the study): yes Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no Drop-out rate & reasons reported: no Outcome · Outcome measure is well-defined, valid and reliable: unclear · Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?:) no (retrospective) Main cofounders taken into account: no

Shammas RL, Cason RW, Sergesketter AR, Glener AD, Broadwater G, Hollins A, Le E, Marks C, Atia AN, Orr JP, Hollenbeck ST. A Comparison of Surgical Complications in Patients Undergoing Delayed versus Staged Tissue-Expander and Free-Flap Breast Reconstruction. Plast Reconstr Surg. 2021 Sep 1;148(3): 501-509. doi: 10.1097/PRS.0000000000008208. PMID: 34270511.				
	BMI (%, n) · Delayed: <25: 16.5% (22/140); 25-30: 46.1% (48/140); < 30: 47.4% (63/140); missing: 7/140 · Delayed-immediate: <25: 24.1% (13/54); 25-30: 38.9% (21/54); < 30: 37.0% (20/54); missing: 0/54 Stadium · Delayed: 0: 10.1% (14/140); I: 23.2% (32/140); IIA: 13.8% (19/140); IIB: 22.5% (31/140); IIIA: 19.6% (27/140); IIIB: 1.4% (2/140); IIIC: 7.2% (310140); IV: 2.2% (3/140); missing: 2 · Delayed-immediate: 0: 20.8% (11/54); I: 18.9% (10/54); IIA: 24.5% (13/54); IIB: 17.0% (9/54) ; IIIA: 11.3% (6/54); IIIB: 3.8% (2/54); IIIC: 1.9% (1/54); IV: 1.9% (1/54); missing: 1 Chemotherapy (% yes)			Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol found **Other limitations or comments:** retrospective design

Shammas RL, Cason RW, Sergesketter AR, Glener AD, Broadwater G, Hollins A, Le E, Marks C, Atia AN, Orr JP, Hollenbeck ST. A Comparison of Surgical Complications in Patients Undergoing Delayed versus Staged Tissue-Expander and Free-Flap Breast Reconstruction. Plast Reconstr Surg. 2021 Sep 1;148(3): 501-509. doi: 10.1097/PRS.0000000000008208. PMID: 34270511.				
	· Delayed: 49.6% (69/140) · Delayed-immediate: 31.5% (17/54) Reconstruction type (flap type) (%) Autologous free flap breast reconstruction in both groups			

Verknüpfte Empfehlungen:

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [374], [375], [376], [377], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [390], [391], [392], [393], [394]

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nr of participants (studies)	Certainty of the evidence (GRADE)
	Risk with delayed	Risk with immediate			
Wound complication	26 per 1.000	**22 per 1.000** (18 to 27)	**OR 0.85** (0.69 to 1.04)	23712 (10 non-randomised studies)	⊕◯◯◯ Very low[a,b]
Mastectomy flap necrosis	35 per 1.000	**114 per 1.000** (52 to 234)	**OR 3.51** (1.48 to 8.30)	416 (4 non-randomised studies)	⊕◯◯◯ Very low[a,d]
Total flap loss	24 per 1.000	**24 per 1.000** (15 to 38)	**OR 0.99** (0.61 to 1.61)	10460 (7 non-randomised studies)	⊕◯◯◯ Very low[a,b]
Local recurrence	18 per 1.000	**16 per 1.000** (6 to 45)	**OR 0.93** (0.33 to 2.60)	924 (2 non-randomised studies)	⊕◯◯◯ Very low[a,b]

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nr of participants (studies)	Certainty of the evidence (GRADE)
	Risk with delayed	Risk with immediate			
Satisfaction with breast	The mean satisfaction with breast was **51**	MD **8.14higher** (11.76 lower to 28.04 higher)	-	1242 (2 non-randomised studies)	⨁◯◯◯ Very low[a,b,c]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

siehe Meta-Analysen

Explanations

a. Downgraded by two levels due to very serious risk of bias: Included studies were observational only, and the majority did not adjust at all for relevant baseline characteristics. Results are thus prone to confounding.

b. Downgraded one level due to serious inconsistency (high heterogeneity).

c. Downgraded by one level due to serious imprecision; the 95% confidence interval includes both in favor of immediate and in favor of delayed.

d. Downgraded one level due to indirectness of the outcome: imprecise definition of the outcome parameter (type and approach of mastectomy were not considered).

Verknüpfte Empfehlungen:

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [374], [375], [376], [377], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [390], [391], [392], [393], [394]

First Author, Year	Country	Journal	Study design	N Patients	N breasts	Age (mean, range)	Follow- up (range), months	Reconstruction method
Maalouf 2017	Canada	Ann Chir Plast Est	Retrospective	62	62	Immediate: 50 (SD. 9.5) Delayed: 47 (SD. 8)	Immediate: 32 (11-67) Delayed: 92 (26-240)	Immediate and delayed autologous

Verknüpfte Empfehlungen:

Empfehlung 7.58:

Der Zeitpunkt der autologen Brustrekonstruktion (primäre Rekonstruktion, primär verzögerte Rekonstruktion über Expander-Implantat-Sequenz, sekundäre Rekonstruktion) soll unter Berücksichtigung der onkologischen Situation und der individuellen Wünsche mit der Patientin besprochen werden.

Literaturreferenzen: [374], [375], [376], [377], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [390], [391], [392], [393], [394]

First Author, Year	Country	Type of study	Procedure type	Npatients	Outcomes
Beugels 2018	Netherlands	Retrospective	DIEP	737	Surgical, Reop, LoS
Chang 2015	USA	Retrospective	DIEP, SIEA, TRAM	376	Surgical, Reop
DeBono 2002	UK	Retrospective	LO	97	Surgical, Reop
Dewael 2019	Belgium	Retrospective	DIEP, SIEA	60	Surgical, Reop
Maalouf 2017	Canada	Retrospective	DIEP	62	Surgical, Reop
Manyam 2019	USA	Retrospective	DIEP, E/ 1, LO, TRAM	204	Surgical, Reop
Prantl 2020	Germany	Retrospective	DIEP	3,913	Surgical, Reop, LoS
Sternberg 2006	USA	Retrospective	LO	100	Surgical, Reop
Tran 2001	USA	Retrospective	TRAM	102	Surgical, Reop

First Author, Year	Country	Type of study	Procedure type	Npatients	Outcomes
Yoon 2018	USA	Retrospective	E/I, DIEP, E/I, SIEA, TRAM	1,957	Surgical, Reop

Abbreviations: ABO, abdominal advance; DIEP, deep inferior epigastric artery perforator; FLAP, autologous flap with no specification; GAP, gluteal artery perforator; LO, latissimus dorsi; MS, muscle-sparing; SIEA, superficial inferior epigastric artery; TRAM, transverse rectus abdominis myocutaneous; R, retrospective; P, prospective; Reop, reoperation; LoS, length of stay.

t

Verknüpfte Empfehlungen:

Empfehlung 7.59:

Die Patientin soll darüber aufgeklärt werden, dass die adjuvante Bestrahlung der autolog rekonstruierten Brust mit einem erhöhten Auftreten von Fettgewebsnekrosen und verminderten Werten der patientenberichteten Outcomeparameter (Zufriedenheit mit der rekonstruierten Brust, körperliche Gesundheit, seelische Gesundheit) assoziiert ist.

Literaturreferenzen: [395], [396], [397], [398], [399], [400], [401], [402], [403], [404], [405], [406], [407], [408], [409], [410], [411]

Liew B, Southall C, Kanapathy M, Nikkhah D. Does post-mastectomy radiation therapy worsen outcomes in immediate autologous breast flap reconstruction? A systematic review and meta-analysis. J Plast Reconstr Aesthet Surg. 2021 Dec;74(12): 3260-3280. doi: 10.1016/j.bjps.2021.08.005. Epub 2021 Aug 28. PMID: 34565703.

Source and Purpose	Design and participants	Intervention	Outcomes	Results	Quality and comment
Country: **Aim**: "The aim of this review is to systematically analyze the existing literature to compare the clinical, aesthetic and patient-reported outcomes in immediately reconstructed autologous flaps exposed to PMRT with the outcomes of flaps with no radiation exposure."	**Design**: Systematic review with Metaanalysis **Search date**: Searched from inception until 19.11.2020 **Searched databases**: Medline, Embase, Cochrane Central **Included study designs**: Cohort studies, prospective studies, retrospective studies	**Intervention** post-mastectomy radiotherapy no post-mastectomy radiotherapy post-mastectomy radiotherapy and delayed reconstruction	1) Fat necrosis 2) Contracture or volume loss 3) Revisional operations	**Fat necrosis** 12 studies PMRT: 81/485 No PMRT: 157/1577 RR: 1.91[1.45, 2.52] p < 0.00001 **Contracture or volume loss** 4 studies PMRT: 32/307 No PMRT: 45/671	**Risk of bias assessment of study:** ROBINS-I tool "Using the ROBINS-I tool, it was found that thirteen studies were at moderate risk of bias and eight studies were at serious risk of bias." **Overall confidence in results of SR (AMSTAR-2):** PICO elements: yes

Liew B, Southall C, Kanapathy M, Nikkhah D. Does post-mastectomy radiation therapy worsen outcomes in immediate autologous breast flap reconstruction? A systematic review and meta-analysis. J Plast Reconstr Aesthet Surg. 2021 Dec;74(12): 3260-3280. doi: 10.1016/j.bjps.2021.08.005. Epub 2021 Aug 28. PMID: 34565703.					
	Number of included studies: n=21 **Number of included patients**: 3,817 pts **Mean/median age**: Not reported. **Inclusion criteria**: Primary data from prospective and retrospective comparative studies Human studies Studies that include data on autologous flap reconstruction **Exclusion criteria:** Review, technique, case report or case series articles Studies not published in English Studies with less than one-year follow-up			RR: 1.62 [1.06, 2.48] p < 0.00001 **Revisional operations** 10 studies PMRT: 111/436 No PMRT: 248/1036 RR: 0.95 [0.80, 1.13] p = 0.54	A priori design: partial yes Justification for design: no Literature search >= 2 databases, search strategy + other sources: partial yes Selection in duplicate: yes Data extraction in duplicate: yes List of excluded studies: no sufficient detail on studies: partial yes RoB assessed: yes Funding of incl. studies: no MA appropriate: no RoB considered in MA: yes

Liew B, Southall C, Kanapathy M, Nikkhah D. Does post-mastectomy radiation therapy worsen outcomes in immediate autologous breast flap reconstruction? A systematic review and meta-analysis. J Plast Reconstr Aesthet Surg. 2021 Dec;74(12): 3260-3280. doi: 10.1016/j.bjps.2021.08.005. Epub 2021 Aug 28. PMID: 34565703.					
	Studies with less than ten patients in each group Studies that do not stratify results by type of reconstruction (autologous vs implant-based) and/or timing of reconstruction (immediate vs delayed) Studies focused solely on chest wall irradiation prior to breast reconstruction Studies focused solely on the elderly (> 65 years) or on obese patients Studies with no relevant extractable				Heterogeneity explained: yes Publication bias investigated: no Sources of CoI: yes **Sources of funding** AG No funding was received for this work.

Verknüpfte Empfehlungen:

Empfehlung 7.59:

Die Patientin soll darüber aufgeklärt werden, dass die adjuvante Bestrahlung der autolog rekonstruierten Brust mit einem erhöhten Auftreten von Fettgewebsnekrosen und verminderten Werten der patientenberichteten Outcomeparameter (Zufriedenheit mit der rekonstruierten Brust, körperliche Gesundheit, seelische Gesundheit) assoziiert ist.

Literaturreferenzen: [395], [396], [397], [398], [399], [400], [401], [402], [403], [404], [405], [406], [407], [408], [409], [410], [411]

Hsieh WC, Tee R, Huang YT, Kuo WL, Huang JJ. Surgical and patient-reported outcomes in an Asian female population with or without adjuvant radiotherapy after immediate free perforator flap breast reconstruction: A retrospective review. JPRAS Open. 2023 Sep 11;38: 237-248. doi: 10.1016/j.jpra.2023.09.001. PMID: 38021323; PMCID: PMC10630550.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Immediate breast reconstruction **Exclusion criteria** (for analysis): Recurrence Previous radiation therapy Lost to follow-up **Enrolment period:** July 2008 - December 2018	**Interventions** RT after autologous reconstruction · N = 15 No RT after autologous reconstruction · N = 86 **Analysis** Frequencies & mean ± standard deviation (range) No matching	**Heamatoma required evacuation (< 30 days)** · RT: 1/15 · No RT: 0/86 **Infections (< 30 days)** · RT: 0/15 · No RT: 0/86 **Wound required surgical intervention (> 30 days)** · RT: 0/15 · No RT: 1/86	**General information** Follow-up: mean 5 years Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. CoI: The authors declare that they have no conflict of interest. **Risk of bias considerations** (adapted from SIGN cohort study checklist)

Hsieh WC, Tee R, Huang YT, Kuo WL, Huang JJ. Surgical and patient-reported outcomes in an Asian female population with or without adjuvant radiotherapy after immediate free perforator flap breast reconstruction: A retrospective review. JPRAS Open. 2023 Sep 11;38: 237-248. doi: 10.1016/j.jpra.2023.09.001. PMID: 38021323; PMCID: PMC10630550.				
	Follow-up (mean, sd): RT: 5.2 (2.48) years (range 2.4–10.5) No RT: 5.73 (2.73) years (range 2.3–12.8) **Descriptive statistics** Age (mean, sd) · RT: 40.0 (7.59; range: 29-53 · No RT: 45.5 (8.3), range: 24 - 65 BMI (mean, sd) · RT: 24.5 (3.7), range: 19.5 - 32.0 <30: 13 (92.9%) >30: 2 (13.3%) · No RT: 24.2 (4.2), range: 17.3 - 40.1 <30: 78 (92.9%) >30: 6 (7.1%) Stadium (TNM)	No adjustment	**Fat necrosis required surgical intervention (< 30 days)** · RT: 0/15 · No RT: 3/86 **NAC necrosis (< 30 days)** · RT: 0/15 · No RT: 0/86 **Local recurrence** · RT: 0/15 · No RT: 0/86 **QoL-outcomes: Breast –Q (mean, sd)** Psychosocial well-being: · RT: 66.2 (20.1) · No RT: 75.1 (17.3) Physical well-being (chest): · RT: 60.1 (20.3) · No RT: 73.9 (17.3) Physical well-being (donor site):	Study type: restrospective cohort study Confounding: probably (high risk risk) Rate of participation/Exclusions reported (selection bias into the study): yes (low risk) Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status: no (low risk due to retrospective data collection and no possible influence) Drop-out rate & reasons reported: not reported Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (àlf not, Knowledge

Hsieh WC, Tee R, Huang YT, Kuo WL, Huang JJ. Surgical and patient-reported outcomes in an Asian female population with or without adjuvant radiotherapy after immediate free perforator flap breast reconstruction: A retrospective review. JPRAS Open. 2023 Sep 11;38: 237-248. doi: 10.1016/j.jpra.2023.09.001. PMID: 38021323; PMCID: PMC10630550.				
	· RT: Stage 0 (DCIS): 0 (0.0%), Stage I: 2 (13.3%), Stage II: 5 (33.3%), Stage III: 8 (53.3%) · No RT: Stage 0 (DCIS): 21 (24.4%), Stage I: 28 (32.6%), Stage II: 37 (43.0%), Stage III: 0 (0.0%) Chemotherapy (% yes) (previous) · RT: 6 (40.0%) · No RT: 7 (8.1%) Reconstruction type (flap type) (%) · RT: DIEP (73.3%), PAP (13.3%), Free ms-TRAM (13.3%) No RT: DIEP (87.2%), PAP (7.0%), Free ms-TRAM (5.8%)		· RT: 73.2 (28.6) · No RT: 78.3 (18.4) <u>Sexual well-being:</u> · RT: 44.1 (18.3) · No RT: 50.8 (22.4) <u>Satisfaction with breast:</u> · RT: 60.1 (10.4) · No RT: 65.1 (14.8) <u>Satisfaction with surgeon:</u> · RT: 95.2 (9.6) · No RT: 92.8 (13.5) <u>Satisfaction with information from surgeon:</u> · RT: 74.0 (15.1) · No RT: 74.8 (18.3) <u>Satisfaction with medical team:</u> · RT: 97.3 (5.5) · No RT: 93.1 (14.5) <u>Satisfaction with other staff:</u>	of exposure status likely to influence the outcome?: no (low risk due to retrospective data collection and no possible influence) Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol found **Other limitations or comments:** retrospective design

Hsieh WC, Tee R, Huang YT, Kuo WL, Huang JJ. Surgical and patient-reported outcomes in an Asian female population with or without adjuvant radiotherapy after immediate free perforator flap breast reconstruction: A retrospective review. JPRAS Open. 2023 Sep 11;38: 237-248. doi: 10.1016/j.jpra.2023.09.001. PMID: 38021323; PMCID: PMC10630550.				
			· RT: 93.9 (13.0) · No RT: 89.7 (17.1) **Aesthetics (mean, sd)** <u>Breast shape of reconstructive site:</u> · RT: 4.0 (0.3) · No RT: 4.12 (0.5) <u>Symmetry of inframammary fold:</u> · RT: 4.3 (0.5) · No RT: 4.1 (0.6) <u>Symmetry of volume:</u> · RT: 4.0 (0.5) · No RT: 4.0 (0.5) <u>Symmetry of shape:</u> · RT: 3.7 (0.5) · No RT: 3.9 (0.6) <u>Overall outcomes:</u> · RT: 3.9 (0.4)	

Hsieh WC, Tee R, Huang YT, Kuo WL, Huang JJ. Surgical and patient-reported outcomes in an Asian female population with or without adjuvant radiotherapy after immediate free perforator flap breast reconstruction: A retrospective review. JPRAS Open. 2023 Sep 11;38: 237-248. doi: 10.1016/j.jpra.2023.09.001. PMID: 38021323; PMCID: PMC10630550.				
			No RT: 4.1 (0.5)	

Verknüpfte Empfehlungen:

Empfehlung 7.59:

Die Patientin soll darüber aufgeklärt werden, dass die adjuvante Bestrahlung der autolog rekonstruierten Brust mit einem erhöhten Auftreten von Fettgewebsnekrosen und verminderten Werten der patientenberichteten Outcomeparameter (Zufriedenheit mit der rekonstruierten Brust, körperliche Gesundheit, seelische Gesundheit) assoziiert ist.

Literaturreferenzen: [395], [396], [397], [398], [399], [400], [401], [402], [403], [404], [405], [406], [407], [408], [409], [410], [411]

Jagsi R, Momoh AO, Qi J, Hamill JB, Billig J, Kim HM, Pusic AL, Wilkins EG. Impact of Radiotherapy on Complications and Patient-Reported Outcomes After Breast Reconstruction. J Natl Cancer Inst. 2018 Feb 1;110(2): 157–65. doi: 10.1093/jnci/djx148. PMID: 28954300; PMCID: PMC6059091.

Study type	Population	Interventions	Main results	Methodological evaluation
Prospective multicenter cohort study	**Inclusion criteria** (for analysis): Female sex Age 18 years or older, Undergoing first-time, immediate, or delayed reconstruction following mastectomy **Exclusion criteria** (for analysis): Patients treated with prophylactic mastectomy (without cancer diagnosis)	**Interventions** RT after autologous reconstruction · N = 236 No RT after autologous reconstruction · N = 407 **Analysis** Frequencies; mixed-effects logistic regression model No matching	**Hematoma** One year post-op: · RT: 9/236 · No RT: 27/407 Two years post-op: · RT: 8/199 · No RT: 21/332 **Wound dehiscence** One year post-op: · RT: 12/236 · No RT: 8/407	**General information** Follow-up: mean 5 years Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. CoI: The authors declare that they have no conflict of interest. **Risk of bias considerations** (adapted from SIGN cohort study checklist)

Jagsi R, Momoh AO, Qi J, Hamill JB, Billig J, Kim HM, Pusic AL, Wilkins EG. Impact of Radiotherapy on Complications and Patient-Reported Outcomes After Breast Reconstruction. J Natl Cancer Inst. 2018 Feb 1;110(2): 157–65. doi: 10.1093/jnci/djx148. PMID: 28954300; PMCID: PMC6059091.				
	Women who had received radiotherapy prior to mastectomy Patients who received bilateral reconstruction with autologous reconstruction techniques on one side and implant-based reconstruction techniques on the other Those who received two-staged crossover of procedure types Those who received immediate reconstruction after mastectomy of one breast but delayed reconstruction of the other **Enrolment period:** 2012 - 2015 **Follow-up:** NR (at least 2 years) **Descriptive statistics** Age (years, %) · RT: <30: 19/622 (3.1%); 30-39: 99/622 (15.9%); 40-49:	Adjusted for Baseline value of the corresponding outcome variable, clinical and demographic characteristics and between-enter variability by including sites (e.g. reconstruction timing, age, extent of disease, bilateral vs unilateral reconstruction, chemotherapy receipt, nodal management, body mass index, smoking, diabetes, race, ethnicity, education, employment, income, and hospital site)	Two years post-op: · RT: 11/199 · No RT: 8/332 **Wound infection requiring oral antibiotics** One year post-op: · RT; 4/236 · No RT: 7/407 Two years post-op: · RT: 3/199 · No RT: 5/332 **Wound infection requiring IV antibiotics** One year post-op: · RT: 5/236 · No RT: 3/407 Two years post-op: · RT: 3/199 · No RT: 3/332	Study type: restrospective cohort study Confounding: probably (high risk risk) Rate of participation/Exclusions reported (selection bias into the study): yes (low risk) Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status: no (low risk due to retrospective data collection and no possible influence) Drop-out rate & reasons reported: not reported Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to

Jagsi R, Momoh AO, Qi J, Hamill JB, Billig J, Kim HM, Pusic AL, Wilkins EG. Impact of Radiotherapy on Complications and Patient-Reported Outcomes After Breast Reconstruction. J Natl Cancer Inst. 2018 Feb 1;110(2): 157–65. doi: 10.1093/jnci/djx148. PMID: 28954300; PMCID: PMC6059091.				
	211/622 (33.9%); 50-59: 191/622 (30.7%); ≥60: 102/622 (16.4%) · No RT: <30: 24/1625 (1.5%); 30-39: 181/1625 (11.1%); 40-49: 586/1625 (36.1%); 50-59: 542/1625 (33.4%); ≥60: 292/1625 (18.0%) BMI (median, range) · RT: <30: 431/622 (69.3%); ≥30: 191/622 (30.7%) · No RT: <30: 1251/1625 (77.0%); ≥30: 374/1625 (23.0%) Stadium · NR Chemotherapy (% yes) · RT: 585/622 (94.1%) · No RT: 588/1625 (36.2%) Reconstruction type (flap type) (%) · NR		**Wound infection requiring surgical repair** One year post-op: · RT: 5/236 · No RT: 4/407 Two years post-op: · RT: 3/199 · No RT: 3/332 **Chronic fat necrosis** One year post-op: · RT: 11/236 · No RT: 33/407 Two years post-op: · RT: 14/199 · No RT: 29/332 **Total flap loss** One year post-op: · RT: 1/236 · No RT: 8/407	influence the outcome?: no (low risk due to retrospective data collection and no possible influence) Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol found **Other limitations or comments:** retrospective design

Jagsi R, Momoh AO, Qi J, Hamill JB, Billig J, Kim HM, Pusic AL, Wilkins EG. Impact of Radiotherapy on Complications and Patient-Reported Outcomes After Breast Reconstruction. J Natl Cancer Inst. 2018 Feb 1;110(2): 157–65. doi: 10.1093/jnci/djx148. PMID: 28954300; PMCID: PMC6059091.				
			Two years post-op: · RT: 1/199 · No RT: 6/332 **QoL-outcomes: Breast –Q (mean, SD)** <u>Satisfaction with breast:</u> One year post-op: · RT: 63.9 (16.9) · No RT: 68.5 (17.5) Two years post-op: · RT: 65.1 (18.2) · No RT: 69 (17.8) <u>Satisfaction with outcome:</u> One year post-op: · RT: 71.8 (21.6) · No RT: 74.3 (20.3) Two years post-op: · RT: 70.1 (22.9) · No RT: 73.6 (20)	

Jagsi R, Momoh AO, Qi J, Hamill JB, Billig J, Kim HM, Pusic AL, Wilkins EG. Impact of Radiotherapy on Complications and Patient-Reported Outcomes After Breast Reconstruction. J Natl Cancer Inst. 2018 Feb 1;110(2): 157–65. doi: 10.1093/jnci/djx148. PMID: 28954300; PMCID: PMC6059091.				
			<u>Psychosocial well-being:</u> One year post-op: · RT: 70.4 (18.6) · No RT: 75.4 (19.6) Two years post-op: · RT: 71.8 (19.4) · No RT: 77.7 (18.9) <u>Physical well-being:</u> One year post-op: · RT: 71.2 (13.9) · No RT: 76.3 (15.8) Two years post-op: · RT: 72 (15.3) · No RT: 77.2 (15.1)	

Verknüpfte Empfehlungen:

Empfehlung 7.59:

Die Patientin soll darüber aufgeklärt werden, dass die adjuvante Bestrahlung der autolog rekonstruierten Brust mit einem erhöhten Auftreten von Fettgewebsnekrosen und verminderten Werten der patientenberichteten Outcomeparameter (Zufriedenheit mit der rekonstruierten Brust, körperliche Gesundheit, seelische Gesundheit) assoziiert ist.

Literaturreferenzen: [395], [396], [397], [398], [399], [400], [401], [402], [403], [404], [405], [406], [407], [408], [409], [410], [411]

Emanuele Lisa AV, Salgarello M, Huscher A, Corsi F, Piovani D, Rubbino F, Andreoletti S, Papa G, Klinger F, Tinterri C, Testori A, Scorsetti M, Veronesi P, Leonardi MC, Rietjens M, Cortinovis U, Summo V, Rampino Cordaro E, Parodi PC, Persichetti P, Barone M, De Santis G, Murolo M, Riccio M, Aquinati A, Cavaliere F, Vaia N, Pagura G, Dalla Venezia E, Bassetto F, Vindigni V, Ciuffreda L, Bocchiotti MA, Sciarillo A, Renzi N, Meneghini G, Kraljic T, Loreti A, Fortunato L, Pino V, Vinci V, Klinger M. The Effect of Adjuvant Radiotherapy on One- and Two-Stage Prosthetic Breast Reconstruction and on Autologous Reconstruction: A Multicenter Italian Study among 18 Senonetwork Breast Centres. Breast J. 2023 May 9;2023: 6688466. doi: 10.1155/2023/6688466. PMID: 37205012; PMCID: PMC10188256.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective case-control multicenter study	**Inclusion criteria** (for analysis): Female patients Age over 18 years at the time of diagnosis Patients who had undergone mastectomy and immediate reconstruction with implant in one or two stages or with autologous flaps with or without adjuvant radiotherapy	**Interventions** RT after autologous reconstruction · N = 79 No RT after autologous reconstruction · N = 108 **Analysis** Multivariable hierarchical logistic regression analyses	**Hematoma** · RT: 7/79 · No RT: 7/108 **Early infection (< 30 days)** · RT: 4/79 · No RT: 2/108 **Late infection (≥ 30 days)** · RT: 2/79 · No RT: 1/108	**General information** Follow-up: average: 2 years Funding: The authors declare that they have no conLicts of interest. CoI: NR **Risk of bias considerations** (adapted from SIGN cohort study checklist)

Emanuele Lisa AV, Salgarello M, Huscher A, Corsi F, Piovani D, Rubbino F, Andreoletti S, Papa G, Klinger F, Tinterri C, Testori A, Scorsetti M, Veronesi P, Leonardi MC, Rietjens M, Cortinovis U, Summo V, Rampino Cordaro E, Parodi PC, Persichetti P, Barone M, De Santis G, Murolo M, Riccio M, Aquinati A, Cavaliere F, Vaia N, Pagura G, Dalla Venezia E, Bassetto F, Vindigni V, Ciuffreda L, Bocchiotti MA, Sciarillo A, Renzi N, Meneghini G, Kraljic T, Loreti A, Fortunato L, Pino V, Vinci V, Klinger M. The Effect of Adjuvant Radiotherapy on One- and Two-Stage Prosthetic Breast Reconstruction and on Autologous Reconstruction: A Multicenter Italian Study among 18 Senonetwork Breast Centres. Breast J. 2023 May 9;2023: 6688466. doi: 10.1155/2023/6688466. PMID: 37205012; PMCID: PMC10188256.

	Exclusion criteria (for analysis): Prior breast or chest wall irradiation Delayed reconstruction Patients lost to follow-up **Enrolment period:** 2001 – 8th April 2020 **Follow-up:** Average 2 years **Descriptive statistics** Age (median, range) · RT: 50 (45-59) · No RT: 50.5 (45-56) BMI (median, range) · RT: 26.5 (24.0 - 28.4) ≥30: 11 (15.3%) · No RT: 25.0 (23.0 - 27.1) ≥30: 9 (9.2%)	No matching Adjusted for age, the BMI, smoking habits, diabetes, other autoimmune diseases, type of chemotherapy, axillary dissection, and type of surgical procedure	**Early and late infection** · RT: 0/79 · No RT: 0/108 **Skin necrosis** · RT: 18/79 · No RT: 10/108 **Liponecrosis** · RT: 9/79 · No RT: 10/108 **Partial flap necrosis** · RT: 10/79 · No RT: 6/108 **Full-thickness flap necrosis** · RT: 3/79 · No RT: 2/108 **Reintervention** · RT: 3/79	Study type: retrospective case-control multicenter study Confounding: probably (high risk risk) Rate of participation/Exclusions reported (selection bias into the study): yes Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status: no (low risk due to retrospective data collection and no possible influence) Drop-out rate & reasons reported: no problems Outcome · Outcome measure is well-defined, valid and reliable: yes

Emanuele Lisa AV, Salgarello M, Huscher A, Corsi F, Piovani D, Rubbino F, Andreoletti S, Papa G, Klinger F, Tinterri C, Testori A, Scorsetti M, Veronesi P, Leonardi MC, Rietjens M, Cortinovis U, Summo V, Rampino Cordaro E, Parodi PC, Persichetti P, Barone M, De Santis G, Murolo M, Riccio M, Aquinati A, Cavaliere F, Vaia N, Pagura G, Dalla Venezia E, Bassetto F, Vindigni V, Ciuffreda L, Bocchiotti MA, Sciarillo A, Renzi N, Meneghini G, Kraljic T, Loreti A, Fortunato L, Pino V, Vinci V, Klinger M. The Effect of Adjuvant Radiotherapy on One- and Two-Stage Prosthetic Breast Reconstruction and on Autologous Reconstruction: A Multicenter Italian Study among 18 Senonetwork Breast Centres. Breast J. 2023 May 9;2023: 6688466. doi: 10.1155/2023/6688466. PMID: 37205012; PMCID: PMC10188256.				
	Stadium · RT: NR · No RT: NR Chemotherapy (% yes) · RT: 25 (31.7%) · No RT: 18 (16.6%) Reconstruction type (flap type) (%) · RT: NR · No RT: NR		· No RT: 3/108	· Blind outcome assessment to exposure: (àIf not, Knowledge of exposure status likely to influence the outcome?: no (low risk due to retrospective data collection and no possible influence) Main confounders taken into account: unclear (no adjusted data reported per outcome) Confidence intervals reported: no Selective reporting (comparison with protocol): registration number available NCT04783818 **Other limitations or comments:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.59:

Die Patientin soll darüber aufgeklärt werden, dass die adjuvante Bestrahlung der autolog rekonstruierten Brust mit einem erhöhten Auftreten von Fettgewebsnekrosen und verminderten Werten der patientenberichteten Outcomeparameter (Zufriedenheit mit der rekonstruierten Brust, körperliche Gesundheit, seelische Gesundheit) assoziiert ist.

Literaturreferenzen: [395], [396], [397], [398], [399], [400], [401], [402], [403], [404], [405], [406], [407], [408], [409], [410], [411]

Ly CL, Khetpal S, Heller DR, Higgins SA, Killelea B, Alperovich M, Avraham T. Comparing complications in irradiated and non-irradiated free-flaps in patients with bilateral immediate breast reconstruction and unilateral post-mastectomy radiotherapy. Microsurgery. 2021 Oct;41(7): 615-621. doi: 10.1002/micr.30747. Epub 2021 Apr 22. PMID: 33886127.

Study type	Population	Interventions	Main results	Methodological evaluation
Retrospective cohort study	**Inclusion criteria** (for analysis): Immediate bilateral breast reconstruction with abdominally based free-flaps followed by unilateral PMRT **Exclusion criteria** (for analysis): Prior breast radiation Implant-based rechonstruction Flap loss prior to radiation Follow-up less than 6 months	**Interventions** RT after autologous reconstruction · N = 29 No RT after autologous reconstruction · N = 28 **Analysis** Frequencies, proportions and poisson regression No matching	**Wound infection** · RT: 0/29 · No RT: 2/28 **Fat necrosis or oil cysts** · RT: 21/29 · No RT: 23/28 **Delayed wound healing or dehiscence** · RT: 1/29 · No RT: 4/28	**General information** Follow-up: mean: 58.9 ± 29.3 Funding: NR CoI: The authors declare no potential conflict of interest. **Risk of bias considerations** (adapted from SIGN cohort study checklist) Study type: retrospective review Confounding: probably (high risk)

Ly CL, Khetpal S, Heller DR, Higgins SA, Killelea B, Alperovich M, Avraham T. Comparing complications in irradiated and non-irradiated free-flaps in patients with bilateral immediate breast reconstruction and unilateral post-mastectomy radiotherapy. Microsurgery. 2021 Oct;41(7): 615-621. doi: 10.1002/micr.30747. Epub 2021 Apr 22. PMID: 33886127.				
	Incomplete radiation data **Enrolment period:** 2007 - 2017 **Follow-up** (mean, sd): 58.9 (29.3) **Descriptive statistics** Age (mean, sd): 48.9 (9.0) BMI (n (%)): · Normal (18.5–24.9): 14 (19.2%) · Overweight (25–29.9): 29 (39.7%) · obese (≥30): 30 (41.1%) Stadium · RT: NR · No RT: NR Previous Chemotherapy (% yes): 29 (39.7%) Reconstruction type (flap type) (%)	No adjustment	**Partial or total flap loss** · RT: 0/29 · No RT: 0/28 **Revision surgeries** · RT: 31/29 No RT: 30/28	Rate of participation/Exclusions reported (selection bias into the study): reasons for exclusion reported Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status: no (low risk due to retrospective data collection and no possible influence) Drop-out rate & reasons reported: not reported Outcome · Outcome measure is well-defined, valid and reliable: yes Blind outcome assessment to exposure: (àIf not, Knowledge of exposure status likely to influence the outcome?: no (low risk due to retrospective data

Ly CL, Khetpal S, Heller DR, Higgins SA, Killelea B, Alperovich M, Avraham T. Comparing complications in irradiated and non-irradiated free-flaps in patients with bilateral immediate breast reconstruction and unilateral post-mastectomy radiotherapy. Microsurgery. 2021 Oct;41(7): 615-621. doi: 10.1002/micr.30747. Epub 2021 Apr 22. PMID: 33886127.				
	· RT: DIEP (64.4%), TRAM (35.6%), SIEA (0.0%) · No RT: DIEP (63.0%), TRAM (35.6%), SIEA (1.4%)			collection and no possible influence) Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): no protocol found **Other limitations or comments:** retrospective design

Verknüpfte Empfehlungen:

Empfehlung 7.59:

Die Patientin soll darüber aufgeklärt werden, dass die adjuvante Bestrahlung der autolog rekonstruierten Brust mit einem erhöhten Auftreten von Fettgewebsnekrosen und verminderten Werten der patientenberichteten Outcomeparameter (Zufriedenheit mit der rekonstruierten Brust, körperliche Gesundheit, seelische Gesundheit) assoziiert ist.

Literaturreferenzen: [395], [396], [397], [398], [399], [400], [401], [402], [403], [404], [405], [406], [407], [408], [409], [410], [411]

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nr of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no radiotherapy	Risk with Radiotherapy			
Fat necrosis	100 per 1.000	154 per 1.000 (110 to 212)	OR 1.63 (1.11 to 2.41)	3139 (16 non-randomised studies)	⊕◯◯◯ Very low[a]
Satisfaction with breast	The mean satisfaction with breast was 69	MD 3.9 lower (7.1 lower to 0.7 lower)	-	521 (1 non-randomised study)	⊕⊕◯◯ Low[a]
Psychosocial well-being	The mean psychosocial well-being was 78	MD 5.9 lower (9.3 lower to 2.5 lower)	-	521 (1 non-randomised study)	⊕⊕◯◯ Low[a]
Physical well-being	The mean physical well-being was 77	MD 5.2 lower (7.9 lower to 2.5 lower)	-	521 (1 non-randomised study)	⊕⊕◯◯ Low[a]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nr of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no radiotherapy	Risk with Radiotherapy			

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

siehe Meta-Analysen

Explanations

a. Downgraded by two levels due to very serious risk of bias: Included studies were observational only, and the majority did not adjust at all for relevant baseline characteristics. Results are thus prone to confounding / bias by indication - those receiving radiotherapy were probably at higher stage or higher likelihood of disease progression.

Verknüpfte Empfehlungen:

Empfehlung 7.59:

Die Patientin soll darüber aufgeklärt werden, dass die adjuvante Bestrahlung der autolog rekonstruierten Brust mit einem erhöhten Auftreten von Fettgewebsnekrosen und verminderten Werten der patientenberichteten Outcomeparameter (Zufriedenheit mit der rekonstruierten Brust, körperliche Gesundheit, seelische Gesundheit) assoziiert ist.

Literaturreferenzen: [395], [396], [397], [398], [399], [400], [401], [402], [403], [404], [405], [406], [407], [408], [409], [410], [411]

Authors (year)	Study design (all cohorts)	No. of patients (R = IBR and PMRT; U = IBR only; D = PMRT and DBR)	Mean age (years)	No. of flaps	Flap type	Mean radiation dose (Gy)	Follow-up duration
Williams 1997	Retrospective	R: 19 U: 572	NK	NK	TRAM	50.3 or 49.9	NK
Tran 2000	Retrospective	R: 14 U: 14	NK	R: 14 U: 14	FTRAM, PTRAM	50.99	1 yr; M3 yrs
Rogers 2002	Retrospective	R: 30 U: 30	R: 48.2 U: 48.2	R: 32 U: 37	DIEP	50.5	R: 19.9 mos U: 17.4 mos
Spear 2005	Retrospective	R: 34 U: 78	R: 44.5 U: 49.4	R: 38 U: 91	PTRAM	NK	NK
Carlson 2008	Retrospective	R: 25 U: 128 D: 15	R: 48.9 U: 48.5 D: 44.1	R: 25 U: 149 D: 15	PTRAM	NK	NK
Mirzabeigi 2013	Retrospective	R: 46 U: 113	R: 47.0 U: 52.0	R: 46 U: 113	DIEP, MSFT, SIEA, SGAP, IGAP	NK	R: 17.8 mos U: 13.1 mos

Authors (year)	Study design (all cohorts)	No. of patients (R = IBR and PMRT; U = IBR only; D = PMRT and DBR)	Mean age (years)	No. of flaps	Flap type	Mean radiation dose (Gy)	Follow-up duration
Taghizadeh 2015	Prospective	R: 50 U: 62	R: 47.5 U: 47.1	R: 61 U: 95	DIEP	40 or 50	R: M 33.3 mos U: M 32.9 mos
Cooke 2017	Prospective	R: 64 U: 61	R: 51.2 U: 53.2	R: 64 U: 61	DIEP, SIEA	50 or 50.4	>1 year
He 2017	Retrospective	R: 61 U: 278 D: 31	NK	NK	PTRAM, DIEP	40-50.4	year
Pont 2017	Prospective	R: 77 U: 87	R: 48.2 U: 49.7	R: 81 U: 109	DIEP, MSFT, SIEA	50	NK
Myung 2018	Retrospective	R: 21 U: 21	R: 46.7 U: 47.1	R: 21 U: 21	FTRAM, DIEP	50	> 18 mos
O' Connell 2018	Retrospective	R: 28 U: 80 D: 38	R: 57.8 U: 56.8 D: 54.3a	R: 28 U: 80 D: 38	DIEP	40	R: Mdn 27.5 mos U: Mdn 48.7 mos

2.1 Evidenztabellen ohne Empfehlungsverknüpfung

2.1.1 AG 19 Lokoregionäres Rezidiv (Spronk et al. 2018)

Verknüpfte Empfehlungen:

5.1

Source: Spronk I, Schellevis FG, Burgers JS, de Bock GH, and Korevaar JC. "Incidence of Isolated Local Breast Cancer Recurrence and Contralateral Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 39 (2018-6 2018): 70-79. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29621695/.					
Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: In order to provide more guidance and an objective risk of recurrence to healthcare professionals and	**Design**: systematic review **Search date**:	**Intervention** No specific intervention stated by the author, however the outcome	**Primary Outcome**: The annual incidence rate of:	**Primary Outcome**: 1. IBTR incidence 1.1. The annual incidence rates ranged from 0.4%	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 5

Source: Spronk I, Schellevis FG, Burgers JS, de Bock GH, and Korevaar JC. "Incidence of Isolated Local Breast Cancer Recurrence and Contralateral Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 39 (2018-6 2018): 70-79. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29621695/.					
patients, we performed a systematic literature review of the incidence of isolated IBTR and CBC in women diagnosed with a first primary breast cancer. In addition, we examined whether the recurrence rates differed according to the treatment received.	from 1 January 2000 to1 October 2015. **Searched databases**: Medline, EMBASE and the Cochrane Library **Included study designs**: 12 studies were observational 8 studies had experimental design **Number of included studies**: 20, 16 studies	reportedcategorized based on the various risk factors including age, ER status, HER2 status, type of treatment **Control** No risk factor	1. Isolated ipsilateral breast tumor recurrence (IBTR) 2.Contralateral breast cancer (CBC) recurrence	to 1.1% for isolated IBTR, with a median of 0.6%.The median of annual IBTR rate decreased for primary breast cancer diagnosed before 1995 from 0.5% to 0.4% for those diagnosed in 2000 and later. 1.2. The cumulative recurrence rates ranged from 1.9% to 11.1%, with a median cumulative recurrence of 6.2%	critical flaws (items 2,4,7,9,13) **Overall quality of evidence**: critically low **Additional concerns about quality**: Limitations are the lack of information about important risk factors and given treatment with regard to the incidence of recurrence. The influence of systemic therapies could not be studied as

Source: Spronk I, Schellevis FG, Burgers JS, de Bock GH, and Korevaar JC. "Incidence of Isolated Local Breast Cancer Recurrence and Contralateral Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 39 (2018-6 2018): 70-79. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29621695/.					
	on isolated ipsilateral breast tumor recurrence (IBTR) and 5 studies on CBC (5 studies were common) **Number of included patients**: NR **Mean/median age**: NR **Inclusion criteria**: 1.Title: Included the words 'recurrence' or			(median follow-up 10.5 year). 1.3. The 5-10 year cumulative recurrence rates ranged from 1.9% to 6.0%, with a median of 3.1%. 1.4. The >10 year cumulative recurrence rates ranged from 4.8% to 11.1%, with a median of 7.9%. 2. CBC incidence	very limited number of studies reported incidence rates according to the systemic treatment given. In addition, no conclusions of the influence of ER, PR and HER2 status could be drawn, due to the low number of studies examining these determinants, varying between zero and three studies. Another limitation is the exclusion

Source: Spronk I, Schellevis FG, Burgers JS, de Bock GH, and Korevaar JC. "Incidence of Isolated Local Breast Cancer Recurrence and Contralateral Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 39 (2018-6 2018): 70-79. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29621695/.					
	‘contralateral breast cancer’ or ‘second primary breast cancer’ or related word 2.Abstract: - The primary cancer was breast cancer - Recurrence, contralateral breast cancer or second primary breast cancer diagnosis was an outcome variable			2.1. Annual incidence rate was reported between 0.2% and 0.7%, with a median rate of 0.5%. The median of annual CBC rate decreased for primary breast cancer diagnosed before 1995 from 0.5% to 0.2% for those diagnosed in 2000 and later. 2.2.Cumulative recurrence rates ranged from 1.1% to 8.3% and the median rate was 3.6%	of studies with a shorter follow-up time than a median of 5 years. The studies included often only described the median follow-up time and did not report the range. Studies with a short follow up time might be underrepresented. However, the incidence estimation might be less reliable in studies with a short follow-up time.

Source: Spronk I, Schellevis FG, Burgers JS, de Bock GH, and Korevaar JC. "Incidence of Isolated Local Breast Cancer Recurrence and Contralateral Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 39 (2018-6 2018): 70-79. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29621695/.					
	- Study was not exclusively on hereditary breast cancer or breast cancer in young women - Data originated from more than one hospital/center 3.Full text: - Original research studies conducted in curative treated female adult populations with invasive breast cancer			(median follow-up 7.5 year). 2.3.Cumulative CBC recurrence rates for 5-10 year follow-up ranged from 1.1% to 3.8% with a median of 2.4%, 2.4. The rates for >10 year follow-up ranged from 3.8% to 8.3%, the median rate was 5.0%. 3.Factors related to recurrence	Detailed information on when recurrences occur was limited in the studies included. Therefore, we were not able to indicate in which time frame after treatment most recurrences occur. The annual incidence rates calculations in present review are therefore based on the evidence that the number of recurrences is almost the same in each year after

Source: Spronk I, Schellevis FG, Burgers JS, de Bock GH, and Korevaar JC. "Incidence of Isolated Local Breast Cancer Recurrence and Contralateral Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 39 (2018-6 2018): 70-79. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29621695/.					
	- Published in peer-reviewed journals - Data originated from more than one hospital/center - Years of primary breast cancer diagnosis included 1995 or more recent - A median follow-up of at least 5 years - Recurrence was isolated IBTR or CBC			3.1.Age A young age (<40) at diagnosis resulted in higher recurrence incidence rates for both isolated IBTR and CBC. 3.2.ER status Annual recurrence rate (range, n = number of studies) for IBTR among patients with positive ER was 0.4% (0.2-0.5%, n =	treatment. Other limitations included the variability in studies. As we expected, the studies were too heterogeneous in study population, length of follow-up and years of primary diagnosis of the included studies to perform a meta-analysis, which would have, strengthen our results.

Source: Spronk I, Schellevis FG, Burgers JS, de Bock GH, and Korevaar JC. "Incidence of Isolated Local Breast Cancer Recurrence and Contralateral Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 39 (2018-6 2018): 70-79. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29621695/.					
	- Incidence, or a denominator and nominator to calculate incidence was provided - The initial breast cancer was an invasive breast cancer ***Exclusion**:* Studies exclusively focusing on hereditary breast cancer and breast cancer in young women were excluded. Conference abstracts,			2) and among ER negative was 0.4% (n = 1) Annual recurrence rate (range, n = number of studies) for CBC among patients with positive ER was 0.3% (0.3-0.5%, n = 3) and among ER negative was 0.5% (0.4-0.6%, n = 2). 3.3.HER2 status Annual recurrence rate (range, n = number of studies) for IBTR among	**Quality of included studies:** **Assessed but not reported** **Planned included studies** As in the review, it is not clear which of recruited articles used to make the evidence for different interventions, GRADE assessment is not possible.

Source: Spronk I, Schellevis FG, Burgers JS, de Bock GH, and Korevaar JC. "Incidence of Isolated Local Breast Cancer Recurrence and Contralateral Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 39 (2018-6 2018): 70-79. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29621695/.					
	expert reviews, reports and these were excluded			patients with positive HER2 was 0.6% (0.6-0.6%, n = 2) and among HER2 negative was 0.5% (0.4-0.5%, n =1) Annual recurrence rate (range, n = number of studies) for CBC among patients with positive HER2 was 0.2% (n = 1) and among ER negative was 0.3% (n = 1) 4.Recurrence rate based on type of treatment	Due to non-RCT nature of included studies, we propose to downgrade the **level of evidence** to **2b** **Sources of funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Source: Spronk I, Schellevis FG, Burgers JS, de Bock GH, and Korevaar JC. "Incidence of Isolated Local Breast Cancer Recurrence and Contralateral Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 39 (2018-6 2018): 70-79. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29621695/.					
				4.1. IBTR Annual recurrence rate (range, n = number of studies) for IBTR among patients: 4.1.1 With Breast conservative surgery with radiotherapy was 0.5% (0.4-1.1%, n = 10). 4.1.2. With Breast conservative surgery without radiotherapy 0.4% (0.4-0.5%, n = 2).	

Source: Spronk I, Schellevis FG, Burgers JS, de Bock GH, and Korevaar JC. "Incidence of Isolated Local Breast Cancer Recurrence and Contralateral Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 39 (2018-6 2018): 70-79. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29621695/.					
				4.1.3. Mastectomy with radiotherapy 0.5% (0.2-0.7%, n = 2). 4.1.4. Mastectomy without radiotherapy 0.7% (0.5-0.9%, n = 4). 4.2.CBC Annual recurrence rate (range, n = number of studies) for Contralateral breast cancer (CBC) recurrence among patients:	

Source: Spronk I, Schellevis FG, Burgers JS, de Bock GH, and Korevaar JC. "Incidence of Isolated Local Breast Cancer Recurrence and Contralateral Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 39 (2018-6 2018): 70-79. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29621695/.					
				4.2.1.With Breast conservative surgery with radiotherapy was 0.5% (0.2-0.5%, n = 3) 4.2.2. with Breast conservative surgery without radiotherapy 0.2% (n = 1)	
Abbreviations: IBTR = ipsilateral breast tumor recurrence					

Source: Spronk I, Schellevis FG, Burgers JS, de Bock GH, and Korevaar JC. "Incidence of Isolated Local Breast Cancer Recurrence and Contralateral Breast Cancer: A Systematic Review." [In eng]. Breast (Edinburgh, Scotland) 39 (2018-6 2018): 70-79. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/29621695/.					
CBC = Contralateral breast cancer ER = Estrogen Receptor PR = Progesterone Receptor HER2 = Human Epidermal Growth Factor Receptor 2 non-RCT = Non-Randomized Controlled Trial NR =					

2.1.2 AG 19 Lokoregionäres Rezidiv (He et al. 2017)

Verknüpfte Empfehlungen:

5.1

Source: XM, He, and Zou DH. 2017: "The Association of Young Age with Local Recurrence in Women with Early-Stage Breast Cancer after Breast-Conserving Therapy: A Meta-Analysis."					
Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: to determine the relationship between young age and local recurrence in patients with early-stage breast cancer after breast-conserving therapy	**Design**: systematic review and meta-analysis **Search date**: until 07/2016 **Search time frame**: **Searched databases**: PubMed, EMBASE, CNKI, CBM, VIP, Wanfang, and CENTRAL **Included study designs**:	**Intervention** younger patients **Control** older patients(older than 35, 40, or 45 years depending on the definition used in individual studies)	**Primary Outcome**: rate of local recurrence of breast cancer **Secondary Outcome:** NR	**Primary Outcome**: 1. 5-year local recurrence rate: young patients were at higher risk of 5-yearlocal recurrence: RR=2.64, 95% CI (1.94–3.60) 2. 10-year local recurrence rate: young patients were at higher risk of 10-year	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 2 critical flaws (items 2,7) **Overall quality of evidence**: critically low **Additional concerns about quality**: Studies included in this meta-analysis are

Source: XM, He, and Zou DH. 2017: "The Association of Young Age with Local Recurrence in Women with Early-Stage Breast Cancer after Breast-Conserving Therapy: A Meta-Analysis."					
	Non RCT **Number of included studies**: 19 studies including 14 studies for 5-year local recurrence rate and 8 studies for 10-year local recurrence rate **Number of included patients**: 1.from the 14 studies included for 5-year local recurrence: 1,285 patients in the young group and 11,830 patients in the old group 2. from the 8 studies included for 5-year local recurrence: 812 patients in the young group and			local recurrence: RR=2.37, 95% CI (1.57–3.58) **Secondary Outcome**: NR **1.Subgroup analysis by age definition:** Based on the definition of young by each study, the could be stratified into three groups of ages ≤35, ≤40, and ≤ 45 1.1. Subgroup analyses by age definitions showed significant differences in the 5-year local recurrence rate between the young and old patients (≤35 years: RR=2.60, 95% CI (1.45–	published studies. The results that achieved statistical signifcance have a greater chance to be reported or published when compared to those results that are invalid or failed to achieve statistical significance. This phenomenon will exaggerate the effect of the group tested. We also did not analyze the effects of other age-related factors, such as the levels of estrogen, progesterone, progesterone receptor, and HER2 receptor, on local recurrence. These factors could be included

Source: XM, He, and Zou DH. 2017: "The Association of Young Age with Local Recurrence in Women with Early-Stage Breast Cancer after Breast-Conserving Therapy: A Meta-Analysis."					
	5059 patients in the old group **Mean/median age**: NR **Inclusion criteria**: Subjects were eligible for inclusion if the following criteria were met: (1) subjects had primary breast cancer without both distant metastasis and other severe concurrent diseases diagnosed by clinical symptoms, physical signs, X-ray, pathology and cytology examinations; (2) underwent conserving surgery followed by standard treatment of			4.69); ≤40 years old: RR=2.98, 95% CI (2.27–3.90); ≤45 years old: RR=2.02, 95% CI (1.40–2.92). 1.2.For the analyses of 10-year local recurrence rate, results showed significant differences in the subgroups of ages≤35 and≤40 (RR=3.52, 95% CI (1.52–8.16), and RR=2.57, 95% CI (1.94–3.41) respectively), but not in the subgroup of age≤45 (RR=1.03, 95% CI (0.80–1.31)) **2.Subgroupanalysis by region:**	in future studies for a more convincing result. **Quality of included studies:** The included studies were assessed for risk of bias using Newcastle-Ottawa Scale(in which the study with the highest quality is awarded a maximum of nine stars).Accordingly: The quality of the included studies ranges between 6–8 stars. There were 3 studies with a score of 6 stars, 11 with 7 stars, and 5 with 8 stars.

Source: XM, He, and Zou DH. 2017: "The Association of Young Age with Local Recurrence in Women with Early-Stage Breast Cancer after Breast-Conserving Therapy: A Meta-Analysis."					
	whole breast radiation; and (3) had a minimum of 5 years follow up. There was no bias related to age, race, ethnicity, or nationality when selecting subjects. ***Exclusion***: Studies were excluded according to the following criteria: (1) studies without clear diagnosis, inclusion and exclusion criteria of subjects; (2) studies with all subjects under the age of 40; (3) subjects who underwent radio- or chemotherapies before conserving therapy; (4)			2.1. The 5-year local recurrence rates were significantly different between the young and old in the United States and (RR=2.95, 95% CI (1.53–5.67)) and Europe (RR=2.52, 95% CI (1.99–3.19)). However, pooled RRs from two studies in the subgroup of others showed no difference in the 5-year local recurrence rate (RR=1.17, 95% CI (0.10–13.39)) 2.2. The 10-year local recurrence rates were significantly different in all of the subgroup analyses (the United States: RR=4.24,95% CI	Overall, the qualities of the included studies were high. **Sources of funding:** NR

Source: XM, He, and Zou DH. 2017: "The Association of Young Age with Local Recurrence in Women with Early-Stage Breast Cancer after Breast-Conserving Therapy: A Meta-Analysis."					
	studies with inaccurate or incomplete data that were unable to provide outcomes; and (5) studies published repeatedly			(1.85–9.73); Europe: RR=1.99,95% CI (1.20–3.29); Others: RR=2.27,95% CI (1.28–4.03))	
Abbreviations: RCT = Randomized Controlled Trial RR = Risk Ratio 95% CI = 95% Confidence Interval NR = not Reported					

2.1.3 Kapitel 7.4 Transgender und Brustkrebs (Hartley et al. 2018)

Verknüpfte Empfehlungen:

Source: RL, Hartley, Stone JP, and Temple-Oberle C. "Breast Cancer in Transgender Patients: A Systematic Review. Part 1: Male to Female." [In eng]. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 44, no. 10 (2018-10 2018): 1455-62. https://doi.org/doi: . https://pubmed.ncbi.nlm.nih.gov/30087072/.					
Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: The objective is to systematically identify and describe breast cancer clinical presentation in Male-to-Female (MtF) transgender	**Design**: Systematic Review **Search date**: from inception to 01. April 2018		**Incidence**	**Incidence**: The reviewers found MtF breast cancer to be uncommon but when	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: 3

Source: RL, Hartley, Stone JP, and Temple-Oberle C. "Breast Cancer in Transgender Patients: A Systematic Review. Part 1: Male to Female." [In eng]. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 44, no. 10 (2018-10 2018): 1455-62. https://doi.org/doi: . https://pubmed.ncbi.nlm.nih.gov/30087072/.					
patients and provide research recommendations.	**Searched databases**: Medline, ProQuest, Pubmed, Cochrane Database of Systematic Review **Included study designs**: Case Report, Retrospective Cohort, Cross-sectional, Case series			present, commonly occurs in younger patients on CSH as a palpable mass. As with natal female patients, physicians should be encouraged to educate their transgender patients on signs and symptoms of	critical flaws (items 2, 7, 13) **Overall quality of evidence**: critically low **Additional concerns about quality**: The major limitation to this study is the quality of evidence upon which the data was drawn.

Source: RL, Hartley, Stone JP, and Temple-Oberle C. "Breast Cancer in Transgender Patients: A Systematic Review. Part 1: Male to Female." [In eng]. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 44, no. 10 (2018-10 2018): 1455-62. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih. gov/30087072/.					
	Number of included studies: 18 **Number of included patients**: 22 MtF **Median age at diagnosis**: 51,5 years (range 27-69) **Exclusion**: Articles with no transgender patients, no			breast cancer.	***Quality of included studies:*** *Overall, study quality was poor.* **Planned included studies**: / Due to the small study population we propose to downgrade the **level of evidence** from 3a to **3b**

Source: RL, Hartley, Stone JP, and Temple-Oberle C. "Breast Cancer in Transgender Patients: A Systematic Review. Part 1: Male to Female." [In eng]. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 44, no. 10 (2018-10 2018): 1455-62. https://doi.org/doi: . https://pubmed.ncbi.nlm.nih.gov/30087072/.					
	confirmed breast cancer events (confirmation by histological examination) in transgender patients or no breast cancer screening in transgender patients.				**Sources of funding:** None financial support.
Abbreviations: MtF = Male-to-Female					

Source: RL, Hartley, Stone JP, and Temple-Oberle C. "Breast Cancer in Transgender Patients: A Systematic Review. Part 1: Male to Female." [In eng]. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 44, no. 10 (2018-10 2018): 1455-62. https://doi.org/doi: . https://pubmed.ncbi.nlm.nih.gov/30087072/.					
CSH = Cross-Sex Hormone					

2.1.4 Kapitel 4.1 Lokoregional begrenzte Primärerkrankung (Jiwa 2022)

Verknüpfte Empfehlungen:

Source: Jiwa, N, Kumar, S, Gandhewar, R, Chauhan, H, Nagarajan, V, Wright, C, et.al. Diagnostic Accuracy of Nipple Discharge Fluid Cytology: A Meta-Analysis and Systematic Review of the Literature.. Ann Surg Oncol, 2022. 29 (3)(3): p. 1774-1786., https://pubmed.ncbi.nlm.nih.gov/34839426/					
Aim	Design and participants	Index and Reference standard	Outcomes	Results	Quality and comment
Aim: Primary aim was to compute the diagnostic accuracy of nipple discharge fluid cytology for symptomatic women presenting to the breast clinic. Secondary aim was to investigate the variations	**Design**: Systematic Review and Meta-Analysis **Search date**: until 03/2020 **Searched databases**: Medline, Embase, Scopus	**Intervention** Nipple discharge fluid cytology **Control/Reference standards** histopathology gold standard	**Outcome** diagnostic accuracy of nipple discharge fluid cytology pathologic nipple discharge (PND):	**Outcome**: **diagnostic accuracy of nipple discharge fluid cytology** nipple aspirate fluid: sensitivity of 0.75 (95 % CI, 0.74–0.77)	**ROBIS** **Risk of bias in the review:** Unclear **Additional concerns about quality**: No protocol

Source: Jiwa, N, Kumar, S, Gandhewar, R, Chauhan, H, Nagarajan, V, Wright, C, et.al. Diagnostic Accuracy of Nipple Discharge Fluid Cytology: A Meta-Analysis and Systematic Review of the Literature.. Ann Surg Oncol, 2022. 29 (3)(3): p. 1774-1786., https://pubmed.ncbi.nlm.nih.gov/34839426/					
in the management of PND in terms of presentation, imaging, pathology, and surgery as well as the diagnostic accuracy of other methods including ultrasound, MRI, and ductoscopy.	**Included study designs**: clinical studies (not further defined) **Number of included studies in Meta-Analysis**: 45 **Number of included cytology samples**: 8,648 **Mean age**: 48.74 ± 4.66 **Inclusion criteria**: clinical studies with primary data on the		diagnostic accuracy of imaging methods	specificity of 0.87 (95 % CI, 0.86–0.87) for a benign diagnosis (Cn2) relative sensitivity of 0.62 (95% CI, 0.53–0.71) specificity 0.71 (95% CI,0.57–0.81) for breast carcinoma (Cn3/4/5) only Cn5 cytology considered absolute sensitivity of cytology 0.35 (95 % CI, 0.26–0.44) specificity 1.00 (95 % CI, 1.00–1.00	Included study designs not further defined **Quality of included studies**: QUADAS-2 heterogeneous Due to the use of gold standards of histopathology as a reference, we suggest **level of evidence 2b** **Sources of funding:** The research was funded by the NIHR Imperial Biomedical Research Centre (BRC). The study

Source: Jiwa, N, Kumar, S, Gandhewar, R, Chauhan, H, Nagarajan, V, Wright, C, et.al. Diagnostic Accuracy of Nipple Discharge Fluid Cytology: A Meta-Analysis and Systematic Review of the Literature.. Ann Surg Oncol, 2022. 29 (3)(3): p. 1774-1786., https: //pubmed.ncbi.nlm.nih. gov/34839426/					
	diagnostic accuracy of nipple discharge fluid cytology versus ductal histology foreign language studies with English translation studies diagnostic information on benign and/or malignant diagnoses from cytology and on pathologic nipple discharge of all clinical descriptions			**pathologic nipple discharge (PND):** **diagnostic accuracy of imaging methods** <u>Ultrasound</u> pooled sensitivity of 0.70 (95 % CI, 0.60–0.80) a pooled specificity of 0.58 (95 % CI, 0.24–0.75) with a positive predictive value (PPV) of 0.78 (95 % CI, 0.56–0.99) <u>Mammogram</u>	had no commercial interest and no external financial or material support.

Source: Jiwa, N, Kumar, S, Gandhewar, R, Chauhan, H, Nagarajan, V, Wright, C, et.al. Diagnostic Accuracy of Nipple Discharge Fluid Cytology: A Meta-Analysis and Systematic Review of the Literature.. Ann Surg Oncol, 2022. 29 (3)(3): p. 1774-1786., https: //pubmed.ncbi.nlm.nih. gov/34839426/					
	(i.e., single duct, blood-stained, clear) studies that included direct expression of discharge as well as dutoscopy to retrieve a fluid sample were included if patients presented with pathologic nipple discharge. **Exclusion**: if English full text not available			pooled sensitivity of 0.38 (95 % CI, 0.23–0.52), pooled specificity of 0.79 (95 % CI, 0.69–0.90) and a PPV of 0.49 (95 % CI, 0.24–0.75) Magnetic resonance imaging pooled sensitivity of 0.70 (95 % CI, 0.61–0.78)	

Source: Jiwa, N, Kumar, S, Gandhewar, R, Chauhan, H, Nagarajan, V, Wright, C, et.al. Diagnostic Accuracy of Nipple Discharge Fluid Cytology: A Meta-Analysis and Systematic Review of the Literature.. Ann Surg Oncol, 2022. 29 (3)(3): p. 1774-1786., https: //pubmed.ncbi.nlm.nih. gov/34839426/					
	Animal studies, case reports, male BC studies, pregnancy-associated BC studies Papers reporting only on brush cytology			pooled specificity of 0.45 (95 % CI, 0.20–0.70) with a PPV of 0.57 (95 % CI, 0.55–0.79) <u>Galactography</u> pooled sensitivity of 0.62 (95 % CI, 0.13–1.11) pooled specificity of 0.52 (95 % CI, 0.04–1.00) and a PPV of 0.48 (95 % CI, 0.00–0.95)	

Source: Jiwa, N, Kumar, S, Gandhewar, R, Chauhan, H, Nagarajan, V, Wright, C, et.al. Diagnostic Accuracy of Nipple Discharge Fluid Cytology: A Meta-Analysis and Systematic Review of the Literature.. Ann Surg Oncol, 2022. 29 (3)(3): p. 1774-1786., https://pubmed.ncbi.nlm.nih.gov/34839426/					
Abbreviations: PND = Pathologic Nipple Discharge BC = Breast Cancer i.e. = id est 95% CI = 95% Confidence Interval PPV = Positive Predictive Value					

2.1.5 Trastuzumab-Emtansin versus Trastuzumab beim HER2-positiven frühen Mammakarzinom und invasiver Resterkrankung in der Brust und / oder den Lymphknoten nach neoadjuvanter Taxan-basierter und HER2-gerichteter Therapie

Verknüpfte Empfehlungen:

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Trastuzumab Emtansin (Neues Anwendungsgebiet: Mammakarzinom, Frühstadium, HER2+, adjuvante Behandlung)			
Wirkstoff	Trastuzumab Emtansin	**Handelsname**	Kadcyla
Pharmazeutischer Unternehmer	Roche Pharma AG	**Beschlussdatum**	02.07.2020
Anwendungsgebiet	Mammakarzinom		

Population/ZVT	Titel	Mortalität	Morbidiät	QoL	Sicherheit	Zusatznutzen
A	Erwachsene Patientinnen und Patienten mit HER2-positivem Brustkrebs im Frühstadium, die nach einer neoadjuvanten	↔ Kein für die Nutzenbewertung relevanter Unterschied, keine finalen Daten.	↑↑ Vorteile bei der Vermeidung von Rezidiven, Nachteile in Symptomskalen.	↓ Nachteile in Funktionsskalen.	↓↓ Nachteile in den Endpunkten schwerwiegenden unerwünschte Ereignisse (UE),	Hinweis: gering

Population/ZVT	Titel	Mortalität	Morbidiät	QoL	Sicherheit	Zusatznutzen
	Taxan-basierten und HER2-gerichteten Therapie eine invasive Resterkrankung in der Brust und / oder den Lymphknoten aufweisen				schweren UE (CTCAE Grad ≥ 3) und Therapieabbrüchen aufgrund von UE sowie im Detail bei spezifischen UE.	
ZVT	Fortführung der präoperativ begonnenen, anti-HER2-gerichteten Therapie mit Trastuzumab					
↑↑/↓↓: positiver/negativer statistisch signifikanter Effekt, hohe Aussagesicherheit; ↑/↓: positiver/negativer statistisch signifkanter Effekt, niedrige oder unklare Aussagesicherheit;						

Population/ZVT	Titel	Mortalität	Morbidiät	QoL	Sicherheit	Zusatznutzen
↔: kein signifikanter/relevanter Unterschied; ↓: n.b.: nicht bewertbar; Ø: keine Daten						

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung eines neuen Anwendungsgebietes für den Wirkstoff Trastuzumab Emtansin.
Das hier bewertete Anwendungsgebiet lautet: Trastuzumab Emtansin wird als Einzelsubstanz zur adjuvanten Behandlung bei erwachsenen Patienten mit HER2-positivem Brustkrebs im Frühstadium angewendet, die nach einer neoadjuvanten Taxan-basierten und HER2-gerichteten Therapie eine invasive Resterkrankung in der Brust und/oder den Lymphknoten aufweisen.
Die zweckmäßige Vergleichstherapie wurde wie folgt vom G-BA bestimmt:
Fortführung der präoperativ begonnenen, anti-HER2-gerichteten Therapie mit Trastuzumab.
Für die Bewertung legt der pharmazeutische Unternehmer Ergebnisse aus der noch laufenden, offenen, kontrollierten, randomisierten Parallelgruppenstudie KATHERINE vor, in der Trastuzumab Emtansin mit Trastuzumab verglichen wird.
Hinsichtlich der Mortalität zeigen die vorliegenden Ergebnisse, auf der Basis einer insgesamt geringen Anzahl an Ereignissen, zum Endpunkt Gesamtüberleben keinen statistisch signifikanten Effekt. Die finalen Daten zum Gesamtüberleben stehen noch aus.
Trastuzumab Emtansin zeigt im Vergleich zu Trastuzumab einen deutlichen Vorteil in der Vermeidung von Rezidiven. Die Vermeidung von Rezidiven stellt ein essentielles Therapieziel in der vorliegenden kurativen Therapiesituation dar.
Hinsichtlich der Symptomatik wird ein deutlicher Nachteil bei der Behandlung mit Trastuzumab Emtansin festgestellt.
Es zeigen sich nachteilige Effekte bei der gesundheitsbezogenen Lebensqualität unter der Behandlung mit Trastuzumab Emtansin.
Bei den Nebenwirkungen wurde eine Zunahme an schwerwiegenden unerwünschten Ereignisse, an schweren unerwünschten Ereignissen (CTCAE-Grad ≥ 3) und Therapieabbrüchen aufgrund von unerwünschten Ereignissen unter Trastuzumab Emtansin beobachtet.
Es verbleiben Unsicherheiten bei der Interpretation der Ergebnisse zum Gesamtüberleben aufgrund der geringen Ereigniszahlen.
In der Gesamtbetrachtung der Ergebnisse stehen einem deutlichen Vorteil in der Vermeidung von Rezidiven bedeutsame negative Effekte bei der Symptomatik, der Lebensqualität und den Nebenwirkungen gegenüber. Die Nachteile werden vor dem Hintergrund des vorliegenden kurativen Therapieanspruches gewichtet.
In der Gesamtschau wird ein Hinweis auf einen geringen Zusatznutzen von Trastuzumab Emtansin gegenüber Trastuzumab festgestellt.
Der Beschluss ist bis zum 30.09.2024 befristet.

Für die erneute Nutzenbewertung nach Fristablauf sollen im Dossier die für das Jahr 2024 erwarteten Ergebnisse aus der finalen Analyse zum Gesamtüberleben sowie zu weiteren patientenrelevanten Endpunkten, die für den Nachweis eines Zusatznutzens herangezogen werden, aus der Studie KATHERINE vorgelegt werden.

A Randomized, Multicenter, Open-Label Phase III Study to Evaluate the Efficacy and Safety of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy for Patients With HER2-Positive Primary Breast Cancer Who Have Residual Tumor Present Pathologically in the Breast or Axillary Lymph Nodes Following Preoperative Therapy (NCT01772472)					
Short Name	Design	Population	Intervention	Comparator	Outcomes
KATHERINEBO27938, 2012-002018-37	Randomized, Parallel Assignment, Phase 3 Open Label study	Latin American, Colored or Asian with ECOG 0-1 Breast Cancer	Trastuzumab emtansine (N=743)[1]	Trastuzumab (N=743)[2]	• Secondary: Overall Survival (OS)
Notes - Study					

A Randomized, Multicenter, Open-Label Phase III Study to Evaluate the Efficacy and Safety of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy for Patients With HER2-Positive Primary Breast Cancer Who Have Residual Tumor Present Pathologically in the Breast or Axillary Lymph Nodes Following Preoperative Therapy (NCT01772472)					
Open Label Study					
Notes - Study Arms					
1: Trastuzumab Emtansin, 3,6 mg/kg i. v. an Tag 1 eines 21-Tage-Zyklus, insgesamt 14 Zyklen2: Trastuzumab, 6 mg/kg i. v.a an Tag 1 eines 21-Tage-Zyklus, insgesamt 14 Zyklen					

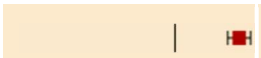
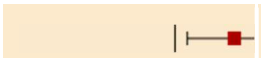
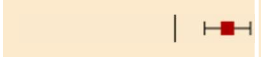
Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
Trastuzumab Emtansin vs. Trastuzumab zur Behandlung von Erwachsenen mit HER2-positivem Brustkrebs im Frühstadium, die nach einer neoadjuvanten Taxan-basierten und HER2-gerichteten Therapie eine invasive Resterkrankung in der Brust und / oder den Lymphknoten aufweisen: Studie KATHERINE							
Dichotomous Outcomes							

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
DFS - Time To Event[2,3]	N=743	NA	N=743	NA	HR 0.53 [0.41; 0.68]; p< 0,001		⊕⊕⊕⊖[a]
OS - Time To Event[1]	N=743	NA42 (5.65%)	N=743	NA56 (7.54%)	HR 0.7 [0.47; 1.05]; p=0.085		⊕⊕⊕⊖[a]
EORTC QLQ-BR23 (SA)[5]	N=534	190 (35.58%)	N=534	150 (28.09%)	RR 1.27 [1.061; 1.512]; p=0.009		⊕⊕⊖⊖[b,c]
EORTC QLQ-BR23 (SCA)[5]	N=534	99 (18.54%)	N=534	88 (16.48%)	RR 1.13 [0.867; 1.46]; p=0.376		⊕⊕⊖⊖[b,c]
EORTC QLQ-BR23 (SEST)[5]	N=534	144 (26.97%)	N=534	94 (17.6%)	RR 1.53 [1.216; 1.929]; p< 0,001		⊕⊕⊖⊖[b,c]
EORTC QLQ-C30 (Diarrhea)[5,6]	N=534	40 (7.49%)	N=536	56 (10.45%)	RR 0.72 [0.487; 1.056]; p=0.091		⊕⊕⊖⊖[b,c]
EORTC QLQ-C30 (Constipation)[5,6]	N=534	159 (29.78%)	N=536	97 (18.1%)	RR 1.65 [1.317; 2.055]; p< 0,001		⊕⊕⊖⊖[b,c]
EORTC QLQ-C30 (Lack of Appetite)[5,6]	N=534	101 (18.91%)	N=536	58 (10.82%)	RR 1.75 [1.295; 2.359]; p< 0,001		⊕⊕⊖⊖[b,c]

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
EORTC QLQ-C30 (Dyspnea)[5,6]	N=534	111 (20.79%)	N=536	111 (20.71%)	RR 1 [0.794; 1.269]; p=0.975		⊕⊕⊖⊖[b,c]
EORTC QLQ-C30 (Pain)[5,6]	N=534	177 (33.15%)	N=536	146 (27.24%)	RR 1.22 [1.013; 1.462]; p=0.036		⊕⊕⊖⊖[b,c]
EORTC QLQ-C30 (Nausea)[5,6]	N=534	89 (16.67%)	N=536	63 (11.75%)	RR 1.42 [1.051; 1.913]; p=0.022		⊕⊕⊖⊖[b,c]
EORTC QLQ-C30 (Fatigue)[5,6]	N=534	211 (39.51%)	N=536	175 (32.65%)	RR 1.21 [1.031; 1.421]; p=0.020		⊕⊕⊖⊖[b,c]
EORTC QLQ-C30 (Insomnia)[5,6]	N=534	140 (26.22%)	N=536	142 (26.49%)	RR 0.99 [0.81; 1.209]; p=0.919		⊕⊕⊖⊖[b,c]
EQ-5D (VAS)[7]	N=526	118 (22.43%)	N=532	97 (18.23%)	RR 1.23 [0.968; 1.564]; p=0.091		⊕⊕⊖⊖[b,c]
Recurrence Rate[4]	N=743	98 (13.19%)	N=743	167 (22.48%)	RR 0.59 [0.467; 0.737]; p< 0,001		⊕⊕⊕⊕
EORTC QLQ-BR23 (Body Image)[5]	N=534	91 (17.04%)	N=534	106 (19.85%)	RR 0.86 [0.667; 1.106]; p=0.237		⊕⊕⊖⊖[b,c]

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
EORTC QLQ-BR23 (Future Perspective)[5]	N=534	106 (19.85%)	N=534	91 (17.04%)	RR 1.16 [0.904; 1.5]; p=0.2374		⊕⊕⊖⊖[b,c]
EORTC QLQ-C30 (Cognitive Function)[5,6]	N=534	201 (37.64%)	N=535	190 (35.51%)	RR 1.06 [0.9; 1.24]; p=0.471		⊕⊕⊖⊖[b,c]
EORTC QLQ-C30 (Social Function)[5,6]	N=534	131 (24.53%)	N=535	102 (19.07%)	RR 1.29 [1.023; 1.618]; p=0.031		⊕⊕⊖⊖[b,c]
EORTC QLQ-C30 (Role Function)[5,6]	N=534	141 (26.4%)	N=536	122 (22.76%)	RR 1.16 [0.94; 1.432]; p=0.167		⊕⊕⊖⊖[b,c]
EORTC QLQ-C30 (Physical Function)[5,6]	N=534	120 (22.47%)	N=535	91 (17.01%)	RR 1.32 [1.034; 1.687]; p=0.025		⊕⊕⊖⊖[b,c]
EORTC QLQ-C30 (Global Health Status)[5,6]	N=534	123 (23.03%)	N=535	112 (20.93%)	RR 1.1 [0.878; 1.38]; p=0.4076		⊕⊕⊖⊖[b,c]

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
EORTC QLQ-C30 (Emotional Function)[5,6]	N=534	208 (38.95%)	N=535	198 (37.01%)	RR 1.05 [0.9; 1.23]; p=0.513		⊕⊕⊖⊖[b,c]
AE - periphere sensorische Neuropathie [22]	N=740	10 (1.35%)	N=720	0 (0%)			⊕⊕⊕⊖
AE - Kopfschmerz[21]	N=740	210 (28.38%)	N=720	122 (16.94%)	RR 1.67 [1.374; 2.042]; p<0.001		⊕⊕⊕⊖[c]
AE - Stomatitis[20]	N=740	80 (10.81%)	N=720	27 (3.75%)	RR 2.88 [1.887; 4.405]; p<0.001		⊕⊕⊕⊖[c]
AE - Mundtrockenheit [19]	N=740	100 (13.51%)	N=720	9 (1.25%)	RR 10.81 [5.508; 21.219]; p<0.001		⊕⊕⊕⊖[c]
AE - Erbrechen[18]	N=740	108 (14.59%)	N=720	37 (5.14%)	RR 2.84 [1.983; 4.067]; p<0.001		⊕⊕⊕⊖[c]
AE - Obstipation[17]	N=740	126 (17.03%)	N=720	59 (8.19%)	RR 2.08 [1.552; 2.782]; p<0.001		⊕⊕⊕⊖[c]

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
AE - Übelkeit[16]	N=740	308 (41.62%)	N=720	94 (13.06%)	RR 3.19 [2.592; 3.921]; p<0.001		⊕⊕⊕⊖[c]
AE - Erkrankungen des Gastrointestinaltrakts [15]	N=740	21 (2.84%)	N=720	7 (0.97%)	RR 2.92 [1.249; 6.824]; p=0.009		⊕⊕⊕⊕
AE - Fieber[14]	N=740	77 (10.41%)	N=720	29 (4.03%)	RR 2.58 [1.707; 3.91]; p<0.001		⊕⊕⊕⊖[c]
AE - Thrombozytenzahl vermindert[12]	N=740	42 (5.68%)	N=720	2 (0.28%)	RR 20.43 [4.964; 84.095]; p<0.001		⊕⊕⊕⊕
AE - Herzerkrankungen[11]	N=740	2 (0.3%)	N=720	7 (1%)	RR 0.28 [0.06; 1.334]; p< 0,088		⊕⊕⊕⊕
AE[10]	N=740	190 (25.68%)	N=720	111 (15.42%)	RR 1.67 [1.349; 2.056]; p< 0,001		⊕⊕⊕⊕
AE[8]	N=740	731 (98.78%)	N=720	672 (93.33%)	RR 1.06 [1.036; 1.081]; p=0.0000		⊕⊕⊕⊖[c]

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
AE - Erkrankungen der Atemwege, des Brustraums und Mediastinums[24]	N=740	329 (44.46%)	N=720	219 (30.42%)	RR 1.46 [1.275; 1.676]; p<0.001		⊕⊕⊕⊖[c]
AE - Ermüdung[13]	N=740	366 (49.46%)	N=720	243 (33.75%)	RR 1.47 [1.292; 1.662]; p<0.001		⊕⊕⊕⊖[c]
AE - Augenerkrankungen[25]	N=740	133 (17.97%)	N=720	63 (8.75%)	RR 2.05 [1.55; 2.722]; p<0.001		⊕⊕⊕⊖[c]
AE-Disc	N=740	133 (17.97%)	N=720	15 (2.08%)	RR 8.63 [5.109; 14.567]; p< 0,001		⊕⊕⊕⊖[d]
SAE[9]	N=740	94 (12.7%)	N=720	58 (8.06%)	RR 1.58 [1.156; 2.152]; p=0.004		⊕⊕⊕⊕
SAE - Infektionen und parasitäre Erkrankungen[23]	N=740	37 (5%)	N=720	21 (2.92%)	RR 1.71 [1.014; 2.9]; p=0.042		⊕⊕⊕⊕

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
*Database cutoff: 23.07.2018							
1: Medianes Gesamtüberleben nicht erreicht;2: Medianes krankheitsfreies Überleben nicht erreicht; 3: im DFS berücksichtigte Ereignisse: siehe Rezidivrate; 4: Rezidivrate: umfasst die Ereignisse: ipsilaterales invasives lokales Brustkrebsrezidiv, ipsilaterales invasives regionäres Brustkrebsrezidiv, Fernrezidiv, kontralateraler invasiver Brustkrebs,							

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
sekundäres Primärkarzinom (kein Brustkrebs), DCIS (ipsilateral oder kontralateral) und Tod jedweder Ursache; 5: Anteil an Personen mit Verschlechterung um ≥ 10 Punkte zum Therapieende; 6: Score range 0-100; 7: Gesundheitszustand (EQ-5D VAS) (Verschlechterung um ≥ 10 Punkte) Therapieende; 8: UE jeglichen Schweregrades - Gesamtrate; 9: Schwerwiegende UE - Gesamtrate; 10: Schwere UE - Gesamtrate; 11: Herzerkrankungen (SOC, CTCAE-Grad							

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
≥ 3); 12: Thrombozytenzahl vermindert (PT, CTCAE-Grad ≥ 3); 13: Ermüdung (PT, UE); 14: Fieber (PT, UE); 15: Erkrankungen des Gastrointestinaltrakts (SOC, CTCAE-Grad ≥ 3); 16: Übelkeit (PT, UE); 17: Obstipation (PT, UE); 18: Erbrechen (PT, UE); 19: Mundtrockenheit (PT,UE); 20: Stomatitis (PT, UE); 21: Kopfschmerz (PT, UE); 22: periphere sensorische Neuropathie (PT, CTCAE-Grad ≥ 3); 23: Infektionen und parasitäre Erkrankungen							

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
(SOC, SUE); 24: Erkrankungen der Atemwege, des Brustraums und Mediastinums (SOC, UE); 25: Augenerkrankungen (SOC, UE)							
a: Mediane Überlebenzeit nicht erreicht;b: hoher Anteil nicht in der Auswertung berücksichtigter Personen (> 10 %); c: fehlende Verblindung bei subjektiver Endpunkterhebung; d: fehlende Verblindung bei subjektiver Entscheidung zum Therapieabbruch							

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
AE: Adverse Events; AE-Disc: Adverse Events Leading to Treatment Discontinuation; Any: Any Grade; Body Image: Body Image; Cognitive Function: Cognitive Function; Constipation: Constipation; CTCAE ≥3: Common Terminology Criteria for Adverse Events, Grade ≥3; DFS: Disease-Free Survival; Diarrhea: Diarrhea; Dyspnea: Dyspnea; Emotional Function: Emotional							

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
Function; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer module ; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; EQ-5D: European Quality of Life 5 Dimensions; Fatigue: Fatigue; Future Perspective: Future Perspective; Global Health Status: Global							

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
Health Status; Insomnia: Insomnia; Lack of Appetite: Lack of Appetite; Nausea: Nausea; OS: Overall Survival; Pain: Pain; Physical Function: Physical Function; Role Function: Role Function; SA: Symptoms in the arm area; SAE: Serious Adverse Events; SCA: Symptoms in the chest area; SEST: Side effects of systemic therapy; Social Function: Social Function; VAS: Visual Analogue Scale							

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
Trastuzumab Emtansin vs. Trastuzumab zur Behandlung von Erwachsenen mit HER2-positivem Brustkrebs im Frühstadium, die nach einer neoadjuvanten Taxan-basierten und HER2-gerichteten Therapie eine invasive Resterkrankung in der Brust und / oder den Lymphknoten aufweisen: Studie KATHERINE							
Continuous Outcomes							
EORTC QLQ-BR23 (SA)[1,2]	N=638	-1.4 ±0.6	N=610	-3.19 ±0.62	LSMD 1.8 [0.1; 3.5];		⊕⊕⊖⊖[a,b]

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
EORTC QLQ-BR23 (SCA)[1,2]	N=638	-2.51 ±0.5	N=610	-3.93 ±0.52	LSMD 1.43 [0.01; 2.84];		⊕⊕⊖⊖[a,b]
EORTC QLQ-BR23 (SEST)[1,2]	N=638	3.39 ±0.42	N=610	1.21 ±0.43	LSMD 2.18 [1.01; 3.35];		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Diarrhea)[1,2]	N=640	-2.62 ±0.4	N=612	-0.95 ±0.41	LSMD -1.67 [-2.78; -0.55];		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Constipation)[1,2]	N=640	5.54 ±0.62	N=612	2.89 ±0.64	LSMD 2.65 [0.9; 4.39];		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Fatigue)[1,2]	N=640	2.48 ±0.63	N=612	0.76 ±0.64	LSMD 1.73 [-0.03; 3.48];		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Insomnia)[1,2]	N=640	0.45 ±0.84	N=612	1.59 ±0.86	LSMD -1.14 [-3.5; 1.22];		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Dyspnea)[1,2]	N=640	3.32 ±0.6	N=612	3.65 ±0.62	LSMD -0.33 [-2.03; 1.37];		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Pain)[1,2]	N=640	1.06 ±0.66	N=612	-0.09 ±0.68	LSMD 1.15 [-0.71; 3.01];		⊕⊕⊖⊖[a,b]

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
EORTC QLQ-C30 (Nausea)[1,2]	N=640	1.94 ±0.29	N=612	1.18 ±0.3	LSMD 0.75 [-0.06; 1.57];		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Lack of Appetite)[1,2]	N=640	1.93 ±0.48	N=612	0.08 ±0.49	LSMD 1.85 [0.5; 3.2];		⊕⊕⊖⊖[a,b]
EQ-5D (VAS)[1,3]	N=618	0.38 (0.47)	N=600	1.95 (0.48)	MD -1.57 [-2.89; -0.24];		⊕⊕⊖⊖[a,b]
EORTC QLQ-BR23 (Enjoyment of Sex)[1,3]	N=216	1 ±1.32	N=218	3.05 ±1.41	LSMD -2.05 [-5.84; 1.74];		⊕⊕⊖⊖[a,b]
EORTC QLQ-BR23 (Body Image)[1,3]	N=638	5.97 ±0.71	N=610	3.6 ±0.72	LSMD 2.38 [0.39; 4.36];		⊕⊕⊖⊖[a,b]
EORTC QLQ-BR23 (Sexual Activity)[1,3]	N=538	3.57 ±0.69	N=517	3.95 ±0.71	LSMD -0.38 [-2.32; 1.57];		⊕⊕⊖⊖[a,b]
EORTC QLQ-BR23 (Future Perspective)[1,3]	N=638	6.43 ±0.81	N=610	6.45 ±0.83	LSMD -0.03 [-2.29; 2.24];		⊕⊕⊖⊖[a,b]

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
EORTC QLQ-C30 (Global Health Status)[1,3]	N=640	0.23 ±0.51	N=612	1.63 ±0.52	LSMD -1.4 [-2.84; 0.04];		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Physical Function)[1,3]	N=640	-0.31 ±0.43	N=612	1.32 ±0.44	LSMD -1.64 [-2.84; -0.44];		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Role Function)[1,3]	N=640	2 ±0.67	N=612	4.20 ±0.69	LSMD -2.21 [-4.09; -0.33];		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Emotional Function)[1,3]	N=640	-1.27 ±0.64	N=612	-2.07 ±0.65	LSMD 0.8 [-0.99; 2.59];		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Cognitive Function)[1,3]	N=640	-5.67 ±0.64	N=612	-5.1 ±0.65	LSMD -0.57 [-2.36; 1.22];		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Social Function)[1,3]	N=640	3.83 ±0.64	N=612	6.21 ±0.65	LSMD -2.38 [-4.17; -0.59];		⊕⊕⊖⊖[a,b]
*Database cutoff: 23.07.2018							

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
1: Mittlere Änderung zum 12-Monats-Follow-Up;2: Eine positive Änderung bedeutet eine Verschlechterung der Symptomatik, eine negative Effektschätzung bedeutet einen Vorteil für die Intervention.; 3: Eine positive Änderung bedeutet eine Verbesserung, eine positive Effektschätzung bedeutet einen Vorteil für die Intervention.							
a: hoher Anteil nicht in der Auswertung berücksichtigter							

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
Personen (> 10 %);b: fehlende Verblindung bei subjektiver Endpunkterhebung							
Body Image: Body Image; Cognitive Function: Cognitive Function; Constipation: Constipation; Diarrhea: Diarrhea; Dyspnea: Dyspnea; Emotional Function: Emotional Function; Enjoyment of Sex: Enjoyment of Sex; EORTC QLQ-BR23: European Organisation for Research and							

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
Treatment of Cancer Quality of Life Questionnaire - Breast Cancer module ; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; EQ-5D: European Quality of Life 5 Dimensions ; Fatigue: Fatigue; Future Perspective: Future Perspective; Global Health Status: Global Health Status; Insomnia: Insomnia; Lack of Appetite: Lack of Appetite; Nausea:							

Outcome	Trastuzumab emtansine N=743	Trastuzumab N=743	Effect Estimate		GRADE		
Nausea; Pain: Pain; Physical Function: Physical Function; Role Function: Role Function; SA: Symptoms in the arm area; SCA: Symptoms in the chest area; SEST: Side effects of systemic therapy; Sexual Activity: Sexual Activity; Social Function: Social Function; VAS: Visual Analogue Scale							

2.1.6 Atezolizumab versus Monochemotherapie als Erstlinientherapie beim triple negativen Mammakarzinom im fortgeschrittenen oder metastasierten Stadium

Verknüpfte Empfehlungen:

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Atezolizumab (neues Anwendungsgebiet: Mammakarzinom, triple-negativ, PD-L1-Expression ≥1%)			
Wirkstoff	Atezolizumab	**Handelsname**	Tecentriq
Pharmazeutischer Unternehmer	Roche Pharma AG	**Beschlussdatum**	02.04.2020
Anwendungsgebiet	Mammakarzinom		

Population/ZVT	Titel	Mortalität	Morbidiät	QoL	Sicherheit	Zusatznutzen
A	Erwachsene Patienten mit nicht resezierbarem lokal fortgeschrittenen oder metastasierten triple-negativem Mammakarzinom (TNBC – triple-negative breast	Keine Bewertung auf Endpunktebene verfügbar	Keine Bewertung auf Endpunktebene verfügbar	Keine Bewertung auf Endpunktebene verfügbar	Keine Bewertung auf Endpunktebene verfügbar	Anhaltspunkt: nicht quantifizierbar

Population/ZVT	Titel	Mortalität	Morbidiät	QoL	Sicherheit	Zusatznutzen
	cancer), deren Tumore eine PD-L1-Expression ≥ 1% aufweisen und die keine vorherige Chemotherapie zur Behandlung der metastasierten Erkrankung erhalten haben					
ZVT	Eine Anthrazyklin- und/oder Taxan-haltige systemische Therapie unter Berücksichtigung der Zulassung der Arzneimittel.					
↑↑/↓↓: positiver/negativer statistisch signifikanter Effekt, hohe Aussagesicherheit; ↑/↓: positiver/negativer statistisch						

Population/ZVT	Titel	Mortalität	Morbidiät	QoL	Sicherheit	Zusatznutzen
signifkanter Effekt, niedrige oder unklare Aussagesicherheit; ↔: kein signifikanter/relevanter Unterschied; ↓: n.b.: nicht bewertbar; Ø: keine Daten						

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung eines neuen Anwendungsgebietes für den Wirkstoff Atezolizumab.
Das hier bewertete Anwendungsgebiet lautet:
Atezolizumab wird angewendet in Kombination mit nab-Paclitaxel bei erwachsenen Patienten zur Behandlung des nicht resezierbaren lokal fortgeschrittenen oder metastasierten triple-negativen Mammakarzinoms (TNBC – triple-negative breast cancer), deren Tumoren eine PD-L1-Expression ≥ 1 % aufweisen und die keine vorherige Chemotherapie zur Behandlung der metastasierten Erkrankung erhalten haben.
Die zweckmäßige Vergleichstherapie wurde vom G-BA wie folgt bestimmt:
Eine Anthrazyklin- und/oder Taxan-haltige systemische Therapie unter Berücksichtigung der Zulassung der Arzneimittel.
Der pharmazeutische Unternehmer hat zum Nachweis des Zusatznutzens Ergebnisse der Studie IMpassion 130 vorgelegt. In dieser wird Atezolizumab in Kombination mit nab-Paclitaxel gegenüber einer Monotherapie mit nab-Paclitaxel verglichen.
nab-Paclitaxel ist in der zu bewertenden Therapiesituation nicht zugelassen. Um einen hinreichend vergleichbaren therapeutischen Nutzen von nab-Paclitaxel gegenüber einem im vorliegenden Anwendungsgebiet zugelassenen Taxan zu belegen, hat der pharmazeutische Unternehmer Daten verschiedener klinischer Studien im Dossier dargestellt.
Vor dem Hintergrund der besonderen Therapie- und Versorgungsituation im vorliegenden Anwendungsgebiet und unter Würdigung entsprechender Stellungnahmen von medizinischen Sachverständigen im vorliegenden Verfahren wird nab-Paclitaxel als hinreichend geeigneter Komparator für die Nutzenbewertung herangezogen.
Hieraus können keine Schlussfolgerungen über die Zweckmäßigkeit von nab-Paclitaxel in der zulassungsüberschreitenden Anwendungsform in der Regelversorgung von Versicherten in der GKV abgeleitet werden.
Bezüglich der Mortalität liegt ein statistisch signifikanter, deutlich positiver Effekt für Atezolizumab + nab-Paclitaxel im Vergleich zu Placebo + nab-Paclitaxel vor.

In der Kategorie Morbidität zeigt sich ein statistisch signifikanter Nachteil für Atezolizumab + nab-Paclitaxel für den Endpunkt „Schmerz“. Aus den weiteren Endpunkten zur Symptomatik sowie für den Gesundheitszustand liegen weder Vor- noch Nachteile vor.
Keine statistisch signifikanten Unterschiede zeigen sich in der Kategorie Lebensqualität.
Innerhalb der Kategorie Nebenwirkungen zeigen sich vereinzelt Nachteile für Atezolizumab + nab-Paclitaxel hinsichtlich des Endpunktes „Abbruch wegen UEs“ und im Detail im Bereich der spezifischen UEs.
Die Nachteile stellen den positiven Effekt auf das Gesamtüberleben jedoch nicht in Frage. Aufgrund von verbleibenden, relevanten Unsicherheiten in Bezug auf den in der Studie IMpassion130 verwendeten Komparator nab-Paclitaxel kann der festgestellte Zusatznutzen in seinem Ausmaß nicht quantifiziert werden.
In der Gesamtschau liegt ein Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen vor.

A Phase III, Multicenter, Randomized, Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) in Combination With Nab-Paclitaxel Compared With Placebo With Nab-Paclitaxel for Patients With Previously Untreated Metastatic Triple-Negative Breast Cancer (NCT02425891)					
Short Name	Design	Population	Intervention	Comparator	Outcomes
IMpassion130WO29522, 2014-005490-37	Randomized, Parallel Assignment, Phase 3 double-blind study	Treatment-naive with ECOG 0-1 Triple Negative Breast Cancer	1. Atezolizumab Plus Nab-Paclitaxel (N=451)[1]2. Atezolizumab Plus Nab-Paclitaxel (N=185) [2]	1. Placebo Plus Nab-Paclitaxel (N=451)[3]2. Placebo Plus Nab-Paclitaxel (N=184) [4]	• Primary: Progression Free Survival (PFS) According to Response Evaluation

A Phase III, Multicenter, Randomized, Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) in Combination With Nab-Paclitaxel Compared With Placebo With Nab-Paclitaxel for Patients With Previously Untreated Metastatic Triple-Negative Breast Cancer (NCT02425891)					
					Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1) in All Randomized Participants • Primary: Overall Survival (OS) in All Randomized Participants
Notes - Study Arms					
1: Participants assigned to atezolizumab plus nab-paclitaxel received					

A Phase III, Multicenter, Randomized, Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) in Combination With Nab-Paclitaxel Compared With Placebo With Nab-Paclitaxel for Patients With Previously Untreated Metastatic Triple-Negative Breast Cancer (NCT02425891)					
both agents until disease progression or unacceptable toxicity.2: Bewertungsrelevante Teilpopulation des Atezolizumab-Arms: Patientinnen, deren Tumoren eine PD-L1-Expression ≥ 1 % der tumorinfiltrierenden Immunzellen aufweisen 3: Participants assigned to placebo plus nab-paclitaxel received both agents until disease progression or unacceptable toxicity. 4:					

A Phase III, Multicenter, Randomized, Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) in Combination With Nab-Paclitaxel Compared With Placebo With Nab-Paclitaxel for Patients With Previously Untreated Metastatic Triple-Negative Breast Cancer (NCT02425891)					
Bewertungsrelevante Teilpopulation des Kontrollarms: Patientinnen, deren Tumoren eine PD-L1-Expression ≥ 1 % der tumorinfiltrierenden Immunzellen aufweisen.					

Outcome	**Atezolizumab Plus Nab-Paclitaxel N=185**	**Placebo Plus Nab-Paclitaxel N=184**	**Effect Estimate**		**GRADE**		
Atezolizumab vs. nab-Paclitaxel zur							

Outcome	Atezolizumab Plus Nab-Paclitaxel N=185	Placebo Plus Nab-Paclitaxel N=184	Effect Estimate		GRADE		
Behandlung von Erwachsenen mit nicht resezierbarem lokal fortgeschrittenen oder metastasierten triple-negativem Mammakarzinom (TNBC – triple-negative breast cancer), deren Tumore eine PD-L1-Expression ≥ 1% aufweisen und die keine vorherige Chemotherapie zur Behandlung der metastasierten Erkrankung erhalten haben: Studie IMpassion130							

Outcome	Atezolizumab Plus Nab-Paclitaxel N=185	Placebo Plus Nab-Paclitaxel N=184	Effect Estimate		GRADE		
Dichotomous Outcomes							
OS - Time To Event[1]	N=185	25 [19.6; 30]94 (50.81%)	N=184	18 [13.6; 20.1]110 (59.78%)	HR 0.71 [0.54; 0.93]; p=0.013		⊕⊕⊕⊕
PFS - Time To Event[2]	N=185	7.5 [6.7; 9.2]149 (80.54%)	N=184	5.3 [3.8; 5.6]163 (88.59%)	HR 0.63 [0.5; 0.8]; p<0.0001		⊕⊕⊕⊕
EORTC QLQ-BR23 (SA) - TTC[3]	N=164	4.6 [2.8; 5.6]103 (62.8%)	N=158	4.1 [2.8; 7.4]93 (58.86%)	HR 0.99 [0.75; 1.31]; p=0.945		⊕⊕⊕⊖[a]
EORTC QLQ-BR23 (SCA) - TTC[3]	N=164	17.4 [9.8; 24.8]67 (40.85%)	N=158	12 [8.2;]60 (37.97%)	HR 0.96 [0.67; 1.37]; p=0.813		⊕⊕⊕⊖[a]
EORTC QLQ-BR23 (SEST) - TTC[3]	N=164	1.1 [1; 1.2]139 (84.76%)	N=158	1.9 [1.1; 1.9]124 (78.48%)	HR 1.18 [0.92; 1.51]; p=0.205		⊕⊕⊕⊖[a]
EORTC QLQ-C30 (Diarrhea) - TTC[3,4]	N=164	4.9 [3.7; 8.3]100 (60.98%)	N=158	6 [4.7; 9.3]87 (55.06%)	HR 1.12 [0.84; 1.49]; p=0.432		⊕⊕⊕⊖[a]
EORTC QLQ-C30 (Lack of Appetite) - TTC[3,4]	N=164	4.9 [3.8; 8.4]97 (59.15%)	N=158	4.3 [3.5; 6.1]93 (58.86%)	HR 0.94 [0.7; 1.25]; p=0.661		⊕⊕⊕⊖[a]

Outcome	Atezolizumab Plus Nab-Paclitaxel N=185	Placebo Plus Nab-Paclitaxel N=184	Effect Estimate		GRADE		
EORTC QLQ-C30 (Constipation) - TTC[3,4]	N=164	4.8 [3.7; 7.8]102 (62.2%)	N=158	5.7 [3.4; 7.6]93 (58.86%)	HR 0.95 [0.72; 1.26]; p=0.744		⊕⊕⊕⊖[a]
EORTC QLQ-C30 (Dyspnea) - TTC[3,4]	N=164	3.9 [3.2; 5.6]103 (62.8%)	N=158	4.8 [2.9; 7.4]90 (56.96%)	HR 1.03 [0.78; 1.37]; p=0.821		⊕⊕⊕⊖[a]
EORTC QLQ-C30 (Pain) - TTC[3,4]	N=164	3.1 [2; 4.6]123 (75%)	N=158	5.1 [3.5; 7.4]100 (63.29%)	HR 1.34 [1.03; 1.76]; p=0.031		⊕⊕⊕⊖[a]
EORTC QLQ-C30 (Nausea) - TTC[3,4]	N=164	3.8 [2.8; 6]115 (70.12%)	N=158	4.3 [2.8; 5.6]102 (64.56%)	HR 1.01 [0.77; 1.33]; p=0.934		⊕⊕⊕⊖[a]
EORTC QLQ-C30 (Fatigue) - TTC[3,4]	N=164	1.8 [1.1; 1.9]142 (86.59%)	N=158	1.9 [1.1; 2.7]126 (79.75%)	HR 1.06 [0.83; 1.35]; p=0.613		⊕⊕⊕⊖[a]
EORTC QLQ-C30 (Insomnia) - TTC[3,4]	N=164	6.6 [4.4; 12.2]90 (54.88%)	N=158	7.3 [4; 15.6]76 (48.1%)	HR 1.03 [0.75; 1.39]; p=0.863		⊕⊕⊕⊖[a]
EQ-5D (VAS) - TTC[3]	N=161	2.8 [1.9; 3.7]122 (75.78%)	N=151	3.7 [2.8; 5.2]102 (67.55%)	HR 1.07 [0.82; 1.4]; p=0.590		⊕⊕⊕⊖[a]

Outcome	Atezolizumab Plus Nab-Paclitaxel N=185	Placebo Plus Nab-Paclitaxel N=184	Effect Estimate		GRADE		
EORTC QLQ-BR23 (Body Image) - TTC[3]	N=164	NA38 (23.17%)	N=158	NA29 (18.35%)	HR 1.19 [0.73; 1.93]; p=0.479		⊕⊕⊕⊖[a]
EORTC QLQ-BR23 (Sexual Activity) - TTC[3]	N=164	23.7 [14.7;]56 (34.15%)	N=158	NA [12;]54 (34.18%)	HR 0.88 [0.6; 1.28]; p=0.495		⊕⊕⊕⊖[a]
EORTC QLQ-BR23 (Future Perspective) - TTC[3]	N=164	3.8 [2.7; 7.4]93 (56.71%)	N=158	4.7 [2.8; 14.3]78 (49.37%)	HR 1.04 [0.77; 1.4]; p=0.777		⊕⊕⊕⊖[a]
EORTC QLQ-C30 (Social Function) - TTC[3,4]	N=164	2.8 [2.1; 4.7]120 (73.17%)	N=158	2.9 [2.8; 3.8]110 (69.62%)	HR 0.96 [0.74; 1.25]; p=0.793		⊕⊕⊕⊖[a]
EORTC QLQ-C30 (Role Function) - TTC[3,4]	N=164	2.8 [1.9; 3.7]122 (74.39%)	N=158	2.8 [2.4; 3.8]119 (75.32%)	HR 0.91 [0.71; 1.18]; p=0.493		⊕⊕⊕⊖[a]
EORTC QLQ-C30 (Emotional Function) - TTC[3,4]	N=164	6.5 [5; 9.5]90 (54.88%)	N=158	6 [3.8; 9.6]86 (54.43%)	HR 0.91 [0.67; 1.22]; p=0.512		⊕⊕⊕⊖[a]

Outcome	Atezolizumab Plus Nab-Paclitaxel N=185	Placebo Plus Nab-Paclitaxel N=184	Effect Estimate		GRADE		
EORTC QLQ-C30 (Physical Function) - TTC[3,4]	N=164	3.1 [2.5; 4.4]120 (73.17%)	N=158	3.8 [3.1; 5.2]116 (73.42%)	HR 0.97 [0.75; 1.25]; p=0.798		⊕⊕⊕⊖[a]
EORTC QLQ-C30 (Global Health Status) - TTC[3,4]	N=164	2.9 [2.1; 3.7]121 (73.78%)	N=158	2.8 [2.4; 3.8]104 (65.82%)	HR 1 [0.77; 1.31]; p=0.982		⊕⊕⊕⊖[a]
EORTC QLQ-C30 (Cognitive Function) - TTC[3,4]	N=164	3 [2.8; 3.9]117 (71.34%)	N=158	3.5 [2.8; 4.4]108 (68.35%)	HR 0.96 [0.74; 1.26]; p=0.792		⊕⊕⊕⊖[a]
AE - Untersuchungen - TTE[6,14]	N=185	NA10 (5.41%)	N=181	NA7 (3.87%)	HR 2.06 [1.02; 4.18]; p=0.041		⊕⊕⊕⊖[b]
AE - TTE[6,7]	N=185	NA97 (52.43%)	N=181	NA73 (40.33%)	HR 1.2 [0.89; 1.63]; p=0.234		⊕⊕⊕⊖[b]
AE - TTE[10,11]	N=185	NA185 (100%)	N=184	NA177 (97.79%)	HR 1.63 [1.2; 2.22]; p=0.002		⊕⊕⊕⊖[b]
AE - TTE[6,12]	N=185	NA107 (57.84%)	N=181	NA66 (36.46%)	HR 0.8 [0.16; 3.96]; p=0.778		⊕⊕⊖⊖[b,d]

Outcome	Atezolizumab Plus Nab-Paclitaxel N=185	Placebo Plus Nab-Paclitaxel N=184	Effect Estimate		GRADE		
AE - TTE[6,13]	N=185	NA3 (1.62%)	N=181	NA3 (1.66%)	HR 1.2 [0.46; 3.17]; p=0.710		⊕⊕⊖⊖[b,d]
AE - TTE[11,15]	N=185	NA26 (14.05%)	N=181	NA11 (6.08%)	HR 1.13 [0.92; 1.39]; p=0.2418		⊕⊕⊕⊕
AE-Disc - TTE[8,9]	N=185	NA37 (20%)	N=181	NA13 (7.18%)	HR 2.34 [1.24; 4.41]; p=0.007		⊕⊕⊕⊖[c]
SAE - TTE[5,6]	N=185	NA43 (23.24%)	N=181	NA31 (17.13%)	HR 1.17 [0.74; 1.87]; p=0.501		⊕⊕⊕⊖[b]
*Database cutoff: 29.12.2018							
1: Medianes Gesamtüberleben (Monate);2: Medianes progressionsfreies Überleben (Monate); 3: Mediane Zeit bis zur ersten Verschlechterung							

Outcome	Atezolizumab Plus Nab-Paclitaxel N=185	Placebo Plus Nab-Paclitaxel N=184	Effect Estimate		GRADE		
um ≥ 10 Punkte (Monate); 4: Score range 0-100; 5: Schwerwiegende UE - Gesamt; 6: keine Angaben zur medianen Zeit bis zum ersten Ereignis (Monate); 7: Schwere UE - Gesamt; 8: Therapieabbruch aufgrund von UE; 9: keine Angaben zur medianen Zeit bis zum Ereignis (Monate); 10: immunvermittelte UE; 11: Keine Angaben zur medianen Zeit bis zum ersten Ereignis (Monate); 12: immunvermittelte SUE; 13: immunvermittelte							

Outcome	Atezolizumab Plus Nab-Paclitaxel N=185	Placebo Plus Nab-Paclitaxel N=184	Effect Estimate		GRADE		
schwere UE (CTCAE-Grad 3-4); 14: Untersuchungen (SOC, UE CTCAE-Grad 3-4); 15: UE jeglichen Schweregrades - Gesamt							
a: hoher Anteil nicht in der Auswertung berücksichtigter Personen (> 10 %);b: unvollständige Beobachtungen aus potenziell informativen Gründen; c: Auftreten konkurrierender Ereignisse für den Endpunkt Therapieabbruch aufgrund von UE							

Outcome	Atezolizumab Plus Nab-Paclitaxel N=185	Placebo Plus Nab-Paclitaxel N=184	Effect Estimate		GRADE		
(Abbruch aufgrund Krankheitsverschlechterung); d: zu geringe Anzahl an aufgetretenen Ereignissen							
AE: Adverse Events; AE-Disc: Adverse Events Leading to Treatment Discontinuation; Any: Any Grade; Body Image: Body Image; Cognitive Function: Cognitive Function; Constipation: Constipation; CTCAE ≥3: Common Terminology Criteria for Adverse Events,							

Outcome	Atezolizumab Plus Nab-Paclitaxel N=185	Placebo Plus Nab-Paclitaxel N=184	Effect Estimate		GRADE		
Grade ≥3; Diarrhea: Diarrhea; Dyspnea: Dyspnea; Emotional Function: Emotional Function; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer module ; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; EQ-5D: European Quality							

Outcome	Atezolizumab Plus Nab-Paclitaxel N=185	Placebo Plus Nab-Paclitaxel N=184	Effect Estimate		GRADE		
of Life 5 Dimensions; Fatigue: Fatigue; Future Perspective: Future Perspective; Global Health Status: Global Health Status; Insomnia: Insomnia; Lack of Appetite: Lack of Appetite; Nausea: Nausea; OS: Overall Survival; Pain: Pain; PFS: Progression-Free Survival; Physical Function: Physical Function; Role Function: Role Function; SA: Symptoms in the arm area; SAE: Serious Adverse Events; SCA:							

Outcome	Atezolizumab Plus Nab-Paclitaxel N=185	Placebo Plus Nab-Paclitaxel N=184	Effect Estimate		GRADE		
Symptoms in the chest area; SEST: Side effects of systemic therapy; Sexual Activity: Sexual Activity; Social Function: Social Function; TTC: Time To Change ; TTE: Time To Event ; VAS: Visual Analogue Scale							

2.1.7 Trastuzumab Deruxtecan versus Monochemotherapie beim HR-positiven/HER low Mammakarzinom im fortgeschrittenen oder metastasierten Stadium

Verknüpfte Empfehlungen:

Zur Methodik und Vorgehensweise zur Erstellung der Evidenztabellen siehe Evidenzbericht

Trastuzumab deruxtecan (Neues Anwendungsgebiet: Mammakarzinom, HER2-low, vorbehandelt)			
Wirkstoff	Trastuzumab deruxtecan	**Handelsname**	Enhertu
Pharmazeutischer Unternehmer	Daiichi Sankyo Deutschland GmbH	**Beschlussdatum**	20.07.2023
Anwendungsgebiet	Mammakarzinom		

Population/ZVT	Titel	Mortalität	Morbidiät	QoL	Sicherheit	Zusatznutzen
A	Erwachsene mit inoperablem oder metastasiertem HER2-low-Brustkrebs, die bereits eine Chemotherapie in der metastasierten Situation erhalten haben oder bei	↑↑ Vorteil im Gesamtüberleben.	↔ Vorteile in Schmerzen und Schlaflosigkeit; Nachteile bei Übelkeit und Erbrechen und Diarrhö; insgesamt	↑ Vorteile in körperliche Funktion, kognitive Funktion, soziale Funktion und Körperbild.	↑↑ Vorteil in den Endpunkten SUE und schwere UE (CTCAE-Grad ≥ 3) und im Detail Vor- und Nachteile in spezifischen UE.	Hinweis: beträchtlich

Population/ZVT	Titel	Mortalität	Morbidiät	QoL	Sicherheit	Zusatznutzen
	denen während oder innerhalb von 6 Monaten nach Beendigung der adjuvanten Chemotherapie ein Rezidiv aufgetreten ist		kein überwiegender Vor- oder Nachteil.			
ZVT	Capecitabin oder- Eribulin oder- Vinorelbin oder- eine Anthrazyklin- oder Taxan-haltige Therapie (nur für Patientinnen und Patienten, die noch keine Anthrazyklin- und/oder Taxan-haltige Therapie erhalten haben oder die für eine erneute Anthrazyklin- oder Taxan-haltige Behandlung infrage kommen.)					

Population/ZVT	Titel	Mortalität	Morbidiät	QoL	Sicherheit	Zusatznutzen
↑↑/↓↓: positiver/negativer statistisch signifikanter Effekt, hohe Aussagesicherheit; ↑/↓: positiver/negativer statistisch signifkanter Effekt, niedrige oder unklare Aussagesicherheit; ↔: kein signifikanter/relevanter Unterschied; ↓: n.b.: nicht bewertbar; Ø: keine Daten						

Bei der vorliegenden Bewertung handelt es sich um die Nutzenbewertung eines neuen Anwendungsgebietes für den Wirkstoff Trastuzumab-Deruxtecan: „Enhertu wird angewendet als Monotherapie zur Behandlung von erwachsenen Patienten mit inoperablem oder metastasiertem HER2-low-Brustkrebs, die bereits eine Chemotherapie in der metastasierten Situation erhalten haben oder bei denen während oder innerhalb von 6 Monaten nach Beendigung der adjuvanten Chemotherapie ein Rezidiv aufgetreten ist.“
Enhertu wurde unter besonderen Bedingungen zugelassen.
Als zweckmäßige Vergleichstherapie wurde vom G-BA Capecitabin oder Eribulin oder Vinorelbin oder eine Anthrazyklin- oder Taxan-haltige Therapie (nur für Patientinnen und Patienten, die noch keine Anthrazyklin- und/oder Taxan-haltige Therapie erhalten haben oder die für eine erneute Anthrazyklin- oder Taxan-haltige Behandlung infrage kommen.) bestimmt.
Für die Bewertung liegt die offene RCT DESTINY-Breast04 vor, in welcher Trastuzumab-Deruxtecan mit einer Therapie nach ärztlicher Maßgabe unter Auswahl

von Capecitabin, Eribulin, Gemcitabin, Paclitaxel oder Nab-Paclitaxel vergleichen wird.
Die Bewertung basiert auf Auswertungen zu einer Teilpopulation, die vor der Randomisierung einer Behandlung mit Capecitabin, Eribulin, Paclitaxel oder Nab-Paclitaxel zugeordnet wurde.
Für den Endpunkt Gesamtüberleben zeigt sich eine statistisch signifikante Verlängerung der Überlebenszeit durch Trastuzumab-Deruxtecan, die als eine deutliche Verbesserung bewertet wird.
Hinsichtlich der Symptomatik wird in der Gesamtschau der Ergebnisse kein überwiegender Vor- oder Nachteil von Trastuzumab-Deruxtecan festgestellt.
Hinsichtlich des Gesundheitszustands zeigen sich weder positive noch negative Effekte.
In Bezug auf die Lebensqualität liegen Vorteile für Trastuzumab-Deruxtecan vor.
Bei den Nebenwirkungen zeigen sich Vorteile von Trastuzumab-Deruxtecan bei den schwerwiegenden UE und schweren UE. Im Detail zeigen sich bei den spezifischen UE sowohl Vor- als auch Nachteile.
Insgesamt ist die Datengrundlage insbesondere angesichts der fehlenden Verblindung mit Unsicherheiten behaftet. Diese werden jedoch nicht als derart hoch beurteilt, als dass eine Herabstufung der Aussagesicherheit für die Gesamtbewertung gerechtfertigt wäre.
Im Ergebnis stellt der G-BA insbesondere aufgrund der deutlichen positiven Effekte auf die Verlängerung der Überlebensdauer und in Anbetracht der Vorteile hinsichtlich der Lebensqualität und der Nebenwirkungen für Trastuzumab-Deruxtecan einen Hinweis auf einen beträchtlichen Zusatznutzen gegenüber Capecitabin, Eribulin, Paclitaxel oder Nab-Paclitaxel fest.

A Phase 3, Multicenter, Randomized, Open-label, Active Controlled Trial of DS-8201a, an Anti-HER2-antibody Drug Conjugate (ADC), Versus Treatment of Physician's Choice for HER2-low, Unresectable and/or Metastatic Breast Cancer Subjects (NCT03734029)					
Short Name	Design	Population	Intervention	Comparator	Outcomes

A Phase 3, Multicenter, Randomized, Open-label, Active Controlled Trial of DS-8201a, an Anti-HER2-antibody Drug Conjugate (ADC), Versus Treatment of Physician's Choice for HER2-low, Unresectable and/or Metastatic Breast Cancer Subjects (NCT03734029)					
DESTINY-Breast04DS8201-A-U303, 2018-003069-33, 184223, DESTINY-B04	Randomized, Parallel Assignment, Phase 3 Open Label study	Treatment-naive with Stage 3 and ECOG 0-1 Breast Cancer	1. Trastuzumab deruxtecan (N=373)[1]2. Trastuzumab-Deruxtecan (N=344) [2]	1. Physician's Choice (N=184)[3]2. Therapie nach ärztlicher Maßgabe (N=165) [4]	• Primary: Progression-free Survival (PFS) Based on Blinded Independent Central Review (BICR) in the Hormone Receptor-Positive Cohort in Participants With HER2-low Breast Cancer • Secondary: Progression-free Survival (PFS) Based on

A Phase 3, Multicenter, Randomized, Open-label, Active Controlled Trial of DS-8201a, an Anti-HER2-antibody Drug Conjugate (ADC), Versus Treatment of Physician's Choice for HER2-low, Unresectable and/or Metastatic Breast Cancer Subjects (NCT03734029)					
					Blinded Independent Central Review (BICR) in Participants With HER2-low Breast Cancer (All Patients) Regardless of Hormone Receptor Status • Secondary: Overall Survival (OS) in All Patients
Notes - Study					

A Phase 3, Multicenter, Randomized, Open-label, Active Controlled Trial of DS-8201a, an Anti-HER2-antibody Drug Conjugate (ADC), Versus Treatment of Physician's Choice for HER2-low, Unresectable and/or Metastatic Breast Cancer Subjects (NCT03734029)					
Open Label Study					
Notes - Study Arms					
1: HER2-low, unresectable, and/or metastatic breast cancer participants previously treated with chemotherapy randomized to Trastuzumab deruxtecan2: bewertungsrelevante Teilpopulation des Trastuzumab-Deruxtecan-Arms für den					

A Phase 3, Multicenter, Randomized, Open-label, Active Controlled Trial of DS-8201a, an Anti-HER2-antibody Drug Conjugate (ADC), Versus Treatment of Physician's Choice for HER2-low, Unresectable and/or Metastatic Breast Cancer Subjects (NCT03734029)					
G-BA-Beschluss: Patientinnen und Patienten, für die vor der Randomisierung eine Behandlung mit Capecitabin, Eribulin, Paclitaxel oder NabPaclitaxel im Falle einer Zuteilung zur Kontrollgruppe festgelegt wurde 3: HER2-low, unresectable, and/or metastatic breast cancer participants previously treated with chemotherapy randomized to Physician's choice from					

A Phase 3, Multicenter, Randomized, Open-label, Active Controlled Trial of DS-8201a, an Anti-HER2-antibody Drug Conjugate (ADC), Versus Treatment of Physician's Choice for HER2-low, Unresectable and/or Metastatic Breast Cancer Subjects (NCT03734029)					
the following options: Capecitabine Eribulin Gemcitabine Paclitaxel Nab-paclitaxel 4: bewertungsrelevante Teilpopulation des Kontrollarms für den G-BA-Beschluss: Patientinnen und Patienten, für die vor der Randomisierung eine Behandlung mit Capecitabin, Eribulin, Paclitaxel oder NabPaclitaxel im Falle einer Zuteilung zur Kontrollgruppe festgelegt wurde					

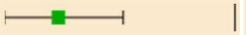
Outcome	Trastuzumab-Deruxtecan N=344	Therapie nach ärztlicher Maßgabe N=165	Effect Estimate		GRADE		
Trastuzumab-Deruxtecan vs. Therapie nach ärztlicher Maßgabe (Capecitabin, Eribulin, Paclitaxel oder Nab-Paclitaxel) zur Behandlung Erwachsener mit inoperablem oder metastasiertem HER2-low-Brustkrebs, die bereits eine Chemotherapie in der metastasierten Situation erhalten haben oder bei denen während oder innerhalb von 6 Monaten nach Beendigung							

Outcome	Trastuzumab-Deruxtecan N=344	Therapie nach ärztlicher Maßgabe N=165	Effect Estimate		GRADE		
der adjuvanten Chemotherapie ein Rezidiv aufgetreten ist: Studie DESTINY-BREAST04							
Dichotomous Outcomes							
OS - Time To Event[1]	N=344	23.4 [20;]137 (39.83%)	N=165	17 [15.1; 20.2]78 (47.27%)	HR 0.64 [0.48; 0.85]; p=0.002		⊕⊕⊕⊕
Viszerale Erkrankung							
Ja	N=306	21.7 [19.5; 24.7]130 (42.4837%)	N=143	17.1 [15.2; 22.4]65 (45.4545%)	HR 0.73 [0.54; 0.99]; p=0.039		
Nein	N=38	7 (18.4211%)	N=22	15.1 [12.6; 20.6]13 (59.0909%)	HR 0.22 [0.09; 0.57]; p=0.001		

Outcome	Trastuzumab-Deruxtecan N=344	Therapie nach ärztlicher Maßgabe N=165	Effect Estimate		GRADE		
PFS - Time To Event[2]	N=344	9.8 [8.5; 11.3]229 (66.57%)	N=165	5.3 [4.3; 6.9]114 (69.09%)	HR 0.53 [0.42; 0.67]; p< 0,0001		⊕⊕⊕⊕
EORTC QLQ-BR23 (SA) - TTC[3]	N=344	7.7 [6.7; 11.2]166 (48.26%)	N=165	5.1 [2.9;]73 (44.24%)	HR 0.78 [0.59; 1.03]; p=0.079		⊕⊕⊖⊖[a,b]
EORTC QLQ-BR23 (SCA) - TTC[3]	N=344	NA [20.3;]93 (27.03%)	N=165	NA37 (22.42%)	HR 0.89 [0.6; 1.31]; p=0.554		⊕⊕⊖⊖[a,b]
EORTC QLQ-BR23 (SEST) - TTC[3]	N=344	4.2 [2.8; 5.9]193 (56.1%)	N=165	2.8 [1.5; 4.5]92 (55.76%)	HR 0.82 [0.64; 1.06]; p=0.131		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Diarrhea) - TTC[3,4]	N=344	9.4 [7; 15.3]	N=165	13.3 [9;]	HR 1.37 [1.003; 1.87]; p=0.049		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Lack of Appetite) - TTC[3,4]	N=344	5.1 [3.2; 6.9]197 (57.27%)	N=165	7 [4.6; 9.8]74 (44.85%)	HR 1.2 [0.92; 1.58]; p=0.190		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Constipation) - TTC[3,4]	N=344	4.2 [2.9; 5.6]205 (59.59%)	N=165	5.9 [4.5; 8.4]73 (44.24%)	HR 1.17 [0.89; 1.54]; p=0.255		⊕⊕⊖⊖[a,b]

Outcome	Trastuzumab-Deruxtecan N=344	Therapie nach ärztlicher Maßgabe N=165	Effect Estimate		GRADE		
EORTC QLQ-C30 (Dyspnea) - TTC[3,4]	N=344	13.2 [8.3; 21.7]148 (43.02%)	N=165	6.8 [5.1;]66 (40%)	HR 0.8 [0.6; 1.08]; p=0.148		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Pain) - TTC[3,4]	N=344	8.5 [5.9; 10.6]177 (51.45%)	N=165	4.4 [2.8; 7.2]86 (52.12%)	HR 0.69 [0.53; 0.898]; p=0.005		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Nausea) - TTC[3,4]	N=344	1.4 [1.4; 1.6]239 (69.48%)	N=165	8.2 [6; 9.8]68 (41.21%)	HR 2.12 [1.61; 2.78]; p< 0,001		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Fatigue) - TTC[3,4]	N=344	4.2 [2.8; 5.5]220 (63.95%)	N=165	2.8 [1.4; 3.3]100 (60.61%)	HR 0.81 [0.63; 1.03]; p=0.081		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Insomnia) - TTC[3,4]	N=344	16 [11.1;]137 (39.83%)	N=165	5.4 [4.2; 7.1]76 (46.06%)	HR 0.56 [0.42; 0.74]; p< 0,001		⊕⊕⊖⊖[a,b]
EQ-5D (VAS) - TTC[5]	N=344	16.4 [11.1;]132 (38.37%)	N=165	8.4 [5.4;]55 (33.33%)	HR 0.82 [0.59; 1.13]; p=0.220		⊕⊕⊖⊖[a,b]
EORTC QLQ-BR23 (Body Image) - TTC[3]	N=344	12.8 [9.6;]143 (41.57%)	N=165	5.1 [2.9; 16.9]75 (45.45%)	HR 0.67 [0.51; 0.897]; p=0.006		⊕⊕⊖⊖[a,b]

Outcome	Trastuzumab-Deruxtecan N=344	Therapie nach ärztlicher Maßgabe N=165	Effect Estimate		GRADE		
EORTC QLQ-BR23 (Future Perspective) - TTC[3]	N=344	16.9 [14.1;]123 (35.76%)	N=165	11.149 (29.7%)	HR 0.98 [0.7; 1.38]; p=0.916		⊕⊕⊖⊖[a,b]
EORTC QLQ-BR23 (Sexual Activity) - TTC[3]	N=344	NA73 (21.22%)	N=165	NA31 (18.79%)	HR 0.91 [0.59; 1.39]; p=0.651		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Social Function) - TTC[3,4]	N=344	5.9 [4.2; 9.7]194 (56.4%)	N=165	3.4 [2.1; 4.7]96 (58.18%)	HR 0.73 [0.57; 0.94]; p=0.014		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Role Function) - TTC[3,4]	N=344	4.2 [2.9; 5.9]198 (57.56%)	N=165	3.2 [1.6; 4.4]93 (56.36%)	HR 0.81 [0.63; 1.04]; p=0.089		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Emotional Function) - TTC[3,4]	N=344	10.4 [8.3; 13.1]161 (46.8%)	N=165	7.1 [5.7; 11.7]64 (38.79%)	HR 0.89 [0.66; 1.2]; p=0.432		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Physical Function) - TTC[3,4]	N=344	8.7 [7.1; 11.3]169 (49.13%)	N=165	4.5 [3; 5.8]87 (52.73%)	HR 0.62 [0.47; 0.81]; p< 0,001		⊕⊕⊖⊖[a,b]

Outcome	Trastuzumab-Deruxtecan N=344	Therapie nach ärztlicher Maßgabe N=165	Effect Estimate		GRADE		
EORTC QLQ-C30 (Global Health Status) - TTC[3,4]	N=344	5.6 [4.2; 7.9]190 (55.23%)	N=165	4 [2.8; 5.9]90 (54.55%)	HR 0.81 [0.63; 1.04]; p=0.097		⊕⊕⊖⊖[a,b]
EORTC QLQ-C30 (Cognitive Function) - TTC[3,4]	N=344	6.5 [5; 7.7]187 (54.36%)	N=165	4.2 [3.1; 6.3]90 (54.55%)	HR 0.75 [0.58; 0.97]; p=0.028		⊕⊕⊖⊖[a,b]
AE - Neutropenie - TTE[7,16]	N=343	NA20 (5.83%)	N=156	NA23 (14.74%)	HR 0.32 [0.17; 0.59]; p< 0,001		⊕⊕⊕⊖[c]
AE - TTE[6,7]	N=343	0.1341 (99.42%)	N=156	0.1 [0.1; 0.1]153 (98.08%)	HR 1.21 [1; 1.46]; p=0.0504		⊕⊕⊕⊖[a]
AE - TTE[7,9]	N=343	7.2 [5; 10.5]184 (53.64%)	N=156	0.9 [0.5; 2]103 (66.03%)	HR 0.5 [0.39; 0.64]; p< 0,001		⊕⊕⊕⊖[c]
AE - Hand-Fuß-Syndrom - TTE[7,12]	N=343	NA4 (1.17%)	N=156	NA24 (15.38%)	HR 0.05 [0.02; 0.15]; p< 0,001		⊕⊕⊖⊖[a,c]
AE - Thrombozytenzahl vermindert - TTE[7,13]	N=343	NA19 (5.54%)	N=156	NA0 (0%)			⊕⊕⊖⊖[c,e]

Outcome	Trastuzumab-Deruxtecan N=344	Therapie nach ärztlicher Maßgabe N=165	Effect Estimate		GRADE		
AE - Erkrankungen des Gastrointestinaltrakts - TTE[7,14]	N=343	0.1 [0.1; 0.1]302 (88.05%)	N=156	0.7 [0.5; 1.5]106 (67.95%)	HR 2.13 [1.69; 2.68]; p< 0,001		⊕⊕⊖⊖[a,c]
AE - Infektionen und parasitäre Erkrankungen - TTE[7,15]	N=343	NA28 (8.16%)	N=156	NA2 (1.28%)	HR 4.22 [0.99; 17.92]; p=0.034		⊕⊕⊖⊖[c,e]
AE - Übelkeit - TTE[7,17]	N=343	NA16 (4.66%)	N=156	NA0 (0%)			⊕⊕⊖⊖[c,e]
AE-Disc - TTE[10,11]	N=343	NA [24.4;]56 (16.33%)	N=156	NA [16.2;]13 (8.33%)	HR 1.09 [0.58; 2.04]; p=0.784		⊕⊕⊕⊖[d]
SAE - TTE[7,8]	N=343	NA [24.4;]97 (28.28%)	N=156	NA [9.2;]41 (26.28%)	HR 0.66 [0.45; 0.97]; p=0.034		⊕⊕⊕⊖[c]
*Database cutoff: 06.01.2022							
1: Medianes Gesamtüberleben							

Outcome	Trastuzumab-Deruxtecan N=344	Therapie nach ärztlicher Maßgabe N=165	Effect Estimate		GRADE		
(Monate);2: Medianes progressionsfreies Überleben (Monate); 3: Mediane Zeit bis zur erstmaligen Verschlechterung um ≥ 10 Punkte (Monate); 4: Score range 0-100; 5: Mediane Zeit bis zur erstmaligen Verschlechterung um ≥ 15 Punkte (Monate); 6: UE jeglichen Schweregrades; 7: Mediane Zeit bis zum ersten Ereignis (Monate); 8: Schwerwiegende UE - Gesamt; 9: Schwere UE - Gesamt; 10: Therapieabbruch							

Outcome	Trastuzumab-Deruxtecan N=344	Therapie nach ärztlicher Maßgabe N=165	Effect Estimate		GRADE		
aufgrund von UE; 11: Mediane Zeit bis zum Ereignis (Monate); 12: Hand-Fuß-Syndrom (PT, UE); 13: Thrombozytenzahl vermindert (PT, schwere UE); 14: Erkrankungen des Gastrointestinaltrakts (SOC, UE); 15: Infektionen und parasitäre Erkrankungen (SOC, SUE); 16: Neutropenie (PT, schwere UE); 17: Übelkeit (PT, schwere UE)							
a: fehlende Verblindung bei subjektiver Endpunkterhebung;b: Hoher Anteil							

Outcome	Trastuzumab-Deruxtecan N=344	Therapie nach ärztlicher Maßgabe N=165	Effect Estimate		GRADE		
an fehlenden Werten im Studienverlauf, der sich zwischen den Armen unterscheidet; c: großer Unterschied in medianer Behandlungsdauer (und damit Beobachtungsdauer) zwischen den Studienarmen d: fehlende Verblindung bei subjektiver Entscheidung zum Therapieabbruch; e: zu geringe Anzahl an aufgetretenen Ereignissen							
AE: Adverse Events; AE-Disc: Adverse Events							

Outcome	Trastuzumab-Deruxtecan N=344	Therapie nach ärztlicher Maßgabe N=165	Effect Estimate		GRADE		
Leading to Treatment Discontinuation; Any: Any Grade; Body Image: Body Image; Cognitive Function: Cognitive Function; Constipation: Constipation; CTCAE ≥3: Common Terminology Criteria for Adverse Events, Grade ≥3; Diarrhea: Diarrhea; Dyspnea: Dyspnea; Emotional Function: Emotional Function; EORTC QLQ-BR23: European							

Outcome	Trastuzumab-Deruxtecan N=344	Therapie nach ärztlicher Maßgabe N=165	Effect Estimate		GRADE		
Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer module ; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; EQ-5D: European Quality of Life 5 Dimensions; Fatigue: Fatigue; Future Perspective: Future Perspective; Global Health Status: Global Health Status; Insomnia:							

Outcome	Trastuzumab-Deruxtecan N=344	Therapie nach ärztlicher Maßgabe N=165	Effect Estimate		GRADE		
Insomnia; Lack of Appetite: Lack of Appetite; Nausea: Nausea; OS: Overall Survival; Pain: Pain; PFS: Progression-Free Survival; Physical Function: Physical Function; Role Function: Role Function; SA: Symptoms in the arm area; SAE: Serious Adverse Events; SCA: Symptoms in the chest area; SEST: Side effects of systemic therapy; Sexual Activity: Sexual Activity; Social Function: Social Function; TTC: Time To Change ; TTE: Time To Event ;							

Outcome	Trastuzumab-Deruxtecan N=344	Therapie nach ärztlicher Maßgabe N=165	Effect Estimate		GRADE		
VAS: Visual Analogue Scale							

2.1.8 Kapitel 4.6 Adjuvante Strahlentherapie des Mammakarzinoms (Galimberti et al. 2013)

Verknüpfte Empfehlungen:

Source: Galimberti V, Cole BF, Zurrida S, et al: International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013 Apr;14(4): 297-305.					
Aim and Country	Design and participants	Intervention	Outcomes	Results	Quality and comment
Acronym of study: IBCSG 23-01 **Aim**: Comparing outcomes in patients with sentinel-node micrometastases treated with axillary dissection with outcomes in those	**Design**: multicenter, randomised, non-inferiority, phase 3 trial **Enrollment**: 27 hospital and cancer centers between 01.04.2001 – 08.02.2010 **Non-inferiority** was defined as a hazard ratio	**Intervention** Axillary dissection **Control** No axillary dissection	**Primary Outcome**: disease-free survival **Secondary Outcome**: overall survival site of recurrence	**Primary Outcome**: disease-free survival (DFS) *5-year DFS* axillary dissection: 84.4%; 95% CI 80.7–88.1	**Quality of study** assessed with SIGN checklist for RCT: acceptable (+) **Limitations by authors** n.a. **Additional concerns about quality**:

Source: Galimberti V, Cole BF, Zurrida S, et al: International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013 Apr;14(4): 297-305.					
receiving no further treatment to the axilla **Country**: Australia, Belgium, Denmark, France, Italy, New Zealand, Peru, Slovenia, and Switzerland	(HR) of less than 1.25 for no axillary dissection versus axillary dissection **Number of included patients**: Randomized: n=934 Analyzed: n=931; axillary dissection: n=464; no axillary dissection: n=467		surgical complications of axillary dissection	no axillary dissection: 87.8% 95% CI 84.4−91.2 ITT-Analysis DFS in the group without axillary dissection was noninferior to the axillary dissection group HR 0.78; 95% CI 0.55–1.11; p=0.0042 **Secondary Outcome**: overall survival (OS)	**Level of Evidence:** Oxford 2011 Level 2 **Sources of funding:** The International Breast Cancer Study Group (IBCSG) sponsored the trial

Source: Galimberti V, Cole BF, Zurrida S, et al: International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013 Apr;14(4): 297-305.					
	Median follow-up time: 5 years (IQR 3.6-7.3) [results presented] **Mean Age (Range):** Axillary dissection: 53 (28-81) No axillary dissection: 54 (26-81) **Inclusion criteria**: clinically non-palpable axillary lymph node(s) and a primary tumour of 5 cm			*5 year OS* 5-year overall survival was Axillary dissection: 97.6%; 95% CI 96.0-99.2 no axillary dissection: 97.5%; 95% CI 95.8-99.1 HR 0.89; 90% CI 0.52–1.54; log-rank p=0.73 site of	

Source: Galimberti V, Cole BF, Zurrida S, et al: International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013 Apr;14(4): 297-305.					
	or less and who, after sentinel-node biopsy, had one or more micrometastatic (=2 mm) sentinel lymph nodes with no extracapsular extension **Exclusion**: not specified			recurrence/axillary recurrences *regional recurrences* Axillary dissection: 1 No axillary dissection: 5 All 6 received breast-conserving surgery and 4 of them radiotherapy surgical complications of axillary dissection *Sensory neuropathy*	

Source: Galimberti V, Cole BF, Zurrida S, et al: International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013 Apr;14(4): 297-305.					
				Axillary dissection: 82 (18%) No axillary dissection: 55 (12%) p=0.012 *Lymphoedema* Axillary dissection: 59 (13%) No axillary dissection: 15 (3%) p<0.0001 *Motor neuropathy*	

Source: Galimberti V, Cole BF, Zurrida S, et al: International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013 Apr;14(4): 297-305.					
				Axillary dissection: 37 (8%) No axillary dissection: 13 (3%) p<0.0004	
Abbreviations: IQR = Interquartile Range DFS = Disease-Free Survival OS = Overall Survival					

Source: Galimberti V, Cole BF, Zurrida S, et al: International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013 Apr;14(4): 297-305.					
RCT = Randomised Controlled Trial ITT = Intention to Treat HR = Hazard Ratio 95% CI = 95% Confidence Interval n.a. = not Available, not Applicable					

2.1.9 Kapitel 4.6 Adjuvante Strahlentherapie des Mammakarzinoms (Giuliano et al. 2011)

Verknüpfte Empfehlungen:

Source: Giuliano AE, Hunt KK, Ballmann KV, et al Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6): 569-575.					
Aim and Country	**Design and participants**	**Intervention**	**Outcomes**	**Results**	**Quality and comment**
Acronym of study: ACOSOG-Z0011 **Aim**: determine the effects of complete axillary lymph node dissection (ALND) on survival of patients with sentinel lymph node (SLN) metastasis of breast cancer **Country**: USA	**Design**: multicenter, randomized phase 3 noninferiority trial **Setting**: 115 sites **Enrollment**: 05/1999 to 12/2004 **Noninferiority**: if the 90% CI for the HR was below 1.3, this would indicate that patients undergoing SLND alone	Before randomization: all women underwent SLND **Intervention** ALND **Control** SLND alone (no further axillary-specific intervention – no third-field nodal irradiation)	**Primary Outcome**: Overall survival (OS) **Secondary Outcome**: Disease-free survival (DFS)	**Primary Outcome**: Overall survival (OS) SLND vs ALND-alone unadjusted HR 0.79; 90% CI 0.56-1.10 *5-year overall survival* SLND-alone: 92.5%; 95% CI 90.0%-95.1%	**Quality of study** assessed with SIGN checklist for RCT: acceptable (+) **Limitations by authors** failure to achieve target accrual and possible randomization imbalance favoring the SLND-alone group

Source: Giuliano AE, Hunt KK, Ballmann KV, et al Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6): 569-575.					
	do not have an unacceptably worse overall survival than patients undergoing SLND plus ALND **Number of included patients**: n=891 randomised; ALND: n=445 SLND alone: n=446 **Median follow-Up:** 6.3 years (IQR 5.2-7.7) **Median Age (Range):** ALND: 56 (24-92) SLND alone: 54			ALND: 91.8%; 95% CI 89.1%-94.5% SLND vs ALND HR (adjusting for adjuvant therapy chemotherapy, endocrine therapy, and/or radiation therapy and age) HR 0.87; 90% CI 0.62-1.23, p=0.03 **Secondary Outcome**: Disease-free survival (DFS) *5-year disease-free survival*	possible randomization imbalance favoring the SLND-alone group **Additional concerns about quality**: Randomization process not described **Level of Evidence:** Oxford 2011 Level 3 (downgrade due to imbalanced groups) **Sources of funding:** supported by National Cancer Institute grant U10 CA 76001 to the American College of

Source: Giuliano AE, Hunt KK, Ballmann KV, et al Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6): 569-575.					
	(25-90) **Inclusion criteria**: women with clinical T1-T2 invasive breast cancer 5cm or less, no palpable adenopathy, and 1 to 2 SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section **Exclusion**:			SLND-alone: 83.9%; 95% CI 80.2%-87.9% ALND: 82.2%; 95% CI 78.3%-86.3% p=0.14 SLND vs ALND unadjusted HR 0.82; 95% CI 0.58-1.17 HR adjusted for adjuvant treatment and age 0.88; 95% CI 0.62-1.25, p=0.47 *5-year rates of local recurrence*	Surgeons Oncology Group (ACOSOG)

Source: Giuliano AE, Hunt KK, Ballmann KV, et al Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6): 569-575.					
	3 or more positive SLNs, matted nodes, or gross extranodal disease, received neoadjuvant hormonal therapy or chemotherapy			SLND: 1.6%; 95% CI 0.7%-3.3% ALND: 3.1%; 95% CI 1.7%-5.2 p=0.11 *Locoregional recurrence-free* *survival at 5 years* SLND 96.7%; 95% CI 94.7%-98.6%ALND 95.7%; 95% CI 93.6%-97.9 p=0.28	
Abbreviations:					

Source: Giuliano AE, Hunt KK, Ballmann KV, et al Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6): 569-575.					
ALND = Axillary Lymph Node Dissection SLN = Sentinel Lymph Node SLND = Sentinel Lymph Node Dissection DFS = Disease-Free Survival IQR = Interquartile Range HR = Hazard Ratio 95% CI = 95% Confidence Interval					

2.1.10 Kapitel 4.7 Systemische Therapie frühes Mammakarzinom: TNBC (An et al. 2020)

Verknüpfte Empfehlungen:

Source: X, An, Lei X, Huang R, Luo R, Li H, Xu F, Yuan Z, et al. Adjuvant Chemotherapy for Small, Lymph Node-Negative, Triple-Negative Breast Cancer: A Single-Center Study and a Meta-Analysis of the Published Literature. Vol. 126, United States, 2020-8-15, 2020. doi: doi: . https: //pubmed.ncbi.nlm.nih.gov/32710666/.					
Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: evaluate the efficacy of adjuvant chemotherapy in patients with small, lymph node-negative TNBC	**Design**: Single-Center Study and a systematic review and meta-analysis **Search date**: n.a. **Searched databases**:	**Intervention** Adjuvant chemotherapy **Control** Without adjuvant chemotherapy **Population**	**Outcome** s overall recurrence rate, including both loco-regional recurrences and distant metastasis events	**Primary Outcome**: Adjuvant chemotherapy significantly reduced the number of recurrence events; the pooled risk ratio (RR) comparing chemotherapy with no chemotherapy was 0.58	**AMSTAR II critical appraisal tool** Overall confidence in the results of the review: critically low; 5 critical flaws (2,4,7,13,15)

Source: X, An, Lei X, Huang R, Luo R, Li H, Xu F, Yuan Z, et al. Adjuvant Chemotherapy for Small, Lymph Node-Negative, Triple-Negative Breast Cancer: A Single-Center Study and a Meta-Analysis of the Published Literature. Vol. 126, United States, 2020-8-15, 2020. doi: doi: . https: //pubmed.ncbi.nlm.nih.gov/32710666/.					
	PubMed, Web of Science, the online proceedings of the American Society of Clinical Oncology annual meetings, the online proceedings of the San Antonio Breast Cancer Symposium, and the CD proceedings of the St. Gallen International Breast Cancer Conference **Included study designs**: Retrospective studies	patients withpT1N0M0 (stage I) or pT1a–bN0M0 TNBC		(95% CI, 0.43-0.78 [P < .001]) **Subgroup analysis** **Among T1a/bN0M0** RR: 0.60 (95% CI, 0.43-0.83 **Among T1bN0M0** RR: 0.62; 95 CI, 0.42-0.92 **Among T1aN0M0**	**Additional concerns about quality**: n.a. **Quality of included studies**: Relatively small sample sizes **Sources of funding:** supported by the Medical Scientific Research Foundation of Guangdong Province, China (A2016206); the

Source: X, An, Lei X, Huang R, Luo R, Li H, Xu F, Yuan Z, et al. Adjuvant Chemotherapy for Small, Lymph Node-Negative, Triple-Negative Breast Cancer: A Single-Center Study and a Meta-Analysis of the Published Literature. Vol. 126, United States, 2020-8-15, 2020. doi: doi: . https: //pubmed.ncbi.nlm.nih.gov/32710666/.					
	Number of included studies: 7 (3 studies enrolled TNBC [T1N0 or T1a/bN0 TNBC] and 4 studies enrolled mixed molecular subtype including TNBC [2 with T1N0 and 2 with T1a/b]) **Number of included patients**: The total number of patients with T1N0M0 TNBC was 1525,			RR: 0.64; 95 CI, 0.31-1.33	International Collaboration Foundation of Science and Technology Planning Project of Guangdong Province of China (2016A050502015); the Key Cultivation Project of Young Teachers of Sun Yat-Sen University (17ykzd33); and the National Natural Science Foundation of China (81902681)

Source: X, An, Lei X, Huang R, Luo R, Li H, Xu F, Yuan Z, et al. Adjuvant Chemotherapy for Small, Lymph Node-Negative, Triple-Negative Breast Cancer: A Single-Center Study and a Meta-Analysis of the Published Literature. Vol. 126, United States, 2020-8-15, 2020. doi: doi: . https: //pubmed.ncbi.nlm.nih.gov/32710666/.					
	including 941 patients with T1a/ bN0M0 TNBC. **Mean/median age**: n.a. **Inclusion criteria**: 1) assessed the benefit of adjuvant chemotherapy among patients with pT1N0M0 (stage I) or pT1a–bN0M0 TNBC; 2) enrolled patients with all molecular subtypes,				

Source: X, An, Lei X, Huang R, Luo R, Li H, Xu F, Yuan Z, et al. Adjuvant Chemotherapy for Small, Lymph Node-Negative, Triple-Negative Breast Cancer: A Single-Center Study and a Meta-Analysis of the Published Literature. Vol. 126, United States, 2020-8-15, 2020. doi: doi: . https: //pubmed.ncbi.nlm.nih.gov/32710666/.					
	including triple-negative types; and 3) clarified the effect of chemotherapy on TNBC. Only studies published in English were included				
Abbreviations: n.a. = not Available, not Applicable RR = Risk Ratio					

Source: X, An, Lei X, Huang R, Luo R, Li H, Xu F, Yuan Z, et al. Adjuvant Chemotherapy for Small, Lymph Node-Negative, Triple-Negative Breast Cancer: A Single-Center Study and a Meta-Analysis of the Published Literature. Vol. 126, United States, 2020-8-15, 2020. doi: doi: . https: //pubmed.ncbi.nlm.nih.gov/32710666/.					
95% CI = 95% Confidence Interval					

2.1.11 Kapitel 4.6 Adjuvante Strahlentherapie (Jia et al. 2021)

Verknüpfte Empfehlungen:

Source: S, Jia, Liu Z, Zhang J, Zhao C, Zhu L, Kong J, Han H, et al. "Can Internal Mammary Lymph Nodes Irradiation Bring Survival Benefits for Breast Cancer Patients? A Systematic Review and Meta-Analysis of 12,705 Patients in 12 Studies." [In eng]. Radiation oncology (London, England) 16, no. 1 (2021-2-23 2021): 42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33622345/.					
Aim	Design and participants	Intervention	Outcomes	Results	Quality and comment
Aim: To evaluate the effect of prophylactic irradiation of internal mammary lymph nodes in breast cancer patients.	**Design**: Systematic review and meta-analysis **Search date**: n.a.	**Intervention** Internal mammary lymph node irradiation (IMNI) **Control**	**Primary Outcome**: Overall survival (OS) Disease-free survival (DFS)	**Primary Outcome**: Overall survival Risk of death reduced by 11% by IMNI:	**AMSTAR II critical appraisal tool**

Source: S, Jia, Liu Z, Zhang J, Zhao C, Zhu L, Kong J, Han H, et al. "Can Internal Mammary Lymph Nodes Irradiation Bring Survival Benefits for Breast Cancer Patients? A Systematic Review and Meta-Analysis of 12,705 Patients in 12 Studies." [In eng]. Radiation oncology (London, England) 16, no. 1 (2021-2-23 2021): 42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33622345/.					
	Searched databases: PubMed, EMBASE, Web of Science, CNKI, Wanfang Medical Network, the Chinese Biomedical Literature Database **Included study designs**: 9 retrospective cohort studies, 1 prospective cohort study, 1 non-	Non-IMNI	**Subgroup analysis:** DFS on key prognostic factors: status of axillary lymph nodes (N_0, N_+) and tumor location (medical/central, lateral) **Secondary Outcome:**	HR 0.89, 95% CI 0.79 to 1.00, I^2=47.5%, p=0.047 (12 studies with 12,705 patients) <u>Disease-free survival</u> HR 0.62, 95% CI 0.47 to 0.82, I^2=79.2%, p=0.001 (8 studies)	Overall confidence in the results of the review: critically low 5 critical flaws (items 2, 4, 7, 11, 13) **Overall quality of evidence**: critically low **Additional concerns about quality**:

Source: S, Jia, Liu Z, Zhang J, Zhao C, Zhu L, Kong J, Han H, et al. "Can Internal Mammary Lymph Nodes Irradiation Bring Survival Benefits for Breast Cancer Patients? A Systematic Review and Meta-Analysis of 12,705 Patients in 12 Studies." [In eng]. Radiation oncology (London, England) 16, no. 1 (2021-2-23 2021): 42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33622345/.					
	randomized controlled trial, 1 randomized controlled trial **Number of included studies**: n=12 **Number of included patients**: n=12,705 **Mean/median age**: n.a. **Inclusion criteria**:		Acute and late side effects	**Subgroup analysis** <u>DFS of high risk group (N_+)</u> HR 0.65, 95% CI 0.53 to 0.80, I^2=71.5%, p<0.0001 <u>DFS in N_0 group</u> HR 1.02, 95% CI 0.87 to 1.20, I^2=0.0%, p=0.794	Some studies had limitations in cohort representation, follow-up time, or description of loss to follow-up **Quality of included studies**: 11 of 12 studies were rated as high quality

Source: S, Jia, Liu Z, Zhang J, Zhao C, Zhu L, Kong J, Han H, et al. "Can Internal Mammary Lymph Nodes Irradiation Bring Survival Benefits for Breast Cancer Patients? A Systematic Review and Meta-Analysis of 12,705 Patients in 12 Studies." [In eng]. Radiation oncology (London, England) 16, no. 1 (2021-2-23 2021): 42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33622345/.					
	Patients without other tumors than BC; no distant metastasis or other complications; Follow-up time at least 5 years			<u>Location of tumor:</u> <u>DFS</u> <u>Central/medical</u> HR 0.55, 95% CI 0.40 to 0.78, p=0.001 <u>Lateral</u> HR 0.77, 95%CI 0.61 to 0.97, p=0.025	(evaluated with Newcastle-Ottawa Scale) **Planned included studies**: Clinical controlled study **Sources of funding**: n.a.

Source: S, Jia, Liu Z, Zhang J, Zhao C, Zhu L, Kong J, Han H, et al. "Can Internal Mammary Lymph Nodes Irradiation Bring Survival Benefits for Breast Cancer Patients? A Systematic Review and Meta-Analysis of 12,705 Patients in 12 Studies." [In eng]. Radiation oncology (London, England) 16, no. 1 (2021-2-23 2021): 42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33622345/.					
				Secondary Outcome: Incidence of radiation pneumonitis/pulmonary fibrosis in the IMNI group (higher: 2 studies; no difference: 1 study) Cardiac toxicity No significant difference (5 studies=all included	

Source: S, Jia, Liu Z, Zhang J, Zhao C, Zhu L, Kong J, Han H, et al. "Can Internal Mammary Lymph Nodes Irradiation Bring Survival Benefits for Breast Cancer Patients? A Systematic Review and Meta-Analysis of 12,705 Patients in 12 Studies." [In eng]. Radiation oncology (London, England) 16, no. 1 (2021-2-23 2021): 42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33622345/.					
				studies comparing cardiac toxicity) <u>Skin reaction</u> Slightly higher in IMNI group (1 study) <u>Incidence of contralateral breast cancer in the long term</u>	

Source: S, Jia, Liu Z, Zhang J, Zhao C, Zhu L, Kong J, Han H, et al. "Can Internal Mammary Lymph Nodes Irradiation Bring Survival Benefits for Breast Cancer Patients? A Systematic Review and Meta-Analysis of 12,705 Patients in 12 Studies." [In eng]. Radiation oncology (London, England) 16, no. 1 (2021-2-23 2021): 42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33622345/.					
				Higher incidence in IMNI group HR 2.47, 95% CI 1.23 to 4.95	
Abbreviations: DFS: disease-free survival HR: Hazard Ratio					

Source: S, Jia, Liu Z, Zhang J, Zhao C, Zhu L, Kong J, Han H, et al. "Can Internal Mammary Lymph Nodes Irradiation Bring Survival Benefits for Breast Cancer Patients? A Systematic Review and Meta-Analysis of 12,705 Patients in 12 Studies." [In eng]. Radiation oncology (London, England) 16, no. 1 (2021-2-23 2021): 42. https: //doi.org/doi: . https: //pubmed.ncbi.nlm.nih.gov/33622345/.					
IMNI: Internal mammary lymph node irradiation OS: Overall survival					

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