

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Early Detection and Diagnosis

Early Detection and Diagnosis

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- **Versions 2005–2024:**

**Albert / Blohmer / Fallenberg / Fersis / Gerber / Heil / Junkermann /
Kühn / Maass / Müller-Schimpfle / Scharl / Schreer / Wöckel**

- **Version 2025:**

Fallenberg / Thomssen

Early Detection with Mammography

<u>Age</u>	<u>Interval (months)</u>	Oxford		
		LOE	GR	AGO
• < 40	na	-	-	--
• 40-44				
• normal risk	na	1b	B	-
• moderately enhanced risk or history of breast cancer*	na	1b	B	+/-
• 45–49 [#]	24-36	1a	A	+
• 50–75 ^{**}	24	1a	A	++
• > 75 ^{***}	24	4	C	+/-

* See Recommendation by the German Commission on Radiological Protection (Strahlenschutzkommission), except INFP (Program of Intensified Early Detection) siehe Chapter 02.

** National Mammography-Screening-Program.

*** Depending on health condition + life expectancy (> 10 yrs).

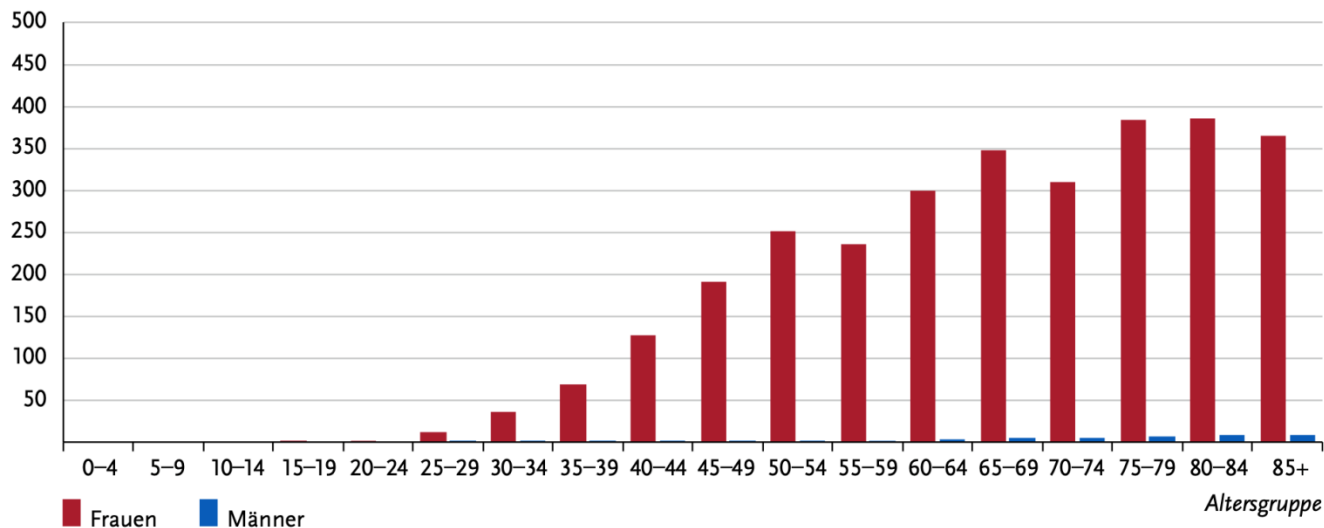
Justifying indication necessary, as long as legal regulations are pending.

Breast Cancer: Age Specific New Cancer Cases

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Abbildung 3.17.2
Altersspezifische Neuerkrankungsraten nach Geschlecht, ICD-10 C50, Deutschland 2019 – 2020
je 100.000



Mammography-Screening Potential Benefit and Harm

Data background: Breast Cancer Surveillance Consortium Registry Data per 10.000 Women screened over 10 years

Age	40-49	50-59	60-69	70-74
Breast cancer death avoided (95% CI)	3 (0-9)	8 (2-17)	21 (11-32)	13 (0-32)
False-positive (n)	1212	932	808	696
Breast biopsies (n)	164	159	165	175
False-negative (n)	10	11	12	13
<u>Calculated from the data above</u>				
False-pos. to be accepted to avoid one breast cancer related death over 10 yrs per 10.000 women	404	117	38	54
Breast biopsies to be accepted to avoid one breast cancer related death over 10 yrs per 10.000 women	55	20	8	13

Mod. acc. Siu AI on behalf of the USPSTF 2016, 164:279–296

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SSK Recommendation Moderate Risk

Women with moderate risk increase from the age of 40: Moderate risk defined as a personal risk of disease of 15% to 29% (depending, for example, on the number and age of diseased family members, histologically proven risk lesions)

Imaging modality	Grade of recommendation	Comment
Mammography	Primary examination	Individually adapted approach (depending on individual risk analysis, taking into account the woman's preferences and objections); in the age group of 50-69 years: Consider participation in the early detection program (mammography screening) and complementary procedures after benefit-risk analysis
US	Primary examination	Consider annually (especially in the case of high breast density)
Breast MRI	Special procedures	Only consider if a malignant finding is not sufficiently to exclude with mammography and sonography. There is insufficient data available for the use of MRI as a primary early detection method in the intermediate risk group

Moderates Risiko berechnet nach Tyrer-Cuzick (QR-code)

Einfluß auf das Risiko haben auch z. B.: Alter, BMI, Brustdichte, frühere Brustbiopsien (Histologie), Vorerkrankungen (Ovarialkarzinom), Hormontherapie, Vorfahren (Ashkenazi Jewish), Alter bei Menarche, Alter bei erster Geburt.



Early Detection in Asymptomatic Women

Digital Breast Tomosynthesis, Endpoint: Cancer Detection Rate

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	Oxford		
	LOE	GR	AGO
Digital Breast Tomosynthesis (DBT ± SM)*	1a	A	+
Replacing FFDM by synthetic MG in addition to DBT**	1a	A	++

The complete DBT dataset of images has to be available for judgment / reporting, the synthetic mammography only is not sufficient.

* To date, no significant reduction of interval cancers to date.

Significantly higher sensitivity, heterogeneous specificity, and higher costs [machine, evaluation, archiving] of DBT in comparison to Full-Field Digital Mammography (FFDM).

** Dose reduction by using calculated synthetic 2D mammography (SM) instead of additional FFDM.

Digital Breast Tomosynthesis

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Screening with tomosynthesis vs. mammography

Issued on: May 2023

Cancer Screening, Diagnosis and Care

European Commission Initiative on Breast Cancer (ECIBC)

Healthcare question

Should screening using digital breast tomosynthesis vs. digital mammography be used in organised screening programmes for early detection of breast cancer in asymptomatic women?

Recommendation

For asymptomatic women with an average risk of breast cancer, the ECIBC's Guidelines Development Group (GDG) suggests using digital breast tomosynthesis (DBT) over digital mammography (DM) in the context of an organised population-based screening programme.

<https://cancer-screening-and-care.jrc.ec.europa.eu/en/ecibc/european-breast-cancer-guidelines?topic=65&usertype=60&updatef2=0>. Download am 09.01.2025

AI for Cancer Detection

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Oxford

AI in screening

Second reader of mammography

LOE

GR

AGO

1b

B

+/-

To reduce workload (AI only)

2b

B

-

Tomosynthesis: stand alone or second reader

2a

B

-

Use of AI too early, no evidence for superiority and transfer into clinical routine, standardisation lacking [Uwimana A et al. 2025, Al-Karawi D et al. 2024]

Artificial Intelligence for Breast Cancer Detection and its Health Technology Assessment

	ML %			ML-unaided radiologist			ML-aided radiologists		
	Median	95%-C.I.		Median	95%-C.I.		Median	95%-C.I.	
Sensitivity [%]	83.6	79.7	86.9	82.2	77.2	86.3	86.2	80.6	90.3
Specificity [%]	88.5	84.0	91.9	86.0	81.9	89.2	77.8	57.1	90.2

While AI systems demonstrated promising applications across diverse breast imaging techniques, as highlighted in the reviewed articles and in our analysis indicating their superior diagnostic and predictive capabilities compared to conventional radiology practices, **our study underscores persistent challenges in developing and validating AI systems for clinical implementation.** These challenges stem from concerns regarding the availability and reliability of breast imaging data and the imperative to ensure the resilience, interpretability, and transparency of AI algorithms while navigating ethical and regulatory compliance considerations.

Early Detection (normal or moderate risk*)

Sonography / MRI



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- **Screening-Breast sonography alone**
 - Automated 3D-sonography
- **Breast sonography as an adjunct to FFDM:**
 - Dense mammogram (heterogeneously dense, extremely dense)
 - Elevated risk
- **MRI if screening MG is negative and breast composition: extremely dense** 45-75 yrs**

	Oxford		
	LoE	GR	AGO
	5	D	--
	3a	C	-
	2a	B	++
	1b	C	++
	1b	B	+

* Except INFP (Program of Intensified Early Detection).

** Definition of extremely dense corresponds to BIRADS-density category D, heterogeneously dense to BIRADS-category C according to ACR BI-RADS-Atlas 5th ed. 2013.

Early Detection (normal risk) Clinical Breast Examination (CBE)

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As stand alone procedure

- Self-examination
- Clinical breast examination (CBE) by health professionals outside checkup for cancer
- Clinical breast examination (CBE) by health professionals during checkup for cancer**
- Medical palpation by blind / visually impaired persons

CBE because of mammographic / sonographic lesion

CBE in combination with imaging

	Oxford		
	LoE	GR	AGO
Self-examination	1a	A	-*
Clinical breast examination (CBE) by health professionals outside checkup for cancer	1a	C	-*
Clinical breast examination (CBE) by health professionals during checkup for cancer**	1a	B	++
Medical palpation by blind / visually impaired persons	3b	C	-
CBE because of mammographic / sonographic lesion	5	D	++
CBE in combination with imaging	1a	A	++

* May increase breast awareness.

** Outside mammography screening.

Assessment of Suspicious Imaging (Screening or Diagnostic) or Breast Symptoms



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	Oxford		
	LoE	GR	AGO
■ Clinical examination	3b	B	++
■ X-ray based imaging			
■ Mammography (if not performed)	1b	A	++
■ Tomosynthesis*	2a	B	+
■ Contrast-enhanced mammography	1b	B	+
■ Sonography (B-mode)	2b	B	++
■ Elastography (shear-wave) **	2b	B	+
■ Automated 3D-sonography	3b	B	+/-
■ Minimally invasive biopsy (CNB, VAB)	1b	A	++
■ MRI***	2a	B	+

* Replacement of additional FFDM by DBT/SM to reduce exposure to radiation.

** Additional assessment

*** If clinical examination, mammography and sonography incl. needle biopsy (CNB, VAB) do not allow a clear assessment.

CEM vs MRI

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Contrast-enhanced mammography

Issued on: October 2021

Cancer Screening, Diagnosis and Care

Healthcare question

European Commission Initiative on Breast Cancer (ECIBC)

Should contrast-enhanced mammography vs. magnetic resonance imaging be used as additional imaging method to assist in surgical treatment planning in women with histologically confirmed invasive breast cancer?

Recommendation

In women with histologically confirmed invasive breast cancer, who require further evaluation, the ECIBC's Guidelines Development Group (GDG) suggests using contrast-enhanced mammography (CEM) over magnetic resonance imaging (MRI) as additional imaging method to assist in surgical treatment planning.

Comparison of Different Assessment Modalities

Summary of pooled performance (95% confidence interval) of imaging modalities for recalled lesions.

Imaging Modality	Sensitivity	Specificity
Digital mammography (DM)	85 (78-90)	77 (66-85)
Digital Breast Tomosynthesis (DBT)	91 (87-94)	85 (75-91)
Handheld Ultrasound (HHUS)	90 (86-93)	65 (46-80)
Contrast-enhanced Mammography (CEM)	95 (90-97)	73 (63-81)
Magnetic Resonance Imaging (MRI)	93 (88-96)	69 (55-81)

Conclusions: The CEM, MRI, DBT, and HHUS demonstrate excellent performance in correctly identifying and classifying cancer lesions referred for diagnostic work-up, but HHUS, MRI, and CEM have a more limited ability to discriminate benign lesions than DBT and DM.

Akwo Cancers (Basel). 2024 Oct 17;16(20):3505. 2024

Contrast enhancement and its pattern in CEM and MRI can be used to determine malignant or benign lesions. As some benign lesions show enhancement on CEM and MRI or hypervascularity on ultrasound, which increase the potential for FP; this may explain the lower overall specificity reported for HHUS, MRI, and CEM. Therefore, enhancement in MRI and CEM, and vascularity in ultrasound can be strengths and drawbacks at the same time.

Pre-Therapeutic Assessment of the Breast

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- **Clinical examination**
- **Sonography (breast)**
- **Mammography (completion of the imaging)**
- **MRI***
- **Contrast-enhanced mammography (alone) if available; consider radiation sensitivity of the breast (age)***
- **Tomosynthesis (DBT) + SM****
- **Breast-CT**
- **Minimally invasive biopsy of further lesions (CNB, VAB)**
- **Tagging the tumor, if neoadjuvant therapy planned**

Oxford		
LoE	GR	AGO
5	D	++
2b	B	++
2b	B	++
1b	A	+
2a	B	+
2b	B	+
4	D	-
1b	A	++
1c	A	++

* MRI- or CEM guided vacuum biopsy is mandatory in case of MRI- or CEM detected additional lesions (in-house or with cooperations). Individual decision for patients at high familiar risk, with dense breast (density C / D), lobular invasive tumors, suspicion of multilocular disease.

** Replacement of additional FFDM by SM in order to reduce the exposure to radiation

Pre-Therapeutic Assessment: Axilla

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- **Clinical examination**
- **Sonography**
- **CNB Axilla, if suspicious LN and marking of the node if TAD planned ≤ 3 susp. LK***
- **MRI**
- **Mammography (FFDM)**
- **Tomosynthesis (DBT)**
- **Contrast-enhanced mammography (CEM, alone)**
- **PET CT / MRI for axillary LN**
- **Breast-CT**

	Oxford		
	LoE	GR	AGO
	5	D	++
	2a	B	++
	2b	B	++
	1b	A	+
	2b	B	-
	2b	B	-
	2a	B	-
	2b	B	-
	4	D	-

Pre-Therapeutic Staging

	Oxford		
	LoE	GR	AGO
	5	D	++
History and clinical examination			
<u>Only in case of high metastatic potential and/or symptoms and/or indication for (neo-) adjuvant chemotherapy and/or antibody-therapy:</u>			
▪ CT scan of thorax / abdomen / pelvis	2a	B	++
▪ Bone scan	2a	B	+
▪ Chest X-ray	5	C	+/-
▪ Liver ultrasound	5	D	+/-
▪ Further investigation in case of additional suspicious lesions (e.g. liver-MRI, CEUS*, biopsy etc.)	2a	B	+
▪ FDG-PET or FDG-PET-CT** FDG-PET-MRI**	2a	B	+/-
▪ Whole body MRI	2a	C	+/-

* Contrast enhanced ultrasound.

** Particularly in patients with high tumor stage (III), if available.

Diagnosing Bone Metastases in Breast Cancer: A Systematic Review and Network Meta-Analysis on Diagnostic Test Accuracy Studies of 2-[18F] FDG-PET/CT, 18F-NaF-PET/CT, MRI, Contrast-Enhanced CT, and Bone Scintigraphy



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Summary of Meta-Analyses. Estimates (and Respective 95% Confidence Intervals) of Sensitivity and Specificity Derived From Bivariate Random Effects Models and Network Meta-Analyzed Differences in Sensitivity and Specificity

Modality	Bivariate random effects models			Network meta-analysis ^o	
	Number of studies	Sensitivity	Specificity	Sensitivity	Specificity
2-[18F]FDG-PET/CT	20	0.94 (0.89-0.97)	0.98 (0.96-0.99)	reference	reference
MRI	7	0.94 (0.82-0.98)	0.93 (0.87-0.96)	n.s.	n.s.
18F-NaF-PET/CT	4	0.95 (0.85-0.98)	1.00 (0.93-1.00)	n.s.	n.s.
CE-CT	5	0.70 (0.62-0.77)	0.98 (0.97-0.99)	p = 0.017	n.s.
Bone scintigraphy	13	0.83 (0.75-0.88)	0.96 (0.87-0.99)	p = 0.017	p = 0.053

^o Network meta-analysis of multimodality studies (n = 16); comparator minus reference.

We concluded that 2-[18F]FDG-PET/CT and MRI have high and comparable accuracy for diagnosing bone metastases in breast cancer patients. Both outperformed CE-CT and bone scintigraphy regarding sensitivity. Future multimodality studies based on consented thresholds are warranted for further exploration, especially in terms of the potential role of 18F-NaF-PET/CT in bone metastasis diagnosis in breast cancer.

mod. from Gerke O et al. Semin Nucl Med. 2025 Jan;55(1):137-151.

Neoadjuvant Systemic Therapy (NST, NACT)

Assessment Methods of Response

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- **Sonography**
- **Clinical examination, Palpation**
- **Mammography (DM)**
- **CEM (contrast-enhanced mammography)**
- **MRI**
- **DBT (Tomosynthesis)**
- **PET(-CT)**

	Oxford		
	LoE	GR	AGO
	2b	B	++
	2b	B	++
	2b	B	++
	2a	B	+
	2a	B	+
	2b	B	+/-
	2b	B	+/-

Assessment of response should be performed by the same modality before, during, and after treatment.

Use of Different Imaging Modalities for Monitoring NACT

Comparison of HHUS, TOMO, MG and MRI: Murakami et al. AR Open 2021

Size difference	<-11 mm	<-6 to -10mm	+/- 5 mm	>-6 to -10mm	>-11 mm
DBT vs. Patho	0%	5.3%	82.1%	8.4%	4.2%
FFDM vs Patho	9.5%	9.5%	62.1%	8.4%	10.5%
US vs Patho	10.5%	9.5%	61.1%	12.6%	6.3%
MRI vs. Patho	3.2%	8.4%	75.8%	6.3%	6.3%

Conclusion:

DBT has good correlation with histopathology for measuring residual tumor size after NST. DBT was comparable to MRI in assessing tumor response after completion of NST.

CEM compared to MRI: Kaiyin et al. BCRT 2023

Six head-to-head comparison studies with 328 patients included.
Pooled **sensitivity, specificity, and diagnostic odds ratio (DOR):**

CEM: 93% (95% CI, 84-97%), 68% (CI, 60-76%), 29.29 (CI, 11.41-75.18)

MRI: 84% (95% CI, 62-95%), 80% (CI, 71-87%), 21.39 (CI, 5.94-77.13).

AUC: CEM: 0.85 (95% CI 0.82-0.88) **MRI:** 85 (95% CI 0.82-0.88)

Conclusion:

This meta-analysis showed that CEM provides an equivalent diagnostic accuracy to MRI in identification of pCR in breast cancer patients receiving NAT. The results support the increasing use of CEM in this setting and would encourage future studies to validate CEM as a suitable replacement for MRI.

CEM depending on Ca-subtype: Vidali et al. 2024

Conclusions:

Overall, CEM is accurate in assessing the pCR and predicting the pathologic-complete response among the different molecular subtypes after NAT.