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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Early Detection and Diagnosis



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Early Detection and Diagnosis

- **Versions 2005–2019:**
**Albert / Blohmer / Fallenberg / Fersis / Junkermann /
Maass / Müller-Schimpfle / Scharl / Schreer**

- **Version 2021**
Fallenberg / Gerber

Screened data bases

Pubmed	2018 - 2020
Medline	2018 - 2020
Cochrane	2018 - 2020

Guidelines

S3 Diagnostik, Therapie und Nachsorge des Mammakarzinoms:

1. Wöckel A, Festl J, Stüber T et al. Interdisciplinary Screening, Diagnosis, Therapy and Follow-up of Breast Cancer. Guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/045OL, December 2017) - Part 1 with Recommendations for the Screening, Diagnosis and Therapy of Breast Cancer. Geburtshilfe Frauenheilkd. 2018 Oct;78(10):927-948. doi: 10.1055/a-0646-4522. Epub 2018 Oct 19.
2. Wöckel A, Festl J, Stüber T et al. Interdisciplinary Screening, Diagnosis, Therapy and Follow-up of Breast Cancer. Guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/045OL, December 2017) - Part 2 with Recommendations for the Therapy of Primary, Recurrent and Advanced Breast Cancer. Geburtshilfe Frauenheilkd. 2018 Nov;78(11):1056-1088. doi:

10.1055/a-0646-4630. Epub 2018 Nov 26.

European Commission Initiative on Breast Cancer (ECIBC)

European guidelines on breast cancer screening and diagnosis

<https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines>

2015 ACS Update Breast Cancer Screening for women at average risk

IARC Handbook 2016

European Commission 2016

(<http://ecibc.jrc.ec.europa.eu/recommendations/list/3>; Update 24.11.2016, Abruf 20122016)

Screened: Metaanalyses/ Systematic reviews / RCT / Cohort studies

Early Detection with Mammography				
Age	Interval	Oxford		
		LOE	GR	AGO
< 40	na	-	-	--
40-44	na	1b	B	-
45-49	24-36	1a	B	+ [#]
50-69*	24	1a	A	++
70-74	24	1a	A	+ [#]
> 75**	24	4	C	+/- [#]

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* National Mammography-Screening-Program
 ** health status + life expectancy more than 10 years
 # clear indication necessary

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Radiation Dose

1. Miglioretti DL, Lange J, van den Broek JJ, et al. Radiation-Induced Breast Cancer Incidence and Mortality from Digital Mammography Screening: A Modeling Study Ann Intern Med. 2016 Feb 16; 164(4):205-14.
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3. (https://healthcare-quality.jrc.ec.europa.eu/sites/default/files/Guidelines/EtDs/ECIBC_GLs_EtD_screening_40-44.pdf)
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	Early Detection in Asymptomatic Women Digital Breast Tomosynthesis		
	Oxford LOE	GR	AGO
Digital Breast Tomosynthesis (DBT in addition to FFDM or SM)*	1a	B	+
Replacing FFDM by synthetic MG in addition to DBT**	2a	B	++
The complete DBT dataset of images has to be available for evaluation/reporting, the synthetic mammography only is not sufficient.			
<ul style="list-style-type: none"> • Sign. higher sensitivity, heterogeneous specificity, and higher costs [machine, evaluation, archiving] of DBT in comparison to Full-Field Digital Mammography (FFDM) • Dose reduction due to calculated synthetic 2D mammography (SM) instead of FFDM 			
** Evaluation for Germany in a randomized prospective trial (TOSYMA)			

1. Hodgson et al 2016 Hodgson R, Heywang-Köbrunner SH, Harvey SC, et al. Systematic review of 3D mammography for breast cancer screening. Breast. 2016 Jun;27:52-61. doi: 10.1016/j.breast.2016.01.002. Review.)
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	Breast Cancer Mortality Reduction	
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2021.1E</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	Meta-Analysis	RR 95%CI
	Independent UK Panel, 2012	
	13-year metaanalysis	0.80 (0.73–0.89)
	Cochrane Review, 2011	
	Fixed-effect metaanalysis of 9 RCT-trials	0.81 (0.74–0.87)
	As above, but excluding women <50 years	0.77 (0.69–0.86)
	Canadian Task Force, 2011	
	Women aged 50–69 years	0.79 (0.68–0.90)
	Duffy et al, 2012	
	Review of all trials and age groups	0.79 (0.73–0.86)
	Duffy et al, 2020	
	Review of 549,091 Women (30% eligible Swedish screening population)	0.59 (0.51-0.68) mortality 0.75 (0.66-0.84) advanced BC

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Breast Cancer Mortality Reduction		
Meta-Analysis		RR 95%CI
Case-Control Studies		
Broeders et al	Screening Mx	0.46 (0.4 – 0.54)
	Corr. for self selection	0.52 (0.42–0.65)
	Invited for screening	0.69 (0.57–0.83)
Incidence-based Mortality Studies		
Broeders et al	Screening Mx	0.62 (0.56–0.69)
	Invited to screening	0.75 (0.69–0.81)
Randomized Clinical Trials		
Gotsche and Jorgenson	Screening Mx	0.81 (0.74–0.87)
ECIBC		
	Screening MX	
	45–49	0.88 (0.76 - 1.02)
	50–69	0.77 (0.66 - 0.90)
	70–75	0.77 (0.54 - 1.09)

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Breast cancer mortality reduction

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2. Johns LE, Coleman DA, Swerdlow JA, Moss SM, et al. Effect of population breast screening on breast cancer mortality up to 2005 in England and Wales: an individual-level cohort study Br J Cancer 2017;116: 246 -252
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Breastcancer: incidence and mortality

■ Annual incidence of breast cancer and mortality in the EU (GLOBOCAN 2012)

Age	Incidence/1000	Mortality/1000
40 to 44	1,2	0,1
45 to 49	1,7	0,2
50 to 69	2,7	0,5
70 to 74	3,0	0,8

From: <http://gco.iarc.fr/>

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Mammography-Screening 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 (CI95%)	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

Siu Al on behalf of the USPSTF 2016, 164:279–296

Siu AL, on behalf of the U.S. Preventive Services Task Force
 Screening for Breast Cancer: U.S. Preventive Services Task Force
 Recommendation Statement. Ann Internal Med 2016 vol 164: 279-296

Early Detection (normal risk) Sonography/MRI			
	Oxford		
	LoE	GR	AGO
■ Screening-Breast Sonography alone	5	D	--
■ Automated 3D-Sonography	3a	C	--
■ Breast sonography as an adjunct:			
■ Dense mammogram (heterogeneously dense, extremely dense)	2a	B	++
■ Elevated risk	1b	C	++
■ Mammographic lesion	2b	B	++
■ Second-look US (MRI-only detected lesions)	2b	C	++
■ MRI if screening MG is negative and breast composition: extremely dense* 50–75 y	1b	B	+

* 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

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2015;34:165-172

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US-Screening

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Dense Breast

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Elevated Risk

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Recommendations International

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cancer screening—viewpoint of the IARC Working Group. N Engl J Med 2015;372:2353-2358

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Early Detection (normal risk) Clinical Breast Examination (CBE)			
	Oxford		
	LoE	GR	AGO
As a stand-alone procedure			
■ 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 thru blind/optically disabled persons	3b	C	-
CBE because of mammographic/sonographic lesion	5	D	++
CBE in combination with imaging	1a	A	++
* May increase breast awareness			

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Assessment of Breast Symptoms or Lesions			
	Oxford		
	LoE	GR	AGO
■ Clinical examination	3b	B	++
■ Mammography	1b	A	++
■ Tomosynthesis***	2b	B	+
■ Contrast-enhanced mammography (alone or as an adjunct)	2a	B	+
■ Sonography	2b	B	++
■ Elastography (shear-wave) *	2b	B	+
■ Automated 3D-sonography	3b	B	+/-
■ Minimally invasive biopsy	1b	A	++
■ MRI**	3a	B	+
* Adjunct assessment			
**If clinical examination, mammography and sonography incl. needle biopsy do not allow a definite diagnosis			
*** replacement of FFDM with SM			

Combined DM + DBT + US + MRI

1. Mariscotti G, Houssami N, Durando M, et al. Accuracy of mammography, digital breast tomosynthesis, ultrasound and MR imaging in preoperative assessment of breast cancer. Anticancer Res. 2014 Mar;34(3):1219-25.

US-Axilla +FNA/CNB

1. Diepstraten SC, Sever AR, Buckens CFM, et al. Value of preoperative ultrasound guided lymphnode biopsy for preventing completion axillary lymphnode dissection in breast cancer: a systematic review and meta-analysis. Ann Surg Oncol 2014;21:51-59
2. Evans A, Rauchhaus P, Whelehan P, et al. Does shear wave ultrasound independently predict axillary lymph node metastasis in women with invasive breast cancer? Breast Cancer Res Treat. 2013 Dec 4. [Epub ahead of print]
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4. Evans A, Trimboli RM, Athanasiou A et al. Breast ultrasound: recommendations for information to women and referring physicians by the European Society of Breast Imaging. European of Breast Imaging (EUSOBI) , with language review by Europa Donna–The

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MRT

1. Mann RM, Loo CE, Wobbles T et al The impact of preoperative MRI on the re-excision rate in invasive lobular carcinoma of the breast. Breast Cancer Res Treat 2010; 119: 415-422
2. Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. Ann Surg. 2013 Feb;257(2):249-55.
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resonance imaging and questions the role of mammography and ultrasonography regardless of patient mutation status, age and breast density. JCO 2015;33(10):1128-1135

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- 15.Houssami N, Turner RM, Morrow M. Meta-analysis of pre-operative magnetic resonance imaging (MRI) and surgical treatment for breast cancer. Breast Cancer Res Treat. 2017 Sep;165(2):273-283
- 16.Achim Wöckel, Jasmin Festl, Tanja Stüber, et al: Interdisciplinary Screening, Diagnosis, Therapy and Follow-up of Breast Cancer. Guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/045OL, December 2017) – Part 1 with Recommendations for the Screening, Diagnosis and Therapy of Breast Cancer. Geburtshilfe Frauenheilkd. 2018 Oct; 78(10): 927–948.

Reviews CESM:

1. Dromain, C., N. Vietti-Viola, and J.Y. Meuwly, Angiomammography: A review of current evidences. Diagn Interv Imaging, 2019.
2. Patel, B.K., M.B.I. Lobbes, and J. Lewin, Contrast Enhanced Spectral Mammography: A Review. Semin Ultrasound CT MR, 2018. 39(1): p. 70-79.
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1. Luczynska, E., et al., Comparison of the Mammography, Contrast-Enhanced Spectral Mammography and Ultrasonography in a Group of 116 patients. *Anticancer Res*, 2016. 36(8): p. 4359-66.
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4. Fallenberg, E.M., et al., Contrast-enhanced spectral mammography vs. mammography and MRI - clinical performance in a multi-reader evaluation. *Eur Radiol*, 2017. 27(7): p. 2752-2764.
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6. Kim, E.Y., et al., Diagnostic Value of Contrast-Enhanced Digital Mammography versus Contrast-Enhanced Magnetic Resonance Imaging for the Preoperative Evaluation of Breast Cancer. *Journal of breast cancer*, 2018. 21(4): p. 453-462.
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Pre-therapeutic Assessment of Breast and Axilla			
	Oxford		
	LoE	GR	AGO
■ Clinical examination	5	D	++
■ Mammography	2b	B	++
■ + Tomosynthesis (DBT)***	2b	B	+
■ Contrast-enhanced mammography (alone or as adjunct)	2a	B	+
■ Sonography (breast and axilla)	2b	B	++
■ MRI*	1b	B	+
■ Minimally invasive biopsy**	1b	A	++
■ Axilla CNB, if lymph node is suspect	2b	B	++
■ Breast-CT	5	D	-

* MRI-guided vacuum biopsy is mandatory in case of MRI-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 multilocal disease. No reduction in re-excision rate.
 ** Histopathology of additional lesions if relevant for treatment
 *** replacement of FFDM with SM

Combined DM + DBT + US + MRI

1. Mariscotti G, Houssami N, Durando M, et al. Accuracy of mammography, digital breast tomosynthesis, ultrasound and MR imaging in preoperative assessment of breast cancer. Anticancer Res. 2014 Mar;34(3):1219-25.
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US-Axilla +FNA/CNB

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Biopsie

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7. Patel, B.K., et al., Value Added of Preoperative Contrast-Enhanced Digital Mammography in Patients With Invasive Lobular Carcinoma of the Breast. Clin Breast Cancer, 2018. 18(6): p. e1339-e1345.
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Screening Women after Breast Conserving Surgery. *Cancers (Basel)*. 2020;12(12).

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Sensitivities CESM						
Author	n	MG	CESM	MRI	US	Analyse
Dromain 2011	110	78	92			Per patient
Fallenberg 2014	118	77.9	94.7			Per patient
Mokhtar 2014	60	93.2	97.7			Per patient
Lobbes 2014*	113	96.9	100			Per patient
Perez 2015 ECR	98		78		66	Per lesion
Luczinska 2014	152	91	100			
Jochelson 2012	52	81 59	96 83	96 93		Per patient Per lesion
Fallenberg 2013	80	81	100	97		Per patient
Fallenberg 2016	155	81 55	94 72	95 76		Index Per Lesion
Lalji 2016*	199	93	96,9			Per patient 10 reader
Tennant 2016	100	84	95			
Luczynska 2016	116	90	100		92	
Xing 2019	235		91,5	91,5		Per lesion

CESM is comparable to MRI regarding index, a bit inferior for additional lesions

* Recall from Screening

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1. Luczynska, E., et al., Comparison of the Mammography, Contrast-Enhanced Spectral Mammography and Ultrasonography in a Group of 116 patients. Anticancer Res, 2016. 36(8): p. 4359-66.
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Pre-therapeutic Staging			
	Oxford		
	LoE	GR	AGO
	5	D	++
History and clinical examination Additional diagnosis for patients with tumors of high metastatic potential and/or symptoms and/or indication for (neo-)adjuvant chemotherapy and/or antibody-therapy):			
■ CT scan of thorax/abdomen	2a	B	+
■ Bone scan	2b	B	+
■ Chest X-ray	5	C	+/-
■ Liver ultrasound	5	D	+/-
■ In case of suspicious lesions further diagnosis (e.g. liver-MRI, CEUS*, biopsy etc.)	2a	B	+
■ FDG-PET or FDG-PET /CT**	2b	B	+/-
■ Whole body MRI	4	C	+/-
* Contrast enhanced ultrasound **especially in patients with high tumor stage(III) if available			

Statement: history and physical examination

1. GCP

Statement: high metastatic potential / symptoms

1. Rutgers, EJ et al: Quality control in the locoregional treatment of breast cancer (2001) EJC 37: 447-453
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