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Version 2020.1

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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 / Fersis / Junkermann /  
Maass / Müller-Schimpfle / Scharl / Schreer
  
- **Version 2020**  
Fallenberg / Maass

### Screened data bases

Pubmed	2013 - 2019
Medline	2013 - 2019
Cochrane	2013 - 2019

### Guidelines

S3 Diagnostik, Therapie und Nachsorge des Mammakarzinoms:

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.

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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.

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 Mammography (normal risk)				
Age	Interval	Oxford		AGO
		LOE	GR	
< 40	na	-	-	--
40–49	12–24	1b	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

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	Oxford		AGO
	LOE	GR	
<b>Digital Breast Tomosynthesis (DBT alone or in addition to FFDM)*</b>	<b>2a</b>	<b>B</b>	<b>+</b>
<b>Replacing FFDM by synthetic MG in addition to DBT**</b>	<b>3b</b>	<b>B</b>	<b>+</b>
The complete DBT dataset of images has to be available for judgment/reporting, the synthetic mammography only is not sufficient.			
* Sign. higher sensitivity, heterogeneous specificity, and higher costs [machine, evaluation, archiving] in comparison to Full-Field Digital Mammography (FFDM)			
** Evaluation for Germany in a current prospective trial (TOSYMA)			

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 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<h2 style="text-align: center;">Breast Cancer Mortality Reduction</h2> <table> <tr> <th>Meta-Analysis</th><th>RR 95%CI</th></tr> <tr> <td><b>Independent UK Panel, 2012</b></td><td></td></tr> <tr> <td>13-year metaanalysis</td><td>0.80 (0.73–0.89)</td></tr> <tr> <td><b>Cochrane Review, 2011</b></td><td></td></tr> <tr> <td>Fixed-effect metaanalysis of 9 RCT-trials</td><td>0.81 (0.74–0.87)</td></tr> <tr> <td>As above, but excluding women &lt;50 years</td><td>0.77 (0.69–0.86)</td></tr> <tr> <td><b>Canadian Task Force, 2011</b></td><td></td></tr> <tr> <td>Women aged 50–69 years</td><td>0.79 (0.68–0.90)</td></tr> <tr> <td><b>Duffy et al, 2012</b></td><td></td></tr> <tr> <td>Review of all trials and age groups</td><td>0.79 (0.73–0.86)</td></tr> </table>	Meta-Analysis	RR 95%CI	<b>Independent UK Panel, 2012</b>		13-year metaanalysis	0.80 (0.73–0.89)	<b>Cochrane Review, 2011</b>		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)	<b>Canadian Task Force, 2011</b>		Women aged 50–69 years	0.79 (0.68–0.90)	<b>Duffy et al, 2012</b>		Review of all trials and age groups	0.79 (0.73–0.86)
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# Breast Cancer Mortality Reduction

Meta-Analysis		RR 95%CI
<b>Case-Control Studies</b>		
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)
<b>Incidence-based Mortality Studies</b>		
Broeders et al	Screening Mx	0.62 (0.56–0.69)
	Invited to screening	0.75 (0.69–0.81)
<b>Randomized Clinical Trials</b>		
Gotsche and Jorgenson	Screening Mx	0.81 (0.74–0.87)
<b>ECIBC</b>		
	<b>Screening MX</b>	
	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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## 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



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# Early Detection Sonography/MRI

	Oxford		
	LoE	GR	AGO
▪ <b>Screening-Breast Sonography allone</b>	5	D	--
▪ Automated 3D-Sonography	3a	C	--
▪ <b>Breast sonography as an adjunct:</b>			
▪ 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	++
▪ <b>MRI if screening MG is negative and breast composition: extremely dense* 50–75 LJ</b>	1b	B	+

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

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## Early Detection Clinical Examination

Oxford		
LoE	GR	AGO
1a	A	-*
3b	C	-*
5	D	++
BCP		++

**As stand alone procedure**


- Self-examination
- Clinical breast examination (CBE) by health professionals
- CBE because of mammographic/sonographic lesion

**CBE in combination with imaging**

\* May increase breast awareness

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 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	Assessment of Breast Symptoms or Lesions		
	Oxford		
	LoE	GR	AGO
■ <b>Clinical examination</b>	3b	B	++
■ <b>Mammography</b>	1b	A	++
■ Tomosynthesis	2b	B	+
■ Contrast-enhanced mammography (alone or as adjunct)	3a	B	+/-
■ <b>Sonography</b>	2b	B	++
■ Elastography (shear-wave) *	2b	B	+
■ Automated 3D-sonography	3b	B	+/-
■ <b>Minimally invasive biopsy</b>	1c	A	++
■ <b>MRI**</b>	1b	B	+
* Adjunct assessment			
**If clinical examination, mammography and sonography incl. needle biopsy do not allow a definite diagnosis			

### 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.
2. Campanino PP, Ruggieri C, Regini E, 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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### Biopsie

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Pre-therapeutic Assessment of Breast and Axilla			
	Oxford		
	LoE	GR	AGO
■ Clinical examination	5	D	++
■ Mammography	2b	B	++
■ + Tomosynthesis (DBT)	3b	B	+
■ Contrast-enhanced mammography (alone or as adjunct)	3a	B	+/-
■ Sonography (breast and axilla)	2b	B	++
■ MRI*	1b	B	+
■ Minimally invasive biopsy**	1b	A	++
■ Breast-CT	5	D	-
* MRI-guided vacuum biopsy is mandatory in case of MRI-detected additional lesions. Individual decision for patients at high familial risk, with dense breast (density 3-4/diagnostic assessability C-D), lobular invasive tumors, suspicion of multilocal disease. No reduction in re-excision rate.			
** Histopathology of lesions if relevant for treatment			



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## MRI: Preoperative Staging

- **9 eligible studies**  
**(2 randomized trials; 7 comparative cohorts)**
- **3112 patients with BC**
- **MRI versus no-MRI:**
  - Initial mastectomy 16.4% versus 8.1%  
[OR, 2.22 (P < 0.001); adjusted OR, 3.06 (P < 0.001)]
  - Re-excision after initial breast conservation 11.6% versus 11.4%  
[OR, 1.02 (P = 0.87); adjusted OR, 0.95 (P = 0.71)]
  - Overall mastectomy 25.5% versus 18.2%  
[OR, 1.54 (P < 0.001); adjusted OR, 1.51 (P < 0.001)]

N Houssami et al. Ann Surg 2013; 257

1. 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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## MRI: Preoperative Staging in Lobular Invasive Breast Cancer

- **766 patients with invasive lobular cancer (ILC)**
  - **Initial mastectomy: 31.1% versus 24.9%**  
[OR, 1.36 (P = 0.056); adjusted OR, 2.12 (P = 0.008)]
  - **Re-excision after initial breast conservation 10.9% versus 18.0%**  
[OR, 0.56 (P = 0.031); adjusted OR, 0.56 (P = 0.09)]
  - **Overall mastectomy 43.0% versus 40.2%**  
[OR, 1.12 (P = 0.45); adjusted OR, 1.64 (P = 0.034)]

N Houssami et al. Ann Surg 2013; 257

1. 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. doi: 10.1097/SLA.0b013e31827a8d17.
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## MRI and DCIS

Study	No. Cases	Overall accuracy (%)	Sens. (%)	Spec. (%)
Gilles et al 1995	172	70	95	51
Westerhof et al 1998	63	56	45	72
Bazzocchi et al 2006	112	80	79	68
Kuhl et al 2007	75	-	88	-
Baur et al. 2013	58	-	79,3	

„Negative breast MRI findings should not be considered a sure marker of benignancy.“


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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
Lobbis 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	

\* Recall from Screening

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

Pre-therapeutic Staging			
	Oxford		
	LoE	GR	AGO
<div>  <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN TEILEN</p> </div> <p>■ History and clinical examination</p> <p><b>Additional diagnosis for patients with high metastatic potential and/or symptoms (in decision making for chemotherapy and/or anti-HER2-therapy):</b></p> <ul style="list-style-type: none"> <li>■ CT scan of thorax/abdomen</li> <li>■ Bone scan</li> <li>■ Chest X-ray</li> <li>■ Liver ultrasound</li> <li>■ In case of suspicious lesions further diagnosis (e.g. liver-MRI, CEUS*, biopsy etc.)</li> <li>■ FDG-PET or FDG-PET /CT</li> <li>■ Whole body MRI</li> </ul> <p>* Contrast enhanced ultrasound</p>	5	D	++
	2a	B	+
	2b	B	+
	5	C	+/-
	5	D	+/-
	2a	B	+
	3a	C	+/-
	4	C	+/-

#### Statement: history and physical examination

1. GCP

#### Statement: high metastatic potential / symptoms

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