Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Early Detection and Diagnosis

Early Detection and Diagnosis

- **Versions 2005–2018:**
  Albert / Blohmer / Fersis / Junkermann / Maass / Müller-Schimpfle / Scharl / Schreer

- **Version 2019:**
  Blohmer / Müller-Schimpfle

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Early Detection Mammography

Age	Interval	Oxford LOE	Oxford GR	AGO
< 40	na	-	-	--
40–49	12–24	1b	B	+
50–69*	24	1a	A	++
70–74	24	1a	A	++
> 75**	24	4	C	+

* National Mammography-Screening-Program
** health status + life expectacy more than 10 years

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Early Detection in Asymptomatic Women
Digital Breast Tomosynthesis

	Oxford		AGO
	LOE	GR	
Digital Breast Tomosynthese (DBT)*	2a	B	+
Supplementary to FFDM	2a	B	+
Replacing FFDM by synthetic DM/DBT**	3b	B	+

***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)**

Breast Cancer Mortality Reduction

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)

Breast Cancer Mortality Reduction

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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)

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Breast Cancer Mortality Reduction

Age Group (yrs)	NNS	
	Reduction 20%	Mortality 40%
40–49	1770	753
50–59	1087	462
60–69	835	355

4 systematic reviews of 8 RCTs,
1 systematic review of 7 cohort studies and metaanalysis of case-control studies

Oeffinger KC et al JAMA 2015;314

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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

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Breast Cancer Screening
ACS Guideline Update 2015

American Cancer Society Guideline for Breast Cancer Screening, 2015
These recommendations represent guidance from the American Cancer Society (ACS) for women at average risk of breast cancer: women without a personal history of breast cancer, a suspected or confirmed genetic mutation known to increase risk of breast cancer (eg, BRCA), or a history of previous radiotherapy to the chest at a young age.
The ACS recommends that all women should become familiar with the potential benefits, limitations, and harms associated with breast cancer screening.

Recommendations

1. Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years. (*Strong Recommendation*)
   1a. Women aged 45 to 54 years should be screened annually. *(Qualified Recommendation)*
   1b. Women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. *(Qualified Recommendation)*
   1c. Women should have the opportunity to begin annual screening between the ages of 40 and 44 years. *(Qualified Recommendation)*
2. Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer. *(Qualified Recommendation)*
3. The ACS does not recommend clinical breast examination for breast cancer screening among average-risk women at any age. *(Qualified Recommendation)*

[a] A strong recommendation conveys the consensus that the benefits of adherence to that intervention outweigh the undesirable effects that may result from screening. Qualified recommendations indicate there is clear evidence of benefit of screening but less certainty about the balance of benefits and harms,
or about patients' values and preferences, which could lead to different decisions about screening.

Breast-Cancer Screening- Viewpoint of the IARC Working Group

Method	Strength of Evidence
Reduces breast-cancer mortality in women 50-69 yr of age	Sufficient
Reduces breast-cancer mortality in women 70-74 yr of age	Sufficient
Reduces breast-cancer mortality in women 40-44 yr of age	Limited
Reduces breast-cancer mortality in women 45-49 yr of age	Limited
Detects breast cancer that would never have been diagnosed or never have caused harm if women had not been screened (overdiagnosis)	Sufficient
Reduces breast-cancer mortality in women 50-74 yr of age to an extent that its benefits substantially outweigh the risk of radiation-induced cancer	Sufficient
Produces short-term negative psychological consequences when the result is false positive	Sufficient
Has a net benefit for women 50-69 yr of age who are invited to attend organized mammographic screening programs	Sufficient

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Mammography-Screening
Women 40–49 years of age

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RR (invited women)	**0.74** (95%CI 0.66–0.83)
40–44 yr of age	**0.83** (95%CI 0.67–1.00)
45–49 yr of age	**0.68** (95%CI 0.59–0.78)
Participants	**0.71** (95%CI 0.62–0.80)
NNS	**1252** (95%CI 958–1915)
(1 live saved / 10 years screening)	

Hellquist BN et al. Cancer 2011; 117(4) : 714-722

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Early Detection Sonography

	Oxford LoE	Oxford GR	AGO
▪ Screening-Breast Sonography	5	D	--
▪ Automated 3D-Sonography	3a	C	--
As an adjunct:			
▪ Dense mammogram (density 3–4/diagnostic assessability C-D)	2a	B	++
▪ Elevated risk	1b	C	++
▪ Mammographic lesion	2b	B	++
▪ Second-look US (MRI-only detected lesions)	2b	C	++

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Early Detection
Clinical Examination

	Oxford LoE	GR	AGO
As stand alone procedure			
▪ Self-examination	1a	A	-*
▪ Clinical breast examination (CBE) by health professionals	3b	C	-*
▪ CBE because of mammo/sonographic lesion	5	D	++
CBE in combination with imaging	BCP		++

* 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	+
▪ Sonography	2b	B	++
▪ Elastography (shear-wave) *	2b	B	+
▪ Automated 3D-sonography	3b	B	+/-
▪ Minimally invasive biopsy	1c	A	++
▪ MRI**	3b	B	+

* Adjunct assessment

**If clinical examination, mammography and sonography incl. needle biopsy do not allow a definite diagnosis

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Pretherapeutic Assessment of the Breast and the Axilla

	Oxford		
	LoE	GR	AGO
▪ Clinical examination	5	D	++
▪ Mammography	2b	B	++
▪ + Tomosynthesis (DBT)	3b	B	+
▪ Sonography	2b	B	++
▪ Axilla + CNB	2b	B	++
▪ Minimally invasive biopsy*	1b	A	++
▪ MRI**	1b	B	+/-

* Histopathology of lesions if relevant for treatment

** MRI-guided vacuum biopsy is mandatory in case of MRI-detected additional lesions. Individual decision for patients at high familiar risk, with dense breast (density 3-4/diagnostic assessability C-D), lobular invasive tumors, suspicion of multilocular disease. No reduction in reexcision rate.

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

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

MRI Screening in Women with High Familiar Risk

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				MRT		Mammography	
Autor	High Risk / Mutation	Number Women	Number Cancers	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Kriege 2004	M	1909	50	80	90	33	95
Warner 2004	M	236	22	77	95	36	99
Hagen 2004	M	491	25	86	-	50	-
Leach 2005	H / M	649	35	94	77	40	93
Riedl 2007	H / M	327	28	50	98	85,7	92
Kuhl 2010	H / M	687	27	93	98,4	33	99,1
Rijnsburger 2010	M	594	97	77,4	89,7	41	-
Sardanelli 2011	H / M	501	52	91	97	50	-
Passaperuma 2012	M	496	57	90	97	19	97
Gareth 2014	H / M	649	139	93	63	60	-

Prospective study results for MRI screening in women with high familiar risk (H) and muatation carriers (M)

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MRI Screening Problems in High Risk Populations

MRI in addition to mammography	RR
False-positive MRI	**3,43–4,86**
Benign biopsies	1,22–9,50
Benign surgical biopsies (MARIBS)	2
False-negative MRI (MRISC)	**22%**

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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Pretherapeutic Staging

	Oxford LoE	GR	AGO
▪ History and clinical examination	5	D	++
Only recommended in high metastatic potential and/or symptoms (in decision making for chemotherapy and/or Her 2 – therapy)			
▪ CT scan od thorax/abdomen	2a	B	+
▪ Bone scan	2b	B	+
▪ Chest X-ray	5	C	+/-
▪ Liver ultrasound	5	D	+/-
▪ FDG-PET or FDG-PET /CT	3a	C	+/-
▪ Whole body MRI	4	C	+/-
▪ Liver – MRI in case of suspected liver metastases	4	C	+