Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Early Detection and Diagnosis
Screened data bases:
Pubmed 2013 - 2017
Medline 2013 - 2017
Cochrane 2013 - 2017

Guidelines:
S3 Diagnostik, Therapie und Nachsorge des Mammakarzinoms
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

- **Versions 2005–2017:**
  Albert / Blohmer / Fersis / Junkermann / Maass / Müller-Schimpfle / Scharl / Schreer

- **Version 2018:**
  Albert / Müller-Schimpfle
24. Walter LC, Schonberg MA Screening mammography in older women: a review.


Tomosynthesis


Radiation Dose

Mammography density assessment
## Breast Cancer Mortality Reduction

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>RR 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent UK Panel, 2012</td>
<td>0.80 (0.73–0.89)</td>
</tr>
<tr>
<td>13-year metaanalysis</td>
<td></td>
</tr>
<tr>
<td>Cochrane Review, 2011</td>
<td>0.81 (0.74–0.87)</td>
</tr>
<tr>
<td>Fixed-effect metaanalysis of 9 RCT-trials</td>
<td></td>
</tr>
<tr>
<td>As above, but excluding women &lt;50 years</td>
<td>0.77 (0.69–0.86)</td>
</tr>
<tr>
<td>Canadian Task Force, 2011</td>
<td>0.79 (0.68–0.90)</td>
</tr>
<tr>
<td>Women aged 50–69 years</td>
<td></td>
</tr>
<tr>
<td>Duffy et al, 2012</td>
<td>0.79 (0.73–0.86)</td>
</tr>
<tr>
<td>Review of all trials and age groups</td>
<td></td>
</tr>
</tbody>
</table>


# Breast Cancer Mortality Reduction

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>RR 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case-Control Studies</strong></td>
<td></td>
</tr>
<tr>
<td>Broeders et al</td>
<td>Screening Mx</td>
</tr>
<tr>
<td></td>
<td>Corr. for self selection</td>
</tr>
<tr>
<td></td>
<td>Invited for screening</td>
</tr>
<tr>
<td><strong>Incidence-based Mortality Studies</strong></td>
<td></td>
</tr>
<tr>
<td>Broeders et al</td>
<td>Screening Mx</td>
</tr>
<tr>
<td></td>
<td>Invited to screening</td>
</tr>
<tr>
<td><strong>Randomized Clinical Trials</strong></td>
<td></td>
</tr>
<tr>
<td>Gotsche and Jorgenson</td>
<td>Screening Mx</td>
</tr>
</tbody>
</table>


**Breast cancer mortality reduction**


# Mammography-Screening Benefit and Harm

Data background: Breast Cancer Surveillance Consortium Registry Data per 10,000 Women screened over 10 years

<table>
<thead>
<tr>
<th>Age</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer death avoided (CI95%)</td>
<td>3 (0-9)</td>
<td>8 (2-17)</td>
<td>21 (11-32)</td>
<td>13 (0-32)</td>
</tr>
<tr>
<td>False-positive (n)</td>
<td>1212</td>
<td>932</td>
<td>808</td>
<td>696</td>
</tr>
<tr>
<td>Breast biopsies (n)</td>
<td>164</td>
<td>159</td>
<td>165</td>
<td>175</td>
</tr>
<tr>
<td>False-negative (n)</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
</tr>
</tbody>
</table>

Siu AL on behalf of the USPSTF 2016, 164:279-296

1. Siu AL, on behalf of the U.S. Preventive Services Task Force
2. Screening for Breast Cancer: U.S. Preventive Services Task Force
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 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

<table>
<thead>
<tr>
<th>Method</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces breast-cancer mortality in women 50-69 yr of age</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Reduces breast-cancer mortality in women 70-74 yr of age</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Reduces breast-cancer mortality in women 40-44 yr of age</td>
<td>Limited</td>
</tr>
<tr>
<td>Reduces breast-cancer mortality in women 45-49 yr of age</td>
<td>Limited</td>
</tr>
<tr>
<td>Detects breast cancer that would never have been diagnosed or never have caused harm if women had not been screened (overdiagnosis)</td>
<td>Sufficient</td>
</tr>
<tr>
<td>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</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Produces short-term negative psychological consequences when the result is false positive</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Has a net benefit for women 50-69 yr of age who are invited to attend organized mammographic screening programs</td>
<td>Sufficient</td>
</tr>
</tbody>
</table>


Mammography-Screening
Women 40–49 years of age

<table>
<thead>
<tr>
<th>RR (invited women)</th>
<th>0.74 (95%CI 0.66-0.83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–44 yr of age</td>
<td>0.83 (95%CI 0.67-1.00)</td>
</tr>
<tr>
<td>45–49 yr of age</td>
<td>0.68 (95%CI 0.59-0.78)</td>
</tr>
<tr>
<td>Participants</td>
<td>0.71 (95%CI 0.62-0.80)</td>
</tr>
</tbody>
</table>

NNS                       1252 (95%CI 958-1915)

(1 live saved / 10 years screening)


ABUS/AVUS


US-Screening


Dense Breast


Elevated Risk


Recommendations International


Early Detection Clinical Examination

As stand alone procedure
- Self-examination
- Clinical breast examination (CBE) by health professionals
- CBE because of mammo/sonographic lesion

CBE in combination with imaging

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1a</td>
<td>A</td>
<td>-*</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>C</td>
<td>-*</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>BCP</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

* May increase breast awareness


Tomosynthese vs Spotkompression / abnormalities in mammography


Tomosynthese for screen-detected abnormalities


**Tomosynthese Accuracy screening population**


**Elastography**


**Automated Breast Ultrasound (ABUS)**


MRT
### Pretherapeutic Assessment of the Breast and the Axilla

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Mammography</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Mammography</td>
<td>3b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Mammography + Tomosyntheses</td>
<td>3b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>3b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Sonography</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>US-Axilla + FNA/CNB</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Minimally invasive biopsy*</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>MRI**</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* 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 multicellular disease. No reduction in reexcision rate.

### Combined DM + DBT + US + MRI


### US-Axilla +FNA/CNB


### Biopsie

2. Lourenco AP, Mainiero MB Incorporating imaging into the locoregional management of breast cancer. Semin Radiat Oncol 2016; 26(1)


MRT


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)]

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)]


MRI Screening (High-risk) Benefit

- Early detection of cancer cases additionally to conventional imaging
- Improved patient prognosis?
  (Mortality reduction? Reduction of interval cancers?)
MRI Screening in Women with High Familiar Risk

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

<table>
<thead>
<tr>
<th>Autor</th>
<th>High Risk / Mutation</th>
<th>Number Women</th>
<th>Number Cancers</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kriege 2004</td>
<td>M</td>
<td>1909</td>
<td>50</td>
<td>80</td>
<td>90</td>
<td>33</td>
<td>95</td>
</tr>
<tr>
<td>Warner 2004</td>
<td>M</td>
<td>236</td>
<td>22</td>
<td>77</td>
<td>95</td>
<td>36</td>
<td>99</td>
</tr>
<tr>
<td>Hagen 2004</td>
<td>M</td>
<td>491</td>
<td>25</td>
<td>86</td>
<td>-</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>Leach 2005</td>
<td>H/M</td>
<td>649</td>
<td>35</td>
<td>94</td>
<td>77</td>
<td>40</td>
<td>93</td>
</tr>
<tr>
<td>Riedl 2007</td>
<td>H/M</td>
<td>327</td>
<td>28</td>
<td>50</td>
<td>98</td>
<td>85.7</td>
<td>92</td>
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<tr>
<td>Kuhl 2010</td>
<td>H/M</td>
<td>687</td>
<td>27</td>
<td>93</td>
<td>98.4</td>
<td>33</td>
<td>99.1</td>
</tr>
<tr>
<td>Rijnsburger 2010</td>
<td>M</td>
<td>594</td>
<td>97</td>
<td>77.4</td>
<td>89.7</td>
<td>41</td>
<td>-</td>
</tr>
<tr>
<td>Sardanelli 2011</td>
<td>H/M</td>
<td>501</td>
<td>52</td>
<td>91</td>
<td>97</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>Passaperuma 2012</td>
<td>M</td>
<td>496</td>
<td>57</td>
<td>90</td>
<td>97</td>
<td>19</td>
<td>97</td>
</tr>
<tr>
<td>Gareth 2014</td>
<td>H/M</td>
<td>649</td>
<td>139</td>
<td>93</td>
<td>63</td>
<td>60</td>
<td>-</td>
</tr>
</tbody>
</table>

14. Saadatmand S, Obdeijn IM, Rutgers EJ, et al. Survival benefit in women with BRCA1 mutation or familial risk in the MRI screening study (MRISC) Int J Cancer 2015;137(7)1729-1738


3. Saadatmand S, Obdeijn IM, Rutgers EJ, et al. Survival benefit in women with BRCA1 mutation or familial risk in the MRI screening study (MRISC) Int J Cancer 2015;137(7)1729-1738

# MRI and DCIS

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Cases</th>
<th>Overall accuracy (%)</th>
<th>Sens. (%)</th>
<th>Spec. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilles et al 1995</td>
<td>172</td>
<td>70</td>
<td>95</td>
<td>51</td>
</tr>
<tr>
<td>Westerhof et al 1998</td>
<td>63</td>
<td>56</td>
<td>45</td>
<td>72</td>
</tr>
<tr>
<td>Bazzocchi et al 2006</td>
<td>112</td>
<td>80</td>
<td>79</td>
<td>68</td>
</tr>
<tr>
<td>Kuhl et al 2007</td>
<td>75</td>
<td>-</td>
<td>88</td>
<td>-</td>
</tr>
<tr>
<td>Baur et al. 2013</td>
<td>58</td>
<td>-</td>
<td>79.3</td>
<td>-</td>
</tr>
</tbody>
</table>

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

Pretherapeutic Staging

- History and clinical examination
  Only recommended in high metastatic potential and/or symptoms (in decision making for chemotherapy and/or Her 2 – therapy)
  - CT scan od thorax/abdomen
  - Bone scan
  - Chest X-ray
  - Liver ultrasound
  - FDG-PET or FDG-PET /CT
  - Whole body MRI
  - Liver – MRI in case of suspected liver metastases

<table>
<thead>
<tr>
<th>Oxford</th>
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<th>GR</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
</tbody>
</table>

Statement: history and physical examination
1. GCP

Statement: high metastatic potential / symptoms

