OVERDIAGNOSIS IN BREAST SCREENING

Ulrich Bick, Charité Berlin, IDKD Pearl 2017
OVERDIAGNOSIS IS THE DIAGNOSIS OF A DISEASE WHO WILL NEVER CAUSE SYMPTOMS OR DEATH DURING AN INDIVIDUALS ORDINARILY EXPECTED LIFETIME
Length Bias in Mammography Screening

• Slow growing cancers are more likely to be detected at mammography screening than aggressive tumors with high growth rate

• This is accentuated by the fact, that low-grade cancers more often show a strong desmoplastic reaction with typical spiculation on mammography

• Detection at mammography screening is even an independent prognostic factor, that means screen-detected cancers have a better prognosis than symptomatic cancers of the same size and stage
Overdiagnosis from Screening

- Probably somewhere between 10% and 20% of all cancers detected in mammography screening represent overdiagnosis.

- This means around 1% of women screened every two years for a period of twenty years from 50 to 70 will have a breast cancer detected and treated, which otherwise would not have surfaced clinically during their lifetime.
All Overdiagnosis explained by DCIS?

- Currently 20 - 25% of all screen detected breast cancers represent DCIS
- This compares to around 5% DCIS in a symptomatic cohort of before introduction of organized mammography screening
- Does all DCIS detected by screening in asymptomatic women represent overdiagnosis?
DCIS

- Very heterogeneous disease
- Low- and intermediate grade DCIS have an excellent long-term prognosis and will more likely represent overdiagnosis
- Lag time before progression to relevant invasive disease much shorter for high-grade DCIS
- Possibility of a distinct low-grade genetic pathway
- Significant contribution to number of mastectomies
Microcalcifications

○ Better visualization with digital mammography (increased detection of both DCIS independent of grade as well as invasive cancer)
  Bluekens et al. 2012 Radiology 265:707-714

○ Adequate pursuit of microcalcifications highly relevant for detection of small invasive cancers

○ Reliable prediction of tumor grade and invasion not possible from microcalcification morphology

○ Follow-up approach for microcalcifications unreliable and associated with risk of rapid progression
DCIS: Overdiagnosis vs. Overtreatment

- Biopsy of microcalcifications necessary to define nature of underlying abnormality
- Morbidity primarily related to therapy (extensive surgery, radiation, psychological effects of being labeled as a breast cancer patient)
- Close radiological surveillance alone may be an option for a certain subgroup of low-risk DCIS patients (*consider patient age!*)
- Possible use of MRI to exclude relevant high-grade or invasive disease?!
A Phase III trial of surgery versus active monitoring for LOw RISk DCIS Trial (LORIS) funded by the National Institute for Health Research Health Technology Assessment Programme (NIHR HTA)
# Low Risk DCIS Trial (LORIS)

Criteria for Low Risk DCIS Trial (LORIS).

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
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<tbody>
<tr>
<td>• Female, age ≥ 46 years</td>
<td>• A mass lesion clinically, on ultrasound scan or mammogram at the site of</td>
</tr>
<tr>
<td>• Screen-detected or incidental microcalcification</td>
<td>the microcalcification before biopsy</td>
</tr>
<tr>
<td>• Low risk DCIS on large volume VAB, confirmed by central pathology review</td>
<td>• Previous invasive breast cancer or DCIS</td>
</tr>
<tr>
<td>• Patient fit to undergo surgery</td>
<td>• Recent onset ipsilateral blood-stained nipple discharge.</td>
</tr>
<tr>
<td>• No previous breast cancer or DCIS diagnosis</td>
<td>• High-risk group for developing breast cancer</td>
</tr>
<tr>
<td>• Written informed consent</td>
<td>(as defined by NICE guidelines, or prior exposure to mantle radiotherapy)</td>
</tr>
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Low-grade DCIS

- May be co-located with risk lesions (FEA, ADH) as well as benign fibrocystic changes within the same microcalcification area
- Possibility of false-negative stereotactic biopsy based on sampling
- Active surveillance approach for low-grade DCIS would also obviate the need for open excisional biopsy of some risk lesions

Transitions Between Flat Epithelial Atypia and Low-grade Ductal Carcinoma In Situ of the Breast
Overdiagnosis: *Invasive Cancers*

- Overdiagnosis in invasive cancers likely related to small slow-growing low-grade cancers
- Currently impossible to predict in advance, which cancer may represent overdiagnosis
- Size change over time excellent predictor of growth potential
- Morbidity from local excision usually low
Population-based Mammography Screening

Factors increasing the risk for overdiagnosis

- Length bias
- Discouragement of short-term follow-up
- Postmenopausal women as target population
- Current surrogate parameters and quality criteria in screening may set the wrong incentives
- Individualized strategies e.g. incorporating personal risk factors difficult to implement in mass screening
# ACRIN 6666 Trial

Influence of tumor biology on mode of detection

<table>
<thead>
<tr>
<th>IDC Grade</th>
<th>Detected with Mammography</th>
<th>Contribution of Ultrasound</th>
<th>Contribution of MRI</th>
<th>Not detected by Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>21% (7/33)</td>
<td>46% (11/24)</td>
<td>57% (4/7)</td>
<td>38% (3/8)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>42% (14/33)</td>
<td>29% (7/24)</td>
<td>14% (1/7)</td>
<td>13% (1/8)</td>
</tr>
<tr>
<td>High</td>
<td>33% (11/33)</td>
<td>25% (6/24)</td>
<td>28% (2/7)</td>
<td>25% (2/8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3% (1/33)</td>
<td>-</td>
<td>-</td>
<td>25% (2/8)</td>
</tr>
<tr>
<td>All</td>
<td>46% (33/72)</td>
<td>33% (24/72)</td>
<td>10% (7/72)</td>
<td>11% (8/72)</td>
</tr>
</tbody>
</table>
Effect of Three Decades of Screening Mammography on Breast-Cancer Incidence

Archie Bleyer, M.D., and H. Gilbert Welch, M.D., M.P.H.

<table>
<thead>
<tr>
<th>Performance indicator</th>
<th>Desirable level</th>
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<tbody>
<tr>
<td>13. Proportion of screened women subjected to early recall following diagnostic assessment</td>
<td>0%</td>
</tr>
<tr>
<td>16. Proportion of screen-detected cancers that are invasive</td>
<td>80-90%</td>
</tr>
<tr>
<td>17. Proportion of screen-detected cancers that are stage II+</td>
<td>&lt; 30%</td>
</tr>
<tr>
<td>- initial screening examinations</td>
<td></td>
</tr>
<tr>
<td>- subsequent-regular screening examinations</td>
<td>&lt; 25%</td>
</tr>
<tr>
<td>19. Proportion of invasive screen-detected cancers that are ≤ 10 mm in size</td>
<td>≥ 25%</td>
</tr>
<tr>
<td>- initial screening examinations</td>
<td></td>
</tr>
<tr>
<td>- subsequent-regular screening examinations</td>
<td>≥ 30%</td>
</tr>
<tr>
<td>20. Proportion of invasive screen-detected cancers that are &lt; 15 mm in size</td>
<td>&gt; 50%</td>
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</table>
New Quality Indicators

- Upper limit for (non high-grade) DCIS
- Incidence (in absolute terms) of advanced-stage breast cancer in the entire target population in comparison to the expected incidence
- Detection rates with breakdown by histological grade to estimate clinical relevance
What can the radiologist do?

- Inform patients about risk of overdiagnosis
- Do not continue to screen if significant comorbidities exist or remaining life expectancy is less than ten years (reduce overutilization)
- Integrate individual risk (age, family history, genetic information) into the decision making process
- More active use of short-term follow-up
- Encourage clinicians to reduce overtreatment
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**Breast Cancer Screening's Triple O:** Overdiagnosis, Overutilization, Overtreatment