Overdiagnosis:
The Role of Pathology

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Overdiagnosis in screening mammography

**Definition:** Overdiagnosis is detection by screening of cancers that never would have come to clinical attention had screening had not taken place


Literature review of overdiagnosis estimates, adjusting for: incidence trends and lead-time

- Netherlands: 2.8%
- Italy: 4.6% / 1.0%
- Denmark: 7.0%
- England: 10% / 3.3%

High expectations to the pathology diagnosis

- Objectively define the type of disease
- Comprehensively describe the individual situation
- Strictly follow standardized nomenclature
- Consider and interpret clinical and radiological findings
- Provide guidance to prognostic and predictive factors
Situations leading to overdiagnosis (and overtreatment)

• Errors in interpretation
  – Diagnostic errors
  – Misclassification

• Terminology issues
  – Overinterpretation of B3 lesions
  – Communication problems

• Lesions with very low mortality
  – Low malignant tumors and Ig-DCIS
  – Rare lesions
Diagnostic errors in breast pathology

- Overdiagnosis may occur, especially with pathologists who are inexperienced or not subspecialized in breast pathology

- Azzopardi (1979):
  - Severe epitheliosis (florid ductal hyperplasia)
  - Sclerosing adenosis
  - Infiltrating epitheliosis (sclerosing lesions w/ hyperplasia)
  - Papilloma
  - Fibrosis, Elastosis
  - Pseudo-lobular carcinoma
  - Fat necrosis
Low frequency of diagnostic errors in pathology but high severity

- Breast cases second most common to skin (melanoma)
- Average cost per claim: $453.200
- High due to failure to detect cancer
- False-negatives more frequent than false-positive cases

Number of medicolegal claims reported in the US each year per 100 insured physicians (Troxel: USCAP 2006).

Examples of common diagnostic problems

- Fat necrosis
- Florid ductal hyperplasia
- Papilloma
- Sclerosing lesion
- Sclerosing adenosis
- Apocrine adenosis
Some sources of diagnostic errors in pathology

- „Hasty“ diagnosis
- Lack of experience
- Bad technical quality of tissue sections
- Mislabelling of specimen
- Incomplete / missing clinical information
Strategies for Minimizing Errors in Breast Pathology

- Quality assurance programs
  - Consensus slide conference
  - Adherence to established guidelines
  - Accreditation, external audits
- Review of outside pathology slides and reports before the initiation of cancer therapy
- Seeking a second opinion in difficult cases

After: Masood ICBDC 2013
Major and minor changes after seeking second opinion in breast pathology

Change in surgical therapy in up to 7.5% of cases

Additional prognostic information in 40% of cases

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**TABLE 1. Major changes in pathologic diagnosis**

<table>
<thead>
<tr>
<th>Initial diagnosis</th>
<th>Second-opinion diagnosis</th>
<th>n</th>
<th>% Total cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCIS</td>
<td>Benign</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>DCIS</td>
<td>Invasive cancer</td>
<td>6</td>
<td>1.7</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>DCIS</td>
<td>7</td>
<td>2.0</td>
</tr>
<tr>
<td>Margins positive</td>
<td>Margins negative</td>
<td>10</td>
<td>4.1</td>
</tr>
<tr>
<td>Margins negative</td>
<td>Margins positive</td>
<td>6</td>
<td>2.5</td>
</tr>
</tbody>
</table>

DCIS, ductal carcinoma-in-situ.

* Includes three cases that had both a margin change and another major change. Thus, major changes occurred in 7.8% of cases.

**TABLE 3. Minor changes in prognostic information**

<table>
<thead>
<tr>
<th>Change</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 to other</td>
<td>18</td>
<td>7.4</td>
</tr>
<tr>
<td>Invasive</td>
<td>9</td>
<td>11.1</td>
</tr>
<tr>
<td>DCIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other grade change</td>
<td>32</td>
<td>13.2</td>
</tr>
<tr>
<td>Invasive</td>
<td>8</td>
<td>9.9</td>
</tr>
<tr>
<td>DCIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No grade on first pathologic report</td>
<td>42</td>
<td>17.4</td>
</tr>
<tr>
<td>Invasive</td>
<td>29</td>
<td>35.8</td>
</tr>
<tr>
<td>Histological changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>61</td>
<td>25.2</td>
</tr>
<tr>
<td>Tubular/colloid to other</td>
<td>18</td>
<td>7.4</td>
</tr>
<tr>
<td>DCIS</td>
<td>36</td>
<td>44.4</td>
</tr>
<tr>
<td>Invasive to invasive + DCIS</td>
<td>43</td>
<td>17.8</td>
</tr>
<tr>
<td>No subtype on initial pathologic report</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>4</td>
<td>1.7</td>
</tr>
<tr>
<td>DCIS</td>
<td>9</td>
<td>11.1</td>
</tr>
</tbody>
</table>

DCIS, ductal carcinoma-in-situ.
Situations leading to overdiagnosis (and overtreatment)

- Errors in interpretation
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  - Misclassification

- Terminology issues
  - Overinterpretation of precancerous lesions
  - Communication problems

- Lesions with very low mortality
  - Low malignant tumors and Ig-DCIS
  - Rare lesions
Lobular Neoplasia (LN)

- Atypical lobular hyperplasia (ALH)
  - Classic LCIS
    - LIN 1
  - Florid LCIS
    - LIN 2
  - Pleomorphic LCIS
    - LIN 1

- Lobular Carcinoma in situ (LCIS)
  - LIN 1
  - LIN 2
  - LIN 3
Natural history: ALH vs. LCIS

- **ALH:**
  - 4 - 5x increased risk for invasive breast ca.
  - Individual risk (15 years): ~8%

- **LCIS**
  - LCIS: 8 - 9x increased risk for invasive breast ca.
  - Individual risk (15 years): ~15-20%

- **Cofactors**
  - Extent / number of lobules involved
  - History of previous breast biopsies
  - Family history

Nashville Breast Cohort
Nurses Health Study
Florid LCIS
aCGH comparison of fLCIS, pLCIS, and cLCIS


- fLCIS in situ shares the cytologic features, E-cadherin loss, and the lobular genetic signature loss found in classic lobular carcinoma in situ.
- fLCIS is genetically more advanced compared with the indolent phenotype of classic lobular carcinoma in situ.
European guidelines

- The pathologist is a key member of the specialist multidisciplinary team and has a primary role in the pre- and postoperative conferences. Patient management is largely based on the pathological findings. They should be sufficiently detailed and accurate.

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  - Rare lesions
Invasive tubular carcinoma

Clinicopathological characteristics (Rakha 2009)

- 68% screen detected
- 59% < 1 cm
- 91% node negative
- 100% good Nottingham prognostic index
Invasive tubular carcinoma – Origin from low grade columnar cell lesions

Histology

Molecular biology

Clonal relationship of FEA and ITC
Annual incidence of invasive ca. and DCIS

Continuous incidence of invasive breast cancer, despite increased detection of DCIS

Source: www.cijfersoverkanker.nl/
Screen detected Ig-DCIS

- How likely is it progression to clinically overt breast cancer during life time?

<table>
<thead>
<tr>
<th>Invasive Cancer Risk</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 yr ipsilateral</td>
</tr>
<tr>
<td>LCIS</td>
<td>3-6%</td>
</tr>
<tr>
<td>Atypia</td>
<td>4-7%</td>
</tr>
<tr>
<td>DCIS Score 10</td>
<td>5,0%</td>
</tr>
<tr>
<td>DCIS Score 30</td>
<td>10,0%</td>
</tr>
<tr>
<td>DCIS Score 65</td>
<td>15,0%</td>
</tr>
<tr>
<td>BRCA 1/2</td>
<td>5-7%</td>
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</table>

After: Essermann ASCO 2012
<table>
<thead>
<tr>
<th>Invasive Cancer Risk</th>
<th>10 yr ipsilateral</th>
<th>5 yr ipsilateral</th>
<th>Lifetime (either breast)</th>
<th>Offered / preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCIS</td>
<td>3-6%</td>
<td>20-40%</td>
<td>Active surveillance</td>
<td></td>
</tr>
<tr>
<td>Atypia</td>
<td>4-7%</td>
<td>20-40%</td>
<td>Active surveillance</td>
<td></td>
</tr>
<tr>
<td>DCIS Score 10</td>
<td>5.0%</td>
<td>2.5%</td>
<td>10-20%</td>
<td>Lumpectomy</td>
</tr>
<tr>
<td>DCIS Score 30</td>
<td>10.0%</td>
<td>3.5%</td>
<td>10-20%</td>
<td>Lumpectomy + XRT +/- Tamoxifen</td>
</tr>
<tr>
<td>DCIS Score 65</td>
<td>15.0%</td>
<td>7.5%</td>
<td>15-30%</td>
<td>Mastectomy</td>
</tr>
<tr>
<td>BRCA 1/2</td>
<td>5-7%</td>
<td>50-85%</td>
<td>Active surveillance/ screening Prophylactic mastectomy and/or oophorectomy</td>
<td></td>
</tr>
</tbody>
</table>

After: Essermann ASCO 2012

**With treatment!**
Risk of invasive cancer after biopsy of DCIS alone

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>All</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis</td>
<td>1938</td>
<td>(8)</td>
<td>6</td>
<td>75</td>
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<tr>
<td>Farrow</td>
<td>1970</td>
<td>(25)</td>
<td>5</td>
<td>20</td>
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<td>Haagensen</td>
<td>1971</td>
<td>(11)</td>
<td>8</td>
<td>73</td>
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<td>Millis</td>
<td>1975</td>
<td>(8)</td>
<td>2</td>
<td>25</td>
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<tr>
<td>Rosen</td>
<td>1980</td>
<td>(15)</td>
<td>8</td>
<td>53</td>
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<td>Eusebi</td>
<td>1994</td>
<td>(80)</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Page</td>
<td>1995</td>
<td>(28)</td>
<td>9</td>
<td>32</td>
</tr>
</tbody>
</table>

Mean = 28%
DCIS associated with IDC is genomically similar to the invasive component and therefore may represent either a clone with high invasive potential or invasive cancer spreading through the ducts.
Low Grade DCIS (LORD) Trial

• Hypothesis: Asymptomatic, low-grade DCIS detected by microcalcifications only can safely be managed by active surveillance

• Aim: To show non-inferiority of active surveillance as compared to standard treatment in low-grade DCIS patients

• Primary end-point: Ipsilateral invasive breast cancer-free rate (IBCF rate) at five years

• Study design:
  – Randomized, non-inferiority trial
  – Age $> 49$ year
  – Asymptomatic, low grade DCIS w/ microcalcifications

Wesseling, EBCC-9, 2014
Should Ig-DCIS and LCIS be considered as a precursor lesions or as risk indicators?

• Histologic and molecular evidence indicate the Ig-DCIS and LCIS are both precursor lesions and also risk indicators

• However, due to the slow progression of the lesions, they may never evolve into an aggressive cancer

Personal view:

• Possibly, there is a balance of progression and regression with low-grade lesions, due to the low proliferation rates of the neoplastic cells, and this may explain for the low risk to the patients.
Summary

Overdiagnosis may occur in three different settings:

- Pathology overdiagnosis (misclassification)
- Terminologic overdiagnosis (overinterpretation)
- Academic overdiagnosis (low mortality lesions)