Rethinking DCIS

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No disclosures
Definition of DCIS

- Proliferation of epithelial cells within the duct system with all features of malignancy
- Changes confined to the basement membrane
- Segmentally spread
- Non obligate precursor lesion of invasive breast cancer (BC)
- Transition into invasive BC in 20-50% within 15-20 years
Frequency and clinical appearance

- **Frequency**
  - Incidence by systemic screening up to 20% of all BC
  - 50% of all screened detected cancers

- **Clinical presentation**
  - Asymptomatic mammographic finding 90%
    - pure micocalcifications 76%
    - solid lesion with microcalcifications 13%
    - solid lesion 11%
  - Palpable tumor, nipple discharge (+/- Mb. Paget) 10%
Histological classification

- High grade (G3 / Comedo type)
  - necroses↑
  - number of mitoses↑
  - atypia↑

- Non high grade (G1,2 / Non comedo type)
  - mostly ER+
  - no aneuploidy
  - no p53-overexpression
  - no Her2-overexpression
DCIS-Standard of Care

- Diagnosis
- Surgery
- Radiotherapy (RT)
- Systemic therapy
Diagnosis I

- Screening mammography (Mgr)
  - ev. additional magnification view
  - ev. additional tomosynthesis
- Ultrasound
  - additional mass?
  - lymph nodes?
Diagnosis II

- Vacuum assisted stereotactic biopsy
  - Minimal sampling error (upgrade 0-20%)
  - Radiography of the samples
  - Clip-application

- Preoperative Mgr
  - Residual calcifications?
  - Where are they located?
Diagnosis III

- Magnetic resonance imaging (MRI)
  - Sensitivity 88-92%
    - i.e. high detection rate for high grade lesions
  - Specificity 87-97%
  - No reduction of local recurrence (LR) rate
  - No routine use in work-up of verified DCIS
    - Optional: measurement of the extent of a large DCIS

Lehmann et al, LNCI Monography 2010
Solin JCO 2008
Overdiagnosis in Screening?

Definition:

Diagnosis of subclinical carcinomas by screening which would not have clinically appeared during lifetime or caused cancer related death.
Notes of overdiagnosis by Mgr-screening

- Missing of „compensatory drop“ in most trials
- Distinct increase of DCIS without decrease of invasive BC
- Change of DCIS to invasive BC only in 20-63%
- DCIS in 37% of autopsys of women with 40-54a
- Observed regression of DCIS
- Increasing sensitivity in screening (e.g. by tomosynthesis)

Alvorcado et al. JCI 2012
Sanders et al. Cancer 2005
Zahl et al. Lancet Oncol 2011
# Overdiagnosis in literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Amount %</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK Panel (meta-analysis of 3 RT-trials), Lancet 2012</td>
<td>11-19</td>
</tr>
<tr>
<td>Pace, JAMA 2014 (medline literature research 1960-2014)</td>
<td>19</td>
</tr>
<tr>
<td>Jorgensen, BMJ 2009 (ecological studies)</td>
<td>46-57</td>
</tr>
<tr>
<td>Bleyer, NEJM 2012 (SEER data 1976-2008)</td>
<td>31</td>
</tr>
<tr>
<td>Njor, BMJ 2013 (2 danish cohort studies)</td>
<td>1-2</td>
</tr>
<tr>
<td>Gunsoy, Br J Cancer 2014 (Markov-simulation model)</td>
<td>6-8</td>
</tr>
<tr>
<td>Heinavaara, Br J Cancer 2014 (finnish cohort study)</td>
<td>5-7</td>
</tr>
<tr>
<td>Puliti, J med Screen 2012 (lit. review of 13 EU observational studies)</td>
<td>1-10</td>
</tr>
<tr>
<td>Yen, Cancer 2012 (two county trial)</td>
<td>0</td>
</tr>
</tbody>
</table>
Future aspects – Diagnosis

- EDRN/NCI (early detection research network)
- FAST MRI (early neovascularisation)
- Personalized Screening?
- Chemoprevention for high risk premalignant lesions
  - multifocal ADH
  - JAK1/2 Inhibitor Ruxolitinib

Morris E, et al, JCO 2014
WISDOM trial (L Esserman)
Denigm A, et al. NEJM 2015
Li. San Antonio 2015
Aim of therapy

- Removal of entire lesion
- Avoidance of local recurrence (LR)
  - 50% invasive BC (can be life threatening)
Surgery: *Breast conserving surgery (BCS)*

- Pre/intraoperative localization
- Segmental surgical excision
  - Oncoplastic techniques
- Specimen radiography
- Clear margins
  - No ink on tumor
  - 1mm

*St. Gallen Consensus, Ann Oncol 2015*
*NCCN Guideines 2015*
Surgery: *Mastectomy* (*Mx*)

- **Indication**
  - Diffuse scattered malignant microcalcifications
  - Multicentricity
  - Persistent positive margins after attempts of BCS

- **Methods**
  
  *Preferred combined with immediate reconstruction*
  
  - Skin sparing mastectomy
  - Nipple sparing mastectomy
Surgery: *Sentinel node biopsy*

Axillary surgery not mandatory for pure DCIS but optional for:
- highly suspicious for invasive cancer
- no possibility to identify a sentinel after surgery
## Omitting surgery in DCIS?

### Small series

<table>
<thead>
<tr>
<th>Author/PY</th>
<th>N</th>
<th>Follow up (years)</th>
<th>Characteristics of DCIS</th>
<th>Symptomatic DCIS</th>
<th>Symptomatic Invasive BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betsil (1978)</td>
<td>10</td>
<td>22</td>
<td>Low grade papillary</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Page (1995)</td>
<td>28</td>
<td>30</td>
<td>Non comedo</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Collins (2005)</td>
<td>13</td>
<td>4-27</td>
<td>Mixed grade</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>
Survival benefit of surgery?
SEER-Data

- N = 57,222
- Retrospective analysis
- 1988-2011
- Treatment:
  - 1,169 (2%) without surgery
  - 56,053 (98%) with surgery
- Median follow-up 57 months

Survival benefit of surgery?
SEER-Data

- All patients 98.5% vs. 93.4%  P < .001
- Low grade DCIS 98.8% vs. 98.6%  P = .95

Future aspects I
LORIS-Trial  Clinical Cancer research UK

Non high grade DCIS
Any size
>46 years
Minimal family history

BCS

Active monitoring
Mammography yearly

Primary endpoint: 5 yr ipsilateral invasive BC free survival

C. Tausch
Future aspects II
LORD-Trial  EORTC BCG 1401 - Dutch Breast Cancer Research Group

Non high grade DCIS
Any size
>45 years
Minimal family history

Conventional treatment
BCS +/-RT  +/-HT
Mastectomy

Active monitoring
Mammography yearly

Primary endpoint: 10 yr ipsilateral invasive BC free survival
Radiotherapy (RT)

- Standard after BCS
- Whole-breast radiation (WBI)
- Avoidance of RT only if VNPI-Score $\leq 5$
  - Tumorsize $< 15$mm and
  - Margin $> 1$mm and
  - Non high grade and
  - Age $> 60$a

Breast cancer mortality after DCIS
SEER-Data

Demographic data

- 1988-2011
- N = 108,196
- SEER 18 (28% of US-population)
- 53.8 years (15-69)
- Mean follow-up 7.5 years (0-23.9)

Narod SA, et al. JAMA 2015
Breast cancer mortality after DCIS
SEER-Data

Results

- 20 ys BC-specific mortality 3.3%
  - Significantly higher for
    - Women < 35ys 7.8% \( P < .001 \)
    - Blacks 7.0% \( P < .001 \)
- Increased BC-specific mortality after invasive local recurrence \( P < .001 \)
- 517 patients (54%) died without invasive recurrence
- RT reduced invasive recurrence \( P < .001 \)
- RT did not reduce BC-specific mortality \( P = .22 \)

*Narod SA, et al. JAMA 2015*
EBCTCG-Meta-analysis for BCS +/- RT
EORTC, NSABP B-17, swe DCIS, UK/ANZ

- N = 3`279
- Median follow-up 13-17 years
- 10 years local recurrence rate 13% vs. 28%
  relative risk reduction:
  - < 50 years 31%
  - > 50 years 62%
- BC mortality rate 4% in both arms
- Contralateral BC rate 3.8% vs. 2.5%

JNCI 2010
Is RT always necessary?  
A matter of selection?

**ECOG E5194 Trial**

- Prospective cohort trial
- 30% endocrine therapy (ET) with Tamoxifen
- Median follow-up 8.8 ys
- Margin width ≥ 3mm

<table>
<thead>
<tr>
<th>N</th>
<th>Size (mm)</th>
<th>Grading</th>
<th>10y LR rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>565</td>
<td>&lt;25</td>
<td>Non high grade</td>
<td>14.6</td>
</tr>
<tr>
<td>105</td>
<td>&lt;10</td>
<td>High grade</td>
<td>19</td>
</tr>
</tbody>
</table>

*Solin LJ, et al. JCO 2015*
Prediction of risk for LR?  
**OncoType Dx 12-gene DCIS score**

- 7 cancer related genes, 5 reference genes
- Validation in 327 patients of ECOG E5194
- 10 year risk for invasive or DCIS LR

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>N</th>
<th>Ipsilateral breast recurrence</th>
<th>Invasive ipsilateral breast recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (&lt;39)</td>
<td>230</td>
<td>10.6%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Intermediate risk (39-54)</td>
<td>53</td>
<td>26.7%</td>
<td>12.3%</td>
</tr>
<tr>
<td>High risk (&gt;55)</td>
<td>44</td>
<td>25.9%</td>
<td>19.2%</td>
</tr>
<tr>
<td>Log rank</td>
<td></td>
<td>$P = .006$</td>
<td>$P = .003$</td>
</tr>
</tbody>
</table>

*Note: Log rank $P$ values are given.*

*Source: Solin LJ, et al. JNCI 2013*
Predictors of ipsilateral recurrence
ECOG E5194

Univariate analysis

- Age
- Size
- Menopausal status
- DCIS Score

Multivariate analysis

- Size
- Menopausal Status
- DCIS Score
**VNPI (Van Nuys Prognostic Index) as predictor for LR**

Size, Margins, Pathologic classification, Age

<table>
<thead>
<tr>
<th>Author (PY)</th>
<th>N</th>
<th>Low risk N (%)</th>
<th>Follow-up (years)</th>
<th>LR (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gillear (2008)</td>
<td>215</td>
<td>65 (30)</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Di Saverio (2008)</td>
<td>186</td>
<td>144 (77)</td>
<td>10</td>
<td>0.6</td>
</tr>
<tr>
<td>MacAusland (2007)</td>
<td>222</td>
<td>136 (61)</td>
<td>5</td>
<td>1.0</td>
</tr>
<tr>
<td>Silverstein MJ (2015)</td>
<td>696</td>
<td>696</td>
<td>12</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Molecular phenotypes as predictor of LR?

Controversial results

- No predictive value for LR

- Molecular phenotypes predict LR
Consistent predictors for invasive LR

<table>
<thead>
<tr>
<th>Predicting factor</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 45</td>
<td>2.0-2.1</td>
</tr>
<tr>
<td>Palpable mass</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td>Comedo type</td>
<td>2.8-3.1</td>
</tr>
<tr>
<td>Positive margin</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Size may be a risk factor: difficult to measure accurately
OncoType-Dx DCIS score promising (promising results)

EBCTCG, J CO 2006
Solin LJ, et al. JNCI 2013
Nested Case-Control Study
San Francisco Bay SEER_Data

- 143 recurrent cases (half DCIS and half invasive BC)
- 186 controls
  - ER
  - Ki67
  - TP53
  - Her2
  - COX2

<table>
<thead>
<tr>
<th>Recurrence risk by biomarker profile (% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P16/COX2/Ki67 (+/+/+</td>
</tr>
<tr>
<td>P16/COX2/Ki67 (+/-/+</td>
</tr>
<tr>
<td>ER/HER2/Ki67 (-/+/+</td>
</tr>
</tbody>
</table>

- An ultra-low-risk group could not be identified!

Kerlikowske K, et al. JNCI 2010
Future aspects RT I
NSABP B-39 / RTOG 0413

DCIS
Any size
>46 years

BCS

WBI

APBI
(Accelerated partial breast irradiation)
- Mammosite 34 Gy
- External catheter 34 Gy
- 3D conformal external beam therapy 38.5 Gy

Mammosite 34 Gy

External catheter 34 Gy

3D conformal external beam therapy 38.5 Gy
DCIS  
G1,2, > 20mm  
G3, any size  
Margin > 1mm

BCS

WBI for 3 weeks  
42.5 Gy

WBI for 5 weeks  
50 Gy

Boost (10Gy)  
nihil

Recruitment 2007 – 2014  
N = 1608
Systemic therapy

- Endocrine Therapy optional for ER+ DCIS
- Tamoxifen 5a
- No chemotherapy
- No anti-Her2 therapy
DCIS-Tamoxifen Trials
BCS + RT +/- Tamoxifen

NSAPB B-24, UK/ANZ 2x2 Design

- LR rate 16.6-17% vs. 13.2% (30% reduction)
  - NSABP B-24: significance only for invasive recurrence
  - UK/ANZ: significance only for DCIS recurrence
- BC mortality rate no difference
- Contralateral BC rate 50% reduction
- UK/ANZ Trial no effect of Tam in combination with RT
- Absolute reduction of invasive BC events by Tam 7%

Allred, et al. JCO 2012
NSABP B-35 Trial
BCS + RT + ET (Tamoxifen vs. Anastrozol)

- N = 3104
- Median follow-up 8.6 years

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Tamoxifen 20mg / 5 years</th>
<th>Anastrozol 1mg / 5 years</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC free survival</td>
<td>89.2%</td>
<td>93.5%</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>BC events</td>
<td>114</td>
<td>84</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>Invasive BC events</td>
<td>63</td>
<td>39</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>Contralateral BC events</td>
<td>55</td>
<td>37</td>
<td>n.s.</td>
</tr>
<tr>
<td>Contralateral invasive BC events</td>
<td>36</td>
<td>20</td>
<td>P = 0.03</td>
</tr>
</tbody>
</table>

DFS n.s. (<60a P = 0.02)
OS n.s.

Margolese ASCO 2015
IBIS II DCIS Trial
International Breast Cancer Intervention Study

N = 2980
Tamoxifen vs. Anastrozol for 5 years
Median follow-up 7.2 years

- No significant difference in recurrence
- No overall effect on other cancers
- No effect on death
- Expected difference in side effect profiles
- Unexpected increase in CVA for anastrozole

Cuzick J, et al. SABCS 2015
Future aspects I

- ECOG-ACRIN E4112: prospective study of MRI and DCIS-Score
- Further investigation in drivers responsible for invasion
  - CD10
  - COX2
  - P38 MAPK
  - RP/PTEN loss
  - BCL-9
  - SIM2s

Kerlikowske K, et al. JNCI 2010
Knudsen ES, et al. JNCI 2012
Elsarraj HS, et al. BCR 2015
Biopsy proven DCIS
Postmenopausal
ER and/or PR (+)
Radiographically measureable disease

3 months letrozole

Stable or response

Progression

3 months letrozole

MRI

Clinical examination

MRI

Mgr Surgery
Future aspects III
NSABP B-43

- DCIS
  - Any size
  - Any age
  - Her 2 (3+)
  - or FISH pos.

- BCS

- WBI

- WBI + Trastuzumab
  - 8 mg/kg iv day 1
  - 6mg/kg iv day 22
Summarizing invasive BC risk by treatment choice

- **EBCTCG**
  - Do nothing: 2.0% per year
  - Excision only: 1.4% per year
  - Excision + RT: 0.7% per year

- **B27**
  - Excision + RT + TAM (ER+): 0.4% per year

- **SEER**
  - Mastectomy: 0.1% per year

Radiation consistently cuts recurrence risk in half regardless of the starting risk level.

*Euhus DM, SABCS 2015*
Take home massage

- Overdiagnosis
- Avoidance of invasive recurrence!
- Overtreatment for non high grade DCIS?
- Decision finding for adjuvant therapy
  - Patients and tumor characteristics
  - Interdisciplinary meeting
  - Patients preference
- More data warranted
  - Current trials
  - Mechanisms leading to invasive recurrence?
Acknowledgements

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