Are We Overtreating DCIS?

Kelly K. Hunt, MD
Department of Surgical Oncology
MD Anderson Cancer Center
| Ductal Carcinoma In Situ (DCIS) |

<table>
<thead>
<tr>
<th><strong>Incidence:</strong></th>
<th>AKA:</th>
</tr>
</thead>
<tbody>
<tr>
<td>≈ 60,000 new cases US 2011</td>
<td>Noninvasive Breast Cancer</td>
</tr>
<tr>
<td>20-25% of our Current practice</td>
<td>Preinvasive Breast Cancer</td>
</tr>
<tr>
<td></td>
<td>Intraductal Carcinoma</td>
</tr>
<tr>
<td></td>
<td>“Precancer”</td>
</tr>
</tbody>
</table>
DCIS Has Increased 500 Fold Since the Advent of Mammographic Screening
DCIS

Course

Amorphous

Linear branching
DCIS

- >90% asymptomatic non-palpable lesions, detected only by mammography
- Multidisciplinary guidelines for management of DCIS (ACR, ACS, CAMPO, NCCN)
- *Most controversial topic in breast cancer therapy*
### Natural History of Untreated DCIS

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>IBC (%)</th>
<th>Follow-up (yrs)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosen 1980</td>
<td>15</td>
<td>53</td>
<td>1-24</td>
<td>9.1</td>
</tr>
<tr>
<td>Page 1982</td>
<td>28</td>
<td>32</td>
<td>3-31</td>
<td>9.1</td>
</tr>
<tr>
<td>Eusebi 1994</td>
<td>80</td>
<td>14</td>
<td>1-14</td>
<td>13.5</td>
</tr>
<tr>
<td>Collins 2005</td>
<td>13</td>
<td>46</td>
<td>4-18</td>
<td></td>
</tr>
</tbody>
</table>

50-70% of women do not develop IBC, even at 20 years. But how to determine who will not progress?
DCIS

Institute of Medicine
Top 100 Conditions
Warranting CER

Under treatment

Over diagnosis
Overtreatment
DCIS ‘Pre-Cancer’ But Treated Like Cancer

- **Surgery**
  - Any? How much? Excision, Mastectomy; Margins

- **Radiation**
  - Any? If so, how much and in whom?

- **Systemic therapy**
  - Any? What agents?
DCIS ‘Pre-Cancer’ But Treated Like Cancer

- DCIS is a marker for development of invasive breast cancer
- Diagnosis and treatment critical
  - Rule out concurrent presence of invasive carcinoma (11-25%)
  - Prevent development of invasive ca
  - Much like LCIS or ADH
NIH Consensus Conference
Recommendations

Determine the molecular events associated with progression of DCIS to invasive cancer
Biology of DCIS

2000’s to Present
Challenges in Studying DCIS Tissue

- SMALL amounts of tissue
  - Detected by microcalcs
  - MMG/ Core biopsy

- Must rule-out invasive cancer

- Fresh tissue? Paraffin embedded?

LCM: Dr. Lavinia Middleton
Breast Cancer Develops Over Time

- Breast cancer cells progress through changes over a period of years

Normal Duct  Ductal Hyperplasia  Ductal Hyperplasia with Atypia  Ductal Carcinoma In situ  Invasive Ductal Carcinoma

Reversible with tamoxifen  Reversible ?
Sequential and Parallel Models of Carcinogenesis

Alternative model
• Imaging features related to molecular phenotype
  – ER-negative disease:
  – more likely to be multicentric/focal
  – more likely to be visible by ultrasound
  – less likely to visible on mammography

Rauch...Yang et al, Submitted, Radiology 2012
BRCA Mutations in Patients with pure DCIS

- MDACC
  - 118 women DCIS counseled and tested
  - 27% tested BRCA positive
  - Fam hx ovarian ca and BRCAPRO score > 10% independent predictors

- High risk patients with DCIS appropriate candidates for BRCA testing

Bayraktar et al CANCER 2012
Treatment for DCIS: Progress

- Randomized Clinical Trials with the NSABP:
  - B-17: Lumpectomy vs. Lumpectomy and Radiation (Completed)
  - B-24: Lumpectomy/XRT with or without Tamoxifen (Completed)
  - B-35: Lumpectomy/XRT with Anastrozole vs. Tam (Completed)
  - B-39: APBI vs. WBXRT (Nearly complete)
  - B-43: Trasuzumab vs. placebo (Open)
Randomized Trials of Conservative Surgery vs CS+Radiation for DCIS:

Local Failure Rates

<table>
<thead>
<tr>
<th>Trial</th>
<th>#</th>
<th>FU</th>
<th>CS</th>
<th>CS+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP</td>
<td>818</td>
<td>12-yr</td>
<td>31%</td>
<td>15%</td>
</tr>
<tr>
<td>EORTC</td>
<td>1010</td>
<td>10-yr</td>
<td>26%</td>
<td>15%</td>
</tr>
<tr>
<td>SweDCIS</td>
<td>1046</td>
<td>10-yr</td>
<td>30%</td>
<td>13%*</td>
</tr>
<tr>
<td>UKCCR</td>
<td>1030</td>
<td>10-yr</td>
<td>19%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Fisher, Semin Oncol 28, 2001 (med FU, 129 mo)
Bijker, J Clin Oncol 24, 2006 (med FU, 126 mo)
Emdin, Acta Oncol 45, 2006 (med FU, 62 mo)
Holmberg, J Clin Oncol 26, 2008 (mean FU, 96 mo, *estimate cum incidence)
Cuzick, Lancet Oncol, 2010 (med FU, 12.7 year)
So why not utilize radiation with everyone?

- Very effective at decreasing local relapse
- High cost
- 6-weeks for WBRT
- Complications of XRT
  - Fibrosis, cosmesis, cardiac/pulmonary morbidity, other cancers
RTOG 9804: Seven year update of a Prospective Randomized Trial for “Good Risk” Ductal Carcinoma in Situ (DCIS) Comparing Radiation to Observation

Beryl McCormick; Jennifer Moughan; Clifford Hudis; Henry Mark Kuerer; Eileen Rakovitch; Barbara L. Smith; Nour Sneige; Amit Shah; Isabelle Germain; and Julia R. White
Overall Survival (%)

log-rank p-value = 0.18
HR = 1.56 (0.81,3.01)

Patients at Risk
Observation | 298 | 295 | 292 | 287 | 273 | 259 | 214 | 161
RT | 287 | 282 | 275 | 268 | 257 | 240 | 207 | 153
### Local Failure: Ipsilateral Breast

<table>
<thead>
<tr>
<th>Year</th>
<th>Failed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19</td>
<td>298</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>287</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gray's test p-value = 0.0003
HR = 0.11 (0.03, 0.47)

#### 7-Year Rates:

- Observation: 6.7%
- RT: 0.9%

**Patients at Risk**

<table>
<thead>
<tr>
<th>Observation</th>
<th>298</th>
<th>287</th>
<th>272</th>
<th>257</th>
<th>240</th>
<th>225</th>
<th>182</th>
<th>126</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>287</td>
<td>278</td>
<td>265</td>
<td>250</td>
<td>235</td>
<td>211</td>
<td>174</td>
<td>128</td>
</tr>
</tbody>
</table>
Contralateral Breast Events

Gray's test p-value = 0.88  
HR = 1.07 (0.48, 2.39)

7-Year Rates:  
4.8%  
3.9%

Patients at Risk  
Observation: 298 293 286 279 258 241 204 144  
RT: 287 279 268 253 241 220 185 137
RTOG 98-04

• Conclusions
  – Patients with low and intermediate grade DCIS
Genetic Profiling of DCIS

Invasive breast cancer, prostate cancer, colon cancer
Unmet Needs in DCIS

- Reliable methods for making treatment decisions based upon patient specific tumor biology in DCIS not established
- Quantitatively assess the risk of invasive breast cancer recurrence in newly-diagnosed patients with DCIS
- Appropriate management
  - low risk disease which may be treated with surgery alone, avoiding toxicities and costs associated with radiation
  - high risk disease for which the addition of radiation may be considered
A QUANTITATIVE MULTIGENE RT-PCR ASSAY FOR PREDICTING RECURRENCE RISK AFTER SURGICAL EXCISION ALONE WITHOUT IRRADIATION FOR DUCTAL CARCINOMA IN SITU (DCIS): A PROSPECTIVE VALIDATION STUDY OF THE DCIS SCORE FROM ECOG E5194


Eastern Cooperative Oncology Group (ECOG)
North Central Cancer Treatment Group (NCCTG)
Genomic Health, Inc (GHI)

2011 San Antonio Breast Cancer Symposium
ECOG E5194 (PARENT STUDY)

Prospective multicenter study 1997-2000 (n = 670)
  Cohort 1: Low/intermediate grade, size ≤ 2.5 cm
  Cohort 2: High grade, size ≤ 1 cm

Study treatment
  - Surgical excision
  - Minimum 3 mm negative margin width
  - No radiation
  - Tamoxifen option beginning May 2000

Reported outcomes at 5 and 7 years (Hughes, JCO, 2009)
  - Currently reporting 10-year outcomes

### ECOG 5194 No Radiation For DCIS
*(med FU, 60 months)*

<table>
<thead>
<tr>
<th></th>
<th>Low-Inter Gr</th>
<th>High Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># Patients</strong></td>
<td>558</td>
<td>103</td>
</tr>
<tr>
<td><strong>5-year IBTR</strong></td>
<td>6.1%</td>
<td>15.3%</td>
</tr>
<tr>
<td><strong>Invasive</strong></td>
<td>50%</td>
<td>47%</td>
</tr>
<tr>
<td><strong>Contralat BC</strong></td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Hughes et al, *J Clin Onc; 2009*
METHODS FOR DCIS SCORE VALIDATION STUDY

Prospective-retrospective study design
Pre-specified: Study objectives, population, laboratory assays, endpoints, statistical methods

Onco\textit{type} DX assay performed (n = 327; 49%)
Standardized methods for 21 gene assay
Central pathology review
Calculated: DCIS Score and Recurrence Score

Study endpoint: Ipsilateral breast events (IBE)
1\textdegree Endpoint: Any IBE (DCIS or invasive carcinoma)
2\textdegree Endpoints: Invasive IBE
DCIS IBE

DCIS Score: Gene Selection

**Proliferation**
- Ki-67
- STK15
- Survivin
- Cyclin B1
- MYBL2

**Hormone Receptor Group**
- PR

**Reference**
- Beta-actin
- GAPDH
- RPLPO
- GUS
- TFRC

**DCIS Score:**
- Continuous variable
- Number between 0 – 100
DCIS SCORE: 10-YEAR IPSILATERAL BREAST EVENTS (IBE) BY RISK GROUP

ANY IBE

DCIS SCORE: 10-YEAR IPSILATERAL BREAST EVENTS (IBE) BY RISK GROUP

**DCIS Multigene Assay**

May provide additional clinical insights

- *Needs further prospective testing: several studies are in development*

- Clinicians and patients desire objective evidence regarding risk of local recurrence (DCIS or invasive) to assist in treatment decision-making
  - Clinicians and patients are uncertain about radiation
  - Clinical and pathological parameters might indicate treatment and the patient does not wish to receive therapy
  - Clinicians recommend forgoing therapy and the patient is not convinced

- **NEW STUDY - DECISION IMPACT?** Any additional value
New Targeted Approaches for DCIS

Elucidating the Biology of the Disease
Hormonal Therapy and DCIS
NSABP B-24 Stratification Based on ER Status

- ER determined in 732 cases
  - Median f/u 14.5 years
- No benefit in ER negative
- HR 0.49 for all breast cancer events among ER+
- 10-year IBTR
  - ER neg = 20%
  - ER+ placebo = 16%
  - ER+ tam = 10%

Allred et al, JCO, 2012
UCSF Preoperative Endocrine Treatment for ER-positive DCIS

3-month

Letrozole 2.5 mg PO QD
Tamoxifen 20 mg PO QD

Exclusion criteria:
- palpable disease
- microinvasion
- not visible on MRI

Chen et al, *BMC Cancer*, 2009
Alteration of biomarker expression is associated with endocrine treatment for DCIS

Chen et al, *BMC Cancer*, 2009
Biomarker changes associated with endocrine treatment

Chen et al, *BMC Cancer*, 2009
MRI assessment of letrozole response

Responder: ER-positive, postmenopausal; “pathologic CR"
Three-Month Pre-op Endocrine Therapy in DCIS

• Preoperative endocrine therapy of ER-positive DCIS
  – Safe
  – Histologic and radiologic changes are evident

• No long term data on efficacy and the question remains in what proportion of women might this therapy actually prevent the occurrence of invasive breast cancer
NEW Trial Alliance-CALGB 40903: Phase II Single-Arm Study of Neoadjuvant letrozole for ER(+) postmenopausal DCIS

3 months Letrozole

stable or responding

3 months Letrozole

progression

MMG MRI core bx

registration

MRI Clinical exam

MMG MRI Surgery

Measure change Ki67, Imaging-path correlation
PI: Shelley Hwang
N=96
Other Preoperative Targeted Systemic Agents for DCIS?

Window Studies Designed to Gain Better Understanding of Biology and Response in DCIS
NIH Recommendations

- Develop risk-stratification models to identify subsets of women who have DCIS who are candidates for:
  - (1) active surveillance only
  - (2) local excision only
  - (3) local excision with radiotherapy
  - (4) Mastectomy
Summary: DCIS

• Novel clinical trial designs
  – New emerging targets for DCIS
  – Multigene RTPCR Biologic Assays
• DCIS may be ideal opportunity to study promising agents for prevention
• VISION:
  – Selective approach for surgery and radiation