Management of DCIS

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Disclosures

- Speaker’s Bureau
  - Genentech
  - Invuity
  - Medtronic
  - Pacira

- Stock
  - Invuity

- Travel expenses
  - Faxitron

- Advisory Boards
  - Dune
  - TransMed7
  - Genomic Health
Historic Surgical Treatment - Mastectomy

Rationale:

- 30% incidence of multicentric disease
- 40% prevalence of residual tumor at mastectomy following wide excision alone
- 25-50% incidence of in-breast recurrence following limited surgery for a palpable tumor
- 50% of recurrences were invasive
- Combined distant and local recurrence rates following a mastectomy is 1-2%
No randomized trials have been performed comparing mastectomy to breast-conserving surgery plus radiation for DCIS

THE DATA HAS BEEN EXTRAPOLATED FROM STUDIES FOR INVASIVE CARCINOMA
The rate of diagnosis of DCIS increased with the use of screening mammography in the 1980’s
Incidence Rate of In Situ Carcinoma

500% increase!

*Rates are age adjusted to the 2000 US standard population within each age group.

American Cancer Society 2013
FACT

Currently 95% of all DCIS is non-palpable
11% of patients with palpable DCIS have invasion
Occult invasion is found in 50% of DCIS >5.5 cm
FACT

DCIS represents 20-27% of all newly diagnosed breast cancer

2014
Invasive 235,030
DCIS 62,570
FACT

The risk factors for DCIS and gene mutation rates are the same as for invasive breast cancer

All of the genetic mutations found in invasive breast cancer have been found in DCIS
Low-grade DCIS progresses to low-grade invasive carcinoma and high-grade DCIS progresses to high grade DCIS
There is an evolutionary process from normal to invasion.
## Risk of Invasive Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>Invasive Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 year ipsilateral</td>
</tr>
<tr>
<td>LIN</td>
<td>3-5%</td>
</tr>
<tr>
<td>Atypia</td>
<td>3-5%</td>
</tr>
<tr>
<td>Low Risk DCIS</td>
<td>2.5%</td>
</tr>
<tr>
<td>Int Risk DCIS</td>
<td>4-5%</td>
</tr>
<tr>
<td>High Risk DCIS</td>
<td>7-15%</td>
</tr>
<tr>
<td>BRCA 1/2</td>
<td>5-7%</td>
</tr>
</tbody>
</table>

Mike Dixon. ASBS.2014
DCIS was found in up to 14% of autopsies on women age 20-54
What % of DCIS Lesions Progress to Invasive Cancer?
DCIS as a non-obligate precursor

- Retrospective pathology studies showed breast cancer developed in 39-53% of patients.
- Margins matter
- Ipsilateral recurrence 11% vs 3% occurrence in the contralateral breast

Treatment Decisions

- DCIS is heterogeneous
- We must accept recurrences
  - 50% of recurrences are invasive, among all subtypes
Treatment Options for Patients with DCIS

- Breast-conserving surgery and radiation therapy with or without tamoxifen
  - SEER data: 74% of patients with DCIS are treated with breast conservation
- Total mastectomy with or without tamoxifen
- Breast conserving surgery without radiation therapy
- Chemoprevention
4 prospective randomized trials

RT vs not after breast-conserving surgery (BCS) for DCIS

- Women treated with BCS alone – 26-36% risk of recurrence
- Radiation reduces the risk by 50%
- Tamoxifen reduces the risk by 30%
- Neither radiation nor tamoxifen improve survival
Ductal Carcinoma In Situ
NSABP B-17  1985-1993

- 818 women-negative surgical margins randomized to receive radiation or not
  - 80% diagnosed by mammography
  - 70% ≤ 1 cm
- 12 year follow-up
  - IBTR 31.7% → 15.7%
  - Occurrence of invasive carcinoma 16.8% → 7.7%
  - Recurrent DCIS 14.6% → 8.0%
- Comedonecrosis was the only significant predictor for recurrence
Long Term Outcomes for In-Breast Recurrence from NSABP B17, B24

Invasive In-breast recurrences

Wapnir et al, JNCI 103: 2011
EORTC-10853

- 1010 women-negative surgical margins randomized to receive radiation or not
  - 71% detected by mammography
- Median follow-up 10.5 years
  - IBTR 26% → 15%
  - Occurrence of invasive carcinoma 13% → 8%
  - Recurrent DCIS 14% → 7%

12 year follow-up B-17:
  - IBTR 31.7% → 15.7%
  - Occurrence of invasive carcinoma 16.8% → 7.7%
  - Recurrent DCIS 14.6% → 8.0%

Donker, et al. JCO. 2013
Early Breast Cancer Trialists’ Collaborative Group

Meta-analysis NSABP B-17, EORTC, Swe DCIS, UK ANZ

Darby, JNCI monograph, 2010
Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ

Steven A Narod, Javaid Iqbal, Vasily Giannakeas, Victoria Sopik, Ping Sun
Objective: Estimate 10- and 20- year mortality from breast cancer following a diagnosis of DCIS

Methods: Observational study using SEER database from 1988-2011

108,196 women included.

Results: 20 year breast cancer specific mortality is 3.3%.

Conclusion: Prevention of invasive recurrence does not diminish breast cancer mortality.

Narod, et al, JAMA Oncol. 2015
Young age and black ethnicity were significant predictors of breast cancer mortality

<table>
<thead>
<tr>
<th>Age</th>
<th>Ethnicity</th>
<th>Risk of Death (20 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>Black</td>
<td>7.8%</td>
</tr>
<tr>
<td>Older (to age 70)</td>
<td>Non-Hispanic white</td>
<td>3.2%</td>
</tr>
<tr>
<td>7.8%</td>
<td>7%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Risk of death from breast cancer among all women with DCIS was 1.8 times greater than that of the US population.
Twenty-year breast cancer-specific survival after DCIS, by age of diagnosis

*Graph showing survival rates by age group: 60 to 69, 297 deaths/32511; 40 to 59, 554 deaths/70431; 35 to 39, 62 deaths/3973; < 35, 36 deaths/1279*. 

*p < 0.0001*
Other predictors of breast cancer mortality

- Larger tumor size
- Higher grade
- ER negative
- Comedonecrosis
## 20 year risk of invasive recurrence

<table>
<thead>
<tr>
<th>IPSILATERAL INVASIVE RECURRENCE</th>
<th>CONTRALATERAL INVASIVE RECURRENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.9%</td>
<td>6.2%</td>
</tr>
<tr>
<td>BCS with RT</td>
<td>BCS without RT</td>
</tr>
<tr>
<td>4.5%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>
Prevention of invasive in-breast recurrence did not prevent death from breast DCIS

54.1% of women who died of breast cancer did NOT experience in-breast invasive recurrence
Mel Silverstein
“The Father of DCIS”
1496 patients treated between 1979-2009
949 breast conserving surgery
  604 (64%) lumpectomy alone
  345 (36%) lumpectomy and RT
No tamoxifen
Goal of USC/VNPI:
  define the parameters necessary to allow a local recurrence rate < 20% at 12 years
## Van Nuys Prognostic Index

**DCIS**

<table>
<thead>
<tr>
<th>Factor</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>&lt;15 mm</td>
<td>16-40 mm</td>
<td>&gt;4 cm</td>
</tr>
<tr>
<td><strong>Margins</strong></td>
<td>&gt; 1 cm</td>
<td>&lt; 1 cm</td>
<td>&lt; 1 mm</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Non-high grade</td>
<td>Non-high grade with necrosis</td>
<td>High grade</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>&gt;60</td>
<td>40-60</td>
<td>&lt;40</td>
</tr>
</tbody>
</table>

Silverstein, Lagios, JNCI mon. 41: 2010
### TABLE 7.2

Treatment Guidelines, University of Southern California/Van Nuys Prognostic Index (USC/VNPI)

<table>
<thead>
<tr>
<th>USC/VNPI Score</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>4, 5, or 6</td>
<td>Excision only</td>
</tr>
<tr>
<td>7, 8, or 9</td>
<td>Excision plus radiation</td>
</tr>
<tr>
<td>10, 11, or 12</td>
<td>Mastectomy</td>
</tr>
</tbody>
</table>
## Treatment Guidelines for DCIS

### USC/ Van Nuys Prognostic Index

<table>
<thead>
<tr>
<th>USC/VNPI</th>
<th>Treatment</th>
<th>12-yr recur, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4, 5 or 6</td>
<td>Excision alone</td>
<td>≤6</td>
</tr>
<tr>
<td>7, margins ≥3 mm</td>
<td>Excision alone</td>
<td>16</td>
</tr>
<tr>
<td>7, margins &lt;3 mm</td>
<td>Radiation</td>
<td>14</td>
</tr>
<tr>
<td>8, margins ≥3 mm</td>
<td>Radiation</td>
<td>15</td>
</tr>
<tr>
<td>8, margins &lt;3 mm</td>
<td>Mastectomy</td>
<td>1</td>
</tr>
<tr>
<td>9, margins ≥5 mm</td>
<td>Radiation</td>
<td>19</td>
</tr>
<tr>
<td>9, margins &lt;5 mm</td>
<td>Mastectomy</td>
<td>1</td>
</tr>
<tr>
<td>10, 11, or 12</td>
<td>Mastectomy</td>
<td>4</td>
</tr>
</tbody>
</table>

Silverstein, Lagios, JNCI mon. 41: 2010
### B-17: 12 year follow-up

Recurrent DCIS 14.6% → 8.0%

### EORTC: Median follow-up 10.5 years

Recurrent DCIS 14% → 7%

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<td>4, 5 or 6</td>
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<td>Mastectomy</td>
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</tr>
<tr>
<td>10, 11, or 12</td>
<td>Mastectomy</td>
<td>4</td>
</tr>
</tbody>
</table>
Studies omitting radiation in low risk DCIS

Recurrence rates following BCS for DCIS have steadily declined since the initiation of the 4 randomized RT trials

- Wong
- RTOG 9804
- ECOG 5194
Wong: 10-year local recurrence of 15.6%

- 143 patients
- 1995 to 2002
- Predominantly low- to intermediate-grade DCIS ≤ 2.5 cm undergoing BCS without RT
- Margins ≥ 1 cm
- No tamoxifen

Randomized 636 patients to RT or not

- Low/intermediate grade DCIS measuring \( \leq 2.5 \text{ cm} \) and with \( \geq 3 \text{ mm} \) margins

- 62\% of the women took tamoxifen

- At 7 years, the local recurrence rate was 0.9\% in the RT arm vs. 6.7\% in the observation arm

McCormick et al. J Clin Oncol. 2015
Single arm observational study
711 DCIS patients enrolled 1997-2002
Lumpectomy with negative margins (3 mm)
Tamoxifen allowed
Median f/u: 6.5 years
Two cohorts:
- High nuclear grade, ≤ 1 cm
- Low-intermediate nuclear grade, ≤ 2.5 cm
  (Limited or no foci of necrosis)

Hughes, JCO, 2009
## ECOG 5194/NCCTG: Omission of RT for “Good Risk” DCIS Results

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age* (yr)</th>
<th>Size* (mm)</th>
<th>% Tam</th>
<th>% Ipsilateral recurrences 5 yr</th>
<th>% Ipsilateral recurrences 7 yr</th>
<th>% Contralateral events 5 yr</th>
<th>% Contralateral events 7 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High grade</strong></td>
<td>105</td>
<td>59</td>
<td>5 (1-25)</td>
<td>31.3</td>
<td>15.3</td>
<td>18</td>
<td>3.9</td>
<td>7.4</td>
</tr>
<tr>
<td><strong>Low-intermed grade</strong></td>
<td>565</td>
<td>60</td>
<td>5 (2-10)</td>
<td>28.6</td>
<td>6.1</td>
<td>10.5</td>
<td>3.7</td>
<td>4.8</td>
</tr>
</tbody>
</table>

* median

Hughes, JCO, 2009
Predicting Local Recurrence

- DCIS nomogram
- Oncotype DCIS score
- DCISionRT-7 biomarkers and 4 clinical factors (age, size, margin and palpability) - PREDICT registry
Age at Diagnosis
Enter age at the time of diagnosis.

Family History?
Select YES if there are first- (e.g., mother or sister) or second-degree (e.g., paternal aunt or grandmother) relatives with breast cancer.

Presentation
Select Clinical if there was an abnormality on physical examination; select Radiologic if an abnormality was seen only on breast imaging studies (e.g., mammography).

Adjuvant Radiation Therapy?
Select YES if radiation therapy is given after breast-conserving surgery.

Adjuvant Endocrine Therapy?
Select YES if anti-estrogen treatment (e.g., tamoxifen, raloxifene).

Nuclear Grade
Select the nuclear grade from the pathology report. (Low = slight or no variation in the size and shape of the cell nuclei; Intermediate/High = moderate to marked variation in the size and shape of the cell nuclei.)

Necrosis?
Select YES if the pathology report states that there was necrosis associated with the DCIS.

Surgical Margins
Select “Negative” if there is a margin width of at least 2 mm. Select “Positive or Close” if margin width is 2 mm or less.

Number of Surgical Excisions
Indicate the number of surgical excisions that were required.

Year of Surgery
Indicate the year surgery was performed.
ECOG 5194: DCIS Recurrence Score

- A genomic based score to predict local recurrence
- Collaboration between: ECOG, NCCTG, and Genomic Health
- Development based on a subset of genes from *Oncotype DX* Recurrence score that were prognostic with and without tamoxifen

Solin et al, SABC 2011
Oncotype DCIS

Panel of 12 genes

**Proliferation group**
- Ki67
- STK15
- Survivin
- CCNB1 (cyclin B1)
- MYBL2

**Hormone receptor group**
- PR

**Reference group**
- ACTB (β-actin)
- GAPDH
- RPLPO
- GUS
- TFRC

GSTM1
Ten year ipsilateral in-breast recurrence by DCIS Score

Solin et al, JNCI 2013
Oncotype DCIS Score

The magnitude of the effect (i.e., hazard ratio) of age, multifocality, tumor size, and DCIS architecture were all greater than that of the DCIS score.
PreludeDX

- SweDCIS trial (n=1046; 1987-1999)
- BCS randomized to RT vs not
- PreludeDX performed in 584 cases
  - Her2, PR, Ki67, COX2, p16/INK4A, FoxA1, SIAH2

### 10-year RT benefit

<table>
<thead>
<tr>
<th>Decision Score Risk Groups</th>
<th>Invasive Breast Cancer (IBC)</th>
<th>n</th>
<th>Absolute RT Benefit</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk (DS≤3)</td>
<td></td>
<td>243</td>
<td>1%</td>
<td>0.84 [0.32 to 2.22]</td>
<td>0.70</td>
</tr>
<tr>
<td>Elevated Risk (DS&gt;3)</td>
<td></td>
<td>263</td>
<td>9%</td>
<td>0.24 [0.08 to 0.76]</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Warnberg F, SABCS, 2017
Is DCIS Cancer?

A neoplasm or cancer is an abnormal mass of tissue, the growth of which is in excess of and uncoordinated with that of normal tissue and whose growth continues in the same excessive manner after removal of the stimulus which evoked the change.
Is DCIS Cancer?

- The cells are
  - The behavior is not
    - Lacks invasion
    - Lacks metastasis
Should we abandon the word “carcinoma” associated with DCIS?
Because of the noninvasive nature of DCIS, coupled with its favorable prognosis, strong consideration should be given to remove the anxiety-producing term "carcinoma" from the description of DCIS.
CONFUSED?

Stolen (with permission) from Yvonne Ottaviano, MD
Lumpectomy without lymph node surgery without radiation therapy (category 2B)

Whole-breast radiation therapy following lumpectomy reduces recurrence in DCIS by about 50%. Approximately half of the recurrences are invasive and half are DCIS. A number of factors determine that local recurrence risk: palpable mass, larger size, higher grade, close or involved margins, and age <50 years. If the patient and the physician view the individual risk as “low”, some patients may be treated by excision alone. Data evaluating the three local treatments show no differences in patient survival.
Goal of lumpectomy margin evaluation in DCIS

- Identify patients who are *unlikely* to have a large residual tumor burden who are suitable for BCS without further surgery
- Identify patients who are *likely* to have a large residual tumor burden and require re-excision or mastectomy
Margins of at least 2 mm are associated with a reduced risk of local recurrence relative to narrower margins in patients receiving WBRT.

The routine practice of obtaining margin widths >2 mm is not supported by the evidence.
Bayesian Analysis
Relative Odds ratio 2 mm vs 1mm vs no ink on tumor
0.72 (95% CrI 0.47-1.08)
Weak Association

Relative Odds Ratio 2 mm vs 10 mm
0.99 (95% CrI 0.61-1.64)
No significant difference
## DCIS Margins-Morrow

### Frequentist Analysis

<table>
<thead>
<tr>
<th></th>
<th>&gt; 0 or 1 mm</th>
<th>2 mm</th>
<th>3 mm</th>
<th>10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>1533</td>
<td>4902</td>
<td>470</td>
<td>978</td>
</tr>
<tr>
<td><strong>Odds Ratio</strong></td>
<td>referent</td>
<td>0.51</td>
<td>0.42</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td></td>
<td>0.31–0.85</td>
<td>0.18–0.97</td>
<td>0.33–1.08</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td></td>
<td>.01</td>
<td>.04</td>
<td>.09</td>
</tr>
</tbody>
</table>

No significant differences between 2, 3, 10 mm

p > 0.40
Clinical judgment must be used in determining whether patients with <2 mm margins require re-excision

- NSABP: “no ink on tumor”
- MSKCC: Margin width not a predictor of LRR
DCIS Margins-Morrow

Use Invasive ca guideline (no ink on tumor)

Use DCIS guideline (2 mm)

Invasive ca with EIC

DCIS with microinvasion

Pure DCIS

Pure Invasive ca
Prospective Studies of Observation in Low-Risk DCIS

- LORIS
  - Surgery versus Active Monitoring for Low-Risk DCIS
- LORD
  - Low Risk DCIS
- COMET
  - Comparison of Operative to Medical Endocrine Therapy for Low Risk DCIS
Newly diagnosed (by core biopsy) clinically “low risk” DCIS

Primary outcome: ipsilateral invasive cancer-free survival

Randomization: Guideline concordant care (GCC) (surgery and/or RT) vs active surveillance (AS)

Intervene if evidence of progression to invasive cancer

Eligibility criteria:
- Age >50
- Grade I/II DCIS
- No invasion
- ER(+) and/or PR(+)
- HER2(-)
- No mass on PE or imaging

Endpoints:
- 5-year invasive cancer dx
- 5-year mastectomy rate
- 5-year OS, DSS
- PRO endpoints (QOL, fear of cancer recurrence, body image)
Registered and randomized (n=1,200)

- GROUP 1: GCC (n=450)
  - Surgery +/- Radiation choice for endocrine therapy
  - MMG q 12 months x 5 years Usual care for recurrent disease

- GROUP 1: AS (n=450)
  - choice for endocrine therapy
  - MMG q 6 months x 5 years GCC for invasive progression

- GROUP 2: Randomized but declined allocated arm (n=300)
  - GCC or AS
  - Follow up per usual care
The Future

- Combine known clinical and biologic risk factors
- Continue to develop tests that can predict which lesions will become invasive, likely based on the genetic make-up (Integrin αvβ6, P13K pathways, Cox-2, p16, etc)
- Could we predict the timeframe to invasion?
- Not one size fits all
Options

- Observation
- Endocrine therapy (ER+, low-grade)
- Wide local excision
- Wide local excision + RT
- Mastectomy
DCIS has a high probability of long-term disease-free survival and all current therapies have short- and long-term side effects.
Thank you!