In situ breast carcinoma

*DCIS and LCIS*

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Case 1

• 66F with MMG-detected 1.5cm area of pleomorphic calcifications in the left breast
• Stereotactic biopsy demonstrates DCIS, high nuclear grade, ER 90%, PR 5%
• Lumpectomy is performed and demonstrates DCIS with positive superior and medial margins
• Reexcision demonstrates positive margins
• Pt opts for mastectomy
Case 1

- Can she have reconstruction?
- Any further therapy?
In situ breast carcinoma

Abnormal cells confined to the lobules, no invasion through basement membrane

Malignant cells confined to the ductal lumen, no invasion through duct basement membrane
**DCIS grading**

**Grade 1:** Monotonous cell nuclei, 1.5 to 2.0 red blood cells in diameter; finely dispersed chromatin & only occasional nucleoli.

**Grade 2:** Neither nuclear grade 1 nor nuclear grade 3.

**Grade 3:** Markedly pleomorphic nuclei, usually greater than 2.5 red blood cells in diameter; coarse chromatin & prominent or multiple nucleoli.
Ductal carcinoma in situ

• Stage 0, Tis breast cancer
• Excellent prognosis with 98% 10 year breast cancer specific survival
• Makes up 20-25% of all breast cancer diagnoses
  – 60,000 cases annually in the U.S.
• Incidence increasing with better/more screening
• No metastatic potential

Why is it called cancer?
Why do we care about picking it up?
Why is it called cancer?

• Some DCIS progresses to invasive cancer if left untreated
  – Limited natural history data
  – Some studies demonstrate 40-50% progress to invasive disease

• Some may be indolent and a risk marker

• We are unable to predict which DCIS will progress to invasive cancer and at what time interval
Why do we care about picking it up?

• Rule out that there is an invasive cancer
  – Sampling error from needle biopsy
  – 20% risk of underlying invasive cancer
  – Grade associated
  – Most are T1

• Screen aggressively and treat all DCIS aggressively to prevent risk of invasive cancer events
Presentation

- Mammographic calcifications
- Rarely mass-forming
Workup

- Stereotactic biopsy
- MRI not helpful in most instances
- Genetic counseling/testing as indicated
  - NCCN criteria
Treatment

• Surgery

• Radiation therapy

• Endocrine therapy
Treatment - Surgery

• Lumpectomy/XRT (Breast conserving surgery)
  – Localized
  – Tumor to breast ratio compatible with good cosmesis
  – No contraindication to radiation therapy

• Mastectomy
  – Multicentric
  – Tumor to breast ratio not compatible with good cosmesis
  – Unable to clear margins
Sentinel lymph node biopsy

• Not necessary in most cases and DCIS cannot invade ducts and cross into lymphatics

• Indications
  – Mass-lesion
  – Mastectomy
Radiation therapy

• Only needed after lumpectomy to treat remaining breast
• 6 weeks, 5 days a week
• Post-mastectomy rarely needed, consider if multiple positive margins
Early Breast Cancer Trialists’ Collaborative Group

XRT for DCIS

• Question:
  – Examine whether there is utility to adding RT to BCS for DCIS

• Methods:
  – Meta-analysis of 4 randomized trials of RT vs. no RT following BCS
  – 3729 women
  – 1985-1990

EBCTCG, J Natl Cancer Inst Monogr 2010;41:162-177
## Results

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>F/U</th>
<th>LR No RT (%)</th>
<th>LR RT (%)</th>
<th>% risk reduction</th>
<th>P-Value</th>
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<td>NSABP B17</td>
<td>813</td>
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<td>15</td>
<td>47</td>
<td>&lt;0.0001</td>
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<td>UK/ANZ</td>
<td>1030</td>
<td>Crude incidence</td>
<td>14</td>
<td>6</td>
<td>62</td>
<td>&lt;0.0001</td>
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<tr>
<td>Swedish</td>
<td>1046</td>
<td>5.2 yr</td>
<td>22</td>
<td>7</td>
<td>67</td>
<td>&lt;0.0001</td>
</tr>
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</table>

All 4 trials demonstrated a significant reduction in ipsilateral breast recurrences

Fisher et al *NEJM* 1993;328:1581-6
Emdin et al *Acta Oncol* 2006;45(5):536-45
Bijker et al *J Clin Oncol* 2006;24:3381
Results

• Reduced absolute 10-year risk of any ipsilateral breast event by 15.2% (SE 1.6%, 12.9-28.1%, p<.00001)
  - Regardless of age at diagnosis, extent of BCS, use of tamoxifen, margin status, focality, grade, size
• Relative risk reduction of 50%
• No significant effect on breast cancer mortality
• Adding RT to BCS for DCIS reduces local recurrence and has no effect on survival

EBCTCG, J Natl Cancer Inst Monogr 2010;41:162-177
Can we eliminate radiation by taking larger margins?

- No consensus on appropriate margin size
- A retrospective study suggested that 1cm margins resulted in local control equivalent to lumpectomy with XRT
- Two prospective studies attempted to duplicate the results and failed
- Even widely excised high grade DCIS had a high risk of local recurrence with excision alone
- Other studies demonstrated high recurrence rates with grade 1 and 2 lesions as well
- Most use 2mm as sufficient and recommend radiation routinely

Silverstein et al., NEJM 1999.
Systemic therapy?

• No potential for metastasis
Endocrine therapy

- Endocrine therapy reduces local recurrence
Question

Does tamoxifen reduce LR in DCIS? By how much?

When should tamoxifen be used in the treatment of DCIS?
Tamoxifen for DCIS

• Tamoxifen usage in DCIS is low
  – Analysis of SEER database found that only 20.6% of patients with DCIS received tamoxifen in 2005

• UK, Australia and New Zealand DCIS trial
  – Tamoxifen reduced the incidence of all new breast events, ipsilateral DCIS, contralateral tumors
  – No effect on ipsilateral invasive disease

• NSABP B-24 RCT showed that tamoxifen use resulted in a 37% relative reduction of all breast cancer events and a 32% relative risk reduction of ipsilateral breast cancer events
  – Compared 900 patients treated with lumpectomy/RT/placebo vs. 899 patients treated with lumpectomy/RT/tamoxifen

• The NSABP B-24 patient population included those with ER-positive and ER-negative DCIS

Retrospective subset analysis of NSABP B-24

- ER and PR status was evaluated in 732 patients with DCIS (41% of the original study population)
  - IHC at a central lab on all available paraffin blocks (n = 449)
  - Additional 283 patient samples evaluated by various methods

- Evaluated benefit of tamoxifen by receptor status at 10 years and overall follow-up (median of 14.5 years)

Breast cancer development by ER status and type of DCIS treatment, overall follow-up

- ER was positive in 76% of patients

<table>
<thead>
<tr>
<th>Type of BC</th>
<th>Placebo (n = 368)</th>
<th>Tamoxifen (n = 364)</th>
<th>Absolute difference</th>
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<tr>
<td><strong>ER positive</strong></td>
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<tr>
<td>Any</td>
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<td>No.</td>
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<td>BC</td>
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<td>31</td>
<td>58</td>
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<td>19</td>
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<tr>
<td>DCIS</td>
<td>32</td>
<td>12</td>
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<tr>
<td><strong>Ipsilateral</strong></td>
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</tr>
<tr>
<td>BC</td>
<td>47</td>
<td>17</td>
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</tr>
<tr>
<td>IBC</td>
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<tr>
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<tr>
<td><strong>Contralateral</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>BC</td>
<td>32</td>
<td>11</td>
<td>18</td>
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<td>12</td>
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<tr>
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</table>

Breast cancer development by ER status and type of DCIS treatment, overall follow-up

- There were no significant reductions associated with ER-negative DCIS

<table>
<thead>
<tr>
<th>Type of BC</th>
<th>Placebo (n = 368)</th>
<th>Tamoxifen (n = 364)</th>
<th>HR*</th>
<th>95% CI</th>
<th>P†</th>
<th>Absolute difference</th>
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<tr>
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<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td></td>
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<tr>
<td>ER negative</td>
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<td>BC</td>
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<td>1</td>
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<td>0.07 to 18.44</td>
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</table>

Tamoxifen reduced CBC in patients with ER-negative DCIS

+4%
Risk of subsequent breast cancer

- Reduction of subsequent breast cancer was restricted to ER-positive DCIS treated with tamoxifen

- Tamoxifen usage resulted in a 42% relative risk reduction of ipsilateral and contralateral breast cancer events in ER-positive DCIS

Treatment

• Surgery

• Radiation therapy

• Endocrine therapy
Recurrence risk

• Local recurrence after lumpectomy alone is 25-35% at 10 years
• Local recurrence after breast conserving therapy is 10-20% at 10 years
• Local recurrence after mastectomy is 1.4% at 10 years
• 50% of recurrences are DCIS
• 50% are invasive
Management of recurrence

• Rule out distant metastases if invasive
Surgical treatment of recurrence

- If prior breast conserving therapy, mastectomy
- If prior mastectomy, wide local excision
But...

- Lack of survival difference with XRT
- Lack of survival difference with tamoxifen
‘What if I decide to just do nothing?’

Breast cancer’s new frontier
By Siobhan O’Connor
What if I do nothing?

• Eliminate surgery
  – No predictors of which DCIS will progress to invasive cancer
  – No prediction of which DCIS already harbors invasive cancer (20%)

• Eliminate radiation

• Eliminate endocrine therapy
Which DCIS will progress to invasive cancer?

• We don’t know

• We need molecular predictors of which lesions will progress to invasive carcinoma
Nomogram for predicting the risk of local recurrence in DCIS

Oncotype DX DCIS Score

• Multigene expression assay
  – 7 cancer genes, 5 reference genes
• Estimates 10 year risk of ipsilateral breast tumor recurrence (DCIS or invasive)
• Does not predict response to radiation therapy
• Expensive
DCIS observation trials

• 2 European trials:

• LORIS
  – Low-risk DCIS: Age 46 or older, no significant FH or personal history, screen-detected calcifications, asymptomatic, non-high grade DCIS
  – Surgery vs. observation alone

• LORD
  – Not started recruiting patients yet
MSKCC study

- Retrospectively analyzed patients meeting eligibility for LORIS
- 20% had invasion on final pathology
- Not all early, ER positive

Case 2

- 44F with MMG-detected 5mm area of branching calcifications in the right breast
- Stereotactic biopsy demonstrates DCIS, low nuclear grade, ER negative, PR negative
- Post-biopsy MMG demonstrates no residual calcifications
- Does she need surgery?
- Any testing prior to surgery?
Case 2

• Surgical pathology demonstrates biopsy site changes but no residual DCIS or invasive carcinoma

• Any further therapy?
LCIS

- Risk indicator
- Either breast
- 30-40% lifetime risk vs. 12.5% for average woman
Presentation

• Abnormal mammogram
• Biopsy
Management

• Surveillance
  – Annual MMG
  – Annual MRI

• Endocrine therapy
  – Tamoxifen
  – Aromatase inhibitor
Surgery

• Not concordant biopsy
• Pleomorphic LCIS
  – Excise because of risk of concomitant invasive malignancy
Case 3

- 50 premenopausal female with strong FH of breast cancer s/p excision of a mass in her breast
- Pathology demonstrates benign fibroadenoma with LCIS incidentally noted
- Does she need further surgery?
- Any further therapy?