DCIS

Clinical Case Conference
Overview

• Patient case
• Introduction (pathophysiology, epidemiology, histology)
• Treatment/evidence
  – Mastectomy
  – Lumpectomy
  – Radiation
  – Tamoxifen
• Prognostication tools
• ML treatment plan
Case

- 57 yo female diagnosed with DCIS on screening mammogram
- 8/25/13 screening mammogram showed new clustered polymorphic calcifications in the left posterior central region of the left breast
- 8/30/13 left diagnostic mammogram showed cluster of calcifications in upper outer quadrant (UOQ)
- 9/6/13 stereotactic core biopsy performed. Pathology showed DCIS, nuclear grade 3, solid with comedonecrosis and microcalcifications, involving multiple cores. No invasive cancer was identified.
- 9/16/13 MRI showed 1.8cm linear area of non-mass-like enhancement in UOQ, appeared to correspond with biopsy-proven lesion.
- 9/26/13 left wire localized lumpectomy by Dr. Jeannie Shen (UCLA Pasadena Oncology). Pathology showed DCIS with solid and cribriform pattern and grade 2 nuclei, measuring 1.2cm with no invasive component. Closest margin deep at 0.3mm.
- Re-excision of left breast inferior, medial, deep cup showed no residual DCIS. Final inked margins inferior 16.2 mm, medial 25mm, and deep 11.3mm. ER was weakly positive (5% of neoplastic cells are 2-3+) and PR was negative (very rare neoplastic nucleus is 1+).
Pathophysiology

- **Ductal Carcinoma in situ (DCIS)** – neoplastic process confined entirely to the duct system of the breast
- Does not disrupt the basement membrane or involve the breast stroma
- Thought to be direct precursor of invasive breast CA
- Risk factors same as invasive disease – family hx, nulliparity, hx of breast bx, alcohol
- Associated with increased risk of invasive cancer in ipsilateral or contralateral breast
Epidemiology

Large increase in DCIS diagnosis since mid-1970s with introduction of screening mammography

- Palpable breast cancer usually has focus of invasion, rarely pure DCIS
- Incidence rose from 4,800 cases in 1983 to 50,000 annually \(\rightarrow\) 10-fold increase in only 20 years
- Of 215,990 cases of breast cancer diagnosed in 2004, 59,390 were **noninvasive, of which 85% were DCIS** (Jemal et al; *Cancer J Clin* 2004)
- 90% of DCIS seen on mammography today is nonpalpable
- Incidence of DCIS per 1,000 mammograms:
  - 0.56 in 40-49yo
  - 1.07 in 70-84yo
Diagnostic Imaging

- **Mammography**
  - 90% microcalcifications
    - Linear and branching more likely high-grade DCIS, necrosis
    - Fine and granular more likely low-grade DCIS
  - 10% asymmetric density
  - Size on mammography typically underestimated by 1-2 cm compared to pathology

- **MRI**
  - Started being used in 2000
  - Better estimate of size
  - Berg WA et al *JAMA* 2012 showed higher sensitivity, but lower specificity

Perez 5th edition
Histologic Classification

- Architecture: Solid, micropapillary, papillary, cribriform, comedo

- Low grade, non-comedo can be difficult to distinguish from ADH

- Other important features: nuclear grade, necrosis, margins, lesion size, microcalcifications

Perez 5th edition
Growth Pattern

• Less than 2% of cases have multicentric patterns
• Of the discontinuous cases:
  • 63% of foci separated by <5 mm
  • 83% separated by <10 mm
  • 8% > 10 mm
• 90% of poorly differentiated tumors are continuous (no gaps)
• Based on this data, surgical margins of 1 cm should completely excise 90% of tumors

Perez 6th edition
Natural History

- Autopsy series review of women not known to have breast cancer during life → median prevalence of DCIS 8.9% (range 0-15%)
- Only a few studies have looked at the progression of DCIS to invasive carcinoma after biopsy alone
- Studies show that most subsequent malignancies occur within 10 years
- Women with DCIS in one breast are at risk for developing a second tumor in contralateral breast at a rate of 0.5% to 1% per year

Perez 6th edition
Treatment Overview

- Surgical resection is primary therapy
  - Mastectomy or breast conservation surgery (BCS)?
- Radiation therapy can be given adjuvantly
  - PORT after mastectomy?
  - Adjuvant RT after BCS?
- Adjuvant systemic therapy?
  - Hormone therapy?
  - Chemo?
Mastectomy

- Mastectomy was historically first-line choice
  - Recall that this began prior to mammography—DCIS often was presenting as a mass, and many cases turned out to be early invasive breast cancer
  - Curative for >98% of patients with DCIS
- Breast conservation surgery (i.e., BCS, “lumpectomy”)
  - Introduced in 1980s for early stage breast cancer and adopted for DCIS as well
  - BCT = BCS + adjuvant RT
- No randomized trials to compare mastectomy vs BCT
Mastectomy vs Lumpectomy

• Schouten van der Velden et al. *IJROBP* 2007
• Retrospective study
• Aim: to assess the risk of local recurrences after different treatment strategies for DCIS and to determine whether RT decreased the risk of local recurrences
• 798 patients with DCIS
  – Treated 1989-2003
• RESULTS: 5-year recurrence-free survival
  – 75% lumpectomy alone
  – 91% for BCS+RT
  – 99% for mastectomy
Mastectomy vs Lumpectomy

- Retrospective study for DCIS pts treated at Netherlands Cancer Institute 1986-2005
- 504 pts
  - 94 WLE
  - 119 WLE+RT
  - 294 mastectomy
- Median f/u 6.7 years
- 8yr LRR
  - 15.6% WLE
  - 8.8% WLE+RT (p=0.16)
  - 0.9% mastectomy

**FIG. 1.** Time to local recurrence by treatment. WLE, wide local excision; WLE+RT, wide local excision with radiotherapy; O, observed; N, number of patients.
Mastectomy vs Lumpectomy

- BCT has higher local recurrence rates
- But survival is not improved with mastectomy
  - Multiple retrospective reports:
    - Fisher et al. Semin Oncol. 2001 (NSABP experience)
    - Solin et al. Cancer 2005
    - Vargas et al. IJROBP 2005
    - Cutuli et al. IJROBP 2002
    - Wapnir et al. JNCI 2011
- Given the morbidity difference, mastectomy is considered by many to be overtreatment for DCIS
  - ~30% of patients still get mastectomy in U.S. (vs 40% BCS+RT and 30% BCS alone)
RT or no RT after BCS?

- Four large prospective trials started 1985-1990:
  - NSABP B-17
  - EORTC 10853
  - SweDCIS
  - UK/ANZ
EBCTCG Meta-analysis *(JNCIM 2010)*

<table>
<thead>
<tr>
<th>Year code, study name (reference)</th>
<th>Entry dates</th>
<th>No. of women randomized</th>
<th>No. of women eligible for analysis†</th>
<th>Median follow-up (yr)</th>
<th>Mammo-graphic detection (%)</th>
<th>Breast and axillary surgery</th>
<th>Negative surgical margins required</th>
<th>Central pathological review</th>
<th>Breast radiotherapy</th>
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<tbody>
<tr>
<td>Data available for overview</td>
<td></td>
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</tr>
<tr>
<td>NSABP B-17 (3, 4, 5)</td>
<td>1985–1990</td>
<td>818</td>
<td>798</td>
<td>16.5</td>
<td>80</td>
<td>Local excision</td>
<td>Yes</td>
<td>623 (76%)</td>
<td>50 Gy (2 Gy/f) 9% with boost</td>
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<tr>
<td>EORTC 10853 (6, 7, 8, 9)</td>
<td>1986–1996</td>
<td>1010</td>
<td>918</td>
<td>10.4</td>
<td>72</td>
<td>Local excision</td>
<td>Yes</td>
<td>824 (82%)</td>
<td>50 Gy (2 Gy/f) 5% with boost</td>
</tr>
<tr>
<td>SweDCIS (10, 11, 12)</td>
<td>1997–1999</td>
<td>1087</td>
<td>1011</td>
<td>8.4</td>
<td>79</td>
<td>Sector resection</td>
<td>No</td>
<td>271 (25%)</td>
<td>50 Gy (2 Gy/f) (80%) or 48 Gy (2.4 Gy/f) (13%) or 54 Gy (2 Gy/f) then 2 wk gap (7%) Boost not recommended</td>
</tr>
<tr>
<td>UK/ANZ DCIS (13)</td>
<td>1990–1998</td>
<td>1030</td>
<td>1002</td>
<td>4.8</td>
<td></td>
<td>Local excision</td>
<td>Yes</td>
<td>0 (0%)</td>
<td>50 Gy (2 Gy/f) Boost not recommended</td>
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</table>
EBCTCG Meta-analysis *(JNCIM 2010)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Events/women Allocated BCS + RT</th>
<th>Allocated BCS</th>
<th>BCS + RT events Logrank Variance O—E</th>
<th>Ratio of annual event rates BCS + RT : BCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-17</td>
<td>78/400 (19.5%)</td>
<td>139/398 (34.9%)</td>
<td>-36.8</td>
<td>0.49 (SE 0.10)</td>
</tr>
<tr>
<td>EORTC 10853</td>
<td>64/462 (13.9%)</td>
<td>118/456 (25.9%)</td>
<td>-28.8</td>
<td>0.52 (SE 0.11)</td>
</tr>
<tr>
<td>SweDCIS</td>
<td>59/511 (11.5%)</td>
<td>131/500 (26.2%)</td>
<td>-41.3</td>
<td>0.41 (SE 0.10)</td>
</tr>
<tr>
<td>UK/ANZ DCIS</td>
<td>28/505 (5.5%)</td>
<td>67/497 (13.5%)</td>
<td>-20.5</td>
<td>0.41 (SE 0.14)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>229/1878 (12.2%)</strong></td>
<td><strong>455/1851 (24.6%)</strong></td>
<td><strong>-127.4</strong></td>
<td><strong>0.46 (SE 0.05)</strong></td>
</tr>
</tbody>
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Heterogeneity between 4 trials: $\chi^2 = 2.0; P = 0.6$

BCS + RT better | BCS + RT worse

Treatment effect $2P < 0.00001$
EBCTCG Meta-analysis (JNCIM 2010)

- 3,729 women from 4 RCTs

- ARR regardless of:
  - age at diagnosis
  - extent of breast-conserving surgery
  - use of tamoxifen (only 15%)
  - method of DCIS detection
  - margin status → CLOSE margin (<2mm) was categorized as NEGATIVE
  - Focality
  - Grade
  - Comedonecrosis
  - Architecture
  - Tumor size

**Absolute risk reduction of IBTR**

- 5-yr gain 10.5% (SE 1.2)
- 10-yr gain 15.2% (SE 1.6)
- logrank 2P < 0.00001
CLOSE margin (<2mm) was categorized as NEGATIVE for this review.
NSABP B17


- 1985-1990
- 818 patients with DCIS
  - Margins “histologically tumor-free”
- Lumpectomy +/- RT
  - 50Gy/25 whole breast
  - only 9% had RT boost to tumor bed
- Main endpoint: local recurrence, invasive or intraductal
• 5yr event free survival = 84.4% vs. 73.8%
  – Lumpectomy alone = 64/391 IBTR $\rightarrow$ 32 non-invasive, 32 invasive
  – Lump+RT = 28/399 IBTR $\rightarrow$ 20 non-invasive, 8 invasive
  – Non-invasive 10.4% to 7.5% (p=0.055)
  – Invasive 10.5% to 2.9%
• This difference has remained at 12-year follow-up
ECOG DCIS Trial

- 1997-2002
- Prospective, nonrandomized
- 670 patients treated with lumpectomy alone
- Eligible:
  - Non-palpable
  - Size:
    - At least 3mm
    - low- or intermediate-grade DCIS measuring ≤2.5 cm (565 patients)
    - high-grade DCIS measuring ≤ 1 cm (105 patients)
  - Margin ≥3 mm
  - No residual calcs on post-op mammogram
- Patients entered in 2000 and later could opt for tamoxifen
ECOG DCIS Trial

- Median age 60yo (at last surgery)
- Median tumor size in two strata were 6 mm and 5 mm*
- Median follow-up of 6.3 years
- 12% took Tamoxifen

- 5-year rate of ipsilateral breast events:
  - 6.1% in low/intermediate grade
  - 15.3% in high grade

- CONCLUSION: appears safe to omit RT for grade 1-2 and small lesions with good margin
ECOG DCIS Trial

LOW-INTERMEDIATE GRADE

- IBE
  - 5-year rate: 6.1% (95% CI: 4.1% to 8.2%)
  - 7-year rate: 10.5% (95% CI: 7.5% to 13.6%)

- Contralateral BE
  - 5-year rate: 3.7% (95% CI: 2.0% to 5.3%)
  - 7-year rate: 4.8% (95% CI: 2.7% to 6.9%)

HIGH GRADE

- IBE
  - 5-year rate: 15.3% (95% CI: 8.2% to 22.5%)
  - 7-year rate: 18.0% (95% CI: 10.2% to 25.9%)

- Contralateral BE
  - 5-year rate: 3.9% (95% CI: 0.15% to 7.7%)
  - 7-year rate: 7.4% (95% CI: 1.4% to 13.3%)

No. of patients at risk:

IBE
- 558
- 546
- 527
- 507
- 489
- 403
- 270
- 183

CBE
- 558
- 548
- 534
- 517
- 500
- 412
- 283
- 197

IBE
- 103
- 99
- 96
- 92
- 89
- 69
- 60
- 39

CBE
- 103
- 102
- 100
- 97
- 96
- 78
- 60
- 41
ECOG DCIS Trial 12 year follow-up

- Grade 1-2 DCIS <2.5cm had ipsilateral breast event rate of 14.4% (Cohort 1)
- Grade 3 <1cm had event rate 24.6% (Cohort 2), noting no plateau and again 50% of recurrences being invasive.
DCIS “Receptor” Status

- ER+ in 70%, more often in low-grade
- HER2+ in 50%, more often in high-grade
Role of Tamoxifen in DCIS

• Selective estrogen receptor modulator (SERM)
  • Widely used in adjuvant treatment for women with hormone receptor positive invasive breast cancer
  • SERMs have estrogen agonist AND antagonist effects
    • Anti-estrogen effect in breast, CNS, and vagina mucosa
    • Pro-estrogen effect in liver (↓cholesterol), bone, and endometrium
RTOG 98-04

- McCormick et al IJROBP 2012
  - 585 patients eligible for analysis, median f/u 7.2 years
  - 62% received tamoxifen (was optional)
- Closed early due to low accrual
- Results at 7 years
  - Local failure 6.4% for observation vs 0.9% for RT
  - 12/18 failures in obs arm in same quadrant, but neither of the 2 failures in RT arm was in same quadrant
  - Grade 1-2 acute toxicity: 30% vs 76%
  - Grade 3 acute toxicity: 4.0% vs 4.2%

Phase III trial of observation versus radiation therapy for good risk DCIS

Stratification:
age, grade, pathologic margins, and mammographic size

Observation
(± tamoxifen)

Radiation therapy to the whole breast
(± tamoxifen)
UK Trial

- 1701 women underwent excision of DCIS with clear margins (1990-98) and randomly assigned to 2x2 factorial design:
  - Excision alone
  - Excision plus RT (50 Gy)
  - Excision plus tamoxifen
  - Excision plus RT plus tamoxifen

- 53 month follow-up results:
  - Observation 22%
  - TAM alone 18%
  - RT alone 8%
  - TAM+RT 6%

*46% of patients chose one therapy, were randomized only to +/- second therapy

Houghton *Lancet* 2003
UK Trial: Tamoxifen

- Benefit for **bilateral DCIS**
- No synergy with RT

<table>
<thead>
<tr>
<th>Patients not receiving radiotherapy (1053)</th>
<th>Randomised to tamoxifen (n=794)</th>
<th>Randomised to no tamoxifen (n=782)</th>
<th>Hazard ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral invasive</td>
<td>37 (5%)</td>
<td>29 (4%)</td>
<td>1.32 (0.81–2.14)</td>
<td>0.26</td>
</tr>
<tr>
<td>Ipsilateral DCIS</td>
<td>50 (6%)</td>
<td>68 (9%)</td>
<td>0.73 (0.51–1.06)</td>
<td>0.10</td>
</tr>
<tr>
<td>Total invasive</td>
<td>42 (5%)</td>
<td>39 (5%)</td>
<td>1.11 (0.72–1.72)</td>
<td>0.64</td>
</tr>
<tr>
<td>Total DCIS</td>
<td>51 (6%)</td>
<td>75 (10%)</td>
<td>0.68 (0.47–0.97)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients receiving radiotherapy (523)</th>
<th>Randomised to tamoxifen</th>
<th>Randomised to no tamoxifen</th>
<th>Hazard ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral invasive</td>
<td>8 (1%)</td>
<td>6 (1%)</td>
<td>1.25 (0.43–3.61)</td>
<td>0.68</td>
</tr>
<tr>
<td>Ipsilateral DCIS</td>
<td>7 (1%)</td>
<td>9 (1%)</td>
<td>0.75 (0.28–2.02)</td>
<td>0.57</td>
</tr>
<tr>
<td>Total invasive</td>
<td>13 (2%)</td>
<td>11 (1%)</td>
<td>1.11 (0.50–2.48)</td>
<td>0.80</td>
</tr>
<tr>
<td>Total DCIS</td>
<td>7 (1%)</td>
<td>9 (1%)</td>
<td>0.75 (0.28–2.02)</td>
<td>0.57</td>
</tr>
<tr>
<td>Total invasive</td>
<td>20 (3%)</td>
<td>20 (3%)</td>
<td>0.95 (0.51–1.77)</td>
<td>0.88</td>
</tr>
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Houghton *Lancet* 2003
NSABP B-24

- 1804 women with DCIS undergoing lumpectomy + RT
  - RT 50Gy, no boost
- Prospective, randomized to adjuvant tamoxifen or placebo
- Stratified by age, tumor type, method of detection
  - 81-84% mammographically detected

- Tamoxifen reduced breast recurrence 13.4% → 8.2%
  → but included 16% with positive margins
  → absolute difference not much larger than in UK trial
- Overall survival at 7 years was same
Tamoxifen Adherence

**NSABP B-24**
- **31%** of patients discontinued treatment
  - 269 in placebo group, 295 in tamoxifen group
- **Why?**
  - Side effects *(98 placebo, 146 tamoxifen)*
  - Personal reasons *(146 placebo, 124 tamoxifen)*
  - Unspecified reasons *(25 placebo, 25 tamoxifen)*

**UK Trial**
- Of 794 patients randomised to tamoxifen, 86 *(11%)* stopped early
- 56/86 patients had taken at least 2 years of treatment
NSABP B-43

• First prospective, randomized phase III multi-institution international clinical trial targeting HER2+ DCIS
• BCS followed by:
  – RT alone vs. RT + concurrent trastuzumab
• Eligible: >18yo, ECOG 0-1, DCIS excised with negative margins, pN0
• Goal to reduce IBTR, increase BCS

• Opened 11/9/08
• As of 7/31/2013 5,861 patients have had specimens received centrally, and 5,645 of those had analyzable blocks 1,969 (34.9 %) were HER2 positive.
Risk stratification

• USC/Van Nuys prognostic index (USC/VNPI)
  • Quantitative algorithm which uses size, margin width, age, and histologic classification to predict likelihood of local recurrence
  • Assigned scores of 1, 2, or 3 to size, margin, histologic type and came up with total
USC/Van Nuys

- 949 pts with DCIS treated at USC through 2009
  - 604 excision alone, 345 excision + RT
- No hormonal therapy
- Used the updated USC / Van Nuys scoring system (size, margin, DCIS classification, age) which gives scores 4-12
- Median f/u 86 months (7.1 yrs)
- 165 local recurrences (103 - excision alone, 62 - RT).
- 12-yr local recurrence:
  - score 4-6, ≤ 6% (NS difference for RT vs no RT)
  - score 10-12, ≥ 40% (for excision + RT)
USC/Van Nuys

New treatment recommendations to achieve a local recurrence rate of less than 20% at 12 years using the University of Southern California/Van Nuys Prognostic Index (USC/VNPI)

Caveat: Single institution study, not validated by other groups

Silverstein *JNCIM* 2010.
MSKCC Nomogram

Rudloff et al *JCO* 2010 (MSKCC) based on 1,868 consecutive DCIS pts treated with BCS

**Nomogram for predicting 5- and 10-year probability of IBTR after BCS for DCIS.** To estimate risk, calculate points for each variable by drawing a straight line from patient’s variable value to the axis labeled “Points.” Sum all points and draw a straight line from the total point axis to the 5- and 10-year local recurrence axis.
Partial Breast

• ASTRO Consensus:
  – “cautionary” for pure DCIS ≤ 3cm
  – “unsuitable” for pure DCIS > 3cm

• ABS guideline for acceptable (published July 2013)

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>Age</td>
<td>≥50 y old</td>
</tr>
<tr>
<td>Size</td>
<td>≤3 cm</td>
</tr>
<tr>
<td>Histology</td>
<td>All invasive subtypes and DCIS</td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>Positive/negative</td>
</tr>
<tr>
<td>Surgical margins</td>
<td>Negative</td>
</tr>
<tr>
<td>Lymphovascular space invasion</td>
<td>Not present</td>
</tr>
<tr>
<td>Nodal status</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Summary

• BCT is the treatment of choice for patients with localized DCIS
  – Mastectomy should be considered for women with multicentric DCIS or extensive/diffuse DCIS
  – PMRT no good evidence to support (Childs S et al. *IJROBP* 2012, Harvard)
  – 2mm path margins sufficient (Dunne et al. *JCO* 2009, meta-analysis)
• General consensus is still for RT after BCT
  – Consider *omitting* RT after BCS if small, widely excised, low-grade DCIS without necrosis
  – Currently, there is a lack of good data identifying subsets of DCIS that don’t require RT
• Tamoxifen for DCIS reduces local recurrence after BCT + RT, although benefit is small. Generally recommended for ER+ DCIS (Kaiser<UCSD)
• Herceptin for HER2+ DCIS is under study
Case

HPI:
• 57 yo F diagnosed with DCIS on screening mammogram
• 9/26/13 left wire loc lumpectomy. Pathology showed DCIS with solid and cribriform pattern and grade 2 nuclei, measuring 1.2cm.
• Closest margin after re-excision was 11.3mm. ER weakly positive (5% of cells).

ASSESSMENT: Advised patient risk of recurrence 7-10%, could omit RT. Patient opted for treatment.

PLAN: Whole breast 50Gy/25 tangents (with heart block) with boost 10Gy to tumor bed (re-scanned for boost). Completed RT with expected minimal radiation dermatitis. Patient still deciding on tamoxifen.
Heart block
Mean heart dose 110cGy
Boost

- Omlin et- Lancet 2006
  - Retrospective. 373 women age 45 or younger from 18 institutions. TisN0, <=45, BCS. 15% no RT, 45% RT 50 Gy, 40% RT 50 Gy + 10 Gy boost. Median F/U 6 years
  - LR rate: LR-free survival at 10 years: No RT 46% vs. 72% RT no boost vs. 86% RT boost (SS)
  - Predictors: age <40, margin, RT boost
  - Conclusion: consider boost in patients <=45 years
Boost and Margin Status

- Institut Curie
- Retrospective. 208 women, DCIS, BCT with close (<2 mm) or involved margins. Re-excision 29% or RT + boost 71%.
- Median RT dose 67 Gy. Median F/U 7.4 years
- Outcome: On re-excision, 56% residual DCIS and 6% residual IDC
- 7-year LRF if re-excision 9.6% vs RT + boost 9.3% (NS)
- Conclusion: In selected patients, re-excision may be avoided by increasing RT dose to tumor bed to at least 66 Gy

Monteau, IJROBP. 2009
Tumor Bed Boost

• No evidence from prospective trials for boost in DCIS
  – In fact, <10% in NSABP B-17 and EORTC, and none in UK and SweDCIS trials got boost

• Retrospective study from McGill (IJROBP 2012)
  – 220 consecutive pts treated with BCS+RT from 2000-2006
  – 36% received boost
  – Boost group more positive and <0.1-cm margins (48% vs. 8%) (p < 0.0001) and more high risk by VNPI (p = 0.006).
  – Median f/u 46 mon → 0/79 w/ boost had LR vs. 8/141 w/o boost (p = 0.03)
  – Only presence of necrosis SS on UVA (p=0.003)
  – Despite close margins and higher VNPI, boost ↓LR

• Extrapolate from invasive studies
  – Continuum of one disease?