Local-Regional Management of Early Stage Breast Cancer

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Disclosure

• I have no conflicts of interest to disclose.
Learning Objectives

• Discuss the data to support local management of ductal carcinoma in-situ +/- radiation.
• Discuss the management options of early stage, invasive breast cancer and the selection of patients for breast conserving therapy +/- radiation
• Review regional management issues in early stage breast cancer
Early Stage Question 1

1. Which of the following statements regarding administration of 5 years of tamoxifen for hormone receptor positive DCIS in the setting of breast conservation therapy is **TRUE**?

A. Tamoxifen results in an additional ~50% relative risk reduction in ipsilateral breast recurrences
B. Tamoxifen results in a ~30% relative risk reduction in contralateral breast recurrences
C. Tamoxifen results in a decrease in invasive breast recurrences, but not non-invasive recurrences
D. Tamoxifen results in a ~50% relative risk reduction in the contralateral breast
E. Tamoxifen results in a ~5% overall survival benefit
Early Stage Question 2

2. Which of the following statements regarding LRR after BCS+WBRT is TRUE?

A. The EBCTCG Meta-analysis has demonstrated a significant ↓ in LRR but no benefit in OS with the use of WBRT.
B. The Meta-analysis has shown that systemic chemotherapy has no effects on LRR but its use ↓ distant metastasis and thus improves OS
C. The Meta-analysis has demonstrated an additional benefit in ↓ LRR with the addition of chemotherapy to RT compared with RT alone.
D. Patients ≥70 with Stage I, hormone receptor+ invasive breast cancer who undergo BCS and take tamoxifen do not have a statistically significant benefit from adjuvant RT to improve LRR
E. For small invasive tumors <1cm in size, tamoxifen or RT confer equal benefits in LRR.
3. What is the approximate risk of locoregional recurrence in a patient with node positive breast cancer (cT2N1) treated with 6 months of anthracycline and taxane containing neoadjuvant chemotherapy with residual nodal disease at the time of modified radical mastectomy (2/17+ nodes)?
   a. 8%
   b. 17%
   c. 23%
   d. 30%
   e. 40%
Ductal Carcinoma
In-Situ
DCIS: Mastectomy vs. BCT

- No randomized comparisons available
- PIII data: Lumpectomy vs. Lumpectomy + WBRT
- Slight greater LR risk for DCIS with BCT (~8-12%) than mastectomy (~1-3%)
- 1%-2% breast cancer mortality regardless of treatment approach
- Since treatment is solely to prevent a local event, BCT is preferable to mastectomy in most cases
DCIS Mastectomy Indications:
DCIS: Randomized RT Trials

- Four randomized controlled trials, n>4000
  - EORTC 10853 (Bijker, *JCO* 2006)
  - SweDCIS (Holmberg, *JCO* 2008)
  - UK/ANZ (Cuzick, *Lancet Oncology* 2011)
- RT dose 50 Gy to whole breast
  - No boost on any of the trials
- Negative Margins: 3/4 trials no tumor at inked margins
  - SweDCIS: no pathologic margin requirement
    - ~20% +/- unknown margins
- Tamoxifen allowed on 1/4 trials
  - UK/ANZ – complicated 2x2 multi-arm
## DCIS Randomized RT Trials:

<table>
<thead>
<tr>
<th>Study</th>
<th>(n)</th>
<th>RT</th>
<th>+RT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSABP B-17</strong></td>
<td>813</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(17.3 year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>35%</td>
<td>20%</td>
<td></td>
<td>p&lt;0.000005</td>
</tr>
<tr>
<td>Invasive</td>
<td>20%</td>
<td>11%</td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>DCIS</td>
<td>15%</td>
<td>9%</td>
<td></td>
<td>p=0.001</td>
</tr>
<tr>
<td><strong>UK/ANZ</strong></td>
<td>1694</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(12.7-year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>21%</td>
<td>8%</td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Invasive</td>
<td>10%</td>
<td>4%</td>
<td></td>
<td>p=0.01</td>
</tr>
<tr>
<td>DCIS</td>
<td>10%</td>
<td>4%</td>
<td></td>
<td>p=0.0004</td>
</tr>
<tr>
<td><strong>EORTC 10853</strong></td>
<td>1010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10.5 year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>26%</td>
<td>15%</td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Invasive</td>
<td>13%</td>
<td>8%</td>
<td></td>
<td>p=0.0065</td>
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<tr>
<td>DCIS</td>
<td>14%</td>
<td>7%</td>
<td></td>
<td>p=0.0011</td>
</tr>
<tr>
<td><strong>SweDCIS</strong></td>
<td>1046</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(8.4 year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>27%</td>
<td>12%</td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Invasive</td>
<td>15%</td>
<td>5%</td>
<td></td>
<td>p&lt;0.05</td>
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<tr>
<td>DCIS</td>
<td>12%</td>
<td>7%</td>
<td></td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>
“Radiotherapy had no significant adverse effect on mortality from non-breast cancer causes, including heart disease.”
Systemic Treatment Effects on DCIS Outcomes
Tamoxifen for DCIS: NSABP B24

- 1800 patients with DCIS
- 10.5 year median follow-up

All IBTR
11%

Lumpectomy + Radiation

Tamoxifen

Placebo

15%

Subsequently found to beneficial in the hormone receptor + subset

Tamoxifen relative risk reduction:
~30% for ipsilateral breast recurrence
~54% for contralateral breast cancer

Tamoxifen in DCIS: NSABP B24

n=1804

Randomized to: BCS+RT
BCS+RT +Tamoxifen

Wapnir et al. JNCI 2011; 103(6)478
WBRT/ Tamoxifen Effects on DCIS Survival: Pooled Data-NSABP B17 & B24

p=NS

Wapnir et. al. JNCI 2011; 103(6)478
NSABP B-35
Accrual Date: 1/03-6/06
Patients: 3,104
Status: Closed to Accrual
*In active follow-up

IBIS II DCIS
Accrual Date: 2/03-present
Patients: 4,000
Status: Closed to Accrual
*In active follow-up
UK ANZ DCIS Trial

- Randomized 2 x 2 trial of RT and Tamoxifen
- Tamoxifen randomized 1536
- RT randomized 1030
- Median F/U 12.7 years

<table>
<thead>
<tr>
<th></th>
<th>% BCE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RT</td>
<td>19.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>RT</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>No Tamoxifen</td>
<td>24.4</td>
<td>0.0002</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>18.8</td>
<td></td>
</tr>
</tbody>
</table>

- RT and No Tamoxifen: ~60 % reduction in recurrence (p < 0.0001)
- Tamoxifen and No RT: ~30 % reduction in recurrence (p < 0.002)
- Take Home Point: Radiation effects of reducing IBTR were significantly greater than Tamoxifen effects

Cuzick SABC 2009
Other Adjuvant Systemic Therapy for DCIS NSABP B43

- HER2+ DCIS
- Targeted Accrual: 2000

Lumpectomy with negative margins

Radiation Therapy + Trastuzumab x 2

Randomized

Stratification:
- Menopausal Status
- Hormonal therapy
- Nuclear Grade

*Trastuzumab boosts the effectiveness of radiation in preclinical studies

Can breast radiation be omitted following lumpectomy for DCIS?
Can we stratify individual patients’ risk for recurrence?

- Subgroups of patients are at higher risk of recurrence
- Risk of recurrence may vary based on:
  - Tumor grade (EORTC)
  - Tumor size (B-24)
  - Margin status (B-17, EORTC, SweDCIS)
  - Comedonecrosis (B-17, B-24)
  - Multifocality (B-24)
  - Age ≤ 40 (EORTC)
- In 4 randomized trials (and meta-analyses), no subsets have been identified in which the benefit from RT in reducing LR was not statistically significant (where RT may possibly be omitted)
BCS +/-RT for Favorable DCIS: RTOG 98-04

- MMG detected
- Grade 1-2
- ≤2.5 cm
- Inked margins ≥3 mm
- age
- grade
- tumor size
- margin size
- tamoxifen use
- RT: 42.5-50 Gy, no boost
- Observation

- Closed in 2006 due to poor accrual (<1/2 of target enrollment)
- Analysis pending but results will be limited
Wide Excision Alone (WEA Trial) for DCIS

**Low risk:**
- ≤2.5cm by mammo
- Widely negative margins (≥1cm)
- Grade 1/2 (50/50)
- No Tamoxifen

**Results:**
- Closed early--met stopping rules
- 158 pts, median age 51

5 year LR: 12%
Rate of IBTR 2.4%/yr

8 yr update: 14.4% (n=19/132)
Invasive rec: 6/132 (4.5%)

*Wong, J et al. JCO, 2005*  
*Update: ASTRO 2011*
ECOG 5194: 6 Year Results

DCIS: Lumpectomy (711 pts)

Low/Int grade
<2.5cm

(580 pts)
• median size 6mm (18% >1cm)
• median margin 5-10mm
• 31% TAM

High grade
<1cm

(102 pts)
• median 7mm
• Median margin 5-10mm
• 30% TAM

*All pts.observed
*30% Tamoxifen
*Margins>3mm

6 yr ➔ 6.8%

50% DCIS and 50% Invasive
Contralateral events 3.5% & 4.2%

13.7%

Hughes, L et al. JCO 08
“The Believers”  
Radiation Can Be Omitted

- **Believe:**  
  - Radiation has side effects  
  - DCIS not ‘life threatening’  
  - Recurrences can be managed

- **Argue:** Based on ECOG (+ retrospective data), recurrence rates in low risk/low-int grade groups support omission of RT

- **Agree:** In high grade tumors or obviously high risk groups, LR is unacceptable and in these patients, RT should be delivered
“Non-Believers”: Radiation Should be Standard

**Believe:** *All* recurrences are psychologically devastating to pts & should be avoided

- RT should be routinely offered to DCIS patients (with few exceptions)

**Argue:**
- 2 Prospective studies have conflicting results (WEA Trial vs. ECOG)
- ECOG study: pts *highly selected* compared to protocol eligibility
  - Smaller tumor size (6mm median, 2.5 cm eligible)
  - Wider margins (5-10 mm, 3 mm required)
- Tamoxifen permitted (30%)
- Pathologic handling not routine: complete embedding/sequential sectioning
- Natural Hx: Low/int DCIS longer time to LR than high grade DCIS
Update ECOG 5194: San Antonio 2011

- Median follow-up: 8.8 years

<table>
<thead>
<tr>
<th>Grade</th>
<th>IBTR 6-yr</th>
<th>IBTR 10-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>low/intermediate</td>
<td>6.1%</td>
<td>15.4</td>
</tr>
<tr>
<td>high-grade</td>
<td>15.3%</td>
<td>15.1</td>
</tr>
</tbody>
</table>

Solin, SABC 2011
OncoType Dx to Predict DCIS Outcomes

• Used ~1/3 of pts from ECOG 5194 with available tissue
• Used modified version of invasive cancer algorithm for DCIS
• Used subset of genes from OncoType DX that was prognostic in tamoxifen treated and untreated DCIS patients

DCIS Oncotype Dx:

• Assay does not use invasion or ER genes
• Only 12 of 21 used
• The Assay includes 5 proliferation genes, PR, GSTM1 & 5 reference genes
• RT-PCR: Continuous variable
• Score: 0 – 100; Low< 39, Inter. 39 – 54, High≥55
Onco
typeDx to Predict DCIS Outcomes

All Breast Recurrences

<table>
<thead>
<tr>
<th>DCIS Risk Score</th>
<th>All Rec</th>
<th>10 Year Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;39)</td>
<td>12.0%</td>
<td>27.3% (15.2, 45.9)</td>
</tr>
<tr>
<td>Intermediate (39-54)</td>
<td>24.5%</td>
<td>24.5% (13.8, 41.1)</td>
</tr>
<tr>
<td>High (≥55)</td>
<td>27.3%</td>
<td>12.0% (8.1, 17.6)</td>
</tr>
</tbody>
</table>

Invasive Breast Recurrences

<table>
<thead>
<tr>
<th>DCIS Risk Score</th>
<th>Inv. Rec</th>
<th>10 Year Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;39)</td>
<td>5.1%</td>
<td>19.1% (9.0, 37.7)</td>
</tr>
<tr>
<td>Intermediate (39-54)</td>
<td>8.9%</td>
<td>8.9% (2.9, 25.6)</td>
</tr>
<tr>
<td>High (≥55)</td>
<td>19.1%</td>
<td>5.1% (2.8, 9.5)</td>
</tr>
</tbody>
</table>

P=0.01

Solin SABC, 2011
The use of radiation therapy is an independent predictor of local control based on Phase III data.

To date, defining subsets with limited benefits to forego adjuvant RT remains unclear.

*Moran M, et.al* Breast J. Dec 2011
BCS + Adjuvant RT  (Level 1 Evidence: Based on high level of evidence [randomized, prospective studies] with uniform NCCN consensus)

BCS (without RT)  (Level 2B  Evidence: Based on lower level of evidence [retrospective and/or single arm prospective trials] and non-uniform NCCN consensus)
Management of
Stage I-II Breast Ca
### Contemporary Trials

**Comparing BCS+/-RT vs. Mastectomy**

<table>
<thead>
<tr>
<th>Institution</th>
<th>Dates</th>
<th># Patients</th>
<th>Equal Survival</th>
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</thead>
<tbody>
<tr>
<td>NCI (France)</td>
<td>1972-1976</td>
<td>179</td>
<td>YES</td>
</tr>
<tr>
<td>NCI (Milan)</td>
<td>1973-1980</td>
<td>705</td>
<td>YES</td>
</tr>
<tr>
<td>NSABP B-06</td>
<td>1976-1984</td>
<td>1843</td>
<td>YES</td>
</tr>
<tr>
<td>NCI (USA)</td>
<td>1979-1987</td>
<td>237</td>
<td>YES</td>
</tr>
<tr>
<td>EORTC</td>
<td>1980-1986</td>
<td>903</td>
<td>YES</td>
</tr>
<tr>
<td>Danish Group</td>
<td>1983-1987</td>
<td>619</td>
<td>YES</td>
</tr>
</tbody>
</table>
EBCTCG Meta-analysis of BCS +/- RT

- Isolated local recurrence:
  - 5-y gain 18.6% (SE 0.9)

- Breast cancer mortality:
  - 15-y gain 5.4% (SE 1.7)
  - Logrank 2p = 0.0002

- Any death:
  - 15-y gain 5.3% (SE 1.8)
  - Logrank 2p = 0.005
**EBCTCG-Meta-analysis-BCS+/- RT**

(EBCTCG, Lancet 366:17, 2005)

Local Relapse Node (-) 15 yr. Overall Survival

Local Relapse Node (+) 15 yr. Overall Survival
EBCTCG: Shift in Paradigm

- Reduction in LRR → Reduction in distant disease and mortality

- No increase in non-breast mortality with RT

- 4:1 Rule: 20% benefit in LRR @ 5yrs → 5% benefit in Survival @ 15 yr (“4:1”)
Systemic Treatment Effects on Early Stage Breast Cancer Outcomes
10-Year LR in +/- Systemic Therapy
Recent NSABP Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>ER Status</th>
<th>10 yr. LR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-14</td>
<td>No Tamoxifen</td>
<td>+</td>
</tr>
<tr>
<td>B-14</td>
<td>Tamoxifen</td>
<td>+</td>
</tr>
<tr>
<td>B-13</td>
<td>No Chemo</td>
<td>-</td>
</tr>
<tr>
<td>B-13</td>
<td>Chemo</td>
<td>-</td>
</tr>
<tr>
<td>B-19</td>
<td>Chemo</td>
<td>-</td>
</tr>
<tr>
<td>B-23</td>
<td>Chemo</td>
<td>-</td>
</tr>
</tbody>
</table>

Wapnir I et al. Proc ASCO 2005
For all women who received adjuvant RT:

- 5y isolated LRR
  - RT Alone: 28%
  - RT + Systemic therapy: 8%
- 15y ↓ breast ca mortality: 6%

Systemic therapy further decreases LRR and breast cancer mortality

Effect greater when both systemic therapy and radiation used vs. either treatment alone
Can breast radiation be omitted following lumpectomy for early-stage invasive cancers?
Radiation has Effects on Survival

- EBCTCG meta-analysis demonstrated benefit in CSS and OS from radiation after BCS
- Reduction in LRR: \( p < 0.00001 \)
  - 7 % BCS + RT
  - 26 % BCS
- 15 yr. Breast Cancer Death Risk: \( p = 0.0002 \)
  - 30.5 % BCS + RT
  - 35.9 % BCS alone

*Clarke, Lancet 366: 2005*
Wide Excision Alone (WEA) Trial for T1N0

- Unicentric pT1N0 infiltrating ductal carcinoma
- At least 1 cm negative margins
- EIC- and LVI-
- Median age = 66 yrs
- Med pT size = 0.9 cm
- Accrual = 87/90 pts,
- Closed early due to stopping rules

Median FU = 86 months
LRR: 23% (n=19 pts)
Average LRR rate = 2.8%/yr
DM: 5% (n=4 pts)
Tubular: 50% LRR (n=3/6)

Finnish WEA Trial

- Median FU = 12.1 years
- LR: 11.6% vs 27.2%

Eligibility:
- T1N0
- Grade I/II
- EIC-
- HR+
- age > 40
- margins > 1 cm

**Holli K et al. JCO 27 (6), 2009**
CALGB 9343: Omission of RT in Elderly Women ≥70

- 636 women ≥ 70 years
- cT1, N0, M0
- ER+

<table>
<thead>
<tr>
<th></th>
<th>4 years</th>
<th>8 years</th>
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<tbody>
<tr>
<td>No RT</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>RT</td>
<td>0.6%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.001)</td>
<td>(p &lt; 0.001)</td>
</tr>
</tbody>
</table>

cN0 w/o ALND ~ 64%
Incidence of Mastectomy: 1% Tam RT vs. 3% Tam (p=0.07)

Hughes, K et al. NEJM Sept 2004
Hughes, Breast CA Res Treat (#11) 2006
CALGB 9343: Cannot Generalize to Other Patients

Smith, JNCI, 98:2006
Canadian Study of Omission of RT in Women ≥50

- 769 women ≥ 50 years
- pT2N0, ER+
- cN0 w/o ALND ~ 64%

Lumpectomy + Tamoxifen

<table>
<thead>
<tr>
<th>5 Year Results</th>
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<tbody>
<tr>
<td>LR</td>
</tr>
<tr>
<td>7.7%</td>
</tr>
<tr>
<td>0.6</td>
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</table>

Fyles, NEJM Sept 2004
Can Tamoxifen Substitute for RT?
Trials of Tam +/- RT

<table>
<thead>
<tr>
<th></th>
<th># Patients: Selection</th>
<th>Median FU</th>
<th>Tam</th>
<th>Tam + RT</th>
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</thead>
<tbody>
<tr>
<td>NSABP B-21</td>
<td>1,009: &lt; 1cm, pN0</td>
<td>87 mo</td>
<td>8.4%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Canadian (Fyles)</td>
<td>769: &gt; 50, T1/2, pN0</td>
<td>5.6 yrs</td>
<td>7%</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17.6%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Scottish</td>
<td>427: &lt; 70, T1,2, pN0</td>
<td>67 mo</td>
<td>25.0%</td>
<td>3.1%</td>
</tr>
<tr>
<td>CALGB (Hughes)</td>
<td>636: &gt; 70, T1, c,pN0</td>
<td>8 yr</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Austrian (Jakeske)</td>
<td>869: &lt; 3cm, GI/II, pN0,Tam/AI</td>
<td>54mo</td>
<td>5.1%</td>
<td>0.4%</td>
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Margins
## Effect of Margins On Local Relapse for Invasive Cancers

<table>
<thead>
<tr>
<th>Study</th>
<th># Pts</th>
<th>F/U (Yrs)</th>
<th>Local Relapse (%)</th>
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<tbody>
<tr>
<td></td>
<td></td>
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<td>Negative</td>
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<tr>
<td>Jobsen et al.</td>
<td>1697</td>
<td>6+</td>
<td>6.9</td>
</tr>
<tr>
<td>Smitt et al.</td>
<td>303</td>
<td>6</td>
<td>2</td>
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<tr>
<td>Vicini et al.</td>
<td>607</td>
<td>8.5</td>
<td>6-9</td>
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<tr>
<td>Freedman et al.</td>
<td>1262</td>
<td>6.3</td>
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<td>Neuschatz et al.</td>
<td>498</td>
<td>12</td>
<td>4</td>
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<tr>
<td>Obedian et al.</td>
<td>871</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Peterson et al.</td>
<td>1021</td>
<td>6.8</td>
<td>9</td>
</tr>
</tbody>
</table>
**Meta-analysis: Effect of Margins On Local Relapse for Invasive Cancers**

**Findings:**
1) Using a threshold distance weakly assoc. w/ reduced odds of LR
2) Adjustment for covariates (adjuvant therapy) removes the significance of this effect

#Studies: 21 (retrospective)

_Houssami, et.al. Eur J Ca, 2010_
## Meta-analysis of Margin Threshold for Women With DCIS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LR +Margin</th>
<th>LR 2mm Margin</th>
<th>LR 10mm Margin</th>
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<tbody>
<tr>
<td>BCS + RT</td>
<td>20%</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>BCS alone</td>
<td>35%</td>
<td>17%</td>
<td>9%</td>
</tr>
</tbody>
</table>

**# Trials:** 21 studies  
**# Patients:** 7564

*Wang, S. et.al., J.NCI, Epub, March 2012*
Boost
What is the rationale for Boost for Stage I-II Disease?

- The 1-2 cm of breast tissue surrounding the lumpectomy cavity is considered the region at highest risk of cancer recurrence.
- Supplemental dose to this region improves local control.
- Maximizing local control can have an impact on mastectomy-free survival and overall survival.
Boost Delivery Methods:

Boost: Single or multiple fractions delivered to the tumor bed either before, after or simultaneously during WBRT

<table>
<thead>
<tr>
<th>External Beam Modalities:</th>
<th>Intra-operative Modalities:</th>
<th>Brachytherapy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Electrons</td>
<td>• Electrons</td>
<td>• Balloon-based</td>
</tr>
<tr>
<td>• Reduced tangent photons</td>
<td>• kVp</td>
<td>• Interstitial catheter</td>
</tr>
<tr>
<td>• IMRT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# The Phase III Trials of Boost vs. No Boost

<table>
<thead>
<tr>
<th></th>
<th>Lyon (^1)</th>
<th>EORTC (^2)</th>
<th>Budapest(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median F/U</strong></td>
<td>3.3 yrs</td>
<td>10.8 yrs</td>
<td>5.3</td>
</tr>
<tr>
<td><strong>#patients</strong></td>
<td>1024</td>
<td>5138</td>
<td>207</td>
</tr>
<tr>
<td><strong>Fractionation</strong></td>
<td>50 Gy/ 2.5 Gy + 10 Gy</td>
<td>50 Gy /2Gy + 16 Gy</td>
<td>50 Gy/2 Gy +12-16 Gy</td>
</tr>
<tr>
<td><strong>LR(Boost vs. no Boost)</strong></td>
<td>3.6% vs. 4.5%</td>
<td>6.2% vs. 10.2%</td>
<td>15.5% vs. 6.7%</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>0.044</td>
<td>0.0001</td>
<td>0.049</td>
</tr>
<tr>
<td><strong>Cosmesis</strong></td>
<td>12.4% vs. 5.9% (GI-II telang)</td>
<td>21.8% vs. 13.2% (severe fibrosis)</td>
<td>No difference in fat necrosis, skin toxicity, fibrosis</td>
</tr>
</tbody>
</table>

1) Romestaing et al., JCO, 1997  
2) Bartelink H, et al., J Clin Oncol 2007  
### Effects of Boost on 10-Year LR by Age & Grade

<table>
<thead>
<tr>
<th>Age</th>
<th>No Boost (%LR)</th>
<th>Boost (%LR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 40</td>
<td>23.9%</td>
<td>13.5%</td>
</tr>
<tr>
<td>41-50</td>
<td>12.5%</td>
<td>8.7%</td>
</tr>
<tr>
<td>51-60</td>
<td>7.8%</td>
<td>4.9%</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>7.3%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

High grade


Low grade
<table>
<thead>
<tr>
<th>Trial</th>
<th># patients</th>
<th>RT Dose</th>
<th>% received boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-17</td>
<td>814</td>
<td>50 Gy/ 2 Gy</td>
<td>9%</td>
</tr>
<tr>
<td>EORTC 10583</td>
<td>1010</td>
<td>50 Gy/2 Gy</td>
<td>5%</td>
</tr>
<tr>
<td>SweDCIS</td>
<td>1046</td>
<td>50 Gy/ 2 Gy or 48 Gy/ 2.4 Gy</td>
<td>0%</td>
</tr>
<tr>
<td>UKCCCR</td>
<td>1030</td>
<td>50 Gy/2 Gy</td>
<td>0%</td>
</tr>
</tbody>
</table>

* No prospective randomized data of boost vs. no boost for DCIS to date
Benefit of DCIS Boost for Young Women

- Multi-institutional, retrospective study (Rare Cancer Network)
- 373 patients
- age < 45
- all stage Tis N0
- no tamoxifen
  - 15% excision
  - 45% excision + WBRT
  - 40% excision + WBRT + boost
- 10-year LRFS (p<0.0001)
  - 46% excision
  - 72% excision + WBRT
  - 86% excision + WBRT + boost

Omlin, et.al. (Lancet Onc, 2006)
Boost for DCIS

- Retrospective Review, McGill (Montreal)
  - 220 DCIS BCS + WBRT (42.4-50.4 Gy in 16-28 fractions)
  - 36% received boost (median dose of 10 Gy, range: 9-16 Gy)
  - Median follow-up: 46 months both cohorts

- Results:
  - Boost cohort had more close/+ margins and were in higher risk category of VNPI (p=0.015)
  - IBTR: Boost 0% vs. no Boost 5.7% (p=0.03)

P. Wong, Int. J. Rad Onc Bio Phy, 2011
Boost for DCIS


n=1800 pts  Follow-up: 14.5 years
Boost (unplanned analysis)=1569 pts

Boost: 38.5 % (85% 10Gy; 13.4% >10 Gy)

lumpectomy  →  WBRT*  +Placebo
WBRT*  + Tamoxifen (5 yrs)

Results:
More high risk features in the “boost” group (p=0.002)

<table>
<thead>
<tr>
<th>All Patients</th>
<th>n</th>
<th>IBTR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boost</td>
<td>692</td>
<td>13.8</td>
</tr>
<tr>
<td>No Boost</td>
<td>877</td>
<td>14.9</td>
</tr>
</tbody>
</table>

Proportional hazards regression: no significant reduction in risk of IBTR with boost, or in interaction with margins, comedo necrosis, age (p>0.05)
PIII Trial of RT fractionation/boost for DCIS: TROG 07.01

**AIMS:**
1. Clinical Outcomes
2. Toxicity
3. Quality of Life
4. Molecular signatures/molecular markers

**Target Accrual:** 650+
**Study Start Date:** 5/08

**Randomization**
- WBI Alone
- WBI Standard 2 Gy x 25
- WBI Accelerated 2.67 Gy x 16
- WBI + Boost RT
  - WBI Standard + Boost 2 Gy x 8
  - WBI Accelerated + Boost 2 Gy x 8

**Surgery**
- Age (<50, 50+)
- Endocrine Rx (Y/N)
- Center
Interval Between RT & Surgery
Meta-Analysis of RT Delay 8 Weeks

5-year LRR in patients treated with RT>8 weeks after Surgery
OR: 1.62, (CI: 1.21-2.16)

Huang, et.al. JCO 2003
Interval to RT

- Interval from Surgery to RT has typically been analyzed as a dichotomous variable.
- Indirect evidence that the relationship may actually be continuous.
- Across studies, the association between length of time to RT and LR appears to increase with longer intervals examined, but not consistent across studies.
<table>
<thead>
<tr>
<th>Author</th>
<th>RT delay (weeks)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puglia</td>
<td>&gt;6 wks</td>
<td>1.19 (1.01 to 1.39)</td>
</tr>
<tr>
<td>Huang (meta-analysis)</td>
<td>&gt;8 wks</td>
<td>1.62 (1.21 to 2.16)</td>
</tr>
<tr>
<td>Hebert-Croteau</td>
<td>&gt;12 wks</td>
<td>1.75 (1.00 to 3.08)</td>
</tr>
<tr>
<td>Olivotto</td>
<td>&gt;20 wks</td>
<td>2.00 (0.79 to 5.08)</td>
</tr>
</tbody>
</table>

- Given small absolute risk of LR, differences in the rates of ↑ LR are very small (i.e. <1% increase in 5 years for delay >12 weeks)
- Should start RT as soon as reasonably possible
- Radiation with delay is better than no RT in terms of LRR
Conclusions:

1) No diff in LR, Distant outcomes (max 6 months)

2) Pts. w/close margins: (RT 1st) 4% vs 32%

3) Pts. w/unknown margins: (RT 1st) 8% vs 20%

Recht, NEJM 1996, Bellon JCO 2001
Management of cN0, pN1:
Patients with clinically N0 disease
1) Total mastectomy + ALND
2) Total mastectomy + XRT
3) Total mastectomy (ALN untreated)
Regional failure

1) MRM (ALND) 4%
2) TM+radiation 4%
3) TM alone 18%

*High axillary recurrence did not translate into distant mets or OS

Importance of Regional Control: Data from PMRT Randomized Trials

Trials of PMRT and Systemic Therapy +/- Radiation

- Danish 82b trial: premenopausal, high-risk
- Danish 82c trial: postmenopausal, high-risk
- Vancouver BC: premenopausal, LN+

All 3 trials found better PMRT improved local-regional control and had better overall survival
N=3,083
Danish Trials significantly influenced meta-analysis due to large # of patients

*median nodes removed 7

LRR as 1\textsuperscript{st} site of Failure

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Chest wall</th>
<th>Axilla</th>
<th>Supra/Infraclav</th>
<th>All recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RT</td>
<td>16%</td>
<td>13%</td>
<td>5%</td>
<td>33%</td>
</tr>
<tr>
<td>+RT</td>
<td>5%</td>
<td>2%</td>
<td>2%</td>
<td>8%</td>
</tr>
</tbody>
</table>

$\Delta \approx 10\%$  
$\Delta \approx 10\%$

Overgaard, *Sem Rad Onc* 1999
Meta-Analysis: PMRT vs None

Lymph Node-Positive Disease

Local-Regional Recurrence w/RT
- 20% reduction

Breast Ca Survival
- 5% improvement

EBCTCG, Lancet, 2005
Benefits of Local-Regional Therapy

- Persistent LR disease leads to LR Relapse
- Persistent LR disease leads to DM and death
- Timing of events:
  - LRR develop within 5 yrs
  - OS differences happen between year 10-15
Indications for Full Axillary RT After ALND:

*Must weigh therapeutic benefit with toxicity

- Clinically positive axilla
- Incomplete (or no) axillary dissection
- High nodal ratio
- Matted/fixed axillary disease
- Extensive extracapsular extension
How to Manage Axilla in cN0 after SLND:

**Negative SLN**
- No additional axillary treatment necessary
- Milan trial, SLN = ALND
- NSABP B-32, SLN = ALND

**Positive SLN**
- Full node dissection
- Axillary RT (B-04)
- No Axillary treatment (Z-11)
Era of Sentinel Lymph Node Surgery

Randomized Trials

- Positive SLN, is additional treatment necessary?
  
  (Standard to date: ALND)

  - Europe: AMAROS, ALND vs XRT
  - US: Z11 trial, ALND vs. no Axillary tx
ACOSOG Z-11

- Clinically negative axilla
- T1-2, 1 or 2 SN +
- Targeted Accrual: 1900
- 115 institutions

Primary Endpoints:
- Overall Survival
- Morbidity

Protocol: Tangents only

*Giuliano et. al., JAMA, 305:2011*
## Z11 Patients by Treatment Arm

<table>
<thead>
<tr>
<th></th>
<th>ALND</th>
<th>SLN only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE</strong></td>
<td>median (yrs)</td>
<td></td>
</tr>
<tr>
<td>% &gt; 50 years</td>
<td>56</td>
<td>54</td>
</tr>
<tr>
<td>%</td>
<td>67.3</td>
<td>67.6</td>
</tr>
<tr>
<td><strong>TUMOR SIZE(%)</strong></td>
<td>T-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>67.9</td>
<td>70.6</td>
</tr>
<tr>
<td></td>
<td>32.4</td>
<td>29.4</td>
</tr>
<tr>
<td><strong>ER + or PR + (%)</strong></td>
<td>83.5</td>
<td>83.7</td>
</tr>
<tr>
<td><strong>GRADE (%)</strong></td>
<td>I/II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70.9</td>
<td>72.4</td>
</tr>
<tr>
<td></td>
<td>29.1</td>
<td>27.5</td>
</tr>
<tr>
<td><strong>LVI (%)</strong></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40.6</td>
<td>35.2</td>
</tr>
<tr>
<td><strong>NODES + (%)</strong></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>19.8</td>
</tr>
<tr>
<td></td>
<td>≥ 3</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.7</td>
</tr>
</tbody>
</table>

Giuliano et. al., Ann. of Surg., 252: 2010

Giuliano et. al., JAMA, 305:2011
Z11 Overall Patient Population

Typical “profile” of patients:
- >50: ~ 67%
- <T-1: ~ 67%
- HR+: >80%
- Grade I-II: ~ 71%
- No LVI ~ 62%
**Limitations:**
- Target accrual not met, n=856/1900
- Study prematurely closed due to ↓ accrual/ ↓ events
- About 20% of patients lost to follow-up
- Not all patients received tx by randomization
  - 11 pts: SLND-only arm had ALND
  - 32 SLNB + ALND had SLND-only
- Study not adequately powered to meet the pre-determined statistical survival endpoints
Most Important Results

27% of SNB+ALND had additional +LN(s)

Yet axillary failure was very low

<table>
<thead>
<tr>
<th></th>
<th>Local Recurrence</th>
<th>Regional Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLNB only</td>
<td>8/425 (1.8%)</td>
<td>4/425 (0.9%)</td>
</tr>
<tr>
<td>ALND</td>
<td>15/388 (3.6%)</td>
<td>2/388 (0.5%)</td>
</tr>
</tbody>
</table>

No p value provided

*Why different than B-04: 18% Ax Rec for Total Mastectomy/untreated axilla arm?
Reasons for Low LRR in Z11?

- ER+ disease still being treated with hormones
- LN disease eradicated by systemic therapy
- LN disease is “biologically irrelevant”
- LN disease eradicated by “breast” radiation
**Z11 Protocol: Tangents Only**

* Z11 was surgical study, thus, no RT QA for tangent field borders
High Tangents Cover Most of Level I/II Axilla

High tangent fields includes most of area at risk

- Superior border: Just below humeral head
- Posterior border: 2 cm within the lung

includes:

- over 95% of SLN
- over 80% of level I and II axilla


*Review of RT fields of pts tx on Z-11 currently being evaluated by ACOSOG*
Patient Eligibility:
1) + axillary nodes
2) Primary tumor > 2 cm in size
3) < 10 nodes dissected
4) ≥1 of the following (with –nodes):
   - Grade 3 histology
   - ER-negative disease
   - Lymphovascular space invasion

n=1832 patients 2000 and 2007
Results:

- Median f/u = 62 months
- Local relapse similar in 2 arms
- Marked decrease in regional recurrences

WBI n=21 vs. WBI+RNI n=4
- 67% isolated RR were in the axilla, 1 isolated recurrence in the IMNs.
### NCIC-CTG MA-20

<table>
<thead>
<tr>
<th>5 year results</th>
<th>WBI</th>
<th>WBI+RNI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR Control</td>
<td>94.5%</td>
<td>96.8%</td>
<td>0.020</td>
</tr>
<tr>
<td>DFS</td>
<td>84%</td>
<td>90%</td>
<td>0.003</td>
</tr>
<tr>
<td>Distant DFS*</td>
<td>87%</td>
<td>92.4%</td>
<td>0.002</td>
</tr>
<tr>
<td>OS</td>
<td>90.7%</td>
<td>92.3%</td>
<td>0.070</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>4.1%</td>
<td>7.3%</td>
<td>0.004</td>
</tr>
<tr>
<td>&gt;GII toxicity</td>
<td>0.2</td>
<td>1.3%</td>
<td>0.010</td>
</tr>
</tbody>
</table>

*The absolute magnitude of the distant DFS benefit larger than absolute benefit in locoregional control.*
Results of MA-20

- WBI
- WBI+RNI

5 year Results:
All benefit was in regional relapse
IBTR was identical in both arms
Benefit in DDFS and trend in OS with RNI
Clinical N0, Pathologic N1: No Additional Treatment vs. Full Axillary RT

*Additional Data Needed!

<table>
<thead>
<tr>
<th></th>
<th>Z-0011</th>
<th>MA-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age med/mean</td>
<td>55 years</td>
<td>53 years</td>
</tr>
<tr>
<td>Tumor Size</td>
<td>32 mm</td>
<td>47 mm</td>
</tr>
<tr>
<td>ER Negative (%)</td>
<td>16.5</td>
<td>25</td>
</tr>
<tr>
<td>Grade III (%)</td>
<td>28</td>
<td>42</td>
</tr>
<tr>
<td>Median Nodes Removed</td>
<td>17</td>
<td>12</td>
</tr>
</tbody>
</table>
Caution in omitting treatment to axilla in patients who do not fit Z-11 profile:

- Clinically positive axilla
- NCT patients with +SN upfront
- ER-disease
- Other considerations
  - Younger age
  - Triple negative disease
AMAROS = After Mapping of the Axilla RT or Surgery?

**Additional Data Needed**

0.5–3.0cm invasive breast cancer clinically negative axilla

Randomization: ALND vs. axillary radiotherapy

Sentinel node biopsy procedure

**Sentinel node negative**

Follow up

**Sentinel node positive**

ALND

Quality of life questionnaire (1, 2, 3, 5, 10 years)
Shoulder function (1, 3, 5, 10 years)

Axillary radiotherapy

Quality of life questionnaire (1, 2, 3, 5, 10 years)
Shoulder function (1, 3, 5, 10 years)

*Results available 2013*
Additional Data Needed

Nodal RT for Intermediate Disease: EORTC 22922

Axillary node+ or central/medial tumor
BCS or mastectomy

RT to breast/CW only

RT to breast/CW + SCV + IM
Patients who can forgo ALND:
- T1 or T2 tumor
- Clinically negative axilla
- 1 or 2 positive nodes on biopsy
- Treatment with breast-conserving surgery
- Treatment with whole-breast radiation therapy
- No neoadjuvant chemotherapy
Summary cN0, SLN+

In pts with cN0 and +SLN, each radiation oncologist will have to decide how to best manage axilla

My approach (until more data is available):

- Discuss issues with patient and individualize treatment
- SN Micromets-Tangents only or high tangents
- 1-2+ SLN macromets-high tangent vs. regional nodal fields
Accelerated Hypofractionated Whole Breast RT:
hf-WBRT: Radiobiology

- Conventional fractionation (CF) based on radiobiologic models
- Because $\alpha/\beta$ ratio for most tumors is high (~10) compared to normal tissue, then CF is needed to improve therapeutic ratio
- If $\alpha/\beta$ ratio of a tumor is low (~2-4), then CF and HF should yield similar effectiveness and toxicity
- Until recently, $\alpha/\beta$ ratio for breast cancer not known
- Combined Data from RMH Pilot & START A demonstrated:
  $\alpha/\beta$ ratio: Breast cancer: 4.6 Gy
  Breast normal tissue: 3.4 Gy

Implication: Due to similar $\alpha/\beta$ ratios (similar sensitivity to fraction size), minimal gain in therapeutic ratio from CF-WBRT in treatment of breast cancer
Trial I: Royal Marsden Pilot Trial

Primary Endpoint: Late normal tissue effects
Population: T1-3, N0-1, n=1410
Median F/U: 9.1 years

- 50 Gy, 25 fractions, (2 Gy)
- 42.9 Gy/13 fractions (3.3 Gy)
- 39 Gy/13 fractions (3 Gy)

<table>
<thead>
<tr>
<th>Cosmesis (%)</th>
<th>50Gy</th>
<th>42.9 Gy</th>
<th>39 Gy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Change</td>
<td>35.6</td>
<td>42.3</td>
<td>27.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marked Change</td>
<td>5.6</td>
<td>10.1</td>
<td>3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fair-Poor</td>
<td>60.9</td>
<td>65.8</td>
<td>50.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Palpable Induration</td>
<td>28.6</td>
<td>40.8</td>
<td>20.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Local Recurrence(%)
(p>0.05)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>50 Gy</td>
<td>12.1</td>
</tr>
<tr>
<td>42.9 Gy/13</td>
<td>9.6</td>
</tr>
<tr>
<td>39 Gy/13</td>
<td>14.8</td>
</tr>
</tbody>
</table>

Owens, Lancet Oncology 7(6), 2006
**Trial II: UK START A Phase III Trial**

- **Population:** T1-3, N0-1
- **Median follow-up:** 5.1 years
- **Local Recurrence (%)**
  - 41.6 Gy / 13 fractions (3.2 Gy): 3.6
  - 39 Gy / 13 fractions (3.0 Gy): 3.5
  - 50 Gy / 25 fractions (2.0 Gy): 5.2

*Maintained the explanatory design of the RMH pilot study*

**Trial III: UK START B Phase III Trial**

- **Population:** T1-T3, N0-N1
- **Median F/U:** 6 yrs
- **Local Recurrence (%)**
  - 40 Gy/15 fractions (2.66 Gy): 3.2
  - 50 Gy/25 fractions (2.0 Gy): 2.2

*Bentzen SM., Lancet Oncology 2008;9:331–*

*Bentzen SM., Lancet 2008;371:1098–1107*
**Trial IV: Canadian Trial**

42.5 Gy/16 fractions  
50 Gy/25 fractions  
n=1234

Population: T1 – T2, N 0 (80% T1, 71% ER+)
Median F/U: 12 years

<table>
<thead>
<tr>
<th>10 year results</th>
<th>In-Breast Recurrence (%)</th>
<th>Excellent/ good Cosmesis (%)</th>
<th>G2-3 Toxicity Subcutaneous Tissue (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hf-WBRT</td>
<td>6.2</td>
<td>71</td>
<td>11</td>
</tr>
<tr>
<td>cf-WBRT</td>
<td>6.7</td>
<td>70</td>
<td>12</td>
</tr>
</tbody>
</table>

*Whelan, NEJM 2010. 362:513–520*
Trial V: UK “FAST Trial”
hf-WBRT (once per week)

n = 915, accrual complete

- 50 Gy, 25 fractions, 2 Gy, 5 wks
- 28.5 Gy, 5 fractions, (5.7 Gy/1x wk) x 5 wks
- 30 Gy, 5 fractions, (6 Gy/1x wk) x 5 wks

*Study not powered to detect significant differences in LR.
* Endpoint: analysis of cosmetic outcomes

Conclusions:
- 5 fx/1x wk=cf50 Gy for breast changes @ 2 yrs & adverse effects @ median of 3.1 years
- Longer f/u of at least 5 years needed

Yarold, Radiother Oncol. 2011 Jul;100(1):93-100
ASTRO Consensus Statement on HF-WBRT Based on Trials I-IV

Patient Criteria:

- ≥50 years or older
- T1–2, N0
- BCS
- No chemotherapy
- Dosimetric criteria
  - \( D_{\text{min}} ≥ 93\% \)
  - \( D_{\text{max}} ≤ 107\% \)
  - (central axis dose + 7% prescribed dose)
  - 2-D planning
  - No heterogeneity corrections

Guideline should not be interpreted to prohibit/oppose HF-WBI for patients not meeting all these criteria; the evidence was not sufficient to reach consensus by the task force for other patients.

Smith B, et.al. IJROBP 2010
ASTRO Consensus Statement on hf-WBRT

**Regimens:**
- For patients not receiving a boost, the task force favored a dose of 42.5 Gy in 16 fractions
- No consensus for optimal HF regimens when using boost

**Role of Boost with HF-WBRT:**
- Task force unable to reach consensus
- General agreement that the indications for boost similar regardless of the HF or CF schemas
- While the majority supported using a tumor-bed boost with HF-WBI when indicated, no data to support how to incorporate it

Smith B, et.al. IJROBP 2010