Evaluating the Z011 study and how local-regional therapy for early breast cancer may change

Karen Hoffman, M.D., M.H.Sc., M.P.H.
Dept of Radiation Oncology
The University of Texas MD Anderson Cancer Center
Overview

- Review the Z11 trial
- Potential reasons for the low regional recurrence rate in patients who did not undergo ALND
- Implementation of Z11 into practice
- Impact of Z11 on radiation treatment field design
Evolution of less extensive and disfiguring procedures

- Radical Mastectomy
- Modified Radical Mastectomy
- Breast Conserving Surgery
ALND can be safely omitted in lymph node negative patients

SLND = ALND
- Locoregional control
- Distant recurrences
- Survival

Sentinel Lymph Node Dissection
*Allows for identification of small volume disease
*Lower morbidity

Axillary Lymph Node Dissection

Krag et al. Lancet Oncol. 2010
Long-term morbidity of ALND

Cross-sectional study of 95 pts

- 70% had at least one complaint
  - 18% moderate to severe
- 21% decreased strength/ROM
- 9% wore compression garments
- 6% quit work or changed vocation because of surgical morbidity

Kakuda et al Amer Surg 1999
SLND has less side effects than ALND

- Morbidity of patients treated on NSABP B-32

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>ALND</th>
<th>SLND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder Abduction Deficit $\geq 10%$ at 1 week</td>
<td>75%</td>
<td>41%</td>
</tr>
<tr>
<td>Arm Volume Difference $\geq 10%$ at 36 months</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Numbness at 6 months</td>
<td>49%</td>
<td>15%</td>
</tr>
</tbody>
</table>
Given the morbidity of ALND, if SLN positive, is ALND necessary?

- Overall, SLN is the only positive LN in 50-70% of patients
Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis
A Randomized Clinical Trial


Giuliano, A. E. et al. *JAMA* 2011;305:569-575
Study objectives

- Primary Objective:
  - To determine the effects of ALND on overall survival in patients with SLN metastases treated in the contemporary era with lumpectomy, adjuvant systemic therapy and tangential breast radiation

- Secondary Objectives:
  - Determine the effects on disease free survival
  - Assess the morbidity of SLND + ALND vs. SLND
Study design

- Phase III Multicenter Non-inferiority Trial
- Enrolled from May 1999-December 2004
Inclusion criteria

- Tumor < 5 cm
- No palpable adenopathy
- Unicentric and unilateral
- Lumpectomy with negative margins
- 1-2 SLN containing metastasis
  - Frozen section, touch prep, or H & E staining
  - Metastasis determined only by IHC omitted
Exclusion criteria

- 3 or more positive SLN
- Matted nodes
- Gross extranodal disease
- Neoadjuvant chemotherapy or endocrine therapy
ACOSOG Z11

Use of adjuvant systemic therapy determined by the treating MD

BCS

cT1-2N0

1-2+ SLN

Age (</> 50)

ER-status

Tumor size

ALND level I & II

Tangential breast radiation without 3rd field nodal radiation

No ALND

ACOSOG Z11
891 Patients Randomized

445 Randomized to ALND
- 25 Withdrew
  - 420 Received ALND
    - 32 did not have ALND
      - 420 Included in Analysis
  - 420 Included in Analysis

446 Randomized to SLND alone
- 10 Withdrew
  - 436 received SLND alone
    - 11 had ALND
      - 436 Included in Analysis
Enrollment

- Target 1900 patients
  - Final analysis planned after 500 deaths
- Closed early because of low event rate
Enrolled patients had favorable characteristics

**Table 1. Baseline Patient and Tumor Characteristics by Study Group**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ALND (n = 420)</th>
<th>SLND Alone (n = 436)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>56 (24-92)</td>
<td>54 (25-90)</td>
</tr>
<tr>
<td>Missing</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Clinical T stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>284 (67.9)</td>
<td>303 (70.6)</td>
</tr>
<tr>
<td>T2</td>
<td>134 (32.1)</td>
<td>126 (29.4)</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Tumor size, median (range), cm</td>
<td>1.7 (0.4-7.0)</td>
<td>1.6 (0.0-5.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Receptor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+/PR+</td>
<td>256 (66.8)</td>
<td>270 (68.9)</td>
</tr>
<tr>
<td>ER+/PR−</td>
<td>61 (15.9)</td>
<td>54 (13.8)</td>
</tr>
<tr>
<td>ER−/PR+</td>
<td>3 (0.8)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>ER−/PR−</td>
<td>63 (16.5)</td>
<td>64 (16.3)</td>
</tr>
<tr>
<td>Missing</td>
<td>37</td>
<td>44</td>
</tr>
<tr>
<td>LVI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>129 (40.6)</td>
<td>113 (35.2)</td>
</tr>
<tr>
<td>No</td>
<td>189 (59.4)</td>
<td>208 (64.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>102</td>
<td>115</td>
</tr>
<tr>
<td>Modified Bloom-Richardson score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>71 (22.0)</td>
<td>81 (25.6)</td>
</tr>
<tr>
<td>2</td>
<td>158 (48.9)</td>
<td>148 (46.8)</td>
</tr>
<tr>
<td>3</td>
<td>94 (29.1)</td>
<td>87 (27.5)</td>
</tr>
<tr>
<td>Missing</td>
<td>97</td>
<td>120</td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infiltrating ductal</td>
<td>344 (82.7)</td>
<td>356 (84.0)</td>
</tr>
<tr>
<td>Infiltrating lobular</td>
<td>27 (6.5)</td>
<td>36 (8.5)</td>
</tr>
<tr>
<td>Other</td>
<td>45 (10.8)</td>
<td>32 (7.5)</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>12</td>
</tr>
</tbody>
</table>

- Age: 65% > 50
- T stage: 69% T1
- ER+: 83%
- LVS: 38%
- IDC: 82%
No difference in the use of adjuvant systemic therapy

<table>
<thead>
<tr>
<th></th>
<th>ALND (n=420)</th>
<th>SLND (n=436)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant Systemic</td>
<td>403 (96%)</td>
<td>423 (97%)</td>
<td>.4</td>
</tr>
<tr>
<td>Hormonal Therapy</td>
<td>195 (46%)</td>
<td>203 (47%)</td>
<td>.97</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>243 (58%)</td>
<td>253 (58%)</td>
<td>.96</td>
</tr>
</tbody>
</table>

LRR Recurrence
Systemic Therapy – 3.3%
No Systemic Therapy – 3.4%

- 96% received systemic therapy
- 60% of these received chemotherapy
Patients had a low nodal burden

<table>
<thead>
<tr>
<th></th>
<th>ALND (n=420)</th>
<th>SLND (n=436)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median nodes removed</td>
<td>17</td>
<td>2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Positive Nodes, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (1.2)</td>
<td>29 (7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1</td>
<td>199 (58)</td>
<td>295 (71)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>68 (19.8)</td>
<td>76 (18.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>72 (21)</td>
<td>15 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Size of Metastasis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micro</td>
<td>137 (37.5)</td>
<td>164 (44.8)</td>
<td>.05</td>
</tr>
<tr>
<td>Macro</td>
<td>228 (62.5)</td>
<td>202 (55.2)</td>
<td></td>
</tr>
<tr>
<td>Additional Positive Non-Sentinel Nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>97 (27.3)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Micromet</td>
<td>14 (10)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- In those undergoing ALND, 27% had additional positive LNs and 14% had 4 or more positive LNs

65% only one positive LN

41% micromet
No difference in survival

- Median follow up 6.3 years

5 Year Overall Survival
SLND – 92.5%
ALND – 91.8%

5 Year Disease Free Survival
SLND – 83.9%
ALND – 82.2%
Recall that among those who had completion ALND:

- 27% had additional positive LNs
- 14% had 4 or more positive LNs
Surgical morbidity higher in patients with ALND

<table>
<thead>
<tr>
<th>Condition</th>
<th>SLND</th>
<th>ALND</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infections</td>
<td>3%</td>
<td>8%</td>
<td>0.0016</td>
</tr>
<tr>
<td>Seromas</td>
<td>6%</td>
<td>14%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>9%</td>
<td>39%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Lymphedema (at 1 year)</td>
<td>2%</td>
<td>13%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total Adverse Effects</td>
<td>25%</td>
<td>70%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Lucci et al. JCO 2007
Early Termination

- Due to lower than anticipated event rate
  - NSABP B-04 40% node positive & 5-year survival was 60%
  - ACOSOG Z0011 100% node positive and 5-year survival was 90%
How do we explain the results of Z11?

Discordance between LN found at ALND and the low regional recurrence rate without ALND?

- LN disease is “biologically irrelevant”
- LN disease eradicated by systemic therapy
- LN disease eradicated by “breast” radiation
Nodal disease is biologically insignificant

**NSABP B-04**
- Chemotherapy not used routinely

- Mastectomy + ALND
  - 38% LN +

- Mastectomy Alone
  - Locoregional Recurrence Rate
    - 18%

- Mastectomy + XRT

*Fisher et al. NEJM 1985*
SLN processing identifies low volume disease

- Higher incidence of metastasis if SLND
- SLN evaluation of more levels and used IHC

Standard ALND (n=134)

- 29% LN + (n=39)
- 10% micromets (4/39)

SLND prior to ALND (n=168)

- 42% LN + (n=68)
- 38% micromets (26/68)

(p < 0.0005)

Nodal disease is eradicated by systemic therapy

Chemotherapy

- NSABP B-18 & B-27, up to 40% were converted from lymph node-positive at diagnosis to lymph node-negative from neoadjuvant chemotherapy

- 74% of patients treated for HER2+ disease with neoadjuvant Trastuzumab were converted from lymph node-positive at diagnosis to lymph node-negative

Endocrine Therapy

Nodal disease is eradicated by “breast” radiation
Many consider this axillary radiation
Breast tangent fields treat low axillary lymph nodes
Breast tangent fields treat low axillary lymph nodes.
Breast tangents treat the low axilla

- Measured the relationship of surgical clips to the tangential radiation field
- SLN clips (level I) within standard fields 85% of the time
- Full ALND clips (I & II) within standard fields 43% of the time
  - If incomplete coverage, 80% of the clips were included in the field

Field design impacts amount of treated axillary lymph nodes

Standard Tangent  High Tangent
High tangents increase axillary coverage

- Compared normal tangents (top 2 cm above breast tissue) to high tangents (inferior to humeral head) on CT imaging
CT based imaging can be used to purposefully target the axilla.
CT based imaging to purposefully target the axilla
CT based imaging to purposefully target the axilla
Patient positioning impacts radiation dose to the axilla

- On average, 50% less dose to level I-III axilla in the prone position

Level I & II axilla can be targeted in the prone position.
Radiation fields used in Z11 are not known

- Required tangential breast radiation without a third field
- Do not know if standard or high tangent fields
- Do not know if supine or prone
- Currently under investigation
Radiation is effective at eradicating microscopic disease

**NSABP B-04**
- Chemotherapy not used routinely

Mastectomy + ALND

- 38% LN +
- 2%

Locoregional Recurrence

Mastectomy

- 18%
- +XRT
- 2%

Mastectomy + XRT

- 2%

*Fisher et al. NEJM 1985*
Low regional recurrence rates in cN0 patients with no axillary surgery when RT is delivered

<table>
<thead>
<tr>
<th>Study</th>
<th>Pts</th>
<th>Design &amp; Follow up</th>
<th>Patient population</th>
<th>RT</th>
<th>Regional Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong</td>
<td>74</td>
<td>Prospective 52 months</td>
<td>Early stage cN0, ER+; median age 75, median size 1.2 cm &amp; 93% LVSI-</td>
<td>High tangents</td>
<td>0%</td>
</tr>
<tr>
<td>Veronisi</td>
<td>221</td>
<td>Arm of RCT 63 months</td>
<td>Less than 1.5 cm, cN0 60% &gt; age 55, 81% ER+, Tangent &amp; axilla</td>
<td></td>
<td>0.5%</td>
</tr>
<tr>
<td>Hoebers</td>
<td>105</td>
<td>Retrospective 41 months</td>
<td>80% 2 cm or less, cN0, Mean age 64, 81% ER+, Tangent, axilla, &amp; SCV</td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>Louis-Sylvestre</td>
<td>332</td>
<td>Arm of RCT 15 yrs</td>
<td>70% 2 cm or less, cN0 Mean age 51, 60% ER+, Breast axilla &amp; IMN</td>
<td></td>
<td>3%</td>
</tr>
</tbody>
</table>
Implementation of Z11 into practice at MDACC…

- Formal multi-disciplinary discussion
- Discussion of who is eligible
- Not changing adjuvant systemic therapy recommendations -- decision to administer systemic therapy dictated largely by tumor biology not number of lymph nodes
- Changing radiation field design

Caudle et al, Ann Surg Oncol 2011
MDACC Interpretation

- Consider omission of ALND on a case-by-case basis
- Now included in the pre-op discussion

Who is eligible:
- T1 or T2 clinically node negative
- 1-2 SLN metastasis
- Planned BCT with whole breast radiation
MDACC Interpretation

Who is not eligible for omission of ALND:

- Clinically node positive
- Neoadjuvant chemotherapy
- Mastectomy patients
- Partial breast irradiation patients

Considerations:

- Young age
- Nodal tumor burden
- Tumor subtype
Younger age and increased nodal burden are associated with LRR after breast conserving therapy

- 1461 pts British Columbia 1986-1992; fup 12 yrs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Local Relapse (n = 1,177)</th>
<th>Regional Relapse (n = 1,177)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 55</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>40-55</td>
<td>1.6</td>
<td>1.0 to 2.4</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>1.7</td>
<td>0.9 to 3.3</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>1-3 positive</td>
<td>1.3</td>
<td>0.8 to 2.2</td>
</tr>
<tr>
<td>≥ 4 positive</td>
<td>2.0</td>
<td>1.0 to 4.3</td>
</tr>
</tbody>
</table>

- MVA that adjusted for size, grade, LVSI, tumor subtype, radiation to nodes, and systemic therapy
Consider nodal burden

- Total number SLN
- Positive to total ratio
- Size of metastasis
- Extra-nodal extension (gross excluded Z11)
- Remember: Z0011 criteria was < 3 positive SLN
  - 71% had 1 positive LN
  - 45% were micromets
Non-luminal subtypes are associated with increased LRR after breast conserving therapy

- 1461 pts British Columbia 1986-1992; fup 12 yrs

![Graph showing cumulative local-relapse-free probabilities over time for different subtypes.](image)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Local Relapse (n = 1,177)</th>
<th>Regional Relapse (n = 1,177)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Luminal A</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Luminal B</td>
<td>1.0</td>
<td>0.6 to 1.7</td>
</tr>
<tr>
<td>Luminal HER2</td>
<td>1.0</td>
<td>0.4 to 2.6</td>
</tr>
<tr>
<td>HER2 enriched</td>
<td>2.7</td>
<td>1.4 to 4.9</td>
</tr>
<tr>
<td>Basal-like</td>
<td>1.2</td>
<td>0.7 to 2.2</td>
</tr>
<tr>
<td>TNP-nonbasal</td>
<td>0.9</td>
<td>0.4 to 1.8</td>
</tr>
</tbody>
</table>

P < .001

Voduc JCO 2010
Subtypes influence effectiveness of radiation therapy

<table>
<thead>
<tr>
<th>Subtype</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>0.09</td>
</tr>
<tr>
<td>Luminal B</td>
<td>0.06</td>
</tr>
<tr>
<td>Triple Negative</td>
<td>0.33</td>
</tr>
<tr>
<td>HER2+</td>
<td>ns: 0.53</td>
</tr>
</tbody>
</table>

Kyndi, JCO 2008
Implementation of Z11 into practice at MDACC…

- Treatment of women meeting criteria for Z11 by 17 breast surgeons

<table>
<thead>
<tr>
<th>Time period</th>
<th>Year prior to Z11</th>
<th>Year after Institutional Meeting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>335</td>
<td>323</td>
</tr>
<tr>
<td>Proportion LN positive on SLND</td>
<td>19%</td>
<td>13%</td>
</tr>
</tbody>
</table>

- Fewer SLN positive patients underwent ALND after Z11
  - 85% before vs. 24% after (p <0.001)
Implementation of Z11 into practice at MDACC...

- After Z11 in SLN positive patients ALND was used selectively

<table>
<thead>
<tr>
<th></th>
<th>ALND</th>
<th>SLND only</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobular histology</td>
<td>30%</td>
<td>3%</td>
<td>0.01</td>
</tr>
<tr>
<td>Higher probability of additional LN by nomogram</td>
<td>25%</td>
<td>14%</td>
<td>0.03</td>
</tr>
<tr>
<td>Size</td>
<td>median 2.2 cm</td>
<td>median 1.5 cm</td>
<td>ns</td>
</tr>
<tr>
<td>Small number of LN removed at SLND</td>
<td>median 1</td>
<td>median 3</td>
<td>ns</td>
</tr>
<tr>
<td>Larger SLN metastasis</td>
<td>median 4 mm</td>
<td>median 2 mm</td>
<td>ns</td>
</tr>
<tr>
<td>Extranodal extension</td>
<td>20%</td>
<td>6%</td>
<td>ns</td>
</tr>
</tbody>
</table>
Implementation of Z11 into practice at MDACC…

- After Z11 surgeons were less likely to perform intra-operative nodal assessment which contributed to a decrease in operative time.

<table>
<thead>
<tr>
<th></th>
<th>Year prior to Z11</th>
<th>Year after Institutional Meeting</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-operative LN assessment</td>
<td>69%</td>
<td>26%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Operative time</td>
<td>median 92 minutes</td>
<td>median 79 minutes</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
We will be seeing more patients in clinic with involved SLN at breast conserving surgery who do not undergo ALND.
What is the appropriate radiation field design for these patients?

- Standard tangents?
- High tangents?
- Regional-nodal irradiation?
- Treatment field design should reflect the lymph node basins at-risk for harboring micrometastatic disease
Nomograms predict risk of non-SLN involvement

- Histology
- Tumor size
- # LN removed
- # Positive LN
- ENE
- LVSI
Should these patients be treated with “high” tangents?

- Historically, tendency to treat undissected axilla with high tangents
- Z11 radiation field design currently being studied
- Believe minimal increase in morbidity from the use of high tangents
Should these patients be treated with “high” tangents?

- Personally, use standard tangents if extremely low risk of additional LN involvement
- Generally use high tangents that treat the level I & II axilla
- Weigh potential morbidity for individual patients
- Primary target is still the breast
Which patients with positive SLNs need regional-nodal radiation?

- Historically, information from axillary lymph node dissection has been used to guide regional-nodal radiation treatment.
Indications for regional-nodal radiation based on ALND

- Stage III disease
- 4 or more positive lymph nodes
- Consider if 1-3 positive LN and adverse features
  - High nodal burden
  - Extra-nodal extension
  - LVSI
Factors that predict at least 25% risk $> 4$ LN

- No drainage on lymphoscintigraphy
- More than 1 + SLN
- LVSI

If didn’t have any of these

- Rate of $>4$ +LN was less than 2%
If we do not have ALND, nomograms predict likelihood of $\geq 4$ LN when SLN positive.

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84

Outperformed two other models in external validation testing
- AUC 0.84
Consider regional nodal radiation for patients with positive SLN expected to have a total of 1-3+ LN.
Preliminary MA 20 results support regional nodal radiation in pts 1-3+ LN

- BCS only
- ALND
- N+ or
- T3 N0 or
- T2 N0 and high risk (ER-, Gr3, LVSI)

Stratify:
- # of nodes +
- chemotherapy
- hormonal therapy
- institute

Randomize:
- of nodes removed
- RT to breast
- RT to breast+ axilla+ SCV+IM

RT to breast
Whole breast RT

Whole breast & regional-nodal RT

- Wire marker on Lumepectomy scar
- Wire marker starts at 3rd intercostal space and marks lower half of breast circumference
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>WBI N=916</th>
<th>WBI + RNI N=916</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>52.7</td>
<td>53.9</td>
</tr>
<tr>
<td>Axillary nodes removed (mean)**</td>
<td>12.3</td>
<td>12.4</td>
</tr>
<tr>
<td>Node –ve</td>
<td>89 (10)</td>
<td>89(10)</td>
</tr>
<tr>
<td>Node +ve (1-3)</td>
<td>780 (85)</td>
<td>776 (85)</td>
</tr>
<tr>
<td>Tumor size &gt; 2 cm</td>
<td>416 (45)</td>
<td>457 (50)</td>
</tr>
<tr>
<td>Grade III</td>
<td>387 (42)</td>
<td>390(43)</td>
</tr>
<tr>
<td>ER –ve</td>
<td>235 (26)</td>
<td>232 (25)</td>
</tr>
<tr>
<td>Adj chemotherapy</td>
<td>829 (91)</td>
<td>830 (91)</td>
</tr>
<tr>
<td>Adj endocrine therapy</td>
<td>705 (77)</td>
<td>700 (76)</td>
</tr>
<tr>
<td>Boost irradiation</td>
<td>221 (24)</td>
<td>206 (22)</td>
</tr>
</tbody>
</table>

* Mean or n (%); ** SN biopsy in 39%
<table>
<thead>
<tr>
<th></th>
<th>WBI</th>
<th>WBI + RNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local only</td>
<td>48 (5.2%)</td>
<td>29 (3.2%)</td>
</tr>
<tr>
<td>Regional only**</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Local &amp; regional</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>5-yr LRDFS</td>
<td>94.5%</td>
<td>96.8%</td>
</tr>
</tbody>
</table>

* Any first local and/or regional recurrence;  
** 67% of regional recurrences were in the axilla
Preliminary MA 20 results support regional nodal radiation in pts 1-3+ LN

- Regional-nodal irradiation improved
  - Local regional control (HR 0.58; p=0.02)
    - 5.2% vs. 3.2%
  - Distant DFS (HR 0.64; p=0.002)
    - 15.7% vs. 11.1
  - Trend toward improvement in OS (HR 0.76; p=0.07)

- Full results await publication and additional details
  - Details of lymph node involvement
RNI increased adverse events*

<table>
<thead>
<tr>
<th></th>
<th>WBI (n=927)</th>
<th>WBI + RNI (n=893)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4/5</td>
</tr>
<tr>
<td><strong>Acute</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rad dermatitis</td>
<td>349</td>
<td>23</td>
<td>-</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Delayed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle wkness</td>
<td>8</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>114</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>34</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

*NCI – Common toxicity criteria v2 1998
Use regional-nodal radiation for patients with 1-3+ LN selectively due to increased side effects
Patients with 1-3+ LN are a heterogeneous group

- Low regional recurrence rate in Z11 without regional-nodal radiation
  - 0.9%
- Also consider other risk factors
  - Number of involved LN
  - Tumor size
  - Extra-nodal extension
  - LVSI
Radiation field design for SLN positive patients

- Deliberate targeting of the at-risk lymph node basins
- CT based planning
- Efficacy is dependent on hitting the target with the right dose
CT based contouring of at-risk lymph nodes

Pectoralis Minor

Level III  Level II  Level I

Practical Essentials Of IMRT, 2004
CT-based delineation is important because LN depth varies

- LN depth correlates with BMI

**SCV**

- Adj. $R^2$ 0.74
- $p < 0.00001$

**Level III**

- Adj. $R^2$ 0.69
- $p < 0.00001$

*Lienssawangwong et al. Int J Rad Oncol Biol Phys, 2007*
For high tangents, be mindful of the superior posterior border.
Implementation of Z11 into practice at MDACC…

- Radiation field design in women meeting criteria for Z11

<table>
<thead>
<tr>
<th></th>
<th>Year prior to Z11</th>
<th>Year after Institutional Meeting</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>“High” tangents</td>
<td>10%</td>
<td>43%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regional-nodal Radiation</td>
<td>8%</td>
<td>8%</td>
<td>ns</td>
</tr>
</tbody>
</table>

- Increased use of “high” tangents, no increase in regional-nodal radiation
Implementation of Z11 into practice at MDACC…

- Increased use of high tangents reflects decrease in ALND among women with positive SLN

<table>
<thead>
<tr>
<th></th>
<th>ALND n=54</th>
<th>SLND without ALND n=26</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>“High” tangents</td>
<td>2% (1/54)</td>
<td>88% (23/26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regional-nodal Radiation</td>
<td>26% (14/54)</td>
<td>23% (6/26)</td>
<td>ns</td>
</tr>
</tbody>
</table>

- SLND without ALND was not associated with increased use of regional-nodal radiation
Based on the results of Z11

ALND can be omitted in:

- T1 or T2 clinically node negative
- 1-2 SLN metastasis
- Planned BCT with whole breast radiation

Special consideration in:

- Young patients
- High nodal burden
- ER-negative tumors
ALND remains standard treatment

Those not included in Z11:

- Clinically positive axilla
- Neoadjuvant chemotherapy patients
- Patients undergoing PBI
- Patients who otherwise would not require radiation therapy
  - Low-risk stage II undergoing mastectomy
Z11 has already changed practice

- Pre-operative discussions
  - Part of BCT versus mastectomy counseling
  - Component of partial breast irradiation discussion
- Intraoperatively, can omit intra-operative SLN assessment
- Radiation treatment design
  - Deliberate targeting of level I/II lymph nodes
  - Use primary tumor and SLN information to select patients for regional-nodal radiation