Radiotherapeutic management of the axilla in breast cancer

Presented by: Kiri Cook, MD, Assistant Professor, Department of Radiation Medicine

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Learning Objectives

• Review the data for axillary radiation in the management of breast cancer
• Discuss the controversies surrounding radiation field design in women with low volume axillary disease
• Review the available data to help guide radiation decision making in controversial areas
• Address some unanswered questions in axillary management

Silverstein et al., World J Surg 2001

Table 1. T-stage value with p-value

<table>
<thead>
<tr>
<th>T-stage</th>
<th>Positive</th>
<th>Radiation sensitivity (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>25% (6)</td>
<td>0.002</td>
</tr>
<tr>
<td>T1a</td>
<td>31.8% (7)</td>
<td>0.002</td>
</tr>
<tr>
<td>T1b</td>
<td>42.8% (2)</td>
<td>0.002</td>
</tr>
<tr>
<td>T1c</td>
<td>18.6% (2)</td>
<td>&gt;0.050</td>
</tr>
<tr>
<td>T2</td>
<td>27.8% (2)</td>
<td>&gt;0.050</td>
</tr>
<tr>
<td>T3</td>
<td>88.0% (1)</td>
<td>0.001</td>
</tr>
<tr>
<td>T4</td>
<td>15.5% (4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td>66.22% (10)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
**Historical Perspective**

- 1800s: William Halsted and the radical mastectomy
- 1930s: Radiation therapy as an alternative to surgery
- 1948: Radiation used adjuvantly post-mastectomy
- 1980s: NSABP B-04
- 1994: Sentinel lymph node biopsy

**cN0 patients – ACOSOG Z0011**

- cT1-T2 N0, post lumpectomy with 1-2 positive sentinel nodes
- Majority ER/PR+
- Randomization: completion ALND vs no completion ALND
- All received adjuvant whole breast radiation (no RT)
- 97% had systemic therapy (chemo or endocrine)
- DFS at 10 years 78% ALND vs 80% SNB
- OS at 10 years 84% vs 86%

**ACOSOG Z0011**

- 27% in ALND group had additional positive nodes
- Median nodes removed = 17
- Radiation can sterilize microscopic nodal disease
- Radiation was tangent only; targeted axilla/3rd field was prohibited

 Giuliano, JAMA 2011 and 2017
Radiation in Z0011

- 456 women enrolled
  - 651 case report forms obtained
  - 228 detailed RT records
  - 142 with sufficient records to evaluate tangent height

- 50% of patients in each group received high tangents
- 19% received a 3rd field
- Those receiving a 3rd field had more nodal involvement

50% of patients in each group received high tangents
- 19% received a 3rd field
- Those receiving a 3rd field had more nodal involvement

AMAROS

- cT1-2 N0 with a positive sentinel node
- Median age 55
- 80% post lumpectomy, majority had 1-2 positive sentinel nodes
  - 60% macromet vs 30% micromet
- 90% received adjuvant systemic treatment
- Randomization: ALND vs adjuvant radiation
- 10 year LRR equivalent (~4%)
- 33% had additional positive nodes on ALND

Radiation in AMAROS

- Axillary RT included all 3 axillary levels and the medial supraclavicular fossa
- Axillary RT allowed after ALND if ≥ 4 positive nodes

<table>
<thead>
<tr>
<th>Node Location</th>
<th>ALND (%)</th>
<th>RT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78%</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>17%</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>&gt;3</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*SN: Sentinel Node*
Z11 and AMAROS

Toxicity

- Z0011
  - ALND group had higher:
    - Surgical complications
    - Lymphedema
    - Axillary parasthesias
  - Radiation is standard of care for cT1-2N0 with 1-2 SN+
  - No or no?

- AMAROS
  - ALND group had higher:
    - Lymphedema
    - Difficulty moving the arm (post hoc analysis)
  - No difference in QoL.

High Risk Breast Cancer

- 82b: Premenopausal women
- LN+, tumor > 5cm, or invasion of skin or pec fascia
- Surgery: total mastectomy and ALND
  - Median LN removed: 7
- Chemo: Cyclophosphamide, MTX, fluorouracil
- Randomized to adjuvant chemo +/- radiation

- 82c: Postmenopausal women randomized to tamoxifen +/- radiation

Ovegaard et al., NEJM 1997 and Lancet 1999
Danish 82b/82C

- Pre-menopausal women
- LN+
- Surgery: Modified radical mastectomy
  - Median LN removed = 11
- Chemo: CMF
- Randomized to chemo +/- radiation
- OS: 54% vs 46% at 15 years (p = .07) 

British Columbia

- Pre-menopausal women
- LN+
- Surgery: Modified radical mastectomy
  - Median LN removed = 11
- Chemo: CMF
- Randomized to chemo +/- radiation
- OS: 54% vs 46% at 15 years (p = .07) 

Field design in PMRT Trials

- Danish 82b/82c: Chest wall, axilla, supraclav, infraclav, IMN
  - 50 Gy in 25 fx or 48 Gy in 22 fx
- British Columbia: Chest wall, axilla, supraclav, infraclav, bilateral IMN
  - 37.5 Gy in 16 fx
Controversy

- Axillary RT well established alternative to ALND for early stage N+ breast cancer
  - AMAROS: RNI covered
  - Z11: ?? covered
- Survival benefit to PMRT with RNI in high risk patients
- RNI for everyone!

MA.20

- S/p lumpectomy and SNB or ALND
- Positive nodes or node negative with “high risk features”
  - T3
  - T2 with <10 nodes removed and at least one of: grade 3, ER-, LVSI
- ALND required if SNB+
- Majority received adjuvant chemo
- Median nodes removed: 13
- Randomization: WBRT +/- RNI

Radiation in MA.20

- 50 Gy in 25 fractions, boost allowed
- RNI group: included supraclavicular, infraclavicular and internal mammary nodes
  - If <10 axillary nodes removed or >3 positive nodes, included level I/II axilla.
**MA.20 Results**

- Improved locoregional recurrence, distant DFS, and DFS, but not OS

**EORTC 22922**

- S/p lumpectomy (76%) or mastectomy + SNB or ALND
- Centrally or medially located N+/–
- Externally located N+
- Majority (85%) had either no involved nodes or 1-3 involved nodes
- Most received systemic therapy
- Median nodes removed: 15
- Randomization: whole breast/chest wall RT +/- RNI

**Radiation in EORTC 22922**

- 50 Gy in 25 fractions, most with boost
- RNI group: medial supraclavicular (to AC joint or apical axillary clips or both) + IMN in first 3 intercostal spaces (or first 5 if LIQ primary)
- Axilla not intentionally targeted in majority of cases
**EORTC 22922 results**

- Improved rate of any first recurrence, distant DFS, and breast cancer mortality, with a marginal effect on OS
- RNI for everyone?!

**Toxicity**

**MA.20**
- Acute dermatitis: 49% vs 40% (S)
- Pneumonitis/fibrosis: 0.4% vs 0.3% (NS)
- Cardiac disease: 0.9% vs 0.4% (NS)
- Lymphedema: 8.4% vs 4.3% (S)

**EORTC**
- Pulmonary fibrosis: 4.4% vs 1.7% (S)
- Cardiac fibrosis: 1.2% vs 0.6% (NS)
- Cardiac disease: 6.5% vs 3.6% (NS)
- Lymphedema: 12% vs 10.5% (NS)

**Lymphedema**

- Prospective screening trial
- 1815 patients from 2005-2018
- Median follow up: 52 months
- Lymphedema: ≥10% relative increase in arm volume >3 months postop

<table>
<thead>
<tr>
<th></th>
<th>SNB</th>
<th>SNB+RNI</th>
<th>ALND</th>
<th>ALND+RNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphedema</td>
<td>8%</td>
<td>10.7%</td>
<td>24.9%</td>
<td>30.1%</td>
</tr>
<tr>
<td>LRR</td>
<td>2.3%</td>
<td>0%</td>
<td>3.8%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>
Controversy?

- MA.20 and EORTC: DFS benefit seen even in low nodal burden/high risk node negative patients
- The classic PMRT trials (Danish 82b/82c and British Columbia) used RN and demonstrated a survival benefit in any number of positive nodes
  - Critics/isms: high rates of locoregional recurrence; inadequate axillary dissection and outdated systemic therapy
- Higher skin, lung toxicity, slightly increased lymphedema risk
- Modern retrospective series show low rates of regional failure in 1-3N+ patients

Supraclavicular failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up</th>
<th>Median age</th>
<th>Number</th>
<th>Median follow-up</th>
<th>S'clav failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livi 2010</td>
<td>6.8 yrs</td>
<td>70</td>
<td>1107</td>
<td>2.1%</td>
<td></td>
</tr>
<tr>
<td>Yu 2010</td>
<td>88 mths</td>
<td>448</td>
<td>294 (144)</td>
<td>1.8%</td>
<td></td>
</tr>
<tr>
<td>WoJY 2010</td>
<td>77 mths</td>
<td>218</td>
<td>100 (77)</td>
<td>2.1%</td>
<td></td>
</tr>
<tr>
<td>Truong 2009</td>
<td>88 mths</td>
<td>1255</td>
<td>100 (200)</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>MacDonald 2009</td>
<td>80 mths</td>
<td>165</td>
<td>100 (30)</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>Reddy 2007</td>
<td>72 mths</td>
<td>202</td>
<td>100 (100)</td>
<td>2.0%</td>
<td></td>
</tr>
<tr>
<td>DBCCG 2006</td>
<td>8 years</td>
<td>1545</td>
<td>100 (150)</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>Strom 2005</td>
<td>116 mths</td>
<td>465</td>
<td>100 (465)</td>
<td>2.3%</td>
<td></td>
</tr>
<tr>
<td>Taghian 2004</td>
<td>11.1 yrs</td>
<td>2957</td>
<td>100 (2957)</td>
<td>2.3-3.5%</td>
<td></td>
</tr>
<tr>
<td>Stranzl 2004</td>
<td>44.4 mths</td>
<td>183</td>
<td>100 (183)</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>Chen 2002</td>
<td>39 mths</td>
<td>2658</td>
<td>307 (2351)</td>
<td>4.3%</td>
<td></td>
</tr>
<tr>
<td>Galper 1999</td>
<td>125 mths</td>
<td>691</td>
<td>0-3LN+ 2351</td>
<td>1.3%</td>
<td></td>
</tr>
</tbody>
</table>

Predicting Supraclavicular Failure

- Age <50
- Grade 3
- ER
- LVI
- >3 positive axillary nodes
- Level II or III nodes pos
- ECE
- >25% nodes pos (only applies to ALND)
- <10 nodes removed
- Largest axillary node >2cm
EBCTCG Meta-analysis

- 22 trials, 3786 women
- Post-mastectomy
- Radiation included chest wall, supraclavicular or axillary fossa (or both) and IMN

A note on IMN

- DBCG-IMN
- 3089 patients, early stage node positive breast cancer
- All received RT to breast/chest wall, supraclav, axilla II-III, and level I if 6 or more nodes involved
- Right sided: received IMN radiation
- Left sided: no IMN radiation
- Breast cancer mortality: 20.9% vs 23.4% (p = .03)
- Overall survival 72.2% vs 75.9% (p = .005)
- Cardiac disease equivalent

What to treat?

<table>
<thead>
<tr>
<th>LN+</th>
<th>Breast/CW</th>
<th>Clav/Iclav</th>
<th>Axilla</th>
<th>IMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>yes</td>
<td>20011-no</td>
<td>Yes if inadequate nodal dissection</td>
<td>20011-no</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MA20-yes</td>
<td></td>
<td>EORTC-yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 RCTs of post mast RT-yes</td>
<td></td>
<td>DBCG-yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retro reviews-select cases</td>
<td></td>
<td>3 RCTs of post mast RT-yes</td>
</tr>
<tr>
<td>3+</td>
<td>yes</td>
<td>3 RCTs of post mast RT-yes</td>
<td>Yes if inadequate nodal dissection or &gt;50% LN+</td>
<td>DBCG-yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 RCTs of post mast RT-yes</td>
</tr>
</tbody>
</table>
What to Treat

- For 1-3 nodes, no high risk features: default to covering regional nodes but can consider sacrificing some coverage if normal tissue constraints hard to treat
- For 4+ nodes, high risk features: cover regional nodes, only sacrifice coverage if all options have been exhausted

Unanswered Questions

- Low volume axillary disease
  - MAJ/Taylor RT: HER2+, Her2-, LN 1-3+, Oncotype < 18
  - Randomization: RNI vs no RNI
- Neoadjuvant chemotherapy
  - NSABP B31: CT: T1N0, 1-3, pCR, nodal pCR
  - Randomization: RNI vs no RNI
- Alliance A011202: cT1-3N1, s/p NACT, positive SNB
  - Randomization: ALND +/- RNI
- Fractionation
  - Standard: 50 Gy in 25 fractions, Hypo: 42.56 Gy in 16 fractions for similar
  - RT-CHARM: Hypofractionated vs standard PMRT in patients planned for breast reconstruction

Thank You!