PMRT

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PGY-2
10/24/12
Staging—Primary Tumor (T)

**T1:** Tumor 2cm or less in greatest dimension
  - **T1mi:** Tumor < 0.1cm in greatest dimension
  - **T1a:** Tumor more than 0.1cm but less than 0.5cm
  - **T1b:** Tumor more than 0.5cm but not more than 1cm
  - **T1c:** Tumor more than 1 cm but not more than 2cm

**T2:** Tumor more than 2-5cm in greatest dimension

**T3:** Tumor >5cm in greatest dimension

**T4:** any size w/ direct extension to (a) chest wall or (b) skin
  - **T4a:** Extension to chest wall, not including pectoralis muscle
  - **T4b:** Edema (including peau d’orange) or ulceration of the skin of the breast, or satellite skin nodules not confined to the same breast
  - **T4c:** Both T4a and T4b
  - **T4d:** Inflammatory carcinoma
Regional Lymph Nodes (N)

• N1  Mets to movable ipsilateral LNs

• N2
  – N2a: Mets to ipsilateral axillary LNs fixed to one another (matted) or to other structures
  – N2b: Mets only in *clinically apparent* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary LN mets

• N3
  – N3a: Mets in ipsilateral infraclavicular LNs
  – N3b: Mets in ipsilateral internal mammary LNs and axillary LNs
  – N3c: Mets in ipsilateral supraclavicular LNs
Stage Grouping

Stage IA: \( T1N0M0 \)
Stage IB: \( T0-1N1 \) (micromets)
Stage IIA: \( T0-1N1M0 \)
\( T2N0M0 \)
\( T2N1M0 \)
\( T3N0M0 \)
Stage IIIB: \( T2N1M0 \)
\( T3N0M0 \)
Stage IIIA: \( T0-3N2, T3N1M0 \)
Stage IIIB: \( T4N0-2 \)
Stage IIIC: \( TxN3M0 \)
Stage IV: \( TxNxM1 \)
Ten-year overall survival rates in patients with breast cancer: stage IIA, 80%; IIB, 70%; IIIA, 60%; IIIB, 50%.
Mastectomy

• Simple mastectomy (or "total mastectomy"):
  – entire breast tissue is removed, but axillary contents are undisturbed with sentinel node bx

• Modified radical mastectomy:
  – The entire breast tissue + ALND

• Radical mastectomy (or "Halsted mastectomy")
  – Removing the entire breast, the axillary lymph nodes, and the pectoralis major and minor muscles behind the breast. Reserved for muscle invasion
Danish trial 82b (1982-89)

Randomized. 1708 pts.
Premenopausal high-risk pts, who had one or more of:
  - positive axillary LN, tumor > 5 cm, invasion of skin or pectoral fascia.

- Randomized after surgery to: RT + CMF chemotherapy, CMF alone, or CMF + tamoxifen. (enrollment in the third group was stopped after 1986 due to higher mortality).

- Surgery consisted of total mastectomy + axillary node dissection (level I and part of level II). Median # of LN removed was 7. RT was to chest wall, SCLV fossa, infraclavicular LN, and IMN in first 4 intercostal spaces. 50 Gy in 25 fx (or 48 Gy in 22 fx, 4days/wk). Recommended use of anterior electron field to treat CW and IMN.

- Chemo: 8 cycles of CMF with RT, or 9 cycles if given alone. RT was sandwiched between first 2 cycles of chemo.

Danish trial 82b (1982-89)

- Median f/u: 114 months. LRR 9% (RT+CMF) vs 32% (CMF). 10-yr DFS 48% vs 34%. 10-yr OS 54% vs 45%.
- RT improved DFS and OS irrespective of tumor size, number of positive LN, or grade, in these high risk pts. More than 50% of local recurrence were on the chest wall.
- **Conclusion:** improved survival with post-op RT
- number of positive LN is difficult to determine from this study because few nodes were removed (median: 7) and many pts had fewer than 4 nodes sampled.

Danish trial 82b (1982-89)

![Graphs showing disease-free survival and overall survival over years after mastectomy for radiotherapy + CMF (54%), CMF (45%), and radiotherapy + CMF (48%), CMF (34%).]

*Figure 1.* Kaplan–Meier Estimates of Disease-free Survival among Women Treated with Radiotherapy plus CMF and CMF Alone. Values in parentheses are disease-free survival at 10 years.

*Figure 2.* Kaplan–Meier Estimates of Overall Survival among Women Treated with Radiotherapy plus CMF and CMF Alone. Values in parentheses are overall survival at 10 years.

Danish trial 82c (1982-90)

- 1375 pts. Stage II or III
- Postmenopausal high-risk pts. Randomized to post-mastectomy: tamoxifen (for 1 yr), or to tam + RT.
- Median f/u 123 months. LRR 8% (RT) vs 35% (No RT). DFS 36% vs 24%. 10-yr OS 45% vs 36%.
- The endpoints were first site of recurrence (locoregional recurrence, distant metastases, or both), and disease-free and overall survival.
- Conclusion: Improved survival with post-op RT

Danish trial 82c (1982-90)

Figure 2: Effect of radiotherapy on disease-free survival and overall survival

Long-Term Results: 82b and c

• Combined 82b and c: 18 year follow up
• probability of any first breast cancer event was
  73%(no RT) and 59%(RT) (P < .001) (relative
  risk [RR], 0.68; 95% CI, 0.63 to 0.75).
• LRR 49% vs 14%(RT). LRR for 1-3 +LN: 27% vs.
  4% (RT) 4+ LN: 51% vs. 10%(RT) All SS.
• DM 64% vs 53%(RT). (P < .001) 73% chance of
  DM after developing LRR; does not depend on
  initial treatment.
• **Conclusion**: PMRT changes the disease recurrence pattern in high-risk breast cancer patients; fewer patients have LRR as first site of recurrence, and overall fewer patients have DM.

Long-Term Results: 82b and c

Overall Survival

• **1-3 LN**: 57% (RT) vs 48%; **4+ LN**: 27% (RT) vs 12%. All SS.

• No OS benefit for patients that were ER/PR- or HER2+.

British Columbia Trial

- CMF 6-12 mo +/- RT
- 318pts With LN+, premenopausal high risk +ALN s/p mastectomy.
- Modified radical mastectomy with median 11 LN removed.
- 20 yr fu

British Columbia Trial

• Radiation:

• 5 field, 37.5Gy/16f Co-60. CW with tangents, supraclavicular/axillary + PAB in 35 Gy/16, bilateral IM 37.5/16 with en face photon field. RT given between cycle 4 and 5.
Treatment of the internal mammary nodes

- Classically done with an en face electron or photon field.
- This field arrangement gave dose not only to the left ventricle but also the coronary arteries.
- Field often treated the supraclavicular fossa in continuity: the “hockey stick”.
British Columbia Trial

• LRR: 26% vs 10%(RT)
• OS: 37% vs 47%(RT) SS
• Similar results for 1-3 LN and >4 LN
• Arm edema in 3.2% vs 9.1%(RT).

British Columbia Trial

Overall Survival

Recurrence free survival

p-value = 0.03  RR: 0.73 (0.55, 0.98)

p-value = 0.002  RR: 0.36 (0.18, 0.71)
## British Columbia Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Chemotherapy-alone arm</th>
<th>Chemotherapy and radiation therapy arm</th>
<th>RR (95% CI)</th>
<th>P†</th>
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<tbody>
<tr>
<td></td>
<td>Survival, %‡</td>
<td>No. of events/ No. of patients</td>
<td>Survival, %‡</td>
<td>No. of events/ No. of patients</td>
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<tr>
<td>All 318 patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Event-free survival</td>
<td>25</td>
<td>116/154</td>
<td>35</td>
<td>105/164</td>
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<tr>
<td>Breast cancer–free survival</td>
<td>30</td>
<td>107/154</td>
<td>48</td>
<td>84/164</td>
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<tr>
<td>Survival free of isolated locoregional disease</td>
<td>74</td>
<td>27/154</td>
<td>90</td>
<td>12/164</td>
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<tr>
<td>Systemic breast cancer–free survival</td>
<td>31</td>
<td>104/154</td>
<td>48</td>
<td>84/164</td>
</tr>
<tr>
<td>Breast cancer–specific survival</td>
<td>38</td>
<td>95/154</td>
<td>53</td>
<td>75/164</td>
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<tr>
<td>Overall survival</td>
<td>37</td>
<td>101/154</td>
<td>47</td>
<td>89/164</td>
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</tbody>
</table>
Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended by international consensus reports?

A subgroup analysis of the DBCG 82 b & c randomized trials.

– Analysis of pts with 8 or more nodes
– 1152 patients

**DBCG 82 b & c randomized trials**

Subanalysis of pts with \( >8 \) LN’s

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1–3 pos. nodes</th>
<th>4+ pos. nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endpoint: loco-regional recurrence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>87%</td>
<td>82%</td>
</tr>
<tr>
<td>Absolute risk reduction</td>
<td>20%</td>
<td>24%</td>
</tr>
<tr>
<td>Number of patients needed to treat to avoid an LRR</td>
<td><strong>5</strong></td>
<td><strong>4</strong></td>
</tr>
<tr>
<td><strong>Endpoint: death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>17%</td>
<td>11%</td>
</tr>
<tr>
<td>Absolute risk reduction</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Number of patients needed to treat to avoid a death</td>
<td><strong>11</strong></td>
<td><strong>10</strong></td>
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</table>

Relative and absolute risk reduction and number of patients needed to treat to achieve benefit of postmastectomy radiotherapy as a function of number of positive lymph nodes. Estimates are calculated for the benefit of avoiding an isolated first loco-regional recurrence or death.

Conclusion:

• The survival benefit after postmastectomy RT was substantial and similar in patients with 1–3 and 4+ positive lymph nodes.
• The indication for RT seems therefore to be at least equally beneficial in patients with 1–3 positive nodes.
Neoadjuvant chemo

MDACC – Retrospective review 1977-2000

• 542 patients treated on six consecutive institutional prospective trials with neoadjuvant chemotherapy, mastectomy, and PMRT
• compared to 134 patients who received similar treatment in these same trials but without radiation
• Median follow up – 10 yr
• RT - CW+LN’s 50 Gy + 10 Gy CW boost.

Huang EH et al. J Clin Oncol. 2004 Dec 1;22(23):4691-9
Neoadjuvant chemo

Table 1. Neoadjuvant Chemotherapy Regimens

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Years of the Study</th>
<th>Neoadjuvant Chemotherapy Regimen</th>
<th>No. of Cycles</th>
<th>CT + M</th>
<th>CT + M + RT</th>
<th>Total Study Population*</th>
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<tr>
<td>Advanced Primary</td>
<td>1974-1985</td>
<td>FAC</td>
<td>3</td>
<td>33</td>
<td>91</td>
<td>191</td>
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<tr>
<td>85-01</td>
<td>1985-1989</td>
<td>VACP</td>
<td>3</td>
<td>19</td>
<td>141</td>
<td>200</td>
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<tr>
<td>89-007</td>
<td>1989-1991</td>
<td>FAC</td>
<td>4</td>
<td>11</td>
<td>104</td>
<td>203</td>
</tr>
<tr>
<td>91-015</td>
<td>1991-1994</td>
<td>FAC or dose-escalated FAC</td>
<td>4</td>
<td>11</td>
<td>101</td>
<td>202</td>
</tr>
<tr>
<td>94-002</td>
<td>1994-1998</td>
<td>FAC or paclitaxel</td>
<td>4</td>
<td>60</td>
<td>41</td>
<td>174</td>
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<tr>
<td>97-099</td>
<td>1998-2000</td>
<td>AT</td>
<td>6</td>
<td>0</td>
<td>64</td>
<td>88</td>
</tr>
<tr>
<td>Total</td>
<td>1974-2000</td>
<td></td>
<td></td>
<td>134</td>
<td>542</td>
<td>1,058</td>
</tr>
</tbody>
</table>

Abbreviations: FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; VACP, vincristine, doxorubicin, cyclophosphamide, and prednisone; AT, doxorubicin, docetaxel; CT, chemotherapy; M, mastectomy; RT, radiation.

*The total study population includes other patients who were not analyzed in this report, such as those receiving breast-conserving surgery with or without radiation.

Huang EH et al. J Clin Oncol. 2004 Dec 1;22(23):4691-9
Neoadjuvant chemo

Outcomes:
• LRR 11%(RT) vs. 22% (SS)
• Clinical stage LRR:
  – I-IIA no benefit for PMRT.
  – Stage IIB+ 11%(RT) vs. 26% (SS)
  – cT3-T4 8%(RT) vs. 22% (SS)
  – cN2-3 12%(RT) vs. 40%.
• Pathologic stage LRR:
  – ypT2+ 14%(RT) vs. 59% (SS)
  – Stage II with 1-3 LN+ no benefit for PMRT (but few pts)
  – pN0 4%(RT) vs. 11% (SS)
  – ≥ 4 LN+ 16%(RT) vs. 59% (SS)

Survival benefit:
• CSS
  – cStage IIIB+ 22%(RT) vs. 44% (SS)
  – cT4 24%(RT) vs. 45% (SS)
  – cN2-3 27%(RT) vs. 49% (SS)
  – ≥ 4 LN+ 18%(RT) vs. 44%
  – *No inflammatory breast ca included
Neoadjuvant chemo

Predictors for LRR:

- no PMRT, >20% LN+, no tamoxifen, cStage IIIB+, no response to neoadjuvant chemo
Neoadjuvant chemo

Conclusion:

- PMRT should be considered for clinical T3, clinical Stage III-IV and patients with $\geq 4$ LN+ at surgery, regardless of response to chemotherapy
T3N0

Ohh no! What do you do??
• MGH/MDACC/Yale - Between 1981 and 2002
• Review of multi-institutional database (Floyd, IJROBP 2006)
• 70 pts
• T3N0
• s/p mastectomy+chemo
  – no PMRT. No neoadj. Median FU 7y.
T3N0

- 5y LRF 7.6%, mostly in CW (4/5)
- LVSI significant prognostic factor
- DFS 83%, OS 86%
T3N0

• Conclusion: No need for PMRT in T3N0, consider if LVSI present

Review of NSABP postmastectomy chemo trials
B-13, B-14, B-19, B-20, and B-23 node-negative trials

• 313 pts, T3N0 treated with MRM +/- chemo, no PMRT, on NSABP trials
  – Therapy included adjuvant chemotherapy in 34.2% of pts; tamoxifen in 21.1%; chemotherapy plus tamoxifen in 19.2%; and no systemic therapy in 25.5%
Review of NSABP postmastectomy chemo trials
B-13, B-14, B-19, B-20, and B-23 node-negative trials

- Median Fu 15.1y.
- 10y isolated LRF 7.1% and LRF +/- DM 10%, mostly at the CW.
- No significant prognostic factors

- Conclusion: Routine use of PMRT in this group is not warranted

Taghian AG, J Clin Oncol. 2006 Aug 20;24(24):3927-32
Who needs PMRT?

• All women with > 3 positive nodes.
• All women with any positive node and a tumor larger than 5 cm.
• ?? Women with positive margins: With other risk factors like size, young age, LVSI or high grade.
• ?? Women with T3N0: Probably not, especially in older women.
• ?? Women with 1-3 positive nodes and T1/T2: Generally yes and especially in women < 45.
• ??After neoadjuvant chemo: If Stage III/IV at diagnosis, if node positive after chemo, if node positive prior to chemo with other high risk features.
Why not PMRT?

- Greater risk for lymphedema of breast and arm
- Increased amount of lung that is fibrosed by radiation, primarily from treatment of either the supraclavicular nodes or internal mammary nodes. EBCTCG also showed increase risk of lung cancer, RR=1.78 but no increase in respiratory disease.
- May expose contralateral breast to radiation.
- Decrease in the quality of the cosmetic outcome following reconstruction, especially with implants.