Postmastectomy Radiotherapy in N1 Breast Cancer: Pros

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   Randomized study of mastectomy +/- PMRT
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Introduction

• Goal of post-mastectomy RT (PMRT)
  – Irradiate residual microscopic disease after mastectomy
  – ↓ local regional recurrence (LRR)
  – ↑ survival

→ Identify high risk patients

<table>
<thead>
<tr>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node +</td>
</tr>
<tr>
<td>T size &gt;5cm</td>
</tr>
</tbody>
</table>

Patient –age
Pathology –margins, grade, LVI, ER status
## Modern Randomized Trials: Mastectomy +/- PMRT

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Treatment</th>
<th>XRT</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Danish 82b</strong></td>
<td>1708 premeno</td>
<td>Mastectomy/CMF +/- XRT</td>
<td>XRT</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>(NEJM 1997)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10-year)</td>
<td></td>
<td>No XRT</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>LRR</td>
<td></td>
<td></td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>23% ↓LRR</td>
<td></td>
<td>Survival</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>9% ↑OS</td>
<td></td>
<td></td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td><strong>Danish 82c</strong></td>
<td>1385 postmeno</td>
<td>Mastectomy/TAM +/- XRT</td>
<td>XRT</td>
<td>p=0.03</td>
</tr>
<tr>
<td>(Lancet 1999)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10-year)</td>
<td></td>
<td>No XRT</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>LRR</td>
<td></td>
<td></td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>27% ↓LRR</td>
<td></td>
<td>Survival</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>9% ↑OS</td>
<td></td>
<td></td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td><strong>British Columbia</strong></td>
<td>318 premeno, +LN</td>
<td>Mastectomy/CMF +/- XRT</td>
<td>XRT</td>
<td>p=0.05</td>
</tr>
<tr>
<td>(NEJM 1997)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(15-year)</td>
<td></td>
<td>No XRT</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>LRR</td>
<td></td>
<td></td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>20% ↓LRR</td>
<td></td>
<td>Survival</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>8% ↑OS</td>
<td></td>
<td>BCa-specific OS</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>57%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td><strong>LRR</strong></td>
<td></td>
<td></td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td><strong>p</strong></td>
<td></td>
<td></td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>
Meta-analysis (Whelan et al., JCO 2000)
Mastectomy +/- RT

1967-1999, 18 trials, 6300 pts, almost post-MRM, pN+
Analyzed only trials that included systemic Tx

Local-regional relapse

Fig 2. Meta-analysis of locoregional radiation therapy randomized trials: locoregional recurrence.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klefstrom</td>
<td>79</td>
<td>0.11</td>
<td>0.04, 0.34</td>
</tr>
<tr>
<td>Blomqvist</td>
<td>99</td>
<td>0.23</td>
<td>0.06, 0.86</td>
</tr>
<tr>
<td>Hayat</td>
<td>112</td>
<td>0.12</td>
<td>0.03, 0.56</td>
</tr>
<tr>
<td>Muss</td>
<td>159</td>
<td>0.33</td>
<td>0.11, 0.95</td>
</tr>
<tr>
<td>Griem</td>
<td>206</td>
<td>0.30</td>
<td>0.11, 0.88</td>
</tr>
<tr>
<td>McArdle</td>
<td>219</td>
<td>0.36</td>
<td>0.17, 0.76</td>
</tr>
<tr>
<td>Velez-Garcia</td>
<td>239</td>
<td>0.44</td>
<td>0.21, 0.93</td>
</tr>
<tr>
<td>Martinez</td>
<td>227</td>
<td>0.24</td>
<td>0.12, 0.51</td>
</tr>
<tr>
<td>Olson</td>
<td>312</td>
<td>0.38</td>
<td>0.19, 0.76</td>
</tr>
<tr>
<td>Ragaz</td>
<td>318</td>
<td>0.43</td>
<td>0.23, 0.79</td>
</tr>
<tr>
<td>Tennvall-Nittby</td>
<td>768</td>
<td>0.31</td>
<td>0.19, 0.51</td>
</tr>
<tr>
<td>Overgaard(TAM)</td>
<td>1375</td>
<td>0.15</td>
<td>0.11, 0.21</td>
</tr>
<tr>
<td>Overgaard(CMF)</td>
<td>1708</td>
<td>0.16</td>
<td>0.11, 0.22</td>
</tr>
</tbody>
</table>

Random Effects OR = 0.25 95% CI = 0.19, 0.34

Radiation reduced odds of LRR by 75%
Meta-analysis (Whelan et al., JCO 2000)
Mastectomy +/- RT

Overall Survival

Radiation reduced odds of death by 17%
PMRT: pN+

British Columbia Randomized Trial, 20-years results (Ragaz JNCI 2005)
N=318 BCa, 1979-1986, premeno, pN+, post-MRM, Median 11 LN sampled
Mastectomy/CMF +/- XRT

LRR 26→10% (p=0.002)  16% ↓LRF
OS 37→47% (p=0.03)        10% ↑OS
Breast ca-specific survival 38→53% (p=0.008)
PMRT: pN+

EBCTCG meta-analysis (Lancet 2005), BCS/Mastectomy +/- RT Trials
1995-2000, N=42000, 78 Randomized Trials

Local Recurrence
• 2/3 reduction in LN- & LN+

Breast Ca Survival
• None in LN-
• 5% for LN+

15-Y LC

15-Y BCa Mortality

8% vs. 3%

28% vs. 31%

29% vs. 8%

60% vs. 55%
PMRT: Failure Pattern

DBCG 82b&82c trials, **10 years results** (Nielsen, JCO 2006)
- DBCG 82b (CMF, premeno) & DBCG 82c (Tamoxifen, postmeno)
- N=3083, 1982-1990, post-MRM, Median 7 LN sampled
- To examine disease recurrence pattern among with or without PMRT
PMRT, pN1 in modern systemic therapy

Cleveland Clinic, Tendulkar et al. IJROBP 2012

- 2000-2007, N=369 (271 No PMRT, 98 PMRT), 1-3 LN+ BCa
- Mastectomy → No PMRT, CTx: 79%, HT: 79%, (***No Systemic Tx: 5%) 
- To report experience of patients with 1-3 LN+ after undergoing a mastectomy
- F/up: 5.2 yrs
- 5-year rate of LRR: 8.9% without PMRT vs. 0% with PMRT (P=0.004)

- Risk factors for LRR in multivariate analysis
  - ECE (HR 4.3, P=0.0006)
  - G III (HR 3.6, P=0.004)

- 5-year LRR in Subgroups (p<0.0001)
  - 4.1% with neither G III nor ECE
  - 8.1% with either G III or ECE
  - 50.4% with both G III and ECE

Fig. Kaplan-Meier curves for locoregional recurrence-free survival, stratified by Bloom-Richardson grade and extracapsular extension (ECE) in 271 patients with 1-3 positive lymph nodes treated with mastectomy with or without systemic therapy but without adjuvant radiotherapy.
PMRT, pN1 in modern systemic therapy

YUMC, Kim et al. BJC 2013

1998~2009, Korean Breast Cancer Registry (KBCR)
N=3477 (3034 No PMRT, 443 PMRT), 1-3 LN+ BCa

To test LNR (ratio of positive nodes to total nodes dissected) as a potential discriminator of higher risk who might benefit from subsequent PMRT

Categorised LNR (cLNR) : verification of the prognostic value of the LNR
Low LNR: <0.18, N=3059
Intermediate : 0.18-0.30, N=418

Table 2. Multivariate analysis of overall survival of breast cancer patients with pN1 disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, &gt;36</td>
<td>0.55</td>
<td>0.41–0.74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tumour size, T2</td>
<td>1.31</td>
<td>1.02–1.67</td>
<td>0.0336</td>
</tr>
<tr>
<td>Oestrogen receptor, positive</td>
<td>0.68</td>
<td>0.53–0.89</td>
<td>0.0042</td>
</tr>
<tr>
<td>Progesterone receptor, positive</td>
<td>0.54</td>
<td>0.42–0.71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Histologic grade, II and III</td>
<td>1.65</td>
<td>1.03–2.63</td>
<td>0.0380</td>
</tr>
<tr>
<td>cLNR, intermediate</td>
<td>1.81</td>
<td>1.34–2.45</td>
<td>0.0001</td>
</tr>
<tr>
<td>cLNR, low: PMRT, yes</td>
<td>1.25</td>
<td>0.86–1.82</td>
<td>0.2415</td>
</tr>
<tr>
<td>cLNR, intermediate: PMRT, yes</td>
<td>0.39</td>
<td>0.17–0.89</td>
<td>0.0248</td>
</tr>
</tbody>
</table>
Who is at Risk in pT1-2N1?

MSKCC, Moo et al. Ann Surg Oncol 2013

- 1995-2006
- N=1087
- pT1/2, 1-3 positive nodes
- Mastectomy ± PMRT
- F/up: 7 yrs (0-17)

- Compared LRR, RFS, OS among patients with and without PMRT

### TABLE I Clinicopathologic and treatment characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Variable</th>
<th>No PMRT (%)</th>
<th>PMRT (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n = 924)</td>
<td>(n = 163)</td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>&lt;0.5–2 cm</td>
<td>55</td>
<td>42</td>
<td>0.0132</td>
</tr>
<tr>
<td></td>
<td>2–5 cm</td>
<td>45</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>≤50 year</td>
<td>44</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;50 year</td>
<td>56</td>
<td>42</td>
<td>0.0011</td>
</tr>
<tr>
<td>Histological grade</td>
<td>I–II</td>
<td>24</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>62</td>
<td>73</td>
<td>0.029</td>
</tr>
<tr>
<td>Extensive intraductal</td>
<td>Yes</td>
<td>27</td>
<td>25</td>
<td>0.74</td>
</tr>
<tr>
<td>component</td>
<td>No</td>
<td>73</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Multifocal/</td>
<td>Yes</td>
<td>42</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>multicentric</td>
<td>No</td>
<td>58</td>
<td>55</td>
<td>0.32</td>
</tr>
<tr>
<td>LVI</td>
<td>Yes</td>
<td>44</td>
<td>64</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>56</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>ECE</td>
<td>Yes</td>
<td>12</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>88</td>
<td>67</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>No. of positive nodes</td>
<td>1</td>
<td>62</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2–3</td>
<td>37</td>
<td>69</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Size of ALN met</td>
<td>Macroscopic</td>
<td>72</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Microscopic</td>
<td>28</td>
<td>12</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Estrogen receptor status</td>
<td>Positive</td>
<td>77</td>
<td>72</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>21</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Progesterone receptor status</td>
<td>Positive</td>
<td>60</td>
<td>61</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>39</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

PMRT group patients were more likely to have adverse factors.
PMRT vs. no-PMRT groups

- LRR ($p = 0.57$)
- RFS ($p = 0.70$)
- OS ($p = 0.28$)

→ No difference

In No PMRT group

- On multivariate analysis
  - age $\leq 50$ years ($p = 0.002$)
  - LVI (+) ($p < 0.0001$)

Among patients not receiving PMRT, **age $\leq 50$ years and LVI** were associated with increased LRR rates and warrant PMRT consideration.
• N= 884 pT1/2, 1-3 positive nodes
• To identify impact of molecular subtype (MST) on LRR among patients with and without PMRT

4 MST
  • HR+/HER2-(luminal A/B), HR+/HER2+(luminal HER2)
  • HR-/HER2+(HER2), HR-/HER2-(basal)

There was no association between MST and LRR, $p=0.35$

Prognostic factors of LRR (on multivariate analysis)
  • age $\leq 50$ yrs ($p = 0.003$), presence of LVI ($p = 0.0003$)
  • MST was not ($p = 0.38$)
Should postmastectomy RT be standard for patients with:

- N+ >3 LN?
- N+ 1-3 LN; all patients?
- N+ 1-3 LN; with adverse pathology?
- N+ 1-3 LN; young age (<40 y)?
**Meta-analysis (EBCTCG, Lancet 2014)**

**Mastectomy +/- RT (20-years report)**

1964-1986, 22 trials, 8135 pts, almost post-MRM, axillary surgery.

RTx at Chest wall, SCL or axillary fossa(or both), IMN.

F/U 10yrs for all recurrence.

---

**Women Deaths Woman-years since diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>Median per woman</th>
<th>Total (x10^4)</th>
<th>Distribution by years (x10^4)</th>
<th>Chemotherapy</th>
<th>Tamoxifen and ER+</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(&lt;10)</td>
<td>10-19</td>
<td>&gt;20</td>
<td>(&lt;10)</td>
<td>10-19</td>
</tr>
<tr>
<td><strong>(A) Axillary dissection (AD) &gt;=10</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN0</td>
<td>700</td>
<td>480</td>
<td>20-1</td>
<td>13.5</td>
<td>6.1</td>
<td>4.4</td>
</tr>
<tr>
<td>pN+</td>
<td>3131</td>
<td>2074</td>
<td>7.2</td>
<td>30.1</td>
<td>20.3</td>
<td>7.9</td>
</tr>
<tr>
<td>pN1-3</td>
<td>1314</td>
<td>759</td>
<td>12.3</td>
<td>17.3</td>
<td>10.3</td>
<td>5.3</td>
</tr>
<tr>
<td>pN4+</td>
<td>1172</td>
<td>1286</td>
<td>4.8</td>
<td>12.4</td>
<td>9.7</td>
<td>2.5</td>
</tr>
<tr>
<td>pN7+</td>
<td>45</td>
<td>29</td>
<td>6.7</td>
<td>0.4</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>pN unknown</td>
<td>56</td>
<td>39</td>
<td>10.6</td>
<td>0.7</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Total</td>
<td>2884</td>
<td>1592</td>
<td>9.0</td>
<td>44.3</td>
<td>26.8</td>
<td>12.5</td>
</tr>
</tbody>
</table>

**Women given systemic therapy (%)**

- 22% 27% 47%
- 75% 22% 91%
- 65% 24% 86%
- 81% 21% 95%
- 100% 0% 100%
- 64% 24% 83%

---

**Women with systemic therapy (AD) >=10**

- pN0: 100% 0% 100%
- pN+: 100% 0% 100%
- pN unknown: 100% 0% 100%
- Total: 100% 0% 100%

---

**Women with systemic therapy (AD) <10**

- pN0: 10% 11% 21%
- pN+: 56% 28% 84%
- pN unknown: 44% 30% 74%
- Total: 44% 25% 69%
Meta-analysis (EBCTCG, Lancet 2014)
Mastectomy +/- RT

1964-1986, 22 trials, 8135 pts, almost post-MRM, axillary surgery
RTx included the chest wall, SCL or axillary fossa (or both), IMN

In N0, No difference
Meta-analysis (EBCTCG, Lancet 2014)

Mastectomy +/- RT

1964-1986, 22 trials, 8135 pts, almost post-MRM, axillary surgery
RTx included the chest wall, SCL or axillary fossa(or both), IMN

3131, N+

Significantly different

Overall recurrence
RTx 10 year gain 10.6%

Breast cancer mortality
RTx 20 year gain 8.1%
Meta-analysis (EBCTCG, Lancet 2014)
Mastectomy +/- RT

1314 N1-3(+) Significantly different

Radiation
10 year gain 11.5%
20 year gain 7.9%
### Overall recurrence

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/women</th>
<th>RT events Log-rank O-E</th>
<th>Variance of O-E</th>
<th>Ratio of annual event rate RT: no RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No systemic therapy</td>
<td>34/93 (36.6%)</td>
<td>-4.1 16.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy and/or ER+ tam+</td>
<td>177/539 (32.8%)</td>
<td>-38.2 94.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>211/632 (33.4%)</td>
<td>-42.3 111.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Difference between treatment effects in two categories: $\chi^2=0.4; 2p>0.1$, NS

Radiation RR 0.68

### Breast cancer mortality

<table>
<thead>
<tr>
<th>Category</th>
<th>Deaths/women</th>
<th>RT deaths Log-rank O-E</th>
<th>Variance of O-E</th>
<th>Ratio of annual death rates RT: no RT</th>
<th>Rate ratio (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No systemic therapy</td>
<td>46/93 (49.5%)</td>
<td>-2.1 21.8</td>
<td></td>
<td></td>
<td>0.91 (SE 0.20)</td>
</tr>
<tr>
<td>Chemotherapy and/or ER+ tam+</td>
<td>202/539 (37.5%)</td>
<td>-25.9 103.7</td>
<td></td>
<td></td>
<td>0.78 (SE 0.09)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>248/632 (39.2%)</td>
<td>-28.0 125.5</td>
<td></td>
<td></td>
<td>0.80 (SE 0.08)</td>
</tr>
</tbody>
</table>

Difference between treatment effects in two categories: $\chi^2=0.4; 2p>0.1$, NS

Radiation RR 0.80

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**Meta-analysis (EBCTCG, Lancet 2014)**

Mastectomy +/- RT

1314, N1-3(+), whether or not systemic therapy
1314 pN1-3 women with Mast+AD

(f) Number of positive nodes ($\chi^2 = 0.2; \ 2p = 0.7$)
- 1 positive node: 3/189 vs 34/209 (RR 0.24, SE 0.17)
- 2–3 positive nodes: 8/218 vs 35/222 (RR 0.24, SE 0.18)
- Unknown but pN1–3: 8/218 vs 43/238 (RR 0.23, SE 0.15)

(g) Any systemic therapy ($\chi^2 = 1.1; \ 2p = 0.3$)
- No systemic: 0/93 vs 12/88 (RR 0.00, SE 0.26)
- Chemo and/or ER+tam+: 19/532 vs 100/581 (RR 0.25, SE 0.10)

(h) Radiotherapy dose ($\chi^2 = 0.9; \ 2p = 0.4$)
- 50+ Gy: 3/173 vs 43/203 (RR 0.19, SE 0.15)
- <50 Gy: 16/452 vs 69/486 (RR 0.12)

(i) Date trial started ($\chi^2 = 0.4; \ 2p = 0.5$)
- Started <1980: 15/426 vs 68/441 (RR 0.20, SE 0.15)
- Started 1980+: 4/199 vs 44/228 (RR 0.12)

(j) Period of follow-up ($\chi^2 = 0.2; \ 2p = 0.7$)
- Years 0–4: 15/2588 vs 95/2633 (RR 0.23, SE 0.10)
- Years 5–9: 4/1878 vs 17/1745 (RR 0.28, SE 0.25)

Total: 19/625 vs 112/669 (RR 0.24, SE 0.10)
(3.0% vs 16.7%)

Global heterogeneity: $\chi^2 = 6.4; \ p > 0.1$: NS
Any first recurrence (years 0-9)

(f) Number of positive nodes ($\chi^2 = 1.1; 2p = 0.3$)
- 1 positive node: 48/191, 80/214, -13.8, 27.8
- 2–3 positive nodes: 89/223, 116/230, -9.8, 41.3
- Unknown but pN1–3: 74/218, 108/238, -18.5, 38.4

(g) Any systemic therapy ($\chi^2 = 0.4; 2p = 0.5$)
- No systemic: 34/93, 42/88, -4.1, 16.8
- Chemo and/or ER+ tam+: 177/539, 262/594, -38.2, 94.5

(h) Radiotherapy dose ($\chi^2 = 0.2; 2p = 0.6$)
- 50+ Gy: 55/180, 97/216, -14.1, 31.2
- <50 Gy: 156/452, 207/466, -28.2, 80.4

(i) Date trial started ($\chi^2 = 1.1; 2p = 0.3$)
- Started <1980: 145/433, 208/454, -34.1, 76.6
- Started 1980+: 66/199, 96/228, -8.1, 35.1

(j) Period of follow-up ($\chi^2 = 0.3; 2p = 0.6$)
- Years 0–4: 157/2816, 235/2686, -34.5, 84.9
- Years 5–9: 54/1898, 89/1782, -7.8, 26.7

Total: 211/632, 304/682, -42.3, 111.6
(33.4%) (44.6%)

Global heterogeneity: $\chi^2 = 13.5; p > 0.1$: NS

Radiation RR 0.68

0.68 (SE 0.08) $2p = 0.00006$
Breast cancer mortality

(f) Number of positive nodes ($x_i^2 = 0.2; 2p = 0.7$)
- 1 positive node: 67/191, 88/214, -7.7, 32.4
- 2–3 positive nodes: 100/223, 124/230, -6.5, 47.8
- Unknown but pN1–3: 81/218, 113/238, -11.4, 41.5

(g) Any systemic therapy ($x_i^2 = 0.4; 2p = 0.5$)
- No systemic: 45/93, 52/88, -2.1, 21.8
- Chemo and/or ER+ tam+: 202/539, 273/594, -25.9, 103.7

(h) Radiotherapy dose ($x_i^2 = 0.0; 2p = 1.0$)
- 50+ Gy: 64/180, 95/216, -7.5, 33.1
- <50 Gy: 184/452, 230/466, -20.9, 92.8

(i) Date trial started ($x_i^2 = 2.0; 2p = 0.2$)
- Started 1960+: 75/199, 93/228, -1.2, 37.4

(j) Period of follow-up ($x_i^2 = 0.0; 2p = 0.9$)
- Years 0–4: 111/2622, 148/3064, -11.2, 58.7
- Years 5–9: 76/2172, 94/2255, -6.5, 37.4
- Years 10–14: 35/1658, 58/1630, -11.0, 29.7
- Years 15–19: 15/1060, 13/986, 0.9, 8.1
- Years 20+: 11/860, 12/757, -0.6, 5.0

Total: 248/632, 325/682, -28.4, 125.9

Global heterogeneity: $x_{18}^2 = 11.4; p > 0.1$: NS

Radiation RR 0.80
Meta-analysis (EBCTCG, Lancet 2014)

Mastectomy +/- RT

In pN1-3, 1133

Significantly different
Meta-analysis (EBCTCG, Lancet 2014)
Mastectomy +/- RT

In 1133, N1-3(+), systemic TX, by number of positive nodes

Overall recurrence

Radiation RR 0.67
Meta-analysis (EBCTCG, Lancet 2014)
Mastectomy +/- RT

In 1133, N1-3(+), systemic TX, by number of positive nodes

Breast cancer mortality

Radiation RR 0.78
Radiation field of PMRT

- Chest wall and regional LN (SCL + axilla +/- IMN)

- Effect of irradiation to IMN in PMRT:
  Negative result in France (IJROBP 2013),
  but ongoing of KROG 0806 in Korea
Selective Use of Postoperative RT after Mastectomy (SUPREMO)

Phase III randomized trial of chest wall RT in intermediate-risk BCa

- pT0-3, N0-1, MO breast cancer
- 1-3 LN+ or LN- with other risk factors (G3 or LVI) treated by mastectomy, axillary clearance and systemic therapy.
- Randomization: Chest wall irradiation vs. None
- 1st end point: OS
- 2nd end point: DFS, Morbidity, QOL, Cost effectiveness, molecular markers of radiation resistance/sensitivity
- Enrollee: 3500 pts (per 1750 per arm) \(\rightarrow\) Need 794 events (deaths)

MRC/EORTC
Summary (I)

- PMRT improves LRR, overall recurrence, and breast cancer mortality for pN1(1-3+) patients

- The proportional reductions in LRR, breast cancer mortality did not differ significantly according to several other prognostic factors such as age, grade, mastectomy type, axillary surgery information, number of (+)LN, any systemic Tx, radiation dose, date trial started and F/U period.

- Absolute gains might be smaller but proportional gains might be larger because of more effective radiotherapy for today’s women.
Summary (II)

- Whether this positive finding of PMRT in N1 breast cancer patients also applies to patients treated with more contemporary regimens remains to be seen.

- In PMRT of pN1 after mastectomy, ALND and systemic therapy, radiation field include chest wall and regional lymph nodes. Chest wall may be important target.

- Benefit of regional nodal irradiation in addition to chest wall or whole breast radiotherapy are investigating and long term result are not yet available.
Postmastectomy Radiotherapy in N1 Breast Cancer: Pros

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