Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

EBCTCG (Early Breast Cancer Trialists’ Collaborative Group)*

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Table 1. Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional nodes following mastectomy and axillary surgery versus no radiotherapy but the same surgery.*

<table>
<thead>
<tr>
<th>Nodal status§</th>
<th>Women</th>
<th>Deaths</th>
<th>Woman-years since diagnosis†</th>
<th>% women given systemic therapy‡</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median/woman</td>
<td>Total (’000s)</td>
<td>Distribution by years (’000s)</td>
</tr>
<tr>
<td>(a) Axillary dissection</td>
<td></td>
<td></td>
<td></td>
<td>10-</td>
<td>20+</td>
</tr>
<tr>
<td>pN0</td>
<td>700</td>
<td>480</td>
<td>20.1</td>
<td>13.5</td>
<td>6.1</td>
</tr>
<tr>
<td>pN+</td>
<td>3131</td>
<td>2074</td>
<td>7.2</td>
<td>30.1</td>
<td>20.3</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>
</tr>
<tr>
<td>pN4+</td>
<td>1772</td>
<td>1286</td>
<td>4.8</td>
<td>12.4</td>
<td>9.7</td>
</tr>
<tr>
<td>pN7+</td>
<td>45</td>
<td>29</td>
<td>6.7</td>
<td>0.4</td>
<td>0.3</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>
</tr>
<tr>
<td>Total for (a)</td>
<td>3887</td>
<td>2593</td>
<td>9.0</td>
<td>44.3</td>
<td>26.8</td>
</tr>
<tr>
<td>(b) Axillary sampling</td>
<td></td>
<td></td>
<td></td>
<td>10-</td>
<td>20+</td>
</tr>
<tr>
<td>pN0</td>
<td>870</td>
<td>595</td>
<td>17.6</td>
<td>15.4</td>
<td>7.5</td>
</tr>
<tr>
<td>pN+</td>
<td>2541</td>
<td>1689</td>
<td>7.8</td>
<td>24.2</td>
<td>17.0</td>
</tr>
<tr>
<td>pN unknown</td>
<td>654</td>
<td>460</td>
<td>9.3</td>
<td>7.1</td>
<td>4.6</td>
</tr>
<tr>
<td>Total for (b)</td>
<td>4065</td>
<td>2744</td>
<td>9.8</td>
<td>46.8</td>
<td>29.1</td>
</tr>
<tr>
<td>(c) Axillary surgery, but extent unknown</td>
<td></td>
<td></td>
<td></td>
<td>10-</td>
<td>20+</td>
</tr>
<tr>
<td>pN0</td>
<td>24</td>
<td>12</td>
<td>8.5</td>
<td>0.2</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>pN+</td>
<td>149</td>
<td>69</td>
<td>11.5</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>pN unknown</td>
<td>10</td>
<td>6</td>
<td>11.0</td>
<td>0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Total for (c)</td>
<td>183</td>
<td>87</td>
<td>10.1</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Total (a)+(b)+(c)</td>
<td>8135</td>
<td>5424</td>
<td>9.4</td>
<td>92.7</td>
<td>57.3</td>
</tr>
</tbody>
</table>

*Data were available for 22 trials, start dates 1964 to 1986, and were unavailable for 4 trials including approximately 400 women. In all 22 trials for which data were available, radiotherapy was given to the chest wall and the supraclavicular and/or the axillary fossa. In 20 of the 22 trials it was also given to the internal mammary chain. Details of the treatments given in these 22 trials are in appendix 10-12. Details of other trials of radiotherapy after mastectomy are in appendix pp 52-53, 64-65, 70-71, 78-79.

†Numbers of woman-years of follow-up for mortality. Many trials followed women for only 10 years for recurrence.

‡Chemotherapy was usually cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). Only 3% of women were classified as oestrogen-receptor positive (ER+) and were in trials where both tamoxifen and chemotherapy were given.

§pN: pathological nodal status, pN+: pathologically node positive, pN1-3: 1-3 pathologically positive nodes, pN4+: at least 4 pathologically positive nodes, pN7+: known to be pN+ but not whether pN1-3 or pN4+, pN unknown: pathological nodal status unknown.

¶Oestrogen-receptor positive.

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Figure 1. Trials included in analysis.

31747 records identified through database searching or other means; abstracts read when available, otherwise titles only

18340 records excluded

13407 papers obtained and read

8520 papers excluded

4887 trial reports filed and assessed for eligibility

4861 trial reports excluded

26 eligible trials identified

4 trials with individual patient data unavailable (around 400 women)

22 trials with data available for 8135 women included in quantitative synthesis (meta-analysis), so individual patient data obtained for around 95% of eligible women
Figure 2. Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 700 women with pathologically node-negative (pN0) disease and in 3131 women with pathologically node-positive (pN+) disease. Analyses of locoregional recurrence first ignore distant recurrences, see appendix pp 8-9 for details. See appendix pp 14, 16, for analyses of both locoregional and distant recurrences and appendix pp 13, 15, for analyses of overall mortality. RR=rate ratio. NS=not significant. Vertical lines indicate 1 SE above or below the 5, 10, 15, and 20 year percentages.

Locoregional recurrence first

700 pN0 women with Mast+AD

- Logrank $p > 0.1$, NS

3131 pN+ women with Mast+AD

- Logrank $p < 0.00001$

Any first recurrence

Breast cancer mortality

- 10-year loss 1.3% (SE 3.3)
  RR 1.06 (95% CI 0.76–1.48)
- Logrank $p > 0.1$, NS

- 20-year loss 2.2% (SE 3.6)
  RR 1.18 (95% CI 0.89–1.55)
- Logrank $p > 0.1$, NS

- 10-year gain 10.6% (SE 2.0)
  RR 0.75 (95% CI 0.67–0.83)
- Logrank $p < 0.00001$

- 20-year gain 8.1% (SE 2.0)
  RR 0.84 (95% CI 0.76–0.94)
- Logrank $p = 0.001$

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Figure 3. Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 1314 women with 1-3 pathologically positive nodes (pN1-3) and in 1772 women with 4+ pathologically positive nodes (pN4+). Analyses of locoregional recurrence first ignore distant recurrences, see appendix pp 8-9 for details. See appendix pp 19, 28, for analyses of both locoregional and distant recurrences and appendix pp 18, 27, for analyses of overall mortality. RR=rate ratio. NS=not significant. Vertical lines indicate 1 SE above or below the 5, 10, 15, and 20 year percentages.

**Locoregional recurrence first**

**B) Any first recurrence**

1314 pN1-3 women with Mast+AD

- Logrank 2p < 0.00001
- No RT 23.1% RT 87.0%
- 10-year gain 11.5% (SE 2.9)
- RR 0.68 (95% CI 0.57–0.82)
- Logrank 2p = 0.00003

1772 pN4+ women with Mast+AD

- Logrank 2p < 0.00001
- No RT 32.1% RT 69.9%
- 10-year gain 8.8% (SE 2.6)
- RR 0.79 (95% CI 0.69–0.90)
- Logrank 2p = 0.00003

**Breast cancer mortality**

- No RT 50.2% RT 42.3%
- 20-year gain 7.9% (SE 3.1)
- RR 0.80 (95% CI 0.67–0.95)
- Logrank 2p = 0.00
Figure 4. Effect of radiotherapy (RT) after mastectomy and axillary dissection on overall recurrence during years 0-9 and on breast cancer mortality for the entire follow-up in 1314 women with one to three pathologically positive nodes (pN1-3), according to whether or not they were in trials in which systemic therapy was given to both randomised treatment groups. Chemotherapy was usually cyclophosphamide, methotrexate, fluorouracil. ER-negative women in trials in which tamoxifen was given to both groups are included in the "no systemic" category. ER=estrogen receptor. Tam=tamoxifen. NS=not significant. SE=standard error. Confidence intervals are 95%.

A) Any first recurrence (years 0-9)

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/Women</th>
<th>RT events</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of annual event rates</th>
<th>Rate Ratio (Standard Error)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated</td>
<td>Allocated</td>
<td>Logrank</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RT No RT</td>
<td>No RT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No systemic</td>
<td>34/3</td>
<td>42/3</td>
<td>-4.1</td>
<td>16.8</td>
<td>0.79 (SE 0.22)</td>
</tr>
<tr>
<td></td>
<td>(68.4%)</td>
<td>(88.9%)</td>
<td>(47.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo and/or Estrogen+</td>
<td>177/392</td>
<td>257/586</td>
<td>-36.2</td>
<td>94.5</td>
<td>0.67 (SE 0.06)</td>
</tr>
<tr>
<td></td>
<td>(23.0%)</td>
<td>(44.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>211/632</td>
<td>304/682</td>
<td>-42.3</td>
<td>111.4</td>
<td>0.69 (SE 0.08)</td>
</tr>
<tr>
<td></td>
<td>(33.4%)</td>
<td>(44.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Difference between treatment effects in 2 categories: $\chi^2 = 0.4; 2p > 0.1; \text{NS}$

B) Breast cancer mortality

<table>
<thead>
<tr>
<th>Category</th>
<th>Deaths/Women</th>
<th>RT deaths</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of annual death rates</th>
<th>Rate Ratio (Standard Error)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated</td>
<td>Allocated</td>
<td>Logrank</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RT No RT</td>
<td>No RT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No systemic</td>
<td>49/3</td>
<td>50/5</td>
<td>-2.1</td>
<td>21.8</td>
<td>0.91 (SE 0.20)</td>
</tr>
<tr>
<td></td>
<td>(44.5%)</td>
<td>(90.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo and/or Estrogen+</td>
<td>222/374</td>
<td>234/276</td>
<td>-25.9</td>
<td>103.7</td>
<td>0.78 (SE 0.09)</td>
</tr>
<tr>
<td></td>
<td>(59.5%)</td>
<td>(54.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>271/663</td>
<td>284/662</td>
<td>-28.0</td>
<td>128.5</td>
<td>0.80 (SE 0.08)</td>
</tr>
<tr>
<td></td>
<td>(39.2%)</td>
<td>(47.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Difference between treatment effects in 2 categories: $\chi^2 = 0.4; 2p > 0.1; \text{NS}$
Figure 5. Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional recurrence and overall recurrence and on 20-year risk of breast cancer mortality in 1133 women with 1-3 pathologically positive nodes (pN1-3) in trials where systemic therapy was given to both randomised treatment groups. Analyses of locoregional recurrence first ignore distant recurrences, see appendix pp 8-9 for details. See appendix pp 22 for analyses of both locoregional and distant recurrences and appendix pp 21 for analyses of overall mortality. RR=rate ratio. NS=not significant. Vertical lines indicate 1 SE above or below the 5, 10, 15, and 20 year percentages.

A) Locoregional recurrence first

B) Any first recurrence

C) Breast cancer mortality

1133 pN1-3 women with Mast+AD and systemic therapy

logrank 2p < 0.00001

No RT 21.0%

RT 4.3%

No RT 45.5%

RT 33.8%

10-year gain 11.7 % (SE 3.2)
RR 0.67 (95% CI 0.55–0.82)
logrank 2p = 0.00009

No RT 49.4%

RT 41.5%

20-year gain 7.9 % (SE 3.3)
RR 0.78 (95% CI 0.64–0.94)
logrank 2p = 0.01
Figure 6. Effect of radiotherapy (RT) after mastectomy and axillary dissection on overall recurrence during years 0–9 and for breast cancer mortality for the entire period of follow-up in 1133 women with one to three pathologically positive nodes (pN1–3) in trials in which systemic therapy was given to both randomised treatment groups, by number of positive nodes. NS=not significant. SE=standard error. Confidence intervals are 95%.

### A) Any first recurrence (years 0–9)

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/Women</th>
<th>RT events</th>
<th>Logrank Variance of O–E</th>
<th>Rate Ratio (Standard Error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 positive node</td>
<td>35/145</td>
<td>62/173</td>
<td>10.5</td>
<td>0.60 (SE 0.17)</td>
</tr>
<tr>
<td>2–3 positive nodes</td>
<td>69/175</td>
<td>92/197</td>
<td>8.6</td>
<td>0.77 (SE 0.15)</td>
</tr>
<tr>
<td>Unknown but (pN1–3)</td>
<td>72/216</td>
<td>107/234</td>
<td>18.3</td>
<td>0.62 (SE 0.13)</td>
</tr>
<tr>
<td>Total</td>
<td>177/539</td>
<td>262/594</td>
<td>37.5</td>
<td>0.67 (SE 0.08)</td>
</tr>
</tbody>
</table>

Difference between treatment effects in 2 categories: $\chi^2 = 9.2; \; p > 0.1; \; \text{NS}$

### B) Breast cancer mortality

<table>
<thead>
<tr>
<th>Category</th>
<th>Deaths/Women</th>
<th>RT deaths</th>
<th>Logrank Variance of O–E</th>
<th>Rate Ratio (Standard Error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 positive node</td>
<td>46/145</td>
<td>60/173</td>
<td>5.7</td>
<td>0.79 (SE 0.16)</td>
</tr>
<tr>
<td>2–3 positive nodes</td>
<td>76/175</td>
<td>96/197</td>
<td>7.0</td>
<td>0.80 (SE 0.15)</td>
</tr>
<tr>
<td>Unknown but (pN1–3)</td>
<td>80/216</td>
<td>111/234</td>
<td>11.4</td>
<td>0.76 (SE 0.14)</td>
</tr>
<tr>
<td>Total</td>
<td>202/539</td>
<td>273/594</td>
<td>24.1</td>
<td>0.78 (SE 0.09)</td>
</tr>
</tbody>
</table>

Difference between treatment effects in 2 categories: $\chi^2 = 9.0; \; p > 0.1; \; \text{NS}$
Webappendix material
Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

EBCTCG (Early Breast Cancer Trialists' Collaborative Group)

Webappendix

Trials of radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD)

Webtable 1 Randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS) – treatment details.

Node negative (pN0)

Webfigure 2 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 700 women with pathologically node-negative (pN0) disease.

Webfigure 3 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 700 women with pathologically node-negative (pN0) disease.

Node positive (pN+)

Webfigure 4 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 3131 women with pathologically node-positive (pN+) disease.

Webfigure 5 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 3131 women with pathologically node-positive (pN+) disease.

Webfigure 6 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): Event rate ratios and 95% confidence intervals for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer mortality in 3131 women with pathologically node-positive (pN+) disease by prognostic and other factors.

1-3 positive nodes (pN1-3)

Webfigure 7 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1314 women with 1-3 pathologically positive nodes (pN1-3).

Webfigure 8 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1314 women with 1-3 pathologically positive nodes (pN1-3).

Webfigure 9 Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): Event rate ratios and 95% confidence intervals for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer mortality in 1314 women with 1-3 pathologically positive nodes (pN1-3) by prognostic and other factors.

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1-3 positive nodes (pN1-3) who received systemic therapy

Webfigure 10  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1133 women with 1-3 pathologically positive nodes (pN1-3) in trials where systemic therapy was given to both randomised treatment groups.

Webfigure 11  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1133 women with 1-3 pathologically positive nodes (pN1-3) in trials where systemic therapy was given to both randomised treatment groups.

1-3 positive nodes (pN1-3) who received systemic therapy subdivided according to number of positive nodes

Webfigure 12  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 15-year risk of breast cancer mortality in 1133 women with 1-3 pathologically positive nodes (pN1-3) in trials where systemic therapy was given to both randomised treatment groups subdivided according to number of positive nodes.

Webfigure 13  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 318 women with 1 pathologically positive node (pN1) and where systemic therapy was given to both randomised treatment groups.

Webfigure 14  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 385 women with 2-3 pathologically positive nodes (pN2-3) and where systemic therapy was given to both randomised treatment groups.

Webfigure 15  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 450 women with 1-3 pathologically positive nodes (pN1-3) but the exact number of positive nodes unknown and where systemic therapy was given to both randomised treatment groups.

4+ positive nodes (pN4+)

Webfigure 16  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1772 women with 4+ pathologically positive nodes (pN4+).

Webfigure 17  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1772 women with 4+ pathologically positive nodes (pN4+).

Webfigure 18  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): Event rate ratios and 95% confidence intervals for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer mortality in 1772 women with 4+ pathologically positive nodes (pN4+) by prognostic and other factors.

4+ positive nodes (pN4+) who received systemic therapy

Webfigure 19  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1677 women with 4+ pathologically positive nodes (pN4+) in trials where systemic therapy was given to both randomised treatment groups.

Webfigure 20  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1677 women with 4+ pathologically positive nodes (pN4+) in trials where systemic therapy was given to both randomised treatment groups.

4+ positive nodes (pN4+) who received systemic therapy subdivided according to number of positive nodes

Webfigure 21  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 15-year risk of breast cancer mortality in 1677 women with 4+ pathologically positive nodes (pN4+) in trials where systemic therapy was given to both randomised treatment groups subdivided according to number of positive nodes.

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Webfigure 22  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 479 women with 4-9 pathologically positive nodes (pN4-9) in trials where systemic therapy was given to both randomised treatment groups.

Webfigure 23  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 403 women with 10+ pathologically positive nodes (pN10+) in trials where systemic therapy was given to both randomised treatment groups.

Webfigure 24  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 795 women with 4+ pathologically positive nodes but the exact number of positive nodes unknown in trials where systemic therapy was given to both randomised treatment groups.

Trials of radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS)

**Node negative (pN0)**

Webfigure 25  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 870 women with pathologically node-negative (pN0) disease.

Webfigure 26  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 870 women with pathologically node-negative (pN0) disease.

**Node positive (pN+)**

Webfigure 27  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 2541 women with pathologically node-positive (pN+) disease.

Webfigure 28  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 2541 women with pathologically node-positive (pN+) disease.

Trials of radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS). Event rate ratios, one line per trial.

Webfigure 29  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 1594 women with pathologically node-negative (pN0) disease.

Webfigure 30  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 5821 women with pathologically node-positive (pN+) disease.

Webfigure 31  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 2801 women with 1-3 pathologically positive nodes (pN1-3).

Webfigure 32  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 2557 women with 4+ pathologically positive nodes (pN4+).

Webfigure 33  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 463 women with pathologically positive nodes (pN7+) but unknown if they were 1-3 or 4+ positive.

Lancet 2014; 383: 2127–35
Trials of radiotherapy to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD)

Webtable 2 Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS).

Webtable 3 Randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS) – treatment details.

Node negative (pN0)

Webfigure 35 Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 465 women with pathologically node-negative (pN0) disease.

Webfigure 36 Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 465 women with pathologically node-negative (pN0) disease.

Node positive (pN+)

Webfigure 37 Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1029 women with pathologically node-positive (pN+) disease.

Webfigure 38 Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1029 women with pathologically node positive (pN+) disease.

Event rate ratios, one line per trial

Webfigure 39 Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 465 women with pathologically node-negative (pN0) disease.

Webfigure 40 Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 for breast cancer and all-cause mortality in 1029 women with pathologically node-positive (pN+) disease.

Webfigure 41 Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 810 women unknown with pathological nodal status (pN?).

Trials of radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy alone (Mast alone)

Webtable 4 Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast).

Webtable 5 Randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast) – treatment details.

Lancet 2014; 383: 2127–35
**Clinically node positive (cN+)**

Webfigure 42  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risks of breast cancer and all-cause mortality in 2896 women with clinically node-negative (cN-) disease.

Webfigure 43  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of recurrence and type of first recurrence in 2896 women with clinically node-negative (cN-) disease.

**Clinically node negative (cN-)**

Webfigure 44  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risks of breast cancer and all-cause mortality in 1481 women with clinically node-positive (cN+) disease.

Webfigure 45  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of recurrence and type of first recurrence in 1481 women with clinically node-positive (cN+) disease.

**Trials of radiotherapy to the regional lymph nodes alone versus not after mastectomy alone (Mast alone)**

Webtable 6  Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast).

Webtable 7  Randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast) – treatment details.

Webfigure 46  Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast): 10-year risks of recurrence, breast cancer and all-cause mortality in 192 clinically node-positive (cN+) women. Note, due to the very small number (6) of clinically node-negative women in this set of trials they are shown only in webfigure 34.

Webfigure 47  Effect of radiotherapy (RT) to the regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of recurrence and type of first recurrence in 192 women with clinically node-positive (cN+) disease.

Webfigure 48  Effect of radiotherapy (RT) versus not after mastectomy but no axillary surgery (Mast): 10-year risks of recurrence during years 0-9, breast cancer mortality, and all-cause mortality in 2904 women with clinically node-negative (cN-) disease. Event rate ratios, one line per trial, trial subdivided according to whether or not radiotherapy was given to the chest wall.

Webfigure 49  Effect of radiotherapy (RT) versus not after mastectomy but no axillary surgery (Mast): 10-year risks of recurrence during years 0-9, breast cancer mortality, and all-cause mortality in 1673 women with clinically node-positive (cN+) disease. Event rate ratios, one line per trial, trial subdivided according to whether or not radiotherapy was given to the chest wall.

**Trials of radiotherapy to the chest wall and regional lymph nodes versus not BEFORE mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS)**

Webtable 8  Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS).

Webtable 9  Randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS) – treatment details.

Webfigure 50  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 15-year risk of breast cancer and all-cause mortality in 255 women with unknown pathological nodal status (pN?) disease.

Webfigure 51  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD): 10-year risk of

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Lancet 2014; 383: 2127–35
recurrence and type of first recurrence, by allocated treatment, in 255 women with unknown pathological nodal status (pN?).

Webfigure 52  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary sampling (Mast+AS): 10-year risk of locoregional recurrence and recurrence of any type and 15-year risk of breast cancer and all-cause mortality in 637 women with unknown pathological nodal status (pN?) disease

Webfigure 53  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary sampling (Mast+AS): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 637 women with unknown pathological nodal status (pN?).

Webfigure 54  Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 892 women with unknown pathological nodal status (pN?).

Webfigure 55  **EBCTCG collaborators, listed alphabetically by institution and then alphabetically by name.**
Webfigure 1. Methodological Note

The analyses presented in the main body of the accompanying paper and also in many of the figures in this webappendix are based on the methodology that has been used throughout by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) and which is described elsewhere. Some of the figures in this webappendix also include additional methodological features. The purpose of this note is to point out some of the features of both types of analysis.

Overall Mortality
In analyses of overall mortality (eg, the lower right-hand panels of webfigures 2, 4, etc), the number of women who are known to have died in each randomised group is related to the number of women at risk of dying and the length of time during which they are at risk of dying in each time-period during follow-up. Some women are, however, lost to follow-up and are withdrawn from the analysis. Thus, whilst it is reported in the lower right-hand panel of webfigure 4 that the cumulative risk of death from any cause among the 1550 women randomised to radiotherapy is 55.4% at 20 years after randomisation, this does not mean that 1014 (ie 0.654x1550) of the women are known to have died. Rather, as shown in webfigure 30, only 1001 (ie 64.6%) of the women are known to have died. The difference between these two percentages is due to the fact that for 390 of these 1550 women the most recent information held in the EBCTCG database indicates only that they were known to be alive at some period less than 20 years after randomisation. These women were withdrawn from the analysis or ‘censored’ on the date they were last known to be alive. Each censored woman is no longer considered to be at risk of dying after her date of censoring and she is excluded from all calculations relating to subsequent time-periods and, in particular, from contributing to the number of years at risk in calculations of the death rate. The technique of censoring has been used routinely by statisticians and actuaries for many decades and theoretical calculations have shown that it is valid, provided that the women who are censored are not different in any respect that affects their mortality rate from the women who remain in the study so that, from the mathematical point of view, the censoring can be considered to be ‘at random’. This assumption is unlikely ever to be precisely true but many of the major factors affecting risk of overall mortality, such as trial, follow-up year, age at trial entry, and nodal status, can be taken into account through stratification, ie by subdividing the data into separate groups according to the stratifying factors, carrying out the analysis separately within each stratum and then combining the results from the separate strata in the form of a weighted average, calculated with weights proportional to the amount of information in each stratum.

Mortality from Causes other than Breast Cancer
Analyses of causes of death other than breast cancer (eg EBCTCG, Lancet 2000; 355:1757-70, and 2005; 366: 2087-2106) are carried out in a fashion similar to that for analyses of overall mortality. Here, however, it is not only women who are lost to follow-up who are censored but all women who have a recurrence of their breast cancer are also censored on the date of that recurrence. This approach enables comparison of mortality rates from non-breast-cancer causes in the two trial arms. However, the resulting estimates of the cumulative risk of death from all non-breast-cancer causes (eg figure 6 lower panel of EBCTCG, Lancet 2000; 355:1757-70) reflect the cumulative risks that would be seen under the hypothetical scenario that no women in the trial die from breast cancer. This scenario is, of course, highly artificial. It is, however, a useful one in that it permits comparison of non-breast-cancer mortality rates in the two trial arms unencumbered by any differences in the rates of breast cancer recurrence/mortality. It therefore enables identification and characterization of specific treatment hazards such as the increased mortality from heart disease or second cancers that has undoubtedly occurred following some of the radiotherapy regimens used in the past (EBCTCG, Lancet 2005; 366: 2087-2106).

Breast Cancer Mortality
The method used in the EBCTCG meta-analyses for studying mortality from breast cancer (eg right-hand panels of figures 1, 2, 4 and lower left-hand panels of webfigures 2, 4, etc) is indirect and makes use of analyses of the two endpoints described above. The data are first subdivided into separate strata (eg, according to trial, follow-up year, age at trial entry, and nodal status). Then, for each trial arm, the mortality rate from non-breast-cancer causes during the period prior to any recurrence of breast cancer is subtracted from the overall mortality rate in the relevant stratum. This method has the advantage that it avoids the difficulties which arise for women who die after a recurrence of their breast cancer and where it is not entirely clear whether their death was, in fact, due to the cancer or due to other causes. As in analyses of non-breast-cancer mortality, the resulting estimates of the cumulative risk of death from breast cancer reflect the cumulative risks that would be seen under the hypothetical scenario that no women in the trial die from causes other than breast cancer. Once again, this is useful in the identification and characterization of the benefits of a randomised treatment separately from its hazards. It also allows comparison of the benefits of the randomised treatment separately from the effects of other factors, such as the increasing overall mortality rate that occurs in all populations with increasing attained age.

continued overleaf
Separate calculation of the effect of a particular treatment on breast cancer mortality and on non-breast-cancer causes can also have substantial advantages even when the main question of interest is the effect of a treatment on overall mortality. For example, information from randomised trials on the effect of radiotherapy in reducing breast cancer mortality can be combined with epidemiological information from other sources on the likely risk of death from the long-term adverse effects of radiotherapy, such as second primary cancers or heart disease.

Analyses of Overall Recurrence
Analyses of overall recurrence are presented in both the main paper (eg middle panels of figures 1, 2 and 4) and in the webappendix (upper right panel of webfigures 2, 4, etc). Rather than using the indirect approach that is taken for analyses of breast cancer mortality, these analyses are carried out in a fashion similar to the analyses of mortality from non-breast-cancer causes in that the first reported recurrence of any type is related to the number of women who have not yet had a recurrence but who, if they did have one, would contribute an event. Women are censored and cease to contribute either events or years at risk after they have had a recurrence, die from a cause other than breast cancer, or are lost to follow-up. Any women who are reported as dying from breast cancer and for whom no recurrence has previously been reported are assumed to have had a distant recurrence immediately preceding their death. As with analyses of mortality from breast cancer and from causes other than breast cancer, these analyses lead to estimates of the cumulative risk of recurrence that would occur under the hypothetical scenario in which no other events occur. For analyses of overall recurrence this involves the assumption that no women in the trial die from causes other than breast cancer. This is similar to the assumption that is made for analyses of breast cancer mortality and, once again, although this assumption is unrealistic it is useful in that it enables identification and characterization of the benefits of the randomised treatment separately from its hazards.

Analyses of Locoregional and Distant Recurrence
Analyses of locoregional recurrence are also presented both in the main paper (eg left panel of figures 1, 2 and 4) and in the webappendix (upper left panel of webfigures 2, 4, etc). These analyses are carried out in similar fashion to the analyses of overall recurrence described above. Only locoregional recurrences that occur before any distant recurrence are counted as events, and women are censored and cease to contribute events or to the years at risk after they have had one recurrence (either a local one or a distant one), or they die from a cause other than breast cancer or are lost to follow-up. The interpretation of analyses of locoregional recurrence is in some respects, similar to that for overall recurrence and breast cancer mortality. Two aspects do, however, differ and, in some contexts it is important to be aware of them. These two aspects are discussed in the following two paragraphs.

Firstly, because estimates of the cumulative risk of locoregional recurrence make the hypothetical assumption that no distant recurrences occur, they over-estimate the cumulative risk of locoregional recurrence. In many circumstances, including most of the analyses presented in this paper and in these webappendices, this is by no means realistic as the number of women whose first recurrence is a distant one is substantial. Insight into the extent of this effect can be gained by considering the distribution of the two different types of recurrence in analyses of overall recurrence, and such analyses have been carried out to accompany all the analyses of locoregional recurrence presented in this paper. For example, webfigure 5 accompanies the analysis of locoregional recurrence shown in the bottom left panel of figure 1 (and also in the top left panel of webfigure 4). The estimated 10-year risk of a recurrence of any type is 62.5% among the women randomised to no radiotherapy (webfigure 5, right-hand panel), of which distant recurrence accounts for 43.1% and locoregional recurrence accounts for the remaining 19.4%. If distant recurrences are censored, as in the analyses of locoregional recurrences, the estimated 10-year risk of locoregional recurrence in this particular example, is 26.0% (bottom left panel of figure 1 and top left panel of webfigure 4). This is 6.8% higher (ie, 26.0% in figure 1 minus 19.4% in webfigure 5) than the estimate derived from an analysis that takes distant recurrences into account.

Secondly, as can be seen in webfigure 5, the 10-year risk of distant recurrence differs between the two treatment groups and in this example, the 10-year risk of distant recurrence is 46.9% among the women allocated to receive radiotherapy and 43.1% among the women allocated not to receive it, ie, the 10-year risk of a distant recurrence is higher in the women randomised to receive radiotherapy than in the women randomised to no radiotherapy. This does not, however, mean that radiotherapy increases the risk of distant recurrence. Rather, it arises from the fact that a proportion of the women who would have had a locoregional recurrence if they had not had radiotherapy have their locoregional recurrence prevented by radiotherapy. These women remain at risk of a distant recurrence for longer and their additional time at risk is taken into account by the fact that, while they remain at risk of a distant recurrence, they continue to contribute to the years at risk and to the denominator in calculation of event rates. However, women who are at a higher risk of locoregional recurrence (eg, because they have more aggressive cancers) are also at a higher risk of distant recurrence. Therefore, the additional contribution to the years at risk from these women whose locoregional recurrence was prevented by the radiotherapy does not compensate fully for the additional risk of distant recurrence that is observed among the women allocated to radiotherapy. Hence the censoring that arises from the distant recurrences cannot be considered to be ‘at random’. The relationship between the risks of locoregional and distant recurrence is unknown, either in the presence of radiotherapy or in its absence – and indeed the relationship is likely to differ between the two. Furthermore, the data from the trial provide no information about this relationship. Therefore it is not possible to carry out analyses of locoregional recurrence that take appropriate account of the occurrence of distant recurrences as a first event.
event, or vice versa. One consequence of this is that, in analyses of locoregional recurrence as a first event (left-hand panels of figures 1, 2, & 5 and top left panels of webfigures 2, 4, 7, 10, 12, 16, 19, 21, 25, 27, 35, 37, 42, 44 and 46), the difference between the cumulative risks in the two treatment arms is a consequence not only of the causal effect of radiotherapy on the local recurrence rate in the two treatment arms, but also of the different extent to which distant recurrence as a first event occurs in each of the two treatment arms. This has consequences both for the interpretation of cumulative risks arising from the analysis of locoregional recurrence and for the interpretation of analyses presenting the ratio of the local recurrence rate in the irradiated group compared with the unirradiated group (figures 3, and 5 and webfigures 30, 6, 9, 18, 29, 30, 31, 32, 33, 34, 39, 40, 41, 48, 49). Analyses of recurrence presenting explicitly the percentages of women whose first recurrence was locoregional or distant respectively are therefore given in this webappendix (webfigures 3,5,8,11,13, 14, 15, 17, 20, 22, 23, 24, 26, 28, 36, 38, 43, 45, 47).

These ideas are not new, but they have not previously been considered in the context of the EBCTCG analyses. A selection of papers either discussing the methodological aspects involved or applying them to other data sets is given below:


- Dignam JJ, Koehrginsky MN. Choice and interpretation of statistical tests used when competing risks are present. *J Clin Oncol* 2008; 26: 4027-34.


Reference

1. http://www.ctsu.ox.ac.uk/research/meta-trials/ebctcg/original-methods-for-ebctcg-meta-analyses
### Webtable 1: Randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS) – treatment details.

<table>
<thead>
<tr>
<th>Year code and study name</th>
<th>Breast surgery</th>
<th>Axillary Surgery* (number of patients)</th>
<th>Chest wall RT</th>
<th>Supraclavicular (SC) and axillary fossa (AF) RT</th>
<th>Internal mammary chain RT</th>
<th>Boost RT to scar</th>
<th>Common systemic chemoendocrine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>64B Oslo X-ray</td>
<td>RM</td>
<td>Axillary dissection (552)</td>
<td>25-41 Gy (1.3-2.1 Gy/f) c or m</td>
<td>36 Gy (1.8 Gy/f) c or m; SC; 18 Gy (u Gy/f) c or m; AF</td>
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<td>None</td>
<td>Ovarian RT</td>
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<tr>
<td>71B Stockholm A</td>
<td>MRM</td>
<td>Axillary sampling (644)</td>
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<td>None</td>
</tr>
<tr>
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<td>55 Gy (2.5 Gy/f) c or m</td>
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<td>None</td>
</tr>
<tr>
<td>74B Edinburgh I</td>
<td>SM</td>
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<td>None</td>
</tr>
<tr>
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<td>MRM or RM</td>
<td>Axillary dissection (215)</td>
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<td>None</td>
</tr>
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<td>Axillary dissection (120)</td>
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<td>None</td>
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<td>MRM or RM</td>
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<td>CMF</td>
</tr>
<tr>
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<td>SM</td>
<td>Axillary dissection (219)</td>
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</tr>
<tr>
<td>77J MD Ander. 7730B</td>
<td>MRM or SM</td>
<td>Axillary dissection (60)</td>
<td>45-60 Gy (1.8-2.0 Gy/f) c or m</td>
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<td>None</td>
</tr>
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<td>Axillary dissection (771)</td>
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<td>48 Gy (2.4 Gy/f) c or m</td>
<td>48 Gy (2.4 Gy/f) c or m</td>
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<td>Premen; C; tam</td>
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<td>MRM</td>
<td>Axillary dissection (318)</td>
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<td>Patey</td>
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<td>40 Gy (2 Gy/f) c</td>
<td>40 Gy (2 Gy/f) c</td>
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<td>LMF</td>
</tr>
<tr>
<td>79F Coimbra</td>
<td>NS</td>
<td>Axillary sampling (124)</td>
<td>36 Gy (3 Gy/f) c or m</td>
<td>39-45 Gy (3-3.6 Gy/f) c or m</td>
<td>39 Gy (3.3 Gy/f) c or m</td>
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<td>AC</td>
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<tr>
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<td>MRM, Patey MR, or RM</td>
<td>Axillary dissection (71)</td>
<td>36 Gy (3 Gy/f) c or m</td>
<td>39-45 Gy (3-3.6 Gy/f) c or m</td>
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<td>CMF &amp; tam; Premon; ovarian RT</td>
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<td>80S Helsinki</td>
<td>RM</td>
<td>Axillary dissection (99)</td>
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<td>45 Gy (3 Gy/f) c</td>
<td>None</td>
<td>CAFT</td>
</tr>
<tr>
<td>80W NSABC Israel</td>
<td>NS</td>
<td>Unknown (112)</td>
<td>46-50 Gy (2 Gy/f) c or m</td>
<td>46-50 Gy (2 Gy/f) c or m</td>
<td>46-50 Gy (2 Gy/f) c or m</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>82B Danish BCG 82b pre</td>
<td>SM</td>
<td>Axillary dissection (416)</td>
<td>36-50 Gy (1.8-2.2 Gy/f) c or m</td>
<td>36-50 Gy (1.8-2.2 Gy/f) c or m</td>
<td>36-50 Gy (1.8-2.2 Gy/f) c or m</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>82C Danish BCG 82c post</td>
<td>SM</td>
<td>Axillary dissection (132)</td>
<td>36-50 Gy (1.8-2.2 Gy/f) c or m</td>
<td>36-50 Gy (1.8-2.2 Gy/f) c or m</td>
<td>36-50 Gy (1.8-2.2 Gy/f) c or m</td>
<td>None</td>
<td>tam</td>
</tr>
<tr>
<td>82Q ECOG EST318</td>
<td>MRM or RM</td>
<td>Axillary dissection (332)</td>
<td>46 Gy (2 Gy/f) c or m</td>
<td>46 Gy (2 Gy/f) c or m</td>
<td>46 Gy (2 Gy/f) c or m</td>
<td>None</td>
<td>CAFT &amp; tam</td>
</tr>
<tr>
<td>84A GBSSG 03 Germany</td>
<td>Patey</td>
<td>Axillary dissection (199)</td>
<td>50 Gy (2 Gy/f) c or m</td>
<td>50 Gy (2 Gy/f) c or m</td>
<td>50 Gy (2 Gy/f) c or m</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>85F Nottingham</td>
<td>SM</td>
<td>Axillary dissection (77)</td>
<td>45 Gy (3 Gy/f) c</td>
<td>45 Gy (3 Gy/f) c</td>
<td>45 Gy (3 Gy/f) c</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>86C CRC, UK</td>
<td>NS</td>
<td>Unknown (71)</td>
<td>Various</td>
<td>Various</td>
<td>Various</td>
<td>Various</td>
<td>None</td>
</tr>
</tbody>
</table>

* Based on the description of axillary surgery in the trial protocol or publications or on information on individual women. Women were classified as having axillary dissection if they were in a trial where the protocol required removal of axillary lymph nodes at least levels II & III or, if individual information available (MD Ander. 7730B, Danish BCG 82b pre, Danish BCG 82c post), resection of ≥10 nodes. In other trials, women were classified as having axillary dissection if the trial publication indicated that the median number of nodes removed was ≥10. Women with less extensive axillary surgery were classified as having axillary sampling. AD=doxorubicin (adriamycin), AC=doxorubicin and cyclophosphamide, AF=axillary fossa, b=additional posterior boost to axilla, BC=bacillus Calmette-Guérin, C=cyclophosphamide, c=ccbalt-60, de=de as depth (of nodes), F=flucarozil, F=Flunariz, r= gunfire, Gy=Gray (intended dose), H=halotestin, L=chlorambucil, m=megavoltage, M=methotrexate, Me=melfalan, MRM=modified radical mastectomy, NS=surgery not specified in detail (Patey mastectomy, or modified radical mastectomy), o=orthovoltage, P=prednisone, P=patey mastectomy, RM=radical mastectomy (Halsted), RT=radiotherapy, SC=supraclavicular, SM=simple (total) mastectomy, tam=tamoxifen, u=unknown.

Lancet 2014; 383: 2127–35
<table>
<thead>
<tr>
<th>Year code and study name</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>Title</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
Webfigure 2. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 700 women with pathologically node-negative (pN0) disease. See webfigure 1 for methodological note and also webfigure 3. Note: 1 locoregional recurrence, 5 recurrences of any type and 5 breast cancer deaths were reported among the 9 pN0 women with tumours ≥ 5 cm who were allocated to receive radiotherapy. 0 locoregional recurrences, 3 recurrences of any type and 4 breast cancer deaths were reported among the 11 pN0 women with tumours ≥ 5 cm who were allocated to not to receive radiotherapy.

700 pN0 women with Mast+AD

Locoregional recurrence first

10-year loss 1.4 % (SE 1.2)
RR 1.81 (95% CI 0.63–5.17)
logrank 2p > 0.1; NS

Any first recurrence

10-year loss 1.3 % (SE 3.3)
RR 1.06 (95% CI 0.76–1.48)
logrank 2p > 0.1; NS

Breast cancer mortality

20-year loss 2.2 % (SE 3.6)
RR 1.18 (95% CI 0.89–1.55)
logrank 2p > 0.1; NS

Any death

20-year loss 6.0 % (SE 3.9)
RR 1.23 (95% CI 1.02–1.49)
logrank 2p = 0.03
Webfigure 3. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 700 women with pathologically node-negative (pN0) disease. ($n_L =$ number of women for whom first recurrence was locoregional, $n_D =$ number women for whom distant recurrence was first.)

700 pN0 women with Mast+AD

347 women allocated RT

Any first recurrence (%)

Locoregional or distant 22.4%
Locoregional first 2.6% ($n_L=9$)
Distant first 19.8% ($n_D=66$)

353 women allocated No RT

Any first recurrence (%)

Locoregional or distant 21.1%
Locoregional first 1.4% ($n_L=5$)
Distant first 19.7% ($n_D=68$)

2$p$ for difference between treatment arms in the proportion of all first recurrences that were locoregional: $> 0.1$; NS

Lancet 2014; 383: 2127–35
Webfigure 4. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 3131 women with pathologically node-positive (pN+) disease. See webfigure 1 for methodological note and also webfigure 5.

3131 pN+ women with Mast+AD

Locoregional recurrence first

10-year gain 17.9% (SE 1.7)
RR 0.32 (95% CI 0.26–0.40)
logrank 2p = 0.00001

Any first recurrence

10-year gain 10.6% (SE 2.0)
RR 0.75 (95% CI 0.67–0.83)
logrank 2p < 0.00001

Breast cancer mortality

20-year gain 8.1% (SE 2.0)
RR 0.94 (95% CI 0.76–0.94)
logrank 2p = 0.001

Any death

20-year gain 5.0% (SE 2.0)
RR 0.89 (95% CI 0.81–0.97)
logrank 2p = 0.01

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Webfigure 5. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 3131 women with pathologically node-positive (pN+) disease. ($n_L$ = number of women for whom first recurrence was locoregional, $n_D$ = number women for whom distant recurrence was first.)

3131 pN+ women with Mast+AD

1550 women allocated RT

- Locoregional or distant 51.9%
- Locoregional first 5.0% ($n_L$=99)
- Distant first 46.9% ($n_D$=703)

1581 women allocated No RT

- Locoregional or distant 62.5%
- Locoregional first 19.4% ($n_L$=297)
- Distant first 43.1% ($n_D$=643)

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Lancet 2014; 383: 2127–35
Webfigure 6. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): Event rate ratios and 95% confidence intervals for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer mortality in 3131 women with pathologically node-positive (pN+) disease by prognostic and other factors. Categories with unknowns are excluded from the heterogeneity and trend tests.

### 3131 pN+ women with Mast+AD

**Locoregional recurrence first (years 0-9)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Absent RT</th>
<th>Absent RT</th>
<th>Absent RT</th>
<th>Age 35-49 yr</th>
<th>Breast cancer mortality</th>
<th>Breast cancer mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 40</td>
<td>0.78 (0.56, 1.09)</td>
<td>0.75 (0.54, 1.04)</td>
<td>0.79 (0.56, 1.14)</td>
<td>0.87 (0.70, 1.09)</td>
<td>0.80 (0.69, 0.93)</td>
<td>0.73 (0.66, 0.82)</td>
</tr>
</tbody>
</table>

**Any first recurrence (years 0-9)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Absent RT</th>
<th>Absent RT</th>
<th>Absent RT</th>
<th>Age 35-49 yr</th>
<th>Breast cancer mortality</th>
<th>Breast cancer mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 40</td>
<td>0.78 (0.56, 1.09)</td>
<td>0.75 (0.54, 1.04)</td>
<td>0.79 (0.56, 1.14)</td>
<td>0.87 (0.70, 1.09)</td>
<td>0.80 (0.69, 0.93)</td>
<td>0.73 (0.66, 0.82)</td>
</tr>
</tbody>
</table>

**Breast cancer mortality**

<table>
<thead>
<tr>
<th>Category</th>
<th>Absent RT</th>
<th>Absent RT</th>
<th>Absent RT</th>
<th>Age 35-49 yr</th>
<th>Breast cancer mortality</th>
<th>Breast cancer mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 40</td>
<td>0.78 (0.56, 1.09)</td>
<td>0.75 (0.54, 1.04)</td>
<td>0.79 (0.56, 1.14)</td>
<td>0.87 (0.70, 1.09)</td>
<td>0.80 (0.69, 0.93)</td>
<td>0.73 (0.66, 0.82)</td>
</tr>
</tbody>
</table>

*Note:* In (g), 181 women who were ER positive with tamoxifen also had chemotherapy. In (b), trials that used orthovoltage irradiation are included in the <50 Gy category.
Webfigure 7. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1314 women with 1-3 pathologically positive nodes (pN1-3). See webfigure 1 for methodological note and also webfigure 8.

1314 pN1-3 women with Mast+AD

**Locoregional recurrence first**

10-year gain 16.5% (SE 2.0)

RR 0.24 (95% CI 0.17–0.34)

Logrank 2p < 0.00001

**Any first recurrence**

10-year gain 11.5% (SE 2.9)

RR 0.68 (95% CI 0.57–0.82)

Logrank 2p = 0.00006

**Breast cancer mortality**

20-year gain 7.9% (SE 3.1)

RR 0.80 (95% CI 0.67–0.95)

Logrank 2p = 0.01

**Any death**

20-year gain 3.0% (SE 3.1)

RR 0.89 (95% CI 0.77–1.04)

Logrank 2p > 0.1; NS

Lancet 2014; 383: 2127–35
Webfigure 8. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1314 women with 1-3 pathologically positive nodes (pN1-3). (nL = number of women for whom first recurrence was locoregional, nD = number women for whom distant recurrence was first.)

1314 pN1-3 women with Mast+AD

632 women allocated RT

682 women allocated No RT

Any first recurrence (%)

Locoregional or distant 34.2%
Locoregional first 2.9% (nL=19)
Distant first 31.3% (nD=192)

Locoregional or distant 45.7%
Locoregional first 17.1% (nL=112)
Distant first 28.6% (nD=192)

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Lancet 2014; 383: 2127–35
### 1314 pN1-3 women with Mast+AD

#### Locoregional recurrence first (years 0-9)

<table>
<thead>
<tr>
<th>Category</th>
<th>pN1-3</th>
<th>Mast-AD</th>
<th>Mast+AD</th>
<th>Ratio of overall event rates</th>
<th>Ratio of locoregional event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 40 yr</td>
<td>0.98</td>
<td>0.567</td>
<td>1.734</td>
<td>1.46</td>
<td>1.24</td>
</tr>
<tr>
<td>Age 41-60 yr</td>
<td>0.51</td>
<td>0.272</td>
<td>0.95</td>
<td>0.97</td>
<td>1.01</td>
</tr>
<tr>
<td>Age &gt; 61 yr</td>
<td>0.35</td>
<td>0.35</td>
<td>1.0</td>
<td>0.97</td>
<td>1.01</td>
</tr>
<tr>
<td>Tumor Grade (T)</td>
<td>0.39</td>
<td>0.21</td>
<td>0.90</td>
<td>0.89</td>
<td>1.01</td>
</tr>
<tr>
<td>received neoad</td>
<td>0.44</td>
<td>0.25</td>
<td>0.90</td>
<td>0.89</td>
<td>1.01</td>
</tr>
<tr>
<td>received adjuv</td>
<td>0.33</td>
<td>0.20</td>
<td>0.77</td>
<td>0.76</td>
<td>0.78</td>
</tr>
<tr>
<td>Total cases</td>
<td>1569</td>
<td>9349</td>
<td>1090</td>
<td>1.64</td>
<td>1.24</td>
</tr>
</tbody>
</table>

#### Any first recurrence (years 0-9)

<table>
<thead>
<tr>
<th>Category</th>
<th>pN1-3</th>
<th>Mast-AD</th>
<th>Mast+AD</th>
<th>Ratio of overall event rates</th>
<th>Ratio of locoregional event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 40 yr</td>
<td>0.62</td>
<td>0.62</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Age 41-60 yr</td>
<td>0.45</td>
<td>0.45</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Age &gt; 61 yr</td>
<td>0.34</td>
<td>0.34</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Tumor Grade (T)</td>
<td>0.45</td>
<td>0.45</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>received neoad</td>
<td>0.49</td>
<td>0.49</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>received adjuv</td>
<td>0.43</td>
<td>0.43</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Total cases</td>
<td>1569</td>
<td>9349</td>
<td>1090</td>
<td>1.64</td>
<td>1.24</td>
</tr>
</tbody>
</table>

#### Breast cancer mortality

<table>
<thead>
<tr>
<th>Category</th>
<th>pN1-3</th>
<th>Mast-AD</th>
<th>Mast+AD</th>
<th>Ratio of overall death rates</th>
<th>Ratio of locoregional death rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 40 yr</td>
<td>0.62</td>
<td>0.62</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Age 41-60 yr</td>
<td>0.45</td>
<td>0.45</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Age &gt; 61 yr</td>
<td>0.34</td>
<td>0.34</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Tumor Grade (T)</td>
<td>0.45</td>
<td>0.45</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>received neoad</td>
<td>0.49</td>
<td>0.49</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>received adjuv</td>
<td>0.43</td>
<td>0.43</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Total cases</td>
<td>1569</td>
<td>9349</td>
<td>1090</td>
<td>1.64</td>
<td>1.24</td>
</tr>
</tbody>
</table>

In (b), trials that used orthovoltage irradiation are included in the <50 Gy category.
Webfigure 10. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1133 women with 1-3 pathologically positive nodes (pN1-3) in trials where systemic therapy was given to both randomised treatment groups. See webfigure 1 for methodological note and also webfigure 11.

1133 pN1-3 women with Mast+AD and systemic therapy

Locoregional recurrence first

Any first recurrence

Breast cancer mortality

Any death

20-year gain 7.9 % (SE 3.3)
RR 0.78 (95% CI 0.64–0.94)
logrank 2p = 0.01

20-year gain 2.9 % (SE 3.4)
RR 0.86 (95% CI 0.72–1.02)
logrank 2p = 0.08

Lancet 2014; 383: 2127–35
Webfigure 11. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1133 women with 1-3 pathologically positive nodes (pN1-3) in trials where systemic therapy was given to both randomised treatment groups. (\(r_L\) = number of women for whom first recurrence was locoregional, \(r_D\) = number women for whom distant recurrence was first.)

**1133 pN1-3 women with Mast+AD and systemic therapy**

**539 women allocated RT**

- Any first recurrence (%)
  - Locoregional or distant 33.8%
  - Locoregional first 3.4% (\(r_L=19\))
  - Distant first 30.4% (\(r_D=158\))

**594 women allocated No RT**

- Any first recurrence (%)
  - Locoregional or distant 45.5%
  - Locoregional first 17.7% (\(r_L=100\))
  - Distant first 27.8% (\(r_D=162\))

\(2p\) for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

*Lancet* 2014; 383: 2127–35
Webfigure 12. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 15-year risk of breast cancer mortality in 1133 women with 1-3 pathologically positive nodes (pN1-3) in trials where systemic therapy was given to both randomised treatment groups subdivided according to number of positive nodes. See webfigure 1 for methodological note and also webfigures 13-15.

Locoregional recurrence first

318 women with Mast+AD, systemic therapy and 1 positive node

Any first recurrence

Breast cancer mortality

365 women with Mast+AD, systemic therapy and 2-3 positive nodes

450 pN1-3 women with exact number of positive nodes unknown, Mast+AD and systemic therapy

Lancet 2014; 383: 2127–35
Webfigure 13. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 318 women with 1 pathologically positive node (pN1) and where systemic therapy was given to both randomised treatment groups. (\(r_l\) = number of women for whom first recurrence was locoregional, \(r_d\) = number women for whom distant recurrence was first.)

318 women with Mast+AD, systemic therapy and 1 positive node

145 women allocated RT

173 women allocated No RT

Any first recurrence (%)

Locoregional or distant 25.3%

Locoregional first 2.3% (\(r_l=3\))

Distant first 23.0% (\(r_d=32\))

Any first recurrence (%)

Locoregional or distant 36.3%

Locoregional first 17.8% (\(r_l=29\))

Distant first 18.5% (\(r_d=34\))

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: = 0.0001
Webfigure 14. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 365 women with 2-3 pathologically positive nodes (pN2-3) and where systemic therapy was given to both randomised treatment groups. \( r_l = \) number of women for whom first recurrence was locoregional, \( r_d = \) number of women for whom distant recurrence was first.

365 women with Mast+AD, systemic therapy and 2-3 positive nodes

178 women allocated RT

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Locoregional or distant (%)</th>
<th>Locoregional first (%) ( (r_l=8) )</th>
<th>Distant first (%) ( (r_d=61) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>3.9 %</td>
<td>36.5 %</td>
</tr>
<tr>
<td>10</td>
<td>58</td>
<td>40.4 %</td>
<td>47.8 %</td>
</tr>
</tbody>
</table>

187 women allocated No RT

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Locoregional or distant (%)</th>
<th>Locoregional first (%) ( (r_l=28) )</th>
<th>Distant first (%) ( (r_d=64) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>15.3 %</td>
<td>32.5 %</td>
</tr>
<tr>
<td>10</td>
<td>58</td>
<td>47.8 %</td>
<td>47.8 %</td>
</tr>
</tbody>
</table>

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: \( = 0.007 \)
Webfigure 15. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 450 women with 1-3 pathologically positive nodes (pN1-3) but the exact number of positive nodes unknown and where systemic therapy was given to both randomised treatment groups. ($r_L =$ number of women for whom first recurrence was locoregional, $r_D =$ number women for whom distant recurrence was first.)

450 pN1-3 women but exact number of positive nodes unknown, Mast+AD and systemic therapy

216 women allocated RT

- Any first recurrence (%)
- 0 10 20 30 40 50 60 70 80 90 100
- 0 5 10 years
- Locoregional or distant 34.0%
- Locoregional first 3.5% ($r_L=8$)
- Distant first 30.5% ($r_D=65$)

234 women allocated No RT

- Any first recurrence (%)
- 0 10 20 30 40 50 60 70 80 90 100
- 0 5 10 years
- Locoregional or distant 48.6%
- Locoregional first 19.4% ($r_L=43$)
- Distant first 29.2% ($r_D=84$)

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: $= 0.00002$

Lancet 2014; 383: 2127–35
1772 pN4+ women with Mast+AD

Webfigure 16. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1772 women with 4+ pathologically positive nodes (pN4+). See webfigure 1 for methodological note and also webfigure 17.

**Locoregional recurrence first**
- 10-year gain 19.1% (SE 2.9)
- RR 0.39 (95% CI 0.30–0.50)
- logrank 2p < 0.00001

**Any first recurrence**
- 10-year gain 8.8% (SE 2.6)
- RR 0.79 (95% CI 0.69–0.90)
- logrank 2p = 0.0003

**Breast cancer mortality**
- 20-year gain 9.3% (SE 2.7)
- RR 0.87 (95% CI 0.77–0.99)
- logrank 2p = 0.04

**Any death**
- 20-year gain 7.6% (SE 2.6)
- RR 0.89 (95% CI 0.78–1.00)
- logrank 2p = 0.05

Lancet 2014; 383: 2127–35
Webfigure 17. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1772 women with 4+ pathologically positive nodes (pN4+). ($n_L$ = number of women for whom first recurrence was locoregional, $n_D$ = number women for whom distant recurrence was first.)

1772 pN4+ women with Mast+AD

893 women allocated RT

Locoregional or distant 66.3%  
Locoregional first 7.1% ($n_L$=78)  
Distant first 59.2% ($n_D$=497)

879 women allocated No RT

Locoregional or distant 75.1%  
Locoregional first 20.5% ($n_L$=179)  
Distant first 54.6% ($n_D$=445)

$2p$ for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001
Webfigure 18. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): Event rate ratios and 95% confidence intervals for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer mortality in 1772 women with pN4+ pathologically positive nodes (pN4+) by prognostic and other factors.

Categories with unknowns are excluded from the heterogeneity and trend tests.

1772 pN4+ women with Mast+AD

### Locoregional recurrence first (years 0-9)

| Category | All N = 1772 | Mast N = 1772 | Adj. N = 1772 | Adj. N = 1772
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate Ratio (95% CI)</td>
<td>29.2 [24.4, 35.0]</td>
<td>32.4 [25.8, 41.0]</td>
<td>27.2 [22.0, 33.6]</td>
<td>25.6 [20.5, 32.6]</td>
</tr>
</tbody>
</table>

### Any first recurrence (years 0-9)

| Category | All N = 1772 | Mast N = 1772 | Adj. N = 1772 | Adj. N = 1772
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate Ratio (95% CI)</td>
<td>36.5 [30.9, 43.6]</td>
<td>40.7 [32.5, 50.7]</td>
<td>32.5 [25.9, 41.9]</td>
<td>30.5 [22.8, 40.6]</td>
</tr>
</tbody>
</table>

### Breast cancer mortality

| Category | All N = 1772 | Mast N = 1772 | Adj. N = 1772 | Adj. N = 1772
<table>
<thead>
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<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Rate Ratio (95% CI)</td>
<td>18.1 [13.0, 24.9]</td>
<td>17.9 [12.8, 25.2]</td>
<td>16.0 [11.4, 22.5]</td>
<td>15.8 [11.0, 22.9]</td>
</tr>
</tbody>
</table>

---

Note In (g), 135 women who were ER positive with tamoxifen also had chemotherapy. In (h), trials that used orthovoltage irradiation are included in the <60 Gy category.
Webfigure 19. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1677 women with 4+ pathologically positive nodes (pN4+) in trials where systemic therapy was given to both randomised treatment groups. See webfigure 1 for methodological note and also webfigure 20.

1677 pN4+ women with Mast+AD and systemic therapy

**Locoregional recurrence first**

- 10-year gain 17.9% (SE 3.0) RR 0.41 (95% CI 0.31–0.53) logrank 2p < 0.000001

**Any first recurrence**

- 10-year gain 8.2% (SE 2.6) RR 0.80 (95% CI 0.70–0.92) logrank 2p = 0.001

**Breast cancer mortality**

- 20-year gain 8.0% (SE 2.8) RR 0.89 (95% CI 0.76–1.01) logrank 2p = 0.08

**Any death**

- 20-year gain 7.1% (SE 2.8) RR 0.90 (95% CI 0.79–1.02) logrank 2p > 0.1; NS
Webfigure 20. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1677 women with 4+ pathologically positive nodes (pN4+) in trials where systemic therapy was given to both randomised treatment groups. ($n_L$ = number of women for whom first recurrence was locoregional, $n_D$ = number women for whom distant recurrence was first.)

1677 pN4+ women with Mast+AD and systemic therapy

837 women allocated RT

- Locoregional or distant 65.8%
- Locoregional first 7.7% ($n_L=77$)
- Distant first 58.1% ($n_D=451$)

840 women allocated No RT

- Locoregional or distant 74.0%
- Locoregional first 20.3% ($n_L=168$)
- Distant first 53.7% ($n_D=420$)

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Lancet 2014; 383: 2127–35
Webfigure 21. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 15-year risk of breast cancer mortality in 1677 women with 4+ pathologically positive nodes (pN4+) in trials where systemic therapy was given to both randomised treatment groups subdivided according to number of positive nodes. See webfigure 1 for methodological note and also webfigures 22-24.

Locoregional recurrence first

479 women with Mast+AD, systemic therapy and 4-9 positive nodes

403 women with Mast+AD, systemic therapy and 10+ positive nodes

795 pN4+ women with exact number of positive nodes unknown, Mast+AD and systemic therapy

Lancet 2014; 383: 2127–35
Webfigure 22. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 479 women with 4-9 pathologically positive nodes (pN4-9) in trials where systemic therapy was given to both randomised treatment groups. \( r_L \) = number of women for whom first recurrence was locoregional, \( r_D \) = number women for whom distant recurrence was first.

479 women with Mast+AD, systemic therapy and 4-9 positive nodes

244 women allocated RT

Locoregional or distant 62.6%

Locoregional first 5.9%
\( (r_L=20) \)

Distant first 56.7%
\( (r_D=134) \)

235 women allocated No RT

Locoregional or distant 69.9%

Locoregional first 24.4%
\( (r_L=58) \)

Distant first 45.5%
\( (r_D=105) \)

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Lancet 2014; 383: 2127–35
Webfigure 23. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 403 women with 10+ pathologically positive nodes (pN10+) in trials where systemic therapy was given to both randomised treatment groups. \( r_L = \) number of women for whom first recurrence was locoregional, \( r_D = \) number women for whom distant recurrence was first.

403 women with Mast+AD, systemic therapy and 10+ positive nodes

194 women allocated RT

- Locoregional or distant 74.3%
- Locoregional first 5.6% \( (r_L=14) \)
- Distant first 68.7% \( (r_D=128) \)

209 women allocated No RT

- Locoregional or distant 81.0%
- Locoregional first 21.9% \( (r_L=50) \)
- Distant first 59.1% \( (r_D=121) \)

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: = 0.00002

Lancet 2014; 383: 2127–35
Webfigure 24. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 795 women with 4+ pathologically positive nodes but the exact number of positive nodes unknown in trials where systemic therapy was given to both randomised treatment groups. ($r_L =$ number of women for whom first recurrence was locoregional, $r_D =$ number women for whom distant recurrence was first.)

**795 pN4+ women but exact number of positive nodes unknown, Mast+AD and systemic therapy**

**399 women allocated RT**

- Locoregional or distant 62.5%
- Locoregional first 10.0% ($r_L=43$)
- Distant first 52.5% ($r_D=189$)

**396 women allocated No RT**

- Locoregional or distant 71.5%
- Locoregional first 16.5% ($r_L=60$)
- Distant first 55.0% ($r_D=194$)

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: > 0.1; NS
Webfigure 25. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 870 women with pathologically node-negative (pN0) disease. See webfigure 1 for methodological note and also webfigure 28. Note: 0 locoregional recurrences, 6 recurrences of any type and 10 breast cancer deaths were reported among the 36 pN0 women with tumours >5 cm who were allocated to receive radiotherapy. 4 locoregional recurrences, 11 recurrences of any type and 9 breast cancer deaths were reported among the 36 pN0 women with tumours ≤5 cm who were allocated to not to receive radiotherapy.

870 pN0 women with Mast+AS

**Locoregional recurrence first**

10-year gain 14.1% (SE 2.3)  
RR 0.25 (95% CI 0.16–0.38)  
logrank 2p < 0.00001

<table>
<thead>
<tr>
<th>Years</th>
<th>RT</th>
<th>No-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>5.91 (2.64-13.52)</td>
<td>3.77 (2.07-6.91)</td>
</tr>
<tr>
<td>5-9</td>
<td>1.13 (0.63-2.04)</td>
<td>1.14 (0.63-2.04)</td>
</tr>
<tr>
<td>10-14</td>
<td>1.09 (0.52-2.31)</td>
<td>1.04 (0.52-2.11)</td>
</tr>
<tr>
<td>RR</td>
<td>0.25</td>
<td>1.00</td>
</tr>
<tr>
<td>CI</td>
<td>0.16-0.38</td>
<td>0.52-2.11</td>
</tr>
<tr>
<td>logrank 2p</td>
<td>&lt;0.00001</td>
<td></td>
</tr>
</tbody>
</table>

**Any first recurrence**

10-year gain 12.1% (SE 3.3)  
RR 0.61 (95% CI 0.47–0.80)  
logrank 2p = 0.0003

<table>
<thead>
<tr>
<th>Years</th>
<th>RT</th>
<th>No-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>4.11 (9.00-16.19)</td>
<td>3.35 (9.00-16.19)</td>
</tr>
<tr>
<td>5-9</td>
<td>1.20 (3.90-16.19)</td>
<td>0.42 (0.80-1.77)</td>
</tr>
<tr>
<td>10-14</td>
<td>0.83 (0.42-1.69)</td>
<td>0.83 (0.42-1.69)</td>
</tr>
<tr>
<td>RR</td>
<td>0.61</td>
<td>1.00</td>
</tr>
<tr>
<td>CI</td>
<td>0.47-0.80</td>
<td>0.80-1.77</td>
</tr>
<tr>
<td>logrank 2p</td>
<td>0.0003</td>
<td></td>
</tr>
</tbody>
</table>

**Breast cancer mortality**

20-year gain 3.8% (SE 3.4)  
RR 0.97 (95% CI 0.77–1.22)  
logrank 2p > 0.1; NS

**Any death**

20-year gain 3.8% (SE 3.6)  
RR 1.00 (95% CI 0.84–1.18)  
logrank 2p > 0.1; NS
Webfigure 26. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 870 women with pathologically node negative (pN0) disease. ($r_L =$ number of women for whom first recurrence was locoregional, $r_D =$ number women for whom distant recurrence was first.)

870 pN0 women with Mast+AS

425 women allocated RT

445 women allocated No RT

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Lancet 2014; 383: 2127–35
Webfigure 27. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 2541 women with pathologically node-positive (pN+) disease. See webfigure 1 for methodological note and also webfigure 28.

**2541 pN+ women with Mast+AS**

**Locoregional recurrence first**

- **10-year gain 30.9% (SE 2.0)***
  - RR 0.21 (95% CI 0.17–0.26)
  - logrank 2p < 0.00001

**Any first recurrence**

- **10-year gain 18.7% (SE 2.2)***
  - RR 0.59 (95% CI 0.53–0.66)
  - logrank 2p < 0.00001

**Breast cancer mortality**

- **20-year gain 12.6% (SE 2.3)***
  - RR 0.74 (95% CI 0.67–0.83)
  - logrank 2p < 0.00001

**Any death**

- **20-year gain 8.7% (SE 2.2)***
  - RR 0.79 (95% CI 0.71–0.87)
  - logrank 2p < 0.00001
Webfigure 28. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary sampling (Mast+AS): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 2541 women with pathologically node-positive (pN+) disease. \( r_l \) = number of women for whom first recurrence was locoregional, \( r_d \) = number women for whom distant recurrence was first.

2541 pN+ women with Mast+AS

1270 women allocated RT

1271 women allocated No RT

Any first recurrence (%)

0 10 20 30 40 50 60 70 80 90 100

0 5 10 years

Locoregional or distant 48.3%

Locoregional first 3.4% \( (r_l=74) \)

Distant first 44.9% \( (r_d=547) \)

Locoregional or distant 67.0%

Locoregional first 29.0% \( (r_l=369) \)

Distant first 38.0% \( (r_d=461) \)

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Lancet 2014; 383: 2127–35
Webfigure 29. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 1594 women with pathologically node-negative (pN0) disease.

### 1594 pN0 women

**Locoregional recurrence first (years 0-9)**

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Women</th>
<th>Ratio of annual event rates (95% CI)</th>
<th>RT : No RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Axillary dissection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64B, Ono X-ray</td>
<td>CW+B + IMC</td>
<td>2/175</td>
<td>2/174</td>
<td>0.0</td>
</tr>
<tr>
<td>74C, DBCG Boston</td>
<td>CW+B + IMC</td>
<td>0/6</td>
<td>0/2</td>
<td>1.0</td>
</tr>
<tr>
<td>76C, Glasgow</td>
<td>CW+B + IMC</td>
<td>0/1</td>
<td>0/1</td>
<td>0.0</td>
</tr>
<tr>
<td>78A, S. Sweden-I</td>
<td>CW+B + IMC</td>
<td>1/36</td>
<td>1/46</td>
<td>1.8</td>
</tr>
<tr>
<td>79C, Metaxetas Athens</td>
<td>CW+B + IMC</td>
<td>0/5</td>
<td>0/5</td>
<td>0.4</td>
</tr>
<tr>
<td>82B, DBCG R2 (pneumol.)</td>
<td>CW+B + IMC</td>
<td>0/9</td>
<td>0/10</td>
<td>0.0</td>
</tr>
<tr>
<td>82C, ECOG EST3161</td>
<td>CW+B + IMC</td>
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<td>0/9</td>
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</tr>
<tr>
<td><strong>(a) Subtotal</strong></td>
<td></td>
<td>3/46</td>
<td>8/5</td>
<td>2.6%</td>
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<tr>
<td></td>
<td></td>
<td>(1.4%)</td>
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<td></td>
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<tr>
<td>(b) Axillary sampling</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>74B, Stockholm B</td>
<td>CW+B + IMC</td>
<td>4/203</td>
<td>3/206</td>
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<td>CW+B + IMC</td>
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<td>4/29</td>
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<tr>
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<td>CW+B + IMC</td>
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<tr>
<td>82B, DBCG R2 (pneumol.)</td>
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<td>0/37</td>
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<tr>
<td>82C, ECOG EST3161</td>
<td>CW+B + IMC</td>
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<td>0/16</td>
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<tr>
<td><strong>(b) Subtotal</strong></td>
<td></td>
<td>14/255</td>
<td>72/359</td>
<td>(21.6%)</td>
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<tr>
<td></td>
<td></td>
<td>(10.2%)</td>
<td></td>
<td></td>
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<tr>
<td>(c) Extent of axillary surgery unknown</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>88C, CRC, UK</td>
<td>CW+B + IMC</td>
<td>0/14</td>
<td>5/10</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>(c) Subtotal</strong></td>
<td></td>
<td>14/289</td>
<td>10/349</td>
<td>(0.9%)</td>
</tr>
<tr>
<td></td>
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<td>(10.0%)</td>
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<tr>
<td>Total</td>
<td></td>
<td>3/334</td>
<td>8/507</td>
<td>(2.9%)</td>
</tr>
</tbody>
</table>

**Heterogeneity between 3 subtotals: \( \chi^2 = 2.9, p = 0.2 \)**

**Heterogeneity within subtotals: \( \chi^2 = 5.6, p > 0.1 \)**

**Heterogeneity between 9 trials: \( \chi^2 = 18.3, p = 0.02 \)**

---

**Any first recurrence (years 0-9)**

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Women</th>
<th>Ratio of annual event rates (95% CI)</th>
<th>RT : No RT</th>
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<tr>
<td>(a) Axillary dissection</td>
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<td></td>
</tr>
<tr>
<td>64B, Ono X-ray</td>
<td>CW+B + IMC</td>
<td>2/175</td>
<td>2/174</td>
<td>0.0</td>
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<tr>
<td>74C, DBCG Boston</td>
<td>CW+B + IMC</td>
<td>0/6</td>
<td>0/2</td>
<td>1.0</td>
</tr>
<tr>
<td>76C, Glasgow</td>
<td>CW+B + IMC</td>
<td>0/1</td>
<td>0/1</td>
<td>0.0</td>
</tr>
<tr>
<td>78A, S. Sweden-I</td>
<td>CW+B + IMC</td>
<td>1/36</td>
<td>1/46</td>
<td>1.8</td>
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<tr>
<td>79C, Metaxetas Athens</td>
<td>CW+B + IMC</td>
<td>0/5</td>
<td>0/5</td>
<td>0.4</td>
</tr>
<tr>
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<td>CW+B + IMC</td>
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<td>0/9</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>(a) Subtotal</strong></td>
<td></td>
<td>3/46</td>
<td>8/5</td>
<td>2.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.4%)</td>
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<td></td>
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<tr>
<td>(b) Axillary sampling</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>74B, Stockholm B</td>
<td>CW+B + IMC</td>
<td>4/203</td>
<td>3/206</td>
<td>0.14</td>
</tr>
<tr>
<td>73A, Southampton UK</td>
<td>CW+B + IMC</td>
<td>3/23</td>
<td>4/29</td>
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</tr>
<tr>
<td>74B, Edinburgh I</td>
<td>CW+B + IMC</td>
<td>0/119</td>
<td>0/114</td>
<td>0.0</td>
</tr>
<tr>
<td>82B, DBCG R2 (pneumol.)</td>
<td>CW+B + IMC</td>
<td>0/36</td>
<td>0/37</td>
<td>0.0</td>
</tr>
<tr>
<td>82C, ECOG EST3161</td>
<td>CW+B + IMC</td>
<td>0/49</td>
<td>0/16</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>(b) Subtotal</strong></td>
<td></td>
<td>14/255</td>
<td>72/359</td>
<td>(21.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(10.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) Extent of axillary surgery unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>88C, CRC, UK</td>
<td>CW+B + IMC</td>
<td>0/14</td>
<td>5/10</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>(c) Subtotal</strong></td>
<td></td>
<td>14/289</td>
<td>10/349</td>
<td>(0.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(10.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>3/334</td>
<td>8/507</td>
<td>(2.9%)</td>
</tr>
</tbody>
</table>

**Heterogeneity between 3 subtotals: \( \chi^2 = 2.9, p = 0.2 \)**

**Heterogeneity within subtotals: \( \chi^2 = 5.6, p > 0.1 \)**

**Heterogeneity between 9 trials: \( \chi^2 = 18.3, p = 0.02 \)**

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=internal mammary chain. Site(s) in brackets were not always treated.
Webfigure 29 cntd.

1594 pN0 women

### Breast cancer mortality

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Deaths/Women</th>
<th>RT deaths</th>
<th>Logrank Hazard Ratio</th>
<th>Ratio of annual death rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Associated RT</td>
<td>Associated No RT</td>
<td>O-E</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Axillary dissection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64B Oslo X-ray</td>
<td>CW=AF+IMC</td>
<td>67/175</td>
<td>62/174</td>
<td>2.0</td>
<td>29.3</td>
</tr>
<tr>
<td>74D DFCS Boston</td>
<td>CW=AF+IMC</td>
<td>1/9</td>
<td>1/10</td>
<td>-0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>76C Dublin</td>
<td>CW=AF+IMC</td>
<td>171</td>
<td>0/1</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>77J N/O Anser. 7700</td>
<td>CW=AF+IMC</td>
<td>0/1</td>
<td>0/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>78A S Sweden 11</td>
<td>CW=AF+IMC</td>
<td>423/134 344/144</td>
<td>8.5</td>
<td>18.2</td>
<td></td>
</tr>
<tr>
<td>79A Mexico Athens</td>
<td>CW=AF+IMC</td>
<td>17/13</td>
<td>16/13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>82B DFCS 68th (premenop)</td>
<td>CW=AF+IMC</td>
<td>38</td>
<td>3/10</td>
<td>-0.2</td>
<td>1.3</td>
</tr>
<tr>
<td>82C DFCS 82nd (postmenop)</td>
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<td>20</td>
<td>1/2</td>
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<td>1.6</td>
</tr>
<tr>
<td>82Q ECOG EST13181</td>
<td>CW=AF+IMC</td>
<td>174</td>
<td>1/4</td>
<td>-0.4</td>
<td>0.5</td>
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**Ratio of annual death rates:**

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<th>RT No RT</th>
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</thead>
<tbody>
<tr>
<td>32.0%</td>
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<tr>
<td>30.0%</td>
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</table>

(b) Axillary sampling

<table>
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<tr>
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<th>Treatment Information</th>
<th>Deaths/Women</th>
<th>RT deaths</th>
<th>Logrank Hazard Ratio</th>
<th>Ratio of annual death rates</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td>Associated RT</td>
<td>Associated No RT</td>
<td>O-E</td>
<td>E-O</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>71B Stockholm A</td>
<td>CW=AF+IMC</td>
<td>77/231</td>
<td>76/236</td>
<td>2.5</td>
<td>35.7</td>
</tr>
<tr>
<td>73A Southampton UK</td>
<td>CW=AF+IMC</td>
<td>9/23</td>
<td>13/29</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>74B Edinburgh I</td>
<td>CW=AF+IMC</td>
<td>44/114</td>
<td>50/114</td>
<td>-1.5</td>
<td>20.7</td>
</tr>
<tr>
<td>82B DFCS 68th (premenop)</td>
<td>CW=AF+IMC</td>
<td>16/63</td>
<td>14/53</td>
<td>-3.3</td>
<td>4.2</td>
</tr>
<tr>
<td>82C DFCS 82nd (postmenop)</td>
<td>CW=AF+IMC</td>
<td>19/49</td>
<td>19/53</td>
<td>0.6</td>
<td>9.0</td>
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</table>

**Ratio of annual death rates:**

<table>
<thead>
<tr>
<th>RT No RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>38.2%</td>
</tr>
<tr>
<td>38.4%</td>
</tr>
</tbody>
</table>

(c) Extent of axillary surgery unknown

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Deaths/Women</th>
<th>RT deaths</th>
<th>Logrank Hazard Ratio</th>
<th>Ratio of annual death rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Associated RT</td>
<td>Associated No RT</td>
<td>O-E</td>
<td>E-O</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>86C CRC, UK</td>
<td>CW=AF+IMC</td>
<td>2/14</td>
<td>5/10</td>
<td>-1.4</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Various</td>
<td>2/6</td>
<td>5/5</td>
<td></td>
<td></td>
</tr>
</tbody>
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**Ratio of annual death rates:**

<table>
<thead>
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<tbody>
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<td>50.0%</td>
</tr>
<tr>
<td>50.0%</td>
</tr>
</tbody>
</table>

**Heterogeneity between 3 subtotals:** $\chi^2 = 2.7; \ p > 0.1; \ NS$

**Heterogeneity within subtotals:** $\chi^2 = 9.8; \ p > 0.1; \ NS$

**Heterogeneity between 14 trials:** $\chi^2 = 12.6; \ p > 0.1; \ NS$

### Any death

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Deaths/Women</th>
<th>RT deaths</th>
<th>Logrank Hazard Ratio</th>
<th>Ratio of annual death rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Associated RT</td>
<td>Associated No RT</td>
<td>O-E</td>
<td>E-O</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Axillary dissection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64B Oslo X-ray</td>
<td>CW=AF+IMC</td>
<td>149/175</td>
<td>150/174</td>
<td>11.3</td>
<td>64.1</td>
</tr>
<tr>
<td>74D DFCS Boston</td>
<td>CW=AF+IMC</td>
<td>58</td>
<td>2/1</td>
<td>-0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>76C Dublin</td>
<td>CW=AF+IMC</td>
<td>1/1</td>
<td>1/1</td>
<td>0.0</td>
<td>0.2</td>
</tr>
<tr>
<td>77J N/O Anser. 7700</td>
<td>CW=AF+IMC</td>
<td>0/1</td>
<td>0/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>78A S Sweden 11</td>
<td>CW=AF+IMC</td>
<td>70/134</td>
<td>73/144</td>
<td>8.7</td>
<td>35.2</td>
</tr>
<tr>
<td>79A Mexico Athens</td>
<td>CW=AF+IMC</td>
<td>208</td>
<td>1/6</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>82B DFCS 68th (premenop)</td>
<td>CW=AF+IMC</td>
<td>3/8</td>
<td>4/10</td>
<td>-0.2</td>
<td>1.3</td>
</tr>
<tr>
<td>82C DFCS 82nd (postmenop)</td>
<td>CW=AF+IMC</td>
<td>6/8</td>
<td>7/12</td>
<td>1.8</td>
<td>2.2</td>
</tr>
<tr>
<td>82Q ECOG EST13181</td>
<td>CW=AF+IMC</td>
<td>4/3</td>
<td>1/4</td>
<td>-0.2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Ratio of annual death rates:**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>69.7%</td>
</tr>
<tr>
<td>67.4%</td>
</tr>
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</table>

(b) Axillary sampling

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Deaths/Women</th>
<th>RT deaths</th>
<th>Logrank Hazard Ratio</th>
<th>Ratio of annual death rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Associated RT</td>
<td>Associated No RT</td>
<td>O-E</td>
<td>E-O</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>71B Stockholm A</td>
<td>CW=AF+IMC</td>
<td>100/203</td>
<td>100/200</td>
<td>0.6</td>
<td>66.3</td>
</tr>
<tr>
<td>73A Southampton UK</td>
<td>CW=AF+IMC</td>
<td>16/23</td>
<td>20/29</td>
<td>1.7</td>
<td>6.8</td>
</tr>
<tr>
<td>74B Edinburgh I</td>
<td>CW=AF+IMC</td>
<td>87/114</td>
<td>83/104</td>
<td>2.8</td>
<td>35.0</td>
</tr>
<tr>
<td>82B DFCS 68th (premenop)</td>
<td>CW=AF+IMC</td>
<td>11/35</td>
<td>19/235</td>
<td>-2.9</td>
<td>6.4</td>
</tr>
<tr>
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<td>31/49</td>
<td>30/39</td>
<td>-1.3</td>
<td>14.1</td>
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</table>

**Ratio of annual death rates:**

<table>
<thead>
<tr>
<th>RT No RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>70.0%</td>
</tr>
<tr>
<td>66.7%</td>
</tr>
</tbody>
</table>

(c) Extent of axillary surgery unknown

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Deaths/Women</th>
<th>RT deaths</th>
<th>Logrank Hazard Ratio</th>
<th>Ratio of annual death rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Associated RT</td>
<td>Associated No RT</td>
<td>O-E</td>
<td>E-O</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>86C CRC, UK</td>
<td>CW=AF+IMC</td>
<td>4/14</td>
<td>5/10</td>
<td>-2.4</td>
<td>2.4</td>
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<tr>
<td></td>
<td>Various</td>
<td>4/8</td>
<td>5/6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Ratio of annual death rates:**

<table>
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<th>RT No RT</th>
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</thead>
<tbody>
<tr>
<td>80.0%</td>
</tr>
<tr>
<td>80.0%</td>
</tr>
</tbody>
</table>

**Heterogeneity between 3 subtotals:** $\chi^2 = 5.4; \ p = 0.07$

**Heterogeneity within subtotals:** $\chi^2 = 5.0; \ p > 0.1; \ NS$

**Heterogeneity between 14 trials:** $\chi^2 = 10.4; \ p > 0.1; \ NS$

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=internal mammary chain. Site(s) in brackets were not always treated.

Lancet 2014; 383: 2127–35
Webfigure 30. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 5821 women with pathologically node-positive (pN+) disease.

### 5821 pN+ women

#### Locoregional recurrence first (years 0-9)

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Women</th>
<th>RT events</th>
<th>Allocated</th>
<th>Alloc. No</th>
<th>Logrank O-E</th>
<th>O-E</th>
<th>Ratio of annual event rates</th>
<th>RT : No RT</th>
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<tbody>
<tr>
<td>(a) Axillary dissection</td>
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<td></td>
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</tr>
<tr>
<td>648 Oulu X-ray</td>
<td>CW+AF+IMC</td>
<td>21/10</td>
<td>10/13</td>
<td>-0.6</td>
<td>2.8</td>
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<td></td>
<td></td>
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<tr>
<td>74D DFCI Boston</td>
<td>CW+AF+IMC</td>
<td>71/10</td>
<td>19/16</td>
<td>-0.2</td>
<td>5.6</td>
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</tr>
<tr>
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<td>CW+AF+IMC</td>
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<td>0/5</td>
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<td>2.9</td>
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<tr>
<td>76A BECCG 1</td>
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<td>12/13</td>
<td>18/12</td>
<td>3.3</td>
<td>7.1</td>
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<tr>
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<td>CW+AF+IMC</td>
<td>21/13</td>
<td>21/10</td>
<td>6.9</td>
<td>9.8</td>
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<td>36/23</td>
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<td>7.1</td>
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<td>6.9</td>
<td>9.8</td>
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<tr>
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<td>CW+AF+IMC</td>
<td>12/16</td>
<td>21/17</td>
<td>8.6</td>
<td>9.8</td>
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<td>(b) Subtotal</td>
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#### Any first recurrence (years 0-9)

<table>
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<th>Year code, and study name</th>
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<th>RT events</th>
<th>Allocated</th>
<th>Alloc. No</th>
<th>Logrank O-E</th>
<th>O-E</th>
<th>Ratio of annual event rates</th>
<th>RT : No RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Axillary dissection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>648 Oulu X-ray</td>
<td>CW+AF+IMC</td>
<td>53/10</td>
<td>53/10</td>
<td>10.2</td>
<td>-0.2</td>
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<tr>
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<td>82/18</td>
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<td>29.7</td>
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<tr>
<td>74D Plockhorst et al (pH+)</td>
<td>CW+AF+IMC</td>
<td>82/10</td>
<td>65/10</td>
<td>2.2</td>
<td>14.4</td>
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</tr>
<tr>
<td>76A BECCG 1</td>
<td>CW+AF+IMC</td>
<td>12/12</td>
<td>62/12</td>
<td>16.6</td>
<td>23.6</td>
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<tr>
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#### Extent of axillary surgery unknown

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<th>Treatment Information</th>
<th>Events/Women</th>
<th>RT events</th>
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<th>Alloc. No</th>
<th>Logrank O-E</th>
<th>O-E</th>
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#### Extent of axillary surgery unknown

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<th>RT events</th>
<th>Allocated</th>
<th>Alloc. No</th>
<th>Logrank O-E</th>
<th>O-E</th>
<th>Ratio of annual event rates</th>
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#### Heterogeneity between 3 subtotals: \( \chi^2 = 8.5; p = 0.01 \)

Heterogeneity within subtotals: \( \chi^2 = 24.8; p = 0.1; NS \)

Heterogeneity between 22 trials: \( \chi^2 = 33.3; p = 0.04 \)

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supracavitary fossa, IMC=internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf
## Breast cancer mortality

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<th>Women</th>
<th>RT deaths</th>
<th>RT deaths</th>
<th>Ratio of annual death rates</th>
<th>RT : No RT</th>
</tr>
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<td><strong>Ratio of annual death rates</strong></td>
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</tbody>
</table>

### (a) Auxillary dissection
- 58.5% of OAC
- 41% of 5-FU
- 18% of RT
- 8% of other

### (b) Auxillary sampling
- 71.9% of 5-FU
- 9.5% of RT
- 18.5% of other

### (c) Extent of auxiliary surgery unknown
- 70% of OAC
- 20% of 5-FU
- 10% of RT

### Any death

<table>
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<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Deaths</th>
<th>Women</th>
<th>RT deaths</th>
<th>RT deaths</th>
<th>Ratio of annual death rates</th>
<th>RT : No RT</th>
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<td><strong>Ratio of annual death rates</strong></td>
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<td></td>
<td></td>
<td></td>
<td><strong>Ratio of annual death rates</strong></td>
<td></td>
</tr>
</tbody>
</table>

### (a) Auxillary dissection
- 101/110 of OAC
- 59/51 of 5-FU
- 15/61 of RT

### (b) Auxillary sampling
- 93/115 of 5-FU
- 65/61 of RT

### (c) Extent of auxillary surgery unknown
- 32/29 of OAC
- 38/33 of RT

### Heterogeneity between 3 subtotals: $\chi^2 = 3.8$; $p > 0.1$; NS

### Heterogeneity within subtotals: $\chi^2 = 34.8$; $p = 0.03$

### Heterogeneity between 24 trials: $\chi^2 = 38.6$; $p = 0.02$

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or suprapubic fossa, IMC=internal mammary chain. Site(s) in brackets were not always treated.

**5821 pN+ women**

Lancet 2014; 383: 2127–35
Webfigure 31. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 2801 women with 1-3 pathologically positive nodes (pN1-3).

### 2801 pN1-3 women

#### Locoregional recurrence first (years 0-9)

<table>
<thead>
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<th>RT events</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of annual event rates (RT/No RT)</th>
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<td></td>
</tr>
<tr>
<td>64B Oslo X-ray</td>
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<td>0/90</td>
<td>673</td>
<td>0.1</td>
<td>1.3</td>
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<td>0</td>
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<td></td>
</tr>
<tr>
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<td>CW-FA+IMC</td>
<td>5/10</td>
<td>1694</td>
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</tr>
<tr>
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<td>25155</td>
<td>-10.8</td>
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<td>111</td>
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<td>0.2</td>
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<td>138</td>
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<td>78.8</td>
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<tr>
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<td>(20.3%)</td>
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Heterogeneity between 3 subtotals: \( \chi^2 = 0.3; p > 0.1: \text{NS} \)

Heterogeneity within subtotals: \( \chi^2 = 7.1; p > 0.1: \text{NS} \)

Heterogeneity between 17 trials: \( \chi^2 = 7.5; p > 0.1: \text{NS} \)

#### Any first recurrence (years 0-9)

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<th>Treatment Information</th>
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<th>RT events</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of annual event rates (RT/No RT)</th>
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<tr>
<td>(3.8%)</td>
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<td>(20.3%)</td>
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Heterogeneity between 3 subtotals: \( \chi^2 = 0.4; p > 0.1: \text{NS} \)

Heterogeneity within subtotals: \( \chi^2 = 25.3; p = 0.07 \)

Heterogeneity between 19 trials: \( \chi^2 = 25.7; p > 0.1: \text{NS} \)

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supracavicular fossa, IMC=internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

Lancet 2014; 383: 2127–35
Webfigure 31 cndt.

2801 pN1-3 women

Breast cancer mortality

| Year code, and study name | Treatment Information | Deaths/Women | Ratio of annual death rates
<table>
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<td></td>
<td>2010-2015</td>
<td>2010-2015</td>
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</table>

(a) Axillary dissection

| Year code, and study name | Treatment Information | Deaths/Women | Ratio of annual death rates
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<td></td>
<td>2010-2015</td>
<td>2010-2015</td>
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</table>

(b) Axillary sampling

| Year code, and study name | Treatment Information | Deaths/Women | Ratio of annual death rates
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<td>2010-2015</td>
<td>2010-2015</td>
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</table>

(c) Extent of axillary surgery unknown

| Year code, and study name | Treatment Information | Deaths/Women | Ratio of annual death rates
<table>
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Any death

| Year code, and study name | Treatment Information | Deaths/Women | Ratio of annual death rates
<table>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Among RT</td>
<td>Among No RT</td>
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<tr>
<td></td>
<td></td>
<td>2010-2015</td>
<td>2010-2015</td>
</tr>
</tbody>
</table>

(a) Axillary dissection

| Year code, and study name | Treatment Information | Deaths/Women | Ratio of annual death rates
<table>
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<td>Among RT</td>
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<td></td>
<td>2010-2015</td>
<td>2010-2015</td>
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</table>

(b) Axillary sampling

| Year code, and study name | Treatment Information | Deaths/Women | Ratio of annual death rates
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<td></td>
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<td>2010-2015</td>
<td>2010-2015</td>
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</tbody>
</table>

(c) Extent of axillary surgery unknown

| Year code, and study name | Treatment Information | Deaths/Women | Ratio of annual death rates
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<td>Among No RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2010-2015</td>
<td>2010-2015</td>
</tr>
</tbody>
</table>

Heterogeneity between 3 subtotals: \( \chi^2 = 0.4 \); p > 0.1; NS
Heterogeneity within subtotals: \( \chi^2 = 15.0 \); p > 0.1; NS
Heterogeneity between 19 trials: \( \chi^2 = 15.4 \); p > 0.1; NS

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
Radiotherapy sites: C/W = chest wall, AF = Axilla and/or supraclavicular fossa, IMC = internal mammary chain. Site(s) in brackets were not always treated.

Lancet 2014; 383: 2127–35
Webfigure 32. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 2557 women with 4+ pathologically positive nodes (pN4+).

### 2557 pN4+ women

#### Locoregional recurrence first (years 0-9)

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Woman</th>
<th>Treatment Information</th>
<th>Events/Woman</th>
<th>Logrank Variance of E</th>
<th>Ratio of annual event rates</th>
</tr>
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<td>RT events</td>
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</tr>
</tbody>
</table>

- **(a) Axillary dissection**
  - 648 Osas X-ray: RT: 0.99
  - 742 PGarion: RT: 0.99
  - 767 SIC SETI: RT: 0.99
  - 786 ESGIT 1: RT: 0.99
  - 788 ESGIT 2: RT: 0.99
  - 822 DBCG 2B: RT: 0.99
  - 855 EECG EST 1018: RT: 0.99

- **(b) Axillary sampling**
  - 777 M stroke: RT: 0.99
  - 838 DBCG 2B: RT: 0.99
  - 855 EECG EST 1018: RT: 0.99

- **(c) Extent of axillary surgery unknown**
  - 800 AEB: RT: 0.99
  - 800 CRC: RT: 0.99

- **(d) Extent of axillary surgery unknown**
  - 800 AEB: RT: 0.99
  - 800 CRC: RT: 0.99

#### Any first recurrence (years 0-9)

<table>
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<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Woman</th>
<th>Treatment Information</th>
<th>Events/Woman</th>
<th>Logrank Variance of E</th>
<th>Ratio of annual event rates</th>
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<tr>
<td></td>
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</tbody>
</table>

- **(a) Axillary dissection**
  - 648 Osas X-ray: RT: 0.99
  - 742 PGarion: RT: 0.99
  - 767 SIC SETI: RT: 0.99
  - 786 ESGIT 1: RT: 0.99
  - 788 ESGIT 2: RT: 0.99
  - 822 DBCG 2B: RT: 0.99
  - 855 EECG EST 1018: RT: 0.99

- **(b) Axillary sampling**
  - 777 M stroke: RT: 0.99
  - 838 DBCG 2B: RT: 0.99
  - 855 EECG EST 1018: RT: 0.99

- **(c) Extent of axillary surgery unknown**
  - 800 AEB: RT: 0.99
  - 800 CRC: RT: 0.99

### Heterogeneity between 3 subtotals:
- χ² = 9.9; p = 0.007
- Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
- Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=internal mammary chain. Site(s) in brackets were not always treated.

### Continued overleaf

Lancet 2014; 383: 2127–35
Breast cancer mortality

Year code, and study name | Treatment Information | Deaths/Women | Logrank Variance of O-E | Ratio of annual death rates
--- | --- | --- | --- | ---

(a) Axillary dissection
649 Oslo X-ray | CW + AF + IMC | 27/30 | 12/20 | -5.9 5.6
742 DFCI Boston | CW + AF + IMC | 30/35 | 33/35 | -2.3 10.6
743 Pechmont OA (PN4+) | CW + AF + IMC | 36/65 | 40/55 | -3.5 14.3
754 ECOG 1 | CW + AF + IMC | 0/125 | 0/125 | 3.7 24.7
756 Single | CW + AF + IMC | 30/40 | 27/31 | -3.8 9.8
774 MD Anderson, 730B | CW + AF | 18/24 | 17/30 | 5.4 5.7
783 S Sweden I:1 | CW + AF + IMC | 28/55 | 50/73 | -4.6 23.9
786 BCCA Vancouver | CW + AF + IMC | 37/60 | 46/54 | -8.8 18.0
790 Clalit Health Services | CW + AF + IMC | 14/40 | 11/54 | -4.9 5.1
791 Hellenic Cooperative | CW + AF | 5/8 | 10/23 | -2.4 4.7
805 ECOG EST 3191 | CW + AF + IMC | 15/15 | 20/23 | 2.8 2.1
823 DBCG 82b (premenop) | CW + AF + IMC | 29/113 | 107/128 | -11.5 30.1
825 DBCG 82b (postmenop) | CW + AF + IMC | 51/100 | 81/94 | -0.4 33.9
825 ECOG EST 3191 | CW + AF + IMC | 64/127 | 80/121 | 1.3 35.7

(a) Subtotal: 657/893 605/879 31.7 237.2 (63.5%) (68.8%)

(b) Axillary sampling
774 MD Anderson, 730B | CW + AF + IMC | 21/232 | 20/229 | 2.1 6.7
735 Clalit Health Services | CW + AF + IMC | 10/116 | 10/163 | -24.8 46.4
786 BCCA Vancouver | CW + AF + IMC | 91/127 | 115/140 | -4.1 44.7
790 Clalit Health Services | CW + AF + IMC | 18/54 | 24/31 | 0.3 8.5

(b) Subtotal: 239/342 293/361 27.0 106.3 (60.9%) (81.2%)

(c) Extent of axillary surgery unknown
800 NW Belgium | CW + AF + IMC | 9/34 | 7/35 | 1.7 3.5
806 CRC UK | CW + AF + IMC | 5/7 | 22/22 | -1.2 3.2

(c) Subtotal: 41/41 41/41 (34.1%) (22.0%)

Total: 820/907 871/971 (64.3%) (70.6%)

0.85 (SE 0.05) (95% CI 0.79-1.00)
Heterogeneity between 3 subtotals: x2 = 2.3; p > 0.1: NS
Heterogeneity within subtotals: x2 = 36.1; p = 0.004
Heterogeneity between 20 trials: x2 = 38.4; p = 0.005
Ratio of annual death rates: RT better 0.89 (SE 0.03) (95% CI 0.85-0.92)
RT worse 0.87 (SE 0.06) (95% CI 0.82-0.94)

Any death

Year code, and study name | Treatment Information | Deaths/Women | Logrank Variance of O-E | Ratio of annual death rates
--- | --- | --- | --- | ---

(a) Axillary dissection
649 Oslo X-ray | CW + AF + IMC | 33/30 | 28/30 | -5.6 6.3
742 DFCI Boston | CW + AF + IMC | 39/35 | 33/35 | 0.9 15.0
743 Pechmont OA (PN4+) | CW + AF + IMC | 41/35 | 40/35 | -1.0 15.2
754 ECOG 1 | CW + AF + IMC | 68/125 | 69/129 | -5.2 29.9
756 Single | CW + AF + IMC | 32/40 | 29/31 | -4.2 13.8
774 MD Anderson, 730B | CW + AF | 19/24 | 17/30 | 5.9 5.9
783 S Sweden I:1 | CW + AF + IMC | 69/92 | 62/73 | -5.0 27.4
786 BCCA Vancouver | CW + AF + IMC | 43/92 | 46/51 | -7.9 18.6
790 Clalit Health Services | CW + AF + IMC | 12/34 | 24/34 | 3.3 1.9
791 Hellenic Cooperative | CW + AF | 5/11 | 18/25 | -2.4 4.7
805 ECOG EST 3191 | CW + AF + IMC | 12/18 | 11/19 | 3.0 2.6
823 DBCG 82b (premenop) | CW + AF + IMC | 85/110 | 106/128 | -9.2 40.0
825 DBCG 82b (postmenop) | CW + AF + IMC | 85/104 | 86/94 | -1.6 36.3
825 ECOG EST 3191 | CW + AF + IMC | 84/127 | 86/121 | -2.9 41.3

(a) Subtotal: 631/893 655/879 31.5 260.5 (70.7%) (74.5%)

(b) Axillary sampling
774 MD Anderson, 730B | CW + AF + IMC | 101/232 | 91/229 | 3.2 7.5
735 Clalit Health Services | CW + AF + IMC | 24/54 | 23/31 | -23.2 48.7
786 BCCA Vancouver | CW + AF + IMC | 107/116 | 135/143 | -10.2 49.3
790 Clalit Health Services | CW + AF + IMC | 23/54 | 27/43 | 9.9 10.5

(b) Subtotal: 264/342 314/361 (77.2%) (87.0%)

(c) Extent of axillary surgery unknown
800 NW Belgium | CW + AF + IMC | 11/34 | 7/39 | 2.7 4.0
806 CRC UK | CW + AF + IMC | 6/7 | 22/22 | -9.2 9.8

(c) Subtotal: 41/41 41/41 (41.5%) (22.0%)

Total: 912/1276 1281/1291 (71.5%) (76.3%)

1.65 (SE 0.03) (95% CI 1.43-1.89)
Heterogeneity between 3 subtotals: x2 = 3.7; p > 0.1: NS
Heterogeneity within subtotals: x2 = 31.6; p = 0.02
Heterogeneity between 20 trials: x2 = 35.2; p = 0.01

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
Radiotherapy sites: CW = chest wall, AF = Axilla and/or supraclavicular fossa, IMC = internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

Lancet 2014; 383: 2127–35
Webfigure 33. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 463 women with pathologically positive nodes (pN?+) but unknown if they were 1-3 or 4+ positive.

463 pN?+ women

Locoregional recurrence first (years 0-9)

Any first recurrence (years 0-9)

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups. Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=internal mammary chain. Site(s) in brackets were not always treated.
Webfigure 33 cntd.

463 pN+ women

Breast cancer mortality

<table>
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<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Allocated RT</th>
<th>Allocated No RT</th>
<th>RT deaths</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of annual death rates</th>
<th>RT : No RT</th>
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<td>(a) Axillary dissection</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>74D DFCI Boston</td>
<td>CW+AF IMC</td>
<td>7/11</td>
<td>4/8</td>
<td>0.2</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>78G BCNC Vancouver</td>
<td>CW+AF IMC</td>
<td>5/12</td>
<td>5/7</td>
<td>1.2</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80G Hiroshi</td>
<td>CW+AF IMC</td>
<td>2/2</td>
<td>2/5</td>
<td>0.0</td>
<td>0.5</td>
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<td>17/11</td>
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</tr>
<tr>
<td>(b) Axillary sampling</td>
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<td>74B Edinburgh I</td>
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<td>0/1</td>
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<td>0.2</td>
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<tr>
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<td>CW+AF IMC</td>
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<td>0.2</td>
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<tr>
<td>82B DCOC B2 (premenop.)</td>
<td>CW+AF IMC</td>
<td>0/0</td>
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<td>0.9</td>
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<td>82C DCOC B2 (postmenop.)</td>
<td>CW+AF IMC</td>
<td>0/0</td>
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<tr>
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<td>28/41</td>
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</table>

Difference between treatment effects in 2 subtotals: χ² = 0.0; p > 0.1; NS
Heterogeneity within subtotals: χ² = 3.1; p > 0.1; NS
Heterogeneity between 8 trials: χ² = 3.1; p > 0.1; NS

Any death

<table>
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<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Allocated RT</th>
<th>Allocated No RT</th>
<th>RT deaths</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of annual death rates</th>
<th>RT : No RT</th>
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<tr>
<td>(a) Axillary dissection</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>74D DFCI Boston</td>
<td>CW+AF IMC</td>
<td>8/11</td>
<td>4/8</td>
<td>0.2</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>78G BCNC Vancouver</td>
<td>CW+AF IMC</td>
<td>5/12</td>
<td>5/7</td>
<td>1.2</td>
<td>2.1</td>
<td></td>
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<tr>
<td>80G Hiroshi</td>
<td>CW+AF IMC</td>
<td>2/2</td>
<td>2/5</td>
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<td>76F Czecelica</td>
<td>CW+AF IMC</td>
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<td>3/3</td>
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<tr>
<td>82B DCOC B2 (premenop.)</td>
<td>CW+AF IMC</td>
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<td>-0.9</td>
<td>0.9</td>
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<tr>
<td>82C DCOC B2 (postmenop.)</td>
<td>CW+AF IMC</td>
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<td>85F Nottingham</td>
<td>CW+AF IMC</td>
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<td>30/41</td>
<td>-3.6</td>
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<td>114/137</td>
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<td>132/148</td>
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</table>

Difference between treatment effects in 2 subtotals: χ² = 0.0; p > 0.1; NS
Heterogeneity within subtotals: χ² = 3.0; p > 0.1; NS
Heterogeneity between 8 trials: χ² = 3.0; p > 0.1; NS

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=internal mammary chain. Site(s) in brackets were not always treated.
Webfigure 34. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 720 women with unknown pathological nodal status (pN?).

720 pN? women

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment</th>
<th>Events/Total</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
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<td><strong>Locoregional recurrence first (years 0-9)</strong></td>
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<tr>
<td><strong>RT events, or No RT</strong></td>
<td>RT: No RT</td>
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<td></td>
<td>Allocated</td>
<td>Allocated</td>
<td>Logrank Variance of O-E</td>
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<tr>
<td>(a) Axillary dissection</td>
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</tr>
<tr>
<td>75A EBCSG 1</td>
<td>CW=AF+MOC</td>
<td>37/</td>
<td>37/</td>
</tr>
<tr>
<td>75C Copenhagen</td>
<td>CW=AF+MOC</td>
<td>31/</td>
<td>31/</td>
</tr>
<tr>
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<td>CW=AF+MOC</td>
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<td>31/</td>
</tr>
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<td>CW=AF+MOC</td>
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<td>21/37</td>
</tr>
<tr>
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</tr>
<tr>
<td>(c) Extent of axillary surgery unknown</td>
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</tr>
<tr>
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<td>CW=AF+MOC</td>
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<td>1/26</td>
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<tr>
<td><strong>Total</strong></td>
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</tr>
</tbody>
</table>

Difference between treatment effects in 2 subtotals: $\chi^2 = 1.2; 2p > 0.1; $ NS
Heterogeneity within subtotals: $\chi^2 = 4.5; p > 0.1; $ NS
Heterogeneity between 7 trials: $\chi^2 = 5.7; p > 0.1; $ NS

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment</th>
<th>Events/Total</th>
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<td>Logrank Variance of O-E</td>
</tr>
<tr>
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</tr>
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<td>37/</td>
<td>37/</td>
</tr>
<tr>
<td>75C Copenhagen</td>
<td>CW=AF+MOC</td>
<td>31/</td>
<td>31/</td>
</tr>
<tr>
<td>75D Stockholm</td>
<td>CW=AF+MOC</td>
<td>31/</td>
<td>31/</td>
</tr>
<tr>
<td>(a) Subtotal</td>
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</tr>
<tr>
<td>75E EBCG 82b (prenone)</td>
<td>CW=AF+MOC</td>
<td>21/37</td>
<td>21/37</td>
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<tr>
<td>(b) Subtotal</td>
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</tr>
<tr>
<td>(c) Extent of axillary surgery unknown</td>
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<tr>
<td>86C CRSG, UK</td>
<td>CW=AF+MOC</td>
<td>1/26</td>
<td>1/26</td>
</tr>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity between 3 subtotals: $\chi^2 = 1.8; p > 0.1; $ NS
Heterogeneity within subtotals: $\chi^2 = 1.3; p > 0.1; $ NS
Heterogeneity between 8 trials: $\chi^2 = 3.1; p > 0.1; $ NS

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

Lancet 2014; 383: 2127–35
### Breast cancer mortality

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Deaths/Women</th>
<th>RT deaths</th>
<th>Ratio of annual death rates</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of RT : No RT</th>
<th>99% CI</th>
<th>95% CI</th>
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<tr>
<td>(a) Axillary dissection</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td>0.96</td>
<td>0.67</td>
</tr>
<tr>
<td>76A Breast Cancer 1</td>
<td>CW/AF+IMC</td>
<td>0/1</td>
<td>0/1</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td>0.97</td>
</tr>
<tr>
<td>76C Breast Cancer 1</td>
<td>CW/AF+IMC</td>
<td>0/1</td>
<td>0/1</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td>0.97</td>
</tr>
<tr>
<td>77.J MD Andor. 77398</td>
<td>CW/AF+IMC</td>
<td>3/4</td>
<td>0/0</td>
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<td>0.98</td>
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<td>79A S Sweden N.1</td>
<td>CW/AF+IMC</td>
<td>11/22</td>
<td>5/18</td>
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<td>0.67</td>
</tr>
<tr>
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<td>CW/AF+IMC</td>
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<td></td>
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<td>0.91</td>
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<tr>
<td>71A Southampton UK</td>
<td>CW/AF+IMC</td>
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<td>0/0</td>
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<td>71C Edinburgh I</td>
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<td>71F Coimbra</td>
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<tr>
<td>82B DCCG 82 (breastop nom)</td>
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<td>80C CRC, UK</td>
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<td>0.91</td>
</tr>
<tr>
<td>82A DCCG, UK</td>
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<tr>
<td><strong>(c) Subtotal</strong></td>
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### Any death

<table>
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<tr>
<th>Year code, and study name</th>
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<th>Deaths/Women</th>
<th>RT deaths</th>
<th>Ratio of annual death rates</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of RT : No RT</th>
<th>99% CI</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>(a) Axillary dissection</td>
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<td></td>
<td>0.96</td>
<td>0.67</td>
</tr>
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<td>76A Breast Cancer 1</td>
<td>CW/AF+IMC</td>
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<td>0/1</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td>0.97</td>
</tr>
<tr>
<td>76C Breast Cancer 1</td>
<td>CW/AF+IMC</td>
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<td>0/1</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td>0.97</td>
</tr>
<tr>
<td>77.J MD Andor. 77398</td>
<td>CW/AF+IMC</td>
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<td>0/0</td>
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<td>0.62</td>
<td>0.98</td>
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<tr>
<td>79A S Sweden N.1</td>
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<td>0.67</td>
</tr>
<tr>
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<td>CW/AF+IMC</td>
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<td>0/0</td>
<td></td>
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<td></td>
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<td>0.91</td>
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<tr>
<td>71A Southampton UK</td>
<td>CW/AF+IMC</td>
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<td>7/10</td>
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<td></td>
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<td>0.98</td>
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<td>71C Edinburgh I</td>
<td>CW/AF</td>
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<td>49/50</td>
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<td>0.97</td>
</tr>
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<td>71F Coimbra</td>
<td>CW/AF+IMC</td>
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<td>1/1</td>
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<td></td>
<td></td>
<td>1.00</td>
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<td>0.97</td>
</tr>
<tr>
<td>82S DCCG 82 (breastop nom)</td>
<td>CW/AF+IMC</td>
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<td>0/1</td>
<td></td>
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<td></td>
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<td>0.97</td>
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<td>(c) Extent of axillary surgery unknown</td>
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<td>0.67</td>
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<td>0/0</td>
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<td>0.91</td>
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<tr>
<td>82A DCCG, UK</td>
<td>Various</td>
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<td>0/0</td>
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<td></td>
<td>0.50</td>
<td>0.91</td>
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<tr>
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</table>

Heterogeneity between 3 subtotals: $\chi^2 = 1.7; p > 0.1: NS$
Heterogeneity within subtotals: $\chi^2 = 5.0; p > 0.1: NS$

† Same polychemotherapy (usually cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=internal mammary chain. Site(s) in brackets were not always treated.
Webtable 2. Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS)*.

<table>
<thead>
<tr>
<th>Nodal status†</th>
<th>Women</th>
<th>Deaths</th>
<th>Woman-years since diagnosis</th>
<th>% women given systemic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median/ woman ('000s)</td>
<td>Total ('000s)</td>
</tr>
<tr>
<td>Axillary dissection</td>
<td></td>
<td></td>
<td>&lt;10</td>
<td>10-</td>
</tr>
<tr>
<td>pN0</td>
<td>465</td>
<td>355</td>
<td>17.3</td>
<td>8.0</td>
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<tr>
<td>pN+</td>
<td>1029</td>
<td>678</td>
<td>6.5</td>
<td>10.1</td>
</tr>
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<td>pN unknown</td>
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<td>Total</td>
<td>2304</td>
<td>1532</td>
<td>7.2</td>
<td>24.5</td>
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</table>

*Data available for 8 trials, start dates 1961 to 1978. In all trials radiotherapy was given to the axilla/supraclavicular fossa and the internal mammary chain. In 3 of the 8 trials radiotherapy to the chest wall was occasionally given. Full details of the trials are given in webtable 3.
† pN0: pathologically node negative, pN+: pathologically node positive, pN unknown: status not reported or staging method was clinical or unknown.
‡ Chemotherapy was cyclophosphamide, methotrexate, 5-fluorouracil [CMF], cyclophosphamide, 5-fluorouracil, prednisone [CFP], or melphalan.
Webtable 3. Randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS) – treatment details.

<table>
<thead>
<tr>
<th>Year code and study name</th>
<th>Breast surgery</th>
<th>Axillary Surgery* (number of patients)</th>
<th>Chest wall RT</th>
<th>Supraclavicular and axillary fossa RT</th>
<th>Internal mammary chain RT</th>
<th>Boost RT to scar</th>
<th>Common systemic chemoendocrine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>61H NSABP B-03</td>
<td>RM</td>
<td>Axillary dissection (748)</td>
<td>None</td>
<td>35-45 Gy (1.8-2.3 Gy/f) o or c</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>64E Oslo Co-60</td>
<td>RM</td>
<td>Axillary dissection (563)</td>
<td>None</td>
<td>50 Gy de (2.5 Gy/f) c</td>
<td>50 Gy de (2.5 Gy/f) c</td>
<td>None</td>
<td>Ovarian irradiation</td>
</tr>
<tr>
<td>69A Heidelberg XRT</td>
<td>MRM</td>
<td>Axillary dissection (143)</td>
<td>None</td>
<td>65 Gy (2.2-2.7 Gy/f) c</td>
<td>65 Gy (2.2-2.7 Gy/f) c</td>
<td>None</td>
<td>None</td>
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<tr>
<td>71D SASIB</td>
<td>RM</td>
<td>Axillary dissection (377)</td>
<td>None for half, others</td>
<td>45 Gy (4.5 Gy/f) o or c</td>
<td>40-60 Gy (2.4-4.5 Gy/f) c or e</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>73C Mayo 70-56-32</td>
<td>MRM or RM</td>
<td>Axillary dissection (241)</td>
<td>None or if skin involvement</td>
<td>50 Gy (2.1 Gy/f) m</td>
<td>50 Gy de (2.1 Gy/f) m</td>
<td>None</td>
<td>CFP or not</td>
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<tr>
<td>73E INT Milan 1</td>
<td>RM</td>
<td>Axillary dissection (22)</td>
<td>None</td>
<td>40-45 Gy (1.8-2.2 Gy/f) c or m</td>
<td>40-45 Gy (1.8-2.2 Gy/f) c or m</td>
<td>None</td>
<td>None*</td>
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<tr>
<td>74Q Piedmont OA (excl phN4+)</td>
<td>MRM or RM</td>
<td>Axillary dissection (160)</td>
<td>None</td>
<td>45 Gy (1.5-2.8 Gy/f) u</td>
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<td>Mel or CMF</td>
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<tr>
<td>78B Toronto-Edmont</td>
<td>RM</td>
<td>Axillary dissection (50)</td>
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<td>40 Gy de (2.5 Gy/f) c</td>
<td>40 Gy de (2.5 Gy/f) c</td>
<td>None</td>
<td>CMF ++ ovar irradiation + P+ bCG</td>
</tr>
</tbody>
</table>

* Based on the description of axillary surgery in the trial protocol or publications or on information on individual women. Women were classified as having axillary dissection if they were in a trial where the protocol required removal of axillary lymph nodes in at least Levels I & II or, if individual information was available, resection of ≥10 nodes. In other trials, women were classified as having axillary dissection if the trial publication indicated that the median number of nodes removed was ≥ 10. BC= bacillus Calmette-Guérin, C=cyclophosphamide, c=coalalt-60, de=dose at depth (of nodes), F=fluorouracil, f=fraction, Gy=Gray (intended dose), m=meagavoltage, M=methotrexate, Mel=melphalan, RM=modified radical mastectomy, NS=surgery not specified (Patéy mastectomy, or modified radical mastectomy), o=orthovoltage, P=prednisone, Patéy=Patéy mastectomy, RM=radical mastectomy (Halsted), RT=radiotherapy, u=unknown. * After 1978 all patients in this trial with positive nodes received CMF chemotherapy.

References for Webtable 3

<table>
<thead>
<tr>
<th>Year code and study name</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>71D SASIB</td>
<td>Personal Correspondence from Dr A Hacking</td>
</tr>
<tr>
<td>78B Toronto-Edmont</td>
<td>Personal Correspondence from Dr K Pritchard</td>
</tr>
</tbody>
</table>

Lancet 2014; 383: 2127–35
Webfigure 35. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 465 women with pathologically node-negative (pN0) disease. See webfigure 1 for methodological note and also webfigure 36.

465 pN0 women with Mast+AD

Locoregional recurrence first

- 10-year loss 0.6 % (SE 1.1)
- RR 2.07 (95% CI 0.21–20.02)
- logrank 2p > 0.1; NS

Any first recurrence

- 10-year loss 1.9 % (SE 4.0)
- RR 1.12 (95% CI 0.72–1.72)
- logrank 2p > 0.1; NS

Breast cancer mortality

- 20-year loss 5.9 % (SE 4.7)
- RR 1.39 (95% CI 0.96–2.01)
- logrank 2p = 0.08

Any death

- 20-year loss 11.1 % (SE 5.0)
- RR 1.58 (95% CI 1.26–1.96)
- logrank 2p = 0.00008

Lancet 2014; 383: 2127–35
Webfigure 36. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 465 women with pathologically node-negative (pN0) disease. ($n_L =$ number of women for whom first recurrence was locoregional, $n_D =$ number women for whom distant recurrence was first.)

465 pN0 women with Mast+AD

233 women allocated RT

Locoregional or distant 20.5%

Locoregional first 3.4% ($n_L=14$)

Distant first 17.1% ($n_D=31$)

232 women allocated No RT

Locoregional or distant 18.6%

Locoregional first 2.0% ($n_L=9$)

Distant first 16.6% ($n_D=36$)

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: $> 0.1$; NS

Lancet 2014; 383: 2127–35
Webfigure 37. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risk of breast cancer and all-cause mortality in 1029 women with pathologically node-positive (pN+) disease. See webfigure 1 for methodological note and also webfigure 38.

1029 pN+ women with Mast+AD

Locoregional recurrence first

- 10-year gain 17.7% (SE 3.0)
- RR 0.30 (95% CI 0.20–0.44)
- logrank 2p < 0.00001

![Graph showing locoregional recurrence rates](image1)

Any first recurrence

- 10-year gain 4.5% (SE 3.6)
- RR 0.88 (95% CI 0.73–1.06)
- logrank 2p > 0.1; NS

![Graph showing any first recurrence rates](image2)

Breast cancer mortality

- 20-year gain 2.7% (SE 3.9)
- RR 1.00 (95% CI 0.82–1.20)
- logrank 2p > 0.1; NS

![Graph showing breast cancer mortality rates](image3)

Any death

- 20-year loss 1.9% (SE 4.0)
- RR 1.09 (95% CI 0.92–1.29)
- logrank 2p > 0.1; NS

![Graph showing any death rates](image4)
Webfigure 38. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1029 women with pathologically node positive (pN+) disease. \( n_L = \) number of women for whom first recurrence was locoregional, \( r_D = \) number women for whom distant recurrence was first.

1029 pN+ women with Mast+AD

531 women allocated RT

498 women allocated No RT

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Lancet 2014; 383: 2127–35
Webfigure 39. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 465 women with pathologically node-negative (pN0) disease.

465 pN0 women

Locoregional recurrence first (years 0-9)

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Women</th>
<th>Log-rank Variance of O-E</th>
<th>Ratio of annual event rates RT : No RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Nodal radiotherapy only, dissection</td>
<td>64E Oslo Co–60 AF+IMC</td>
<td>2/179 1/187 0.5 0.7</td>
<td>2.07 (SE 1.70)</td>
<td>99% &lt;= 99% CI</td>
</tr>
<tr>
<td>74Q Redmont OA (FMH+)</td>
<td>1 AF+IMC</td>
<td>0 0</td>
<td>0.1% (0.5%)</td>
<td></td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td>2 1</td>
<td>0.5 0.7</td>
<td>2.07 (SE 1.70)</td>
<td>99% &lt;= 99% CI</td>
</tr>
<tr>
<td>(b) Some with chest wall radiotherapy, dissection</td>
<td>71D SABSE (CW)+AF+IMC</td>
<td>1/6 0/0</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>(b) Subtotal</td>
<td>6 5 (16.7%)</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3 1</td>
<td>0.5 0.7</td>
<td>2.07 (SE 1.70)</td>
<td>99% &lt;= 99% CI</td>
</tr>
</tbody>
</table>

Heterogeneity between 1 subtotals: $\chi^2 = 0.0; p > 0.1; NS$

Any first recurrence (years 0-9)

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Women</th>
<th>Log-rank Variance of O-E</th>
<th>Ratio of annual event rates RT : No RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Nodal radiotherapy only, dissection</td>
<td>64E Oslo Co–60 AF+IMC</td>
<td>31/179 51/187 1.3 15.1</td>
<td>1.12 (SE 0.24)</td>
<td>99% &lt;= 99% CI</td>
</tr>
<tr>
<td>63A Heidelberg X01</td>
<td>AF+IMC</td>
<td>11/64 0/31 1.0 4.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>74Q Redmont OA (FMH+)</td>
<td>AF+IMC</td>
<td>1/4 0/5 0.0 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td>43 43</td>
<td>18.3%</td>
<td>19.9</td>
<td>1.12 (SE 0.24)</td>
</tr>
<tr>
<td>(b) Some with chest wall radiotherapy, dissection</td>
<td>71D SABSE (CW)+AF+IMC</td>
<td>26 25</td>
<td>0.0 0.6</td>
<td></td>
</tr>
<tr>
<td>(b) Subtotal</td>
<td>6 5 (33.3%)</td>
<td>0.0 0.5</td>
<td>1.00 (SE 1.41)</td>
<td>99% &lt;= 99% CI</td>
</tr>
<tr>
<td>Total</td>
<td>45 45</td>
<td>19.7%</td>
<td>20.4</td>
<td>1.12 (SE 0.23)</td>
</tr>
</tbody>
</table>

Heterogeneity between 2 subtotals: $\chi^2 = 0.0; p > 0.1; NS$

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

† Same polychemotherapy and/or tamoxifen in both groups.

Lancet 2014; 383: 2127–35

continued overleaf
# Breast cancer mortality

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Deaths/Women</th>
<th>RT deaths</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of annual death rates</th>
<th>RT : No RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>64E Oslo Co=00</td>
<td>AF=IMC</td>
<td>55/79</td>
<td>47/97</td>
<td>7.9 22.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>69A Heidelberg XRT</td>
<td>AF=IMC</td>
<td>14/44</td>
<td>8/31</td>
<td>1.8 4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>74G Sheffield OA (BN1+)</td>
<td>AF=IMC</td>
<td>114</td>
<td>40/9</td>
<td>0.2 0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td></td>
<td>227</td>
<td>227</td>
<td>9.4 27.8 1.40 (SE 0.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Some with chest wall radiotherapy, dissection</td>
<td></td>
<td>227</td>
<td>227</td>
<td>9.4 27.8 1.40 (SE 0.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>71D SAE38</td>
<td>(CW)=AF+IMC</td>
<td>2/2</td>
<td>0.0 0.0</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td></td>
<td>6/2</td>
<td>0.0 0.0</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>72/61</td>
<td>233</td>
<td>232</td>
<td>9.4 28.3 1.39 (SE 0.22)</td>
<td>1.59</td>
</tr>
</tbody>
</table>

Difference between treatment effects in 2 subtotals: $X^2 = 0.1; 2p > 0.1$: NS
Heterogeneity within subtotals: $X^2 = 0.1; p > 0.1$: NS
Heterogeneity between 4 trials: $X^2 = 0.1; p > 0.1$: NS

# Any death

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Deaths/Women</th>
<th>RT deaths</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of annual death rates</th>
<th>RT : No RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>64E Oslo Co=00</td>
<td>AF=IMC</td>
<td>154/179</td>
<td>134/157</td>
<td>28.7 91.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>69A Heidelberg XRT</td>
<td>AF=IMC</td>
<td>36/44</td>
<td>19/31</td>
<td>5.6 12.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>74G Sheffield OA (BN1+)</td>
<td>AF=IMC</td>
<td>114</td>
<td>69/9</td>
<td>0.2 0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td></td>
<td>227</td>
<td>227</td>
<td>9.4 27.8 1.40 (SE 0.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Some with chest wall radiotherapy, dissection</td>
<td></td>
<td>227</td>
<td>227</td>
<td>9.4 27.8 1.40 (SE 0.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>71D SAE38</td>
<td>(CW)=AF+IMC</td>
<td>36/27</td>
<td>3/15</td>
<td>0.0 0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td></td>
<td>6/5</td>
<td>0.0 0.0</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>194/161</td>
<td>233</td>
<td>232</td>
<td>9.4 28.3 1.39 (SE 0.22)</td>
<td>1.58</td>
</tr>
</tbody>
</table>

Difference between treatment effects in 2 subtotals: $X^2 = 0.1; 2p > 0.1$: NS
Heterogeneity within subtotals: $X^2 = 0.1; p > 0.1$: NS
Heterogeneity between 4 trials: $X^2 = 1.0; p > 0.1$: NS

† Same polychemotherapy and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.
Webfigure 40. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 1029 women with pathologically node-positive (pN+) disease.

1029 pN+ women

Locoregional recurrence first (years 0-9)

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Women</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated RT</td>
<td>Allocated No RT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Nodal radiotherapy only, dissection</td>
<td>64E Oslo Cc-60</td>
<td>AF+IMC</td>
<td>1/69</td>
<td>49/69</td>
</tr>
<tr>
<td></td>
<td>73E INT Milan 1</td>
<td>AF+IMC</td>
<td>8/55</td>
<td>1/57</td>
</tr>
<tr>
<td></td>
<td>76E Pudumt-Edmont.</td>
<td>1AF+IMC</td>
<td>6/29</td>
<td>4/21</td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td>7/18</td>
<td>20/187</td>
<td>-7.0</td>
<td>5.1</td>
</tr>
<tr>
<td>(b) Some with chest wall radiotherapy, dissection</td>
<td>71D SASB</td>
<td>CW+AF+IMC</td>
<td>39/162</td>
<td>38/164</td>
</tr>
<tr>
<td></td>
<td>73C Mayo 75-56-32</td>
<td>1(CW)+AF+IMC</td>
<td>28/121</td>
<td>28/127</td>
</tr>
<tr>
<td>(b) Subtotal</td>
<td>27/78</td>
<td>28/86</td>
<td>-25.5</td>
<td>21.8</td>
</tr>
<tr>
<td>Total</td>
<td>34/99</td>
<td>105/273</td>
<td>-32.5</td>
<td>26.9</td>
</tr>
</tbody>
</table>

Any first recurrence (years 0-9)

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Women</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated RT</td>
<td>Allocated No RT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Nodal radiotherapy only, dissection</td>
<td>64E Oslo Cc-60</td>
<td>AF+IMC</td>
<td>33/99</td>
<td>47/98</td>
</tr>
<tr>
<td></td>
<td>79A Heidelberg XRT</td>
<td>AF+IMC</td>
<td>25/99</td>
<td>16/97</td>
</tr>
<tr>
<td></td>
<td>73C INT Milan 1</td>
<td>AF+IMC</td>
<td>9/55</td>
<td>7/57</td>
</tr>
<tr>
<td></td>
<td>76E Pudumt-Edmont.</td>
<td>1AF+IMC</td>
<td>32/67</td>
<td>18/61</td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td>113/</td>
<td>94/207</td>
<td>1.3</td>
<td>41.7</td>
</tr>
<tr>
<td>(b) Some with chest wall radiotherapy, dissection</td>
<td>71D SASB</td>
<td>CW+AF+IMC</td>
<td>53/162</td>
<td>53/166</td>
</tr>
<tr>
<td></td>
<td>73C Mayo 75-56-32</td>
<td>1(CW)+AF+IMC</td>
<td>75/121</td>
<td>75/120</td>
</tr>
<tr>
<td>(b) Subtotal</td>
<td>162/283</td>
<td>168/284</td>
<td>-15.0</td>
<td>63.8</td>
</tr>
<tr>
<td>Total</td>
<td>265/</td>
<td>262/527</td>
<td>-13.7</td>
<td>105.5</td>
</tr>
</tbody>
</table>

Difference between treatment effects in 2 subtotals: $\chi^2 = 0.2; \ p > 0.1; \ NS$

Heterogeneity within subtotals: $\chi^2 = 3.3; \ p > 0.1; \ NS$

Heterogeneity between 5 trials: $\chi^2 = 3.5; \ p > 0.1; \ NS$

† Same polychemotherapy and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf
Breast cancer mortality

(a) Nodal radiotherapy only, dissection

(b) Some with chest wall radiotherapy, dissection

Difference between treatment effects in 2 subtotals: \( \chi^2 = 0.0; \ t = 1.0; \ p > 0.1; \ NS \)

- Same polychemotherapy and/or tamoxifen in both groups.
- Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=internal mammary chain. Site(s) in brackets were not always treated.
Webfigure 41. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 810 women with unknown pathological nodal status (pN?).

810 pN? women

Locoregional recurrence first (years 0-9)

<table>
<thead>
<tr>
<th>Year code, study name</th>
<th>Treatment Information</th>
<th>Events/Women Allocated RT</th>
<th>Events/Women Allocated No RT</th>
<th>Logrank Variance O-E</th>
<th>Ratio of annual event rates RT : No RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Nodal radiotherapy only, dissection</td>
<td>74L Piedmont (GA) (2N4+) (1) AF=IMC</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>74B Toronto-Edmonton</td>
<td>1 AF=IMC</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td>0/1</td>
<td>0/1</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td></td>
</tr>
<tr>
<td>(b) Some with chest wall radiotherapy, dissection</td>
<td>71D SASB</td>
<td>(CW) AF=HMC</td>
<td>4/18</td>
<td>4/22</td>
<td>0.3</td>
</tr>
<tr>
<td>(b) Subtotal</td>
<td>18</td>
<td>22</td>
<td>(22.2%)</td>
<td>(18.2%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>34</td>
<td>(15.4%)</td>
<td>(11.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity between 1 subtotals: \( \chi^2 = 0.0, \ p > 0.1; \) NS

Any first recurrence (years 0-9)

<table>
<thead>
<tr>
<th>Year code, study name</th>
<th>Treatment Information</th>
<th>Events/Women Allocated RT</th>
<th>Events/Women Allocated No RT</th>
<th>Logrank Variance O-E</th>
<th>Ratio of annual event rates RT : No RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Nodal radiotherapy only, dissection</td>
<td>61H NSABP B-03+</td>
<td>AF=IMC</td>
<td>195/476</td>
<td>246/544</td>
<td>0.3</td>
</tr>
<tr>
<td>65A Holdenberg XRT</td>
<td>AF=IMC</td>
<td>0/2</td>
<td>0/1</td>
<td>0.1</td>
<td>1.6</td>
</tr>
<tr>
<td>74L Piedmont (GA) (3N4+)</td>
<td>1 AF=IMC</td>
<td>4/10</td>
<td>5/11</td>
<td>0.1</td>
<td>1.6</td>
</tr>
<tr>
<td>74B Toronto-Edmonton</td>
<td>1 AF=IMC</td>
<td>0/0</td>
<td>1/1</td>
<td>0.1</td>
<td>1.6</td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td>200</td>
<td>222</td>
<td>46/566</td>
<td>39.5%</td>
<td></td>
</tr>
<tr>
<td>(b) Some with chest wall radiotherapy, dissection</td>
<td>71D SASB</td>
<td>(CW) AF=HMC</td>
<td>15/18</td>
<td>11/22</td>
<td>4.3</td>
</tr>
<tr>
<td>(b) Subtotal</td>
<td>15</td>
<td>22</td>
<td>(83.3%)</td>
<td>(50.0%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>215/233</td>
<td>504</td>
<td>578</td>
<td>3.8</td>
<td>63.5</td>
</tr>
</tbody>
</table>

Heterogeneity between 1 subtotals: \( \chi^2 = 3.6, \ p > 0.06; \) NS

Heterogeneity within subtotals: \( \chi^2 = 0.0, \ p > 0.1; \) NS

* For balance, control patients in NSABP B-03 count twice in subtotal and final total of events/deaths/women.
† Same polychemotherapy and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf
810 pN? women

Breast cancer mortality

Year code, and study name | Treatment Information | Allocated RT | Allocated No RT | RT deaths (D-E) | Ratio of annual death rates |
---------------------------|-----------------------|--------------|----------------|------------------|-----------------------------|
(a) Nodal radiotherapy only, dissection
61H NSABP B-03 | AF=IMC | 166/476 | 198/514 | 2.7 | 54.8 |
69A Hollandberg XRT | AF=IMC | 52 | 0 | 0.6 | 1.8 |
74Q Piedmont GA (BN4+) | AF=IMC | 53 | 11 | 0.8 | 1.8 |
78B Toronto-Edmonton | AF=IMC | 50 | 0 | 0.6 | 1.8 |
(b) Some with chest wall radiotherapy, dissection
71D SABG | CW=AF=IMC | 918 | 722 | 2.6 | 3.3 |
(b) Subtotal
9 | 71 | 0.0 | 3.3 |
Total
199 | 211 | 5.9 | 59.8 |
Difference between treatment effects in 2 subtotals: \( \chi^2 = 1.7; \quad 2p = 0.1; \quad NS \)
Heterogeneity within subtotals: \( \chi^2 = 0.1; \quad p = 0.1; \quad NS \)
Heterogeneity between 2 trials: \( \chi^2 = 1.8; \quad p = 0.1; \quad NS \)

Any death

Year code, and study name | Treatment Information | Allocated RT | Allocated No RT | RT deaths (D-E) | Ratio of annual death rates |
---------------------------|-----------------------|--------------|----------------|------------------|-----------------------------|
(a) Nodal radiotherapy only, dissection
61H NSABP B-03 | AF=IMC | 320/476 | 334/514 | 1.2 | 89.8 |
69A Hollandberg XRT | AF=IMC | 12 | 0 | 0.6 | 1.8 |
74Q Piedmont GA (BN4+) | AF=IMC | 50 | 11 | 0.6 | 1.8 |
78B Toronto-Edmonton | AF=IMC | 90 | 0 | 0.6 | 1.8 |
(b) Some with chest wall radiotherapy, dissection
71D SABG | CW=AF=IMC | 1018 | 722 | 3.3 | 3.5 |
(b) Subtotal
10 | 71 | 0.0 | 3.5 |
Total
319 | 347 | 5.1 | 59.8 |
Difference between treatment effects in 2 subtotals: \( \chi^2 = 2.8; \quad 2p = 0.09 \)
Heterogeneity within subtotals: \( \chi^2 = 0.2; \quad p = 0.1; \quad NS \)
Heterogeneity between 2 trials: \( \chi^2 = 3.8; \quad p = 0.1; \quad NS \)

* For balance, control patients in NSABP B-03 count twice in subtotal and final total of events/deaths/women.
† Same polychemotherapy and/or tamoxifen in both groups.
Radiotherapy sites. CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.

Lancet 2014; 383: 2127–35
Webtable 4. Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast)*.

<table>
<thead>
<tr>
<th>Nodal status†</th>
<th>Women</th>
<th>Deaths</th>
<th>Woman-years since diagnosis</th>
<th>% women given systemic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median/woman ('000s)</td>
<td>Total ('000s)</td>
</tr>
<tr>
<td>Axillary dissection</td>
<td></td>
<td></td>
<td>&lt;10</td>
<td>10-</td>
</tr>
<tr>
<td>cN-</td>
<td>2896</td>
<td>2098</td>
<td>12.4</td>
<td>45.3</td>
</tr>
<tr>
<td>cN+</td>
<td>1481</td>
<td>1188</td>
<td>9.6</td>
<td>21.5</td>
</tr>
<tr>
<td>Total</td>
<td>4377</td>
<td>3286</td>
<td>11.5</td>
<td>66.8</td>
</tr>
</tbody>
</table>

*Data available for 4 trials, start dates 1970 to 1978. In all trials radiotherapy was given to the axilla/supraclavicular fossa and the internal mammary chain. Full details of the trials are given in webtable 5.
† cN-: negative clinical nodal status, cN+: positive clinical nodal status.
Webtable 5: Randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast) – treatment details.

<table>
<thead>
<tr>
<th>Year code and study name</th>
<th>Breast surgery</th>
<th>Axillary Surgery* (number of patients)</th>
<th>Chest wall RT</th>
<th>Supraclavicular and axillary fossa RT</th>
<th>Internal mammary chain RT</th>
<th>Boost RT to scar</th>
<th>Common systemic chemoendocrine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>70A Manchester RBS1</td>
<td>SM</td>
<td>Axillary sampling (714)</td>
<td>30-37 Gy (2-2.5 Gy/f) o or m</td>
<td>37-40 Gy (2.5-2.7 Gy/f) o or m</td>
<td>37-40 Gy (2.5-2.7 Gy/f) o or m</td>
<td>None</td>
<td>Ovarian ablation</td>
</tr>
<tr>
<td>70B Kings/Cambridge</td>
<td>SM</td>
<td>Axillary sampling (2,800)</td>
<td>28.5-46 Gy (1.5-3.2 Gy/f) o or s</td>
<td>28.5-46 Gy (1.5-3.2 Gy/f) o or s</td>
<td>28.5-46 Gy (1.5-3.2 Gy/f) o or s</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>71C NSABP B-04</td>
<td>SM</td>
<td>Axillary sampling (770)</td>
<td>50 Gy (2 Gy/f) s</td>
<td>45-50 Gy de (1.8-2.0 Gy/f) s</td>
<td>45 Gy de (1.8 Gy/f) s</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>78D Scottish D</td>
<td>SM</td>
<td>Axillary sampling (93)</td>
<td>37-45 Gy (2.3-3.7 Gy/f) o or m</td>
<td>38.4-45.9 Gy (2.3-3.8 Gy/f) o or m</td>
<td>40-45 Gy (2.3-2.7 Gy/f) o or m</td>
<td>None</td>
<td>Tamoxifen or not</td>
</tr>
</tbody>
</table>

* Based on the description of axillary surgery in the trial protocol or publications or on lymph node information on individual women. Women were classified as having axillary sampling if they were in a trial where the protocol specified axillary sampling or, if individual information was available, resection of <10 nodes. In other trials, women were classified as having axillary sampling if the trial publication indicated that the median number of nodes removed was < 10, f=fraction, Gy=Gray (intended dose), m=megavoltage, RM=modified radical mastectomy, o=orthovoltage, RM=radical mastectomy (Halsted), RT=radiotherapy, SM=simple (total) mastectomy.

References for Webtable 5

<table>
<thead>
<tr>
<th>Year code and study name</th>
<th>Reference</th>
</tr>
</thead>
</table>

Lancet 2014; 383: 2127–35
Webfigure 42. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus no axillary surgery (Mast): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risks of breast cancer and all-cause mortality in 2896 women with clinically node-negative (cN-) disease. See webfigure 1 for methodological note and also webfigure 43.
Webfigure 43. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of recurrence and type of first recurrence in 2896 women with clinically node-negative (cN-) disease. \( r_L \) = number of women for whom first recurrence was locoregional, \( r_D \) = number women for whom distant recurrence was first.

2896 cN- women with Mast

1424 women allocated RT

1472 women allocated No RT

Any first recurrence (%)

Locoregional or distant 44.5%

Locoregional first 12.1% \( (r_L=175) \)

Distant first 32.4% \( (r_D=418) \)

Locoregional or distant 51.8%

Locoregional first 31.4% \( (r_L=451) \)

Distant first 20.4% \( (r_D=274) \)

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Lancet 2014; 383: 2127–35
Webfigure 44. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of locoregional recurrence and recurrence of any type and 20-year risks of breast cancer and all-cause mortality in 1481 women with clinically node-positive (cN+) disease. See webfigure 1 for methodological note and also webfigure 45.

1481 cN+ women with Mast

Locoregional recurrence first

10-year gain 27.0 % (SE 2.8)
RR 0.35 (95% CI 0.28–0.43)
logrank 2p < 0.00001

Any first recurrence

10-year gain 13.2 % (SE 2.8)
RR 0.66 (95% CI 0.57–0.76)
logrank 2p < 0.00001

Breast cancer mortality

20-year gain 6.7 % (SE 2.6)
RR 0.95 (95% CI 0.79–1.13)
logrank 2p = 0.03

Any death

20-year gain 4.4 % (SE 2.5)
RR 0.99 (95% CI 0.81–1.02)
logrank 2p > 0.1; NS

Lancet 2014; 383: 2127–35
Webfigure 45. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of recurrence and type of first recurrence in 1481 women with clinically node-positive (cN+) disease. \( r_L = \) number of women for whom first recurrence was locoregional, \( r_D = \) number women for whom distant recurrence was first.

1481 cN+ women with Mast

740 women allocated RT

Any first recurrence (%)

Locoregional or distant 48.6%

Locoregional first 13.8% \((r_L=116)\)

Distant first 34.8% \((r_D=236)\)

0 5 10 years

741 women allocated No RT

Any first recurrence (%)

Locoregional or distant 61.8%

Locoregional first 39.2% \((r_L=291)\)

Distant first 22.6% \((r_D=154)\)

0 5 10 years

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: < 0.00001

Lancet 2014; 383: 2127–35
Webtable 6. Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast)*.

![Table](https://i.imgur.com/3.jpg)

*Data available for 2 trials, start dates 1985 to 1988. In all trials radiotherapy was given to the axilla/supraclavicular fossa and the internal mammary chain. Full details of the trials are given in webtable 7.

†cN−: negative clinical nodal status, cN+: positive clinical nodal status.

‡Chemotherapy was cyclophosphamide, methotrexate, 5-fluorouracil [CMF].
Webtable 7. Randomised trials beginning before the year 2000 and comparing radiotherapy to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast) – treatment details.

<table>
<thead>
<tr>
<th>Year code and study name</th>
<th>Breast surgery</th>
<th>Axillary dissection* (number of patients)</th>
<th>Chest wall RT</th>
<th>Supraclavicular and axillary fossa RT</th>
<th>Internal mammary chain RT</th>
<th>Boost RT to scar</th>
<th>Common systemic chemoendocrine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>85Z Tokyo CIH PS</td>
<td>EM</td>
<td>Axillary sampling (100)</td>
<td>None</td>
<td>42-48 Gy (2-3 Gy/f)</td>
<td>42-48 Gy (2-3 Gy/f)</td>
<td>None</td>
<td>CMF</td>
</tr>
<tr>
<td>88U Tokyo CIH CZ</td>
<td>EM</td>
<td>Axillary sampling (100)</td>
<td>None</td>
<td>42-48 Gy (2-3 Gy/f)</td>
<td>42-48 Gy (2-3 Gy/f)</td>
<td>None</td>
<td>CMF</td>
</tr>
</tbody>
</table>

*Based on the description of axillary surgery in the trial protocol or publications or on information on individual women. Women were classified as having axillary sampling if they were in a trial where the protocol specified no axillary dissection or, if individual information was available, resection of <10 nodes. In other trials, women were classified as having axillary sampling if the trial publication indicated that the median number of nodes removed was < 10, C=cyclophosphamide, EM=Extended mastectomy (ipsilateral paraaerial and supraclavicular lymph node dissection), F=fluorouracil, f=fractiion, Gy=Gray (intended dose), M=methotrexate, RT=radiotherapy.

References for Webtable 7

<table>
<thead>
<tr>
<th>Year code and study name</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>88U Tokyo CIH CZ</td>
<td>Personal Correspondence from Dr M Yoshimoto</td>
</tr>
</tbody>
</table>
Webfigure 46. Effect of radiotherapy (RT) to the regional lymph nodes alone versus not after mastectomy but no axillary surgery (Mast): 10-year risks of recurrence, breast cancer and all-cause mortality in 192 clinically node-positive (cN+) women. See webfigure 1 for methodological note and also webfigure 47. Due to the very small number (8) of clinically node-negative women in this set of trials they are shown only in webfigure 48.

192 cN+ women with Mast

**Locoregional recurrence first**

10-year gain 6.3% (SE 9.1)
RR 0.64 (95% CI 0.30–1.37)
logrank 2p > 0.1; NS

**Any first recurrence**

10-year loss 2.1% (SE 8.4)
RR 0.95 (95% CI 0.63–1.44)
logrank 2p > 0.1; NS

**Breast cancer mortality**

10-year gain 3.8% (SE 8.7)
RR 0.93 (95% CI 0.59–1.46)
logrank 2p > 0.1; NS

**Any death**

10-year loss 0.7% (SE 8.7)
RR 0.96 (95% CI 0.62–1.48)
logrank 2p > 0.1; NS
Webfigure 47. Effect of radiotherapy (RT) to the regional lymph nodes versus not after mastectomy but no axillary surgery (Mast): 10-year risk of recurrence and type of first recurrence in 192 women with clinically node-positive (cN+) disease. ($r_L =$ number of women for whom first recurrence was locoregional, $r_D =$ number women for whom distant recurrence was first.)

192 cN+ women with Mast

97 women allocated RT

Locoregional or distant 66.5%
Locoregional first 12.0% ($r_L = 13$)
Distant first 54.5% ($r_D = 48$)

95 women allocated No RT

Locoregional or distant 64.4%
Locoregional first 18.8% ($r_L = 18$)
Distant first 45.6% ($r_D = 43$)

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: $> 0.1$; NS
Webfigure 48. Effect of radiotherapy (RT) versus not after mastectomy but no axillary surgery (Mast): 10 year risks of recurrence during years 0-9, breast cancer mortality, and all-cause mortality in 2904 women with clinically node-negative (cN-) disease. Event rate ratios, one line per trial, trial subdivided according to whether or not radiotherapy was given to the chest wall.

### 2904 cN- women

#### Locoregional recurrence first (years 0-9)

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Women</th>
<th>Allocated RT</th>
<th>Allocated No RT</th>
<th>RT events</th>
<th>Logrank Variance O-E</th>
<th>Ratio of annual event rates</th>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Women</th>
<th>Allocated RT</th>
<th>Allocated No RT</th>
<th>RT events</th>
<th>Logrank Variance O-E</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Mastectomy without axillary surgery but with CW radiotherapy</td>
<td>708 Kings/Cambridge</td>
<td>CW+AF+IMC</td>
<td>1539/696</td>
<td>348/1049</td>
<td>−100.0</td>
<td>119.7</td>
<td>175/451</td>
<td>1424</td>
<td>1472</td>
<td>−143.0</td>
<td>148.0</td>
<td>0.38 (SE 0.05)</td>
<td>20 + 0.0094</td>
<td>(a) Subtotal</td>
<td>0.38 (SE 0.05)</td>
</tr>
<tr>
<td>(b) Mastectomy without axillary surgery and no CW radiotherapy</td>
<td>822 Tokyo CH FIB</td>
<td>AF+IMC</td>
<td>0/2</td>
<td>3/1</td>
<td>−0.2</td>
<td>0.2</td>
<td>3/5</td>
<td>5</td>
<td>0.26 (SE 1.28)</td>
<td>20 + 0.12.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>175/452</td>
<td>1427</td>
<td>1477</td>
<td>−143.2</td>
<td>148.2</td>
<td>0.38 (SE 0.05)</td>
<td>20 + 0.0094</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Any first recurrence (years 0-9)

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Women</th>
<th>Allocated RT</th>
<th>Allocated No RT</th>
<th>RT events</th>
<th>Logrank Variance O-E</th>
<th>Ratio of annual event rates</th>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Women</th>
<th>Allocated RT</th>
<th>Allocated No RT</th>
<th>RT events</th>
<th>Logrank Variance O-E</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Mastectomy without axillary surgery but with CW radiotherapy</td>
<td>708 Kings/Cambridge</td>
<td>CW+AF+IMC</td>
<td>4359/696</td>
<td>532/1049</td>
<td>−55.7</td>
<td>222.2</td>
<td>593/725</td>
<td>1424</td>
<td>1472</td>
<td>−59.9</td>
<td>298.9</td>
<td>0.75 (SE 0.05)</td>
<td>20 + 0.0095</td>
<td>(a) Subtotal</td>
<td>0.75 (SE 0.05)</td>
</tr>
<tr>
<td>(b) Mastectomy without axillary surgery and no CW radiotherapy</td>
<td>822 Tokyo CH FIB</td>
<td>AF+IMC</td>
<td>3/3</td>
<td>3/3</td>
<td>1.2</td>
<td>0.9</td>
<td>3/5</td>
<td>5</td>
<td>1.2</td>
<td>0.9</td>
<td>4.13 (SE 2.35)</td>
<td>20 + 0.01.9</td>
<td>(b) Subtotal</td>
<td>4.13 (SE 2.35)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>596/728</td>
<td>1427</td>
<td>1477</td>
<td>−54.6</td>
<td>298.9</td>
<td>0.75 (SE 0.05)</td>
<td>20 + 0.0095</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Difference between treatment effects in 2 subtotals: χ² = 0.8; 2p > 0.1: NS
Heterogeneity within subtotals: χ² = 13.4; p = 0.001
Heterogeneity between 4 trials: χ² = 13.5; p = 0.004

† Same polychemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.
Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=internal mammary chain. Site(s) in brackets were not always treated.

continued overleaf

Lancet 2014; 383: 2127–35
Webfigure 48 cntd.

![Breast cancer mortality and Any death tables]

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Deaths/Women</th>
<th>RT deaths</th>
<th>Ratio of annual death rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3/5</td>
<td></td>
<td>2/5</td>
<td></td>
</tr>
</tbody>
</table>

(a) Mastectomy without axillary surgery but with CW radiotherapy

(b) Mastectomy without axillary surgery and no CW radiotherapy

Total

Difference between treatment effects in 2 subtotals: \( \chi^2 = 1.8; \ p > 0.1; \ NS \)

Heterogeneity within subtotals: \( \chi^2 = 0.3; \ p > 0.1; \ NS \)

Heterogeneity between 4 trials: \( \chi^2 = 1.3; \ p > 0.1; \ NS \)

† Same polychemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain. Site(s) in brackets were not always treated.
Webfigure 49. Effect of radiotherapy (RT) versus not after mastectomy but no axillary surgery (Mast): 10 year risks of recurrence during years 0-9, breast cancer mortality, and all-cause mortality in 1673 women with clinically node-positive (cN+) disease. Event rate ratios, one line per trial, trial subdivided according to whether or not radiotherapy was given to the chest wall.

### 1673 cN+ women

#### Locoregional recurrence first (years 0-9)

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Women</th>
<th>Ratio of annual event rates</th>
<th>Logrank Variance of O-E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment Information</td>
<td>Allocated RT</td>
<td>RT events</td>
<td>No RT</td>
</tr>
<tr>
<td>(a) Mastectomy without axillary surgery but with CW radiotherapy</td>
<td>73A Manchester RBS1</td>
<td>CW=AF+IMC</td>
<td>120/395</td>
<td>120/395</td>
</tr>
<tr>
<td></td>
<td>73B Kings/Cambridge</td>
<td>CW=AF+IMC</td>
<td>158/375</td>
<td>158/375</td>
</tr>
<tr>
<td></td>
<td>73C Scottish D</td>
<td>CW=AF+IMC</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td></td>
<td></td>
<td>313/395</td>
<td>313/395</td>
</tr>
<tr>
<td>(b) Mastectomy without axillary surgery and no CW radiotherapy</td>
<td>85Z Tokyo CH/P</td>
<td>TA=IMC</td>
<td>74/740</td>
<td>74/740</td>
</tr>
<tr>
<td></td>
<td>85U Tokyo CH/N</td>
<td>TA=IMC</td>
<td>8/790</td>
<td>8/790</td>
</tr>
<tr>
<td>(b) Subtotal</td>
<td></td>
<td></td>
<td>82/748</td>
<td>82/748</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>395/395</td>
<td>395/395</td>
</tr>
</tbody>
</table>

#### Any first recurrence (years 0-9)

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Women</th>
<th>Ratio of annual event rates</th>
<th>Logrank Variance of O-E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment Information</td>
<td>Allocated RT</td>
<td>RT events</td>
<td>No RT</td>
</tr>
<tr>
<td>(a) Mastectomy without axillary surgery but with CW radiotherapy</td>
<td>73A Manchester RBS1</td>
<td>CW=AF+IMC</td>
<td>140/395</td>
<td>140/395</td>
</tr>
<tr>
<td></td>
<td>73B Kings/Cambridge</td>
<td>CW=AF+IMC</td>
<td>299/395</td>
<td>299/395</td>
</tr>
<tr>
<td></td>
<td>73C Scottish D</td>
<td>CW=AF+IMC</td>
<td>35</td>
<td>47</td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td></td>
<td></td>
<td>352/395</td>
<td>352/395</td>
</tr>
<tr>
<td>(b) Mastectomy without axillary surgery and no CW radiotherapy</td>
<td>85Z Tokyo CH/P</td>
<td>TA=IMC</td>
<td>27/447</td>
<td>27/447</td>
</tr>
<tr>
<td></td>
<td>85U Tokyo CH/N</td>
<td>TA=IMC</td>
<td>34/550</td>
<td>34/550</td>
</tr>
<tr>
<td>(b) Subtotal</td>
<td></td>
<td></td>
<td>61/524</td>
<td>61/524</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>413/524</td>
<td>413/524</td>
</tr>
</tbody>
</table>

† Same polychemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups. Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=internal mammary chain. Site(s) in brackets were not always treated.

**difference between treatment effects in 2 subtotals:** \( \chi^2 = 2.4; \ p > 0.1: \text{NS} \)

Heterogeneity within subtotals: \( \chi^2 = 0.5; \ p > 0.1: \text{NS} \)

Heterogeneity between 4 trials: \( \chi^2 = 2.9; \ p > 0.1: \text{NS} \)

**difference between treatment effects in 3 subtotals:** \( \chi^2 = 2.7; \ p > 0.1: \text{NS} \)

Heterogeneity within subtotals: \( \chi^2 = 2.6; \ p > 0.1: \text{NS} \)

Heterogeneity between 5 trials: \( \chi^2 = 5.3; \ p > 0.1: \text{NS} \)

**continued overleaf**

Lancet 2014; 383: 2127–35
1673 cN+ women

**Breast cancer mortality**

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Deaths/Women</th>
<th>Ratio of annual death rates</th>
<th>(RT : No RT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Mastectomy without axillary surgery but with CW radiotherapy</td>
<td>70A Manchester RBS1 CW/AF=IMC</td>
<td>178/355</td>
<td>215/359</td>
<td>14.5 : 93.7</td>
</tr>
<tr>
<td>70B Kings/Cambridge CW/AF=IMC</td>
<td>235/389</td>
<td>256/375</td>
<td>17.3 : 114.6</td>
<td></td>
</tr>
<tr>
<td>75D Scottish D CW/AF=IMC</td>
<td>3%</td>
<td>47</td>
<td>0.5 : 0.2</td>
<td></td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td>416/</td>
<td>474/</td>
<td>0.86 (SE 0.06)</td>
<td>96% (95% CI)</td>
</tr>
<tr>
<td>(56.2%)</td>
<td>(64.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Mastectomy without axillary surgery and no CW radiotherapy</td>
<td>92Z Tokyo CIH PA</td>
<td>1AF=IMC</td>
<td>99/47</td>
<td>214/55</td>
</tr>
<tr>
<td>88U Tokyo CIH N2</td>
<td>1AF=IMC</td>
<td>29/50</td>
<td>27/50</td>
<td>-1.2 : 11.1</td>
</tr>
<tr>
<td>(b) Subtotal</td>
<td>43/</td>
<td>48/</td>
<td>0.93 (SE 0.22)</td>
<td>96% (95% CI)</td>
</tr>
<tr>
<td>(44.3%)</td>
<td>(50.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>459/</td>
<td>522/</td>
<td>0.87 (SE 0.06)</td>
<td>96% (95% CI)</td>
</tr>
<tr>
<td>(54.8%)</td>
<td>(62.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Any death**

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Deaths/Women</th>
<th>Ratio of annual death rates</th>
<th>(RT : No RT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Mastectomy without axillary surgery but with CW radiotherapy</td>
<td>70A Manchester RBS1 CW/AF=IMC</td>
<td>274/355</td>
<td>285/359</td>
<td>-11.9 : 130.0</td>
</tr>
<tr>
<td>70B Kings/Cambridge CW/AF=IMC</td>
<td>303/380</td>
<td>316/375</td>
<td>-14.4 : 140.5</td>
<td></td>
</tr>
<tr>
<td>75D Scottish D CW/AF=IMC</td>
<td>5/5</td>
<td>47</td>
<td>0.5 : 0.2</td>
<td></td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td>583/</td>
<td>606/</td>
<td>0.91 (SE 0.06)</td>
<td>96% (95% CI)</td>
</tr>
<tr>
<td>(78.6%)</td>
<td>(81.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Mastectomy without axillary surgery and no CW radiotherapy</td>
<td>85Z Tokyo CIH PA</td>
<td>1AF=IMC</td>
<td>234/7</td>
<td>234/5</td>
</tr>
<tr>
<td>88U Tokyo CIH N2</td>
<td>1AF=IMC</td>
<td>25/50</td>
<td>20/50</td>
<td>-1.3 : 11.6</td>
</tr>
<tr>
<td>(b) Subtotal</td>
<td>48/</td>
<td>51/</td>
<td>0.96 (SE 0.22)</td>
<td>96% (95% CI)</td>
</tr>
<tr>
<td>(47.4%)</td>
<td>(53.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>628/</td>
<td>657/</td>
<td>0.91 (SE 0.06)</td>
<td>96% (95% CI)</td>
</tr>
<tr>
<td>(75.0%)</td>
<td>(78.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Same polychemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil), and/or tamoxifen in both groups.

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=internal mammary chain. Site(s) in brackets were not always treated.
Webtable 8. Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS) *

<table>
<thead>
<tr>
<th>Nodal status†</th>
<th>Women</th>
<th>Deaths</th>
<th>Woman-years since diagnosis</th>
<th>% women given systemic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median/</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>woman</td>
<td>(‘000s)</td>
</tr>
<tr>
<td>Axillary dissection</td>
<td>255</td>
<td>201</td>
<td>6.6</td>
<td>2.0</td>
</tr>
<tr>
<td>pN unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axillary sampling</td>
<td>637</td>
<td>497</td>
<td>16.6</td>
<td>10.7</td>
</tr>
<tr>
<td>pN unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>892</td>
<td>698</td>
<td>12.1</td>
<td>12.7</td>
</tr>
</tbody>
</table>

*Data available for 2 trials, start dates 1962 to 1971. In all trials radiotherapy was given to the axilla/supraclavicular fossa and the internal mammary chain. Full details of the trials are given in webtable 9.
† pN unknown: as radiotherapy was given before surgery, to avoid bias pathological nodal status is regarded as unknown.
**Webtable 9.** Randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS) – treatment details.

<table>
<thead>
<tr>
<th>Year code and study name</th>
<th>Breast surgery</th>
<th>Axillary Surgery* (number of patients)</th>
<th>Chest wall RT</th>
<th>Supraclavicular and axillary fossa RT</th>
<th>Internal mammary chain RT</th>
<th>Boost RT to scar</th>
<th>Common systemic chemoendocrine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>62B Berlin-Bruch</td>
<td>RM</td>
<td>Axillary clearance (255)</td>
<td>55 Gy (u Gy/f) c</td>
<td>55 Gy (u Gy/f) c</td>
<td>55 Gy (u Gy/f) c</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>71B Stockholm A</td>
<td>MRM</td>
<td>Axillary sampling (637)</td>
<td>45 Gy (1.8 Gy/f) e</td>
<td>45 Gy de (1.8 Gy/f) c</td>
<td>45 Gy (1.8 Gy/f) e</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

* Based on the description of axillary surgery in the trial protocol or publications or on information on individual women. Women were classified as having axillary dissection if they were in a trial where the protocol required removal of axillary lymph nodes in at least Level I & II or, if individual information was available, resection of ≥10 nodes. In other trials, women were classified as having axillary dissection if the trial publication indicated that the median number of nodes removed was ≥ 10. c=cobalt-60, e=electron, f=fracton, Gy=Gray (intended dose), MRM=modified radical mastectomy, RM=radical mastectomy (Halsted), RT=radiotherapy, u=unknown.

**References for Webtable 9**

<table>
<thead>
<tr>
<th>Year code and study name</th>
<th>Reference</th>
</tr>
</thead>
</table>

Lancet 2014; 383: 2127–35
Webfigure 50. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD): 10-year risk of locoregional recurrence and recurrence of any type and 15-year risk of breast cancer and all-cause mortality in 255 women with unknown pathological nodal status (pN?) disease. See webfigure 1 for methodological note and also webfigure 51.

255 pN? women with Mast+AD

**Locoregional recurrence first**

10-year gain 7.7% (SE 5.2)
RR 0.52 (95% CI 0.22–1.20)
logrank 2p > 0.1; NS

**Any first recurrence**

10-year loss, 3.3% (SE 7.1)
RR 1.08 (95% CI 0.74–1.58)
logrank 2p > 0.1; NS

**Breast cancer mortality**

15-year loss, 3.1% (SE 7.3)
RR 1.13 (95% CI 0.79–1.63)
logrank 2p > 0.1; NS

**Any death**

15-year loss, 5.4% (SE 6.1)
RR 1.21 (95% CI 0.90–1.63)
logrank 2p > 0.1; NS

Lancet 2014; 383: 2127–35
Webfigure 51. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 255 women with unknown pathological nodal status (pN?). ($r_L$ = number of women for whom first recurrence was locoregional, $r_D$ = number women for whom distant recurrence was first.)

255 pN? women with Mast+AD

123 women allocated RT

132 women allocated No RT

Any first recurrence (%)

Locoregional or distant 54.7%

Locoregional first 6.2% ($r_L=7$)

Distant first 48.5% ($r_D=53$)

Locoregional or distant 51.4%

Locoregional first 12.6% ($r_L=17$)

Distant first 38.8% ($r_D=47$)

2p for difference between treatment arms in the proportion of all first recurrences that were locoregional: = 0.04

Lancet 2014; 383: 2127–35
Webfigure 52. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary sampling (Mast+AS): 10-year risk of locoregional recurrence and recurrence of any type and 15-year risk of breast cancer and all-cause mortality in 637 women with unknown pathological nodal status (pN?) disease. See webfigure 1 for methodological note and also webfigure 53.

637 pN? women with Mast+AS

Locoregional recurrence first

10-year gain 21.1 % (SE 3.4)
RR 0.27 (95% CI 0.18–0.40)
logrank 2p < 0.00001

Any first recurrence

10-year gain 13.8 % (SE 4.2)
RR 0.63 (95% CI 0.49–0.82)
logrank 2p = 0.0005

Breast cancer mortality

15-year gain 4.9 % (SE 4.0)
RR 0.89 (95% CI 0.72–1.12)
logrank 2p > 0.1; NS

Any death

15-year gain 4.6 % (SE 4.1)
RR 0.90 (95% CI 0.75–1.08)
logrank 2p > 0.1; NS

Lancet 2014; 383: 2127–35
Webfigure 53. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary sampling (Mast+AS): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 637 women with unknown pathological nodal status (pN?). \((r_L = \text{number of women for whom first recurrence was locoregional}, \ r_D = \text{number women for whom distant recurrence was first.})\)

637 pN? women with Mast+AS

316 women allocated RT

321 women allocated No RT

2*p for difference between treatment arms in the proportion of all first recurrences that were locoregional: \(< 0.00001\)
Webfigure 54. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not before mastectomy and axillary dissection (Mast+AD) or axillary sampling (Mast+AS): Event rate ratios, one line per trial, for locoregional recurrence and recurrence of any type during years 0-9 and for breast cancer and all-cause mortality in 892 women with unknown pathological nodal status (pN?).

892 pN? women

### Locoregional recurrence first (years 0-9)

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Woman</th>
<th>RT events</th>
<th>Logrank Verance of O-E</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Allocated RT</td>
<td>Allocated No RT</td>
<td>RT : No RT</td>
<td>20% CI</td>
</tr>
<tr>
<td>(a) Axillary dissection</td>
<td>CW+AF+IMC</td>
<td>71/125</td>
<td>17/132</td>
<td>−3.6  5.4</td>
<td>0.52 (SE 0.31) 2p&lt;0.01 0.03</td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td></td>
<td>123/312</td>
<td>132/312</td>
<td>−3.6  5.4</td>
<td>0.52 (SE 0.31) 2p&lt;0.01 0.03</td>
</tr>
<tr>
<td>(b) Axillary sampling</td>
<td>71B Stockholm A</td>
<td>20/316</td>
<td>76/321</td>
<td>−30.5 23.1</td>
<td>0.27 (SE 0.12) 2p&lt;0.0001</td>
</tr>
<tr>
<td>(b) Subtotal</td>
<td></td>
<td>20/316</td>
<td>76/321</td>
<td>−30.5 23.1</td>
<td>0.27 (SE 0.12) 2p&lt;0.0001</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>27/439</td>
<td>93/453</td>
<td>−34.1 28.5</td>
<td>0.30 (SE 0.11) 2p&lt;0.0001</td>
</tr>
</tbody>
</table>

Difference between treatment effects in 2 subtotals: χ² = 1.9; 2p > 0.1; NS

### Any first recurrence (years 0-9)

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Events/Woman</th>
<th>RT events</th>
<th>Logrank Verance of O-E</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Allocated RT</td>
<td>Allocated No RT</td>
<td>RT : No RT</td>
<td>20% CI</td>
</tr>
<tr>
<td>(a) Axillary dissection</td>
<td>CW+AF+IMC</td>
<td>60/132</td>
<td>64/132</td>
<td>2.0  26.8</td>
<td>1.08 (SE 0.20) 2p&lt;0.1 0.03</td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td></td>
<td>60/132</td>
<td>64/132</td>
<td>2.0  26.8</td>
<td>1.08 (SE 0.20) 2p&lt;0.1 0.03</td>
</tr>
<tr>
<td>(b) Axillary sampling</td>
<td>71B Stockholm A</td>
<td>110/316</td>
<td>148/321</td>
<td>−26.7 58.5</td>
<td>0.63 (SE 0.11) 2p&lt;0.0001</td>
</tr>
<tr>
<td>(b) Subtotal</td>
<td></td>
<td>110/316</td>
<td>148/321</td>
<td>−26.7 58.5</td>
<td>0.63 (SE 0.11) 2p&lt;0.0001</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>170/439</td>
<td>212/453</td>
<td>−24.6 85.2</td>
<td>0.75 (SE 0.09) 2p&lt;0.001</td>
</tr>
</tbody>
</table>

Difference between treatment effects in 2 subtotals: χ² = 5.2; 2p = 0.02

Difference between treatment effects in 2 trials: χ² = 5.2; 2p = 0.02

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=internal mammary chain.

continued overleaf
### Breast cancer mortality

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Deaths/Women</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of annual death rates</th>
<th>RT : No RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Axillary dissection</td>
<td>628 Berlin-Buch ABC</td>
<td>CW+AF+IMC</td>
<td>67/123</td>
<td>3.6 [SE 0.20]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>67/123</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(54.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td>123/132</td>
<td>(53.0%)</td>
<td>3.6</td>
<td>2p &lt; 0.1; NS</td>
<td></td>
</tr>
<tr>
<td>(b) Axillary sampling</td>
<td>718 Stockholm A</td>
<td>CW+AF+IMC</td>
<td>152/316</td>
<td>-8.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>175/321</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>152/316</td>
<td>(48.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Subtotal</td>
<td>316/321</td>
<td>(54.5%)</td>
<td>-8.6</td>
<td>0.89 [SE 0.11]</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>219/453</td>
<td>(49.8%)</td>
<td>-4.9</td>
<td>0.95 [SE 0.09]</td>
<td></td>
</tr>
</tbody>
</table>

#### Difference between treatment effects in 2 subtotals: \( \chi^2 = 1.2; 2p > 0.1; NS \)

#### Difference between treatment effects in 2 trials: \( \chi^2 = 1.2; 2p > 0.1; NS \)

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain.

### Any death

<table>
<thead>
<tr>
<th>Year code, and study name</th>
<th>Treatment Information</th>
<th>Deaths/Women</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of annual death rates</th>
<th>RT : No RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Axillary dissection</td>
<td>628 Berlin-Buch ABC</td>
<td>CW+AF+IMC</td>
<td>105/123</td>
<td>8.1 [SE 0.17]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>105/123</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(85.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Subtotal</td>
<td>123/132</td>
<td>(72.7%)</td>
<td>8.1</td>
<td>1.21 [SE 0.09]</td>
<td></td>
</tr>
<tr>
<td>(b) Axillary sampling</td>
<td>718 Stockholm A</td>
<td>CW+AF+IMC</td>
<td>244/316</td>
<td>-12.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>253/321</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>244/316</td>
<td>(77.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Subtotal</td>
<td>316/321</td>
<td>(78.8%)</td>
<td>-12.3</td>
<td>0.90 [SE 0.09]</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>340/453</td>
<td>(79.0%)</td>
<td>-4.1</td>
<td>0.97 [SE 0.08]</td>
<td></td>
</tr>
</tbody>
</table>

#### Difference between treatment effects in 2 subtotals: \( \chi^2 = 2.7; 2p = 0.10 \)

#### Difference between treatment effects in 2 trials: \( \chi^2 = 2.7; 2p = 0.10 \)

Radiotherapy sites: CW=chest wall, AF=Axilla and/or supraclavicular fossa, IMC=Internal mammary chain.
Webfigure 55. EBCTCG collaborators, listed alphabetically by institution and then name

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Centre Regional Français Baclesse, Caen, France—T Delozier, B Griffon, J Mace Lescot.

Centre René Huguenin, Paris, St Cloud, France—E Brain, B de La Lande, E Mouret-Fourme.

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