Effect of adjuvant radiotherapy to the internal mammary lymph nodes in patients with early node-positive breast cancer

Lise B J Thorsen
On behalf of the DBCG Radiotherapy Committee
**DBCG-IMN**

- IMN metastasis
  - Often w. medial tumor/N+ disease
  - A poor prognostic sign
- Surgical studies: no beneficial effect IMN dissection
- IMN-RT: increased toxicity with earlier techniques
- No consensus on whether IMN-RT is useful
1980’s
Internal mammary node (IMN) RT for all N+ breast cancer patients

1990’s
Increased awareness on RT-induced heart disease

2000
Anthracyclines

2003
No evidence for effect of IMN-RT

Right side + IMN RT
Left side No IMN-RT

Left side heart dose high
DBCG-IMN

↑ Breast cancer death
↓ Heart death

Right side
+ IMN RT

Left side
No IMN-RT
Hypotheses

In patients with early node positive breast cancer, IMN-RT

- Improves overall survival
- Prevents distant recurrence
- Decreases breast cancer mortality
DBCG-IMN: Design

- Nation-wide population based cohort study
- Inclusion: 2003-2007
  - operable unilateral early BC
  - one or more macrometastatic axillary lymph nodes
  - no prior malignancies
  - age<70 years
  - Treated with standard RT after introduction of new internal mammary node guidelines
  - No recurrence earlier than 30 days after RT
DBCG-IMN: Design

Ineligible
No or non-standard RT 134
Early recurrence 52
Micrometastases 33
Stage 4 disease at diagnosis 38

Primary endpoint: Overall Survival
Secondary endpoints: Metastatic disease, Breast cancer death

Multivariate model adjusting for known prognostic factors: age, menopausal status, pT, pN, and grade, tumor location, stratified for receptor status and histological type
<table>
<thead>
<tr>
<th>Patient and tumor characteristics</th>
<th>IMN RT (n=1485)</th>
<th>No IMN RT (n=1586)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range)</strong></td>
<td>56 (23-70)</td>
<td>57 (27-70)</td>
</tr>
<tr>
<td>Pre-menopausal</td>
<td>611 (41%)</td>
<td>646 (40%)</td>
</tr>
<tr>
<td>Estrogen receptor positive (%)</td>
<td>1202 (81%)</td>
<td>1274 (80%)</td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>1305 (88%)*</td>
<td>1346 (85%)*</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>134 (9%)</td>
<td>163 (10%)</td>
</tr>
<tr>
<td>Other</td>
<td>46 (3%)</td>
<td>77 (5%)</td>
</tr>
<tr>
<td>Grade I</td>
<td>307 (19%)</td>
<td>307 (19%)</td>
</tr>
<tr>
<td>Grade II</td>
<td>710 (48%)</td>
<td>743 (47%)</td>
</tr>
<tr>
<td>Grade III</td>
<td>414 (28%)</td>
<td>456 (29%)</td>
</tr>
<tr>
<td>pT1</td>
<td>527 (36%)</td>
<td>556 (35%)</td>
</tr>
<tr>
<td>pT2</td>
<td>830 (56%)</td>
<td>905 (57%)</td>
</tr>
<tr>
<td>pT3</td>
<td>126 (9%)</td>
<td>124 (8%)</td>
</tr>
<tr>
<td>pN1</td>
<td>867 (58%)</td>
<td>949 (60%)</td>
</tr>
<tr>
<td>pN2</td>
<td>396 (27%)</td>
<td>412 (26%)</td>
</tr>
<tr>
<td>pN3</td>
<td>222 (15%)</td>
<td>225 (14%)</td>
</tr>
<tr>
<td>Lateral</td>
<td>904 (61%)</td>
<td>943 (60%)</td>
</tr>
<tr>
<td>Medial/central</td>
<td>578 (39%)</td>
<td>640 (40%)</td>
</tr>
</tbody>
</table>
### DBCG-IMN: Treatment

<table>
<thead>
<tr>
<th></th>
<th>IMN RT (n=1485)</th>
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</tr>
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<tbody>
<tr>
<td>Radiotherapy: 48 Gy/24 F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMN-RT (%)</td>
<td>1431 (96%)</td>
<td>161 (10%)</td>
</tr>
<tr>
<td>Axillary level II-III (%)</td>
<td>1213 (82%)</td>
<td>1294 (82%)</td>
</tr>
<tr>
<td>Axillary level I-II-III (%)</td>
<td>272 (18%)</td>
<td>292 (18%)</td>
</tr>
<tr>
<td>Boost after BCS (%)</td>
<td>176 (33%)</td>
<td>164 (30%)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy + AC(%)</td>
<td>959 (65%)</td>
<td>1048 (66%)</td>
</tr>
<tr>
<td>Breast conserving +AC(%)</td>
<td>526 (35%)</td>
<td>538 (34%)</td>
</tr>
<tr>
<td>Systemic treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-hormonal therapy (%)</td>
<td>697 (47%)</td>
<td>741 (47%)</td>
</tr>
<tr>
<td>Chemotherapy (%)</td>
<td>274 (19%)</td>
<td>304 (19%)</td>
</tr>
<tr>
<td>Both (%)</td>
<td>514 (35%)</td>
<td>541 (34%)</td>
</tr>
</tbody>
</table>
DBCG-IMN: QA RT-techniques

- Doses to normal tissues acceptable
- IMN-RT intended: Some underdosage
- IMN-RT NOT intended: Some dose unavoidable
- ->Possible dilution of measurable IMN-RT effect!
## Pattern of recurrence

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<th>IMN RT (n=1485)</th>
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<tr>
<td><strong>Local recurrence</strong></td>
<td>29 (2.0 %)</td>
<td>21 (1.3 %)</td>
</tr>
<tr>
<td><strong>Regional lymph node recurrence</strong></td>
<td>10 (0.7 %)</td>
<td>15 (0.9 %)</td>
</tr>
<tr>
<td><strong>Contralateral breast cancer</strong></td>
<td>39 (2.6 %)</td>
<td>36 (2.3 %)</td>
</tr>
</tbody>
</table>

Pattern of recurrence Median FU= 8.0 years
Distant recurrence

Cumulative incidence (%)

Distant recurrence

Adjusted HR: 0.88 (0.77; 1.01)  
P = 0.07

Difference: 2.1%

Events All
IMN RT  410  1485
No IMN RT  467  1586

At risk
IMN RT  1485  1322  1193  1043  521
No IMN RT  1586  1401  1229  1075  500
## Secondary endpoint
Breast cancer mortality

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>IMN RT (n=1485)</th>
<th>No IMN RT (n=1586)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>324</td>
<td>390</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Other malignancy</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>Other</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>
Breast cancer mortality

Cumulative incidence (%)
Breast cancer death

Events All
IMN RT 324 1485
No IMN RT 390 1586

Difference: 2.4%
Adjusted HR: 0.85 (0.73; 0.98)
P = 0.03

Years since radiotherapy

At risk
IMN RT 1485 1406 1299 1203 782
No IMN RT 1586 1507 1352 1246 790
Primary endpoint: Overall Survival

Adjusted HR: 0.83 (0.72; 0.95) p = 0.006

Difference: 3.5%
Association: ✔ - Causality?

- Increasing risk of IMN metastasis with:
  - Increasing number of positive axillary lymph nodes
  - Medial/central tumor location
Subgroup analysis
Endpoint: Overall survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/patients</th>
<th>IMN-RT</th>
<th>No IMN-RT</th>
<th>HR (95% CI)</th>
<th>8-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral 1-3 nodes</td>
<td></td>
<td>91/511</td>
<td>91/563</td>
<td>1.13 (0.84 - 1.51)</td>
<td>82.9% 85.7%</td>
</tr>
<tr>
<td>Medial/central 1-3 nodes</td>
<td></td>
<td>66/352</td>
<td>88/382</td>
<td>0.79 (0.58 - 1.09)</td>
<td>83.4% 78.8%</td>
</tr>
<tr>
<td>Lateral ≥ 4 nodes</td>
<td></td>
<td>135/389</td>
<td>164/378</td>
<td>0.72 (0.57 - 0.90)</td>
<td>68.3% 59.0%</td>
</tr>
<tr>
<td>Medial/central ≥ 4 nodes</td>
<td></td>
<td>84/221</td>
<td>128/256</td>
<td>0.81 (0.61 - 1.07)</td>
<td>62.5% 54.6%</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td>376/1473</td>
<td>471/1579</td>
<td>0.83 (0.72 - 0.95)</td>
<td>76.1% 72.6%</td>
</tr>
</tbody>
</table>
DBCG-IMN: Conclusion

- Overall survival improved with IMN-RT
- Risk of metastatic disease decreased with IMN-RT
- Risk of breast cancer death decreased with IMN-RT
DBCG-IMN: Conclusion

Benefit increased with

• Increasing number of lymph nodes involved
• Medial or central tumor location
Acknowledgements

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Evidence 2013-14

- **EBCTCG meta-analysis**
  - RT after mastectomy+axillary dissection
  - 20 years results: RT reduced breast cancer mortality (BCM) for all (n=3086) N+ patients, effect both in pts with 1-3 and 4+ positive nodes

- **EORTC 22922-10925**
  - 4004 pts. with medial/central tumor and/or N+ disease randomised to medial supraclavicular (MS) and IMN-RT
  - 10 year results: Improved DFS and D-DFS with MS+IMN-RT, OS borderline significant

- **MA.20**
  - 1832 pts. randomised to whole breast irradiation (WBI) versus WBI + regional RT, 85 % of patients with 1-3 nodes positive
  - 5 year results: Improved DFS and D-DFS with addition of regional RT, OS borderline significant
Retrospective and non-randomized: Bias and confounding
Small: Insufficient power to detect an effect
Old: Surgical and systemic treatment (if any) are outdated