OVERVIEW OF DANISH BREAST CANCER TRIALS

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• Introduction
• DBC 82b
• DBC 82c
• Combined Analysis of 82b & c.
• High local recurrence risk & survival analysis.
• Second Primary cancers after RT.
• Estrogen Receptor, Progesterone Receptor, HER-2, and Response to Postmastectomy Radiotherapy in High-Risk Breast Cancer
• Gene profile predicting PMRT.
• The Danish Breast Cancer Cooperative Group (DBCG) was established as a nationwide multidisciplinary organization in 1977 on the initiative from the Danish Surgical Society.

• The organization comprises all the departments in Denmark responsible for
diagnosis,
treatment,
follow-up, and
research in breast cancer.

Includes a central database.
AIM of the Organization

To offer *similar* nationwide diagnostic and therapeutic procedures to all patients with *primary breast cancer* and to improve the prognosis.
From 1977 through 2014, ~110,000 women with early unilateral non metastatic invasive breast cancer, have been entered into the database.

In the case of bilateral cancer, a detailed registration is restricted to the most advanced tumor.

Men with breast cancer and women with a second primary breast cancer are not registered.
Civil Registration System
(to obtain vital status)

National Pathology Registry
(to monitor the completeness of the reporting)

Danish Cancer Registry
(monitors the presence of other malignant diseases and second primaries)

Danish National Patient Registry
(monitor comorbidity and late adverse events)
<table>
<thead>
<tr>
<th>Main groups</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td>Age, menopausal status, comorbidity</td>
</tr>
<tr>
<td>Reasons not to enter standard treatment program for primary breast cancer.</td>
<td>Distant metastases, previous malignant disease (except cancer cutis/cancer coli uteri in situ), bilateral breast cancer, technically inoperable or not operated according to guidelines, patient preference.</td>
</tr>
<tr>
<td>Tumour characteristics</td>
<td>Histological diagnosis, tumor size, number of examined nodes, number of positive nodes, grade, ER status, HER-2 status</td>
</tr>
<tr>
<td>Surgery</td>
<td>Type of preoperative biopsy, sentinel node biopsy, axillary dissection, lumpectomy +/- oncoplastic surgery, mastectomy +/- reconstruction</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>Radiotherapy, chemotherapy, endocrine therapy, anti-HER-2 therapy</td>
</tr>
<tr>
<td>Follow-up</td>
<td>vital status, recurrence, contralateral breast cancer, other malignant disease</td>
</tr>
</tbody>
</table>
Database

• Used to assess the quality of potential prognostic and predictive factors and surgical and oncological procedures to ensure similar quality on a nationwide basis.

• Through numerous national and international studies, DBCG has contributed to an improvement of the evidence-based guidelines for diagnostic aspects and treatment.

• The results achieved by DBCG have been published in 430 peer-reviewed papers, and the data have contributed to several theses and to the meta-analyses conducted by Early Breast Cancer Trialists’ Collaborative Group.
Major achievements in Surgery for Breast Cancer

Change in treatment strategy: Mastectomy to breast-conserving surgery (BCS)

- 2008, (DBCG study): Similar outcomes of local and distant recurrences and survival with BCS compared with mastectomy.
- BCS: ~70% of patients with primary breast cancer.
- Danish guidelines defined “no tumor on ink” as sufficient for invasive cancer and 2 mm free margin in case of ductal carcinoma in situ.
- According to international evidence, the sentinel node technique was introduced in Denmark on the initiative by DBCG.

Sentinel node technique: decreasing proportion of breast cancer patients are exposed to axillary dissection, which is omitted in the case of negative nodal status.

Risk of late adverse effects in terms of pain, sensations, reduced mobility, and lymphedema is reduced.
Radiotherapy

- When the DBCG 77 program was introduced, the staging procedure was improved, and radiotherapy following mastectomy was restricted to patients with positive axillary nodes or a primary tumor exceeding 5 cm or deep invasion.
- (DBCG 82), DBCG tested the hypothesis of lack of effect by radiotherapy when administered in addition to systemic therapy.
- Two large national studies demonstrated a significant reduction in the rate of local recurrence and improved survival.
- However, a recent very large Danish study demonstrated that additional radiation to the parasternal nodes was associated with a significant gain in terms of breast cancer mortality and overall survival.
DBCG has conducted trials to evaluate the morbidity following reduction of the irradiated breast volume after breast conserving surgery and following hypofractionation (less numbers of fractions with higher dose per fraction) in patients eligible for irradiation of the residual breast only.
Systemic therapy

• Selection of the patients for systemic therapy has been according to classical prognostic factors, from the late eighties complemented with a predictive Factor for Endocrine therapy (estrogen receptor status) and from 2007 for biological therapy (human epidermal growth factor receptor [HER2]-status).

• The proportion of patients offered adjuvant systemic therapy has been increasing since the late seventies from ~50% to close to 90%.

• Large proportion of the patients are overtreated and DBCG : heavily involved in the search for valid genomic assays to better identify the patients who are estimated to benefit from a specific treatment.
• The DBCG database provides data to a vast array of both **clinical** and **epidemiological** studies.

• The **quality** of the data is consecutively assessed by the clinical quality indicators, and studies utilizing the data have contributed substantially to the evidence-based guidelines on diagnosis and treatment of breast cancer prepared by DBCG.

• Since the establishment of DBCG, the **prognosis** in breast cancer has continuously improved with a **decrease in 5-year mortality from ~37% to 15%**.
Aim: To evaluate whether the addition of radiotherapy to total mastectomy with axillary dissection and adjuvant chemotherapy influenced locoregional control of tumors, the likelihood of Freedom from distant metastases, & overall survival in high-risk Premenopausal patients.
Protocol Design  The Danish Breast Cancer Cooperative Group protocol 82b includes premenopausal high-risk patients with breast cancer.

- High-risk status: involvement of axillary lymph nodes, tumor size of more than 5 cm, and invasion of the cancer to skin or pectoral fascia (pathological stage II or III).

- Premenopausal: if amenorrheic for less than five years or had a hysterectomy before the age of 55.

- No evidence of metastatic disease
Danish 82b Trial
November 1982 to December 1989

Randomized After Sx (N= 1706)

CMF + PMRT

CMF

CMF plus tamoxifen

enrolment in the third subgroup was stopped in June 1986
Adjuvant Systemic Therapy

Cyclophosphamide 600 mg/m³
Methotrexate 40 mg/m³
Fluorouracil 600 mg/m³ x every four weeks,

Patients the planned chemotherapy consisted of eight cycles of CMF, whereas the patients who were assigned to CMF without radiotherapy Total of nine cycles of CMF.

Compliance with chemotherapy was the same in both groups, and at least 85 percent.

Radiation therapy:
Delivered to the chest wall, including the surgical scar and regional lymph nodes i.e., supraclavicular, infraclavicular, axillary nodes, internal mammary nodes.

Dose: Median absorbed dose
50 Gy/25 fractions over a period of 5 weeks, or 48 Gy, given in 22 fractions over a period of 5 1/2 weeks.

Radiotherapy within one week after the first cycle of chemotherapy.
• F/U:
  Clinical examination at regular intervals for up to 10 years
  Further tested only if they had symptoms or evidence of recurrent disease.
• All diagnostic, therapeutic, and follow-up data were validated and processed by the Danish Breast Cancer Cooperative Group's data center.
• No interim analysis.
• Study monitored regularly by the data center for excess mortality in either treatment group.

• Results confirm that tumor size, number of pathologic nodes, and the grade of anaplasia are the major prognostic factors in breast cancer.
• Addition of irradiation to chemotherapy reduced the frequency of locoregional recurrence to about one fourth that found in the groups that did not receive radiotherapy.
• The fact that 255 patients had fewer than four nodes removed weakens our analysis of the influence of having more than three positive nodes in the study group.

Median potential follow-up was 114 months. (range: 78 - 167).
<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>Radiotherapy and CMF</th>
<th>CMF Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of Patients</td>
<td>Locoregional Recurrences*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>percent</td>
<td>percent</td>
</tr>
<tr>
<td>All patients</td>
<td>1708</td>
<td>852</td>
<td>9</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;40</td>
<td>323</td>
<td>156</td>
<td>11</td>
</tr>
<tr>
<td>40–49</td>
<td>934</td>
<td>459</td>
<td>8</td>
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<tr>
<td>50–59</td>
<td>451</td>
<td>237</td>
<td>10</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;21</td>
<td>674</td>
<td>329</td>
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<tr>
<td>21–50</td>
<td>772</td>
<td>402</td>
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</tr>
<tr>
<td>&gt;50</td>
<td>234</td>
<td>99</td>
<td>12</td>
</tr>
<tr>
<td>Unknown</td>
<td>28</td>
<td>12</td>
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</tr>
<tr>
<td>No. of nodes removed</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0–3</td>
<td>255</td>
<td>122</td>
<td>10</td>
</tr>
<tr>
<td>4–9</td>
<td>1042</td>
<td>581</td>
<td>8</td>
</tr>
<tr>
<td>&gt;9</td>
<td>409</td>
<td>198</td>
<td>9</td>
</tr>
<tr>
<td>Unknown</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>No. of positive nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>135</td>
<td>58</td>
<td>3</td>
</tr>
<tr>
<td>1–3</td>
<td>1061</td>
<td>545</td>
<td>7</td>
</tr>
<tr>
<td>&gt;3</td>
<td>510</td>
<td>248</td>
<td>14</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Frequency of positive nodes (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;34</td>
<td>715</td>
<td>360</td>
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<tr>
<td>34–67</td>
<td>446</td>
<td>217</td>
<td>7</td>
</tr>
<tr>
<td>&gt;67</td>
<td>532</td>
<td>269</td>
<td>15</td>
</tr>
<tr>
<td>Unknown</td>
<td>15</td>
<td>6</td>
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<td>Histopathological classification of tumor§</td>
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<td></td>
</tr>
<tr>
<td>Ductal</td>
<td>1461</td>
<td>741</td>
<td>10</td>
</tr>
<tr>
<td>Lobular</td>
<td>162</td>
<td>69</td>
<td>4</td>
</tr>
<tr>
<td>Medullary</td>
<td>45</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Unknown or other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade of anaplasia (ductal carcinoma only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>363</td>
<td>182</td>
<td>6</td>
</tr>
<tr>
<td>Grade II</td>
<td>701</td>
<td>361</td>
<td>7</td>
</tr>
<tr>
<td>Grade III</td>
<td>351</td>
<td>176</td>
<td>18</td>
</tr>
<tr>
<td>Unknown</td>
<td>46</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>No. of Patients</td>
<td>Distant Metastases Alone</td>
<td>Locoregional Recurrence</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Radiotherapy + CMF</td>
<td>852</td>
<td>287 (34)</td>
<td>75 (9)</td>
</tr>
<tr>
<td>CMF alone</td>
<td>856</td>
<td>219 (26)</td>
<td>277 (32)</td>
</tr>
<tr>
<td>All patients</td>
<td>1708</td>
<td>506 (30)</td>
<td>352 (21)</td>
</tr>
</tbody>
</table>

number of patients (percent)
Disease free Survival

Overall Survival

Disease free Survival

Overall Survival

P<0.001

Years after Mastectomy

Radiotherapy + CMF (48%)

CMF (34%)

Radiotherapy + CMF (54%)

CMF (45%)

Radiotherapy 852  643  505  429  308  102

Radiotherapy + CMF 852  755  641  555  392  188

CMF 856  537  382  327  216  74

CMF 856  738  587  494  329  163
LRF  ➕ (↓23%)
RT 9% vs CMF 32%, $p < 0.001$

- 5-year DFS (⬆14%)
CMF 34% vs RT 48%, $p < 0.001$

- Overall survival (⬆11%)
CMF 45% v. RT 54%, $p < 0.001$

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**Table 4. Cox Multivariate Proportional-Hazards Analysis of the Relative Risk of Any Type of Recurrence or Death or of Death from Any Cause.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Any Type of Recurrence or Death</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P$ Value</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Tumor size ($&lt;21$ mm, $21–50$ mm, $&gt;50$ mm)†</td>
<td>$&lt;0.001$</td>
<td>1.43 (1.30–1.58)</td>
</tr>
<tr>
<td>No. of positive nodes ($0$, $1–3$, $&gt;3$)†</td>
<td>$&lt;0.001$</td>
<td>1.57 (1.36–1.81)</td>
</tr>
<tr>
<td>Frequency of positive nodes ($&lt;34$, $34–67$, $&gt;67$)†</td>
<td>$&lt;0.001$</td>
<td>1.44 (1.30–1.58)</td>
</tr>
<tr>
<td>Grade of anaplasia ($I$, $II$, $III$)†</td>
<td>$&lt;0.001$</td>
<td>1.44 (1.31–1.59)</td>
</tr>
<tr>
<td>Age of 40 to 49 yr (vs. $&lt;40$ yr and $50–59$ yr)</td>
<td>$&lt;0.001$</td>
<td>0.73 (0.64–0.83)</td>
</tr>
<tr>
<td>Radiotherapy + CMF (vs. CMF alone)</td>
<td>$&lt;0.001$</td>
<td>0.59 (0.51–0.67)</td>
</tr>
</tbody>
</table>
Postmastectomy radiotherapy is associated with a lower locoregional recurrence rate and improved disease-free and overall survival when combined with chemotherapy in postmenopausal women.

**Methods:** Between 1982 and 1990, postmenopausal women with high-risk breast cancer (stage II or III) were randomly assigned adjuvant tamoxifen (30 mg daily for 1 year) alone (689) or with postoperative radiotherapy to the chest wall and regional lymph nodes (686). Median followup was 123 months.

The endpoints were first site of recurrence (locoregional recurrence, distant metastases, or both), and disease-free and overall survival.
Danish 82c Trial

Included postmenopausal high-risk breast cancer Patients < 70 years of age.

High - risk status: node positive, tumour size greater than 5 cm, invasion to skin or pectoral fascia, or any combination of these characteristics.

Postmenopausal status was defined as 5 years or more of amenorrhoea or, for women who had undergone hysterectomy, age over 55 years.
Surgical: total mastectomy and axillary-node dissection.

Included removal of the central axillary lymph nodes involving level I and part of level II.

Median of seven lymph nodes were removed.

Tamoxifen was started 2–4 weeks after surgery, and was given concomitantly with PORT.

Patients were followed up with clinical examinations regularly for 10 years.
Radiotherapy was directed towards the chest wall, which included the surgical scar and regional lymph nodes (the supraclavicular, infraclavicular, and axillary nodes, and IMC. The intended dose was either a median absorbed dose in the target mammary nodes in the four upper intercostal spaces).

Dose: 50·0 Gy / 25 fractions in 35 days, 48·0 Gy / 22 fractions in 38 days.

Anterior photon field: supraclavicular and axillary region, and an anterior electron field against the internal mammary nodes and the chest wall. Posterior axillary fields for patients with large anterior to posterior diameter to limit the maximum absorbed dose to 55·0 Gy in 25 fractions, or 52·8 Gy in 22 fractions.
Most patients were treated at six departments with a linear accelerator. However, 69 patients (10% of the patients) were treated at small departments with 250 kV X-rays, the lowest intended dose was 36·0 Gy in 20 fractions in 4 weeks.

- Compliance to radiotherapy was high, and only 30 (4%) patients did not complete the treatment.
- Patients received adjuvant tamoxifen 30 mg daily for 1 year.
- Tamoxifen was started 2–4 weeks after surgery, and was given concomitantly with postoperative radiotherapy.
The effect of treatment was assessed by intention to treat. The primary endpoint was survival (all deaths from any cause were included in the analysis) and locoregional recurrence.
The definition of the endpoint of locoregional recurrence was first site of failure (chest wall, axilla, supra/infraclavicular), alone or together with distant metastases (diagnosed within 1 month).

<table>
<thead>
<tr>
<th>Site of first recurrence</th>
<th>Radiotherapy plus tamoxifen</th>
<th>Tamoxifen only</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>637</td>
<td>444</td>
<td>1081</td>
</tr>
<tr>
<td>Chest wall</td>
<td>31 (16)</td>
<td>123 (17)</td>
<td>154 (33)</td>
</tr>
<tr>
<td>Axillary nodes</td>
<td>9 (2)</td>
<td>73 (8)</td>
<td>82 (10)</td>
</tr>
<tr>
<td>Intraclavicular nodes</td>
<td>7 (2)</td>
<td>29 (8)</td>
<td>36 (10)</td>
</tr>
<tr>
<td>Axilla and chest wall</td>
<td>3 (1)</td>
<td>9 (2)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Axilla and S/I nodes</td>
<td>0</td>
<td>5 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Chest wall plus S/I nodes</td>
<td>2 (1)</td>
<td>3 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Total recurrences</td>
<td>52 (22)</td>
<td>242 (39)</td>
<td>294 (61)</td>
</tr>
</tbody>
</table>
Danish 82c Trial

• Results:

Tamoxifen ± PMRT, N=1374

LRF (↓27%)
35% v 8%, p < 0.001

DFS (↑12%)
36% v. 24%, p < 0.001

Overall survival (↑9%)
45% vs 36%, p = 0.03
PURPOSE:

- Radiation Decrease
  ↓
- Loco regional recurrences [LRRS]
  ↓
- Disease free Survival

AIM: To examine the overall disease recurrence pattern among patients randomly assigned to receive treatment with or without RT.
Patients and Methods

PATIENTS & METHODS:

3083 patients from DBCCG 82 b & 82 c

END POINTS

LRR  DM  CBC

Follow-up continued until DM, CBC, emigration, or death.

Information was selected from medical records, general practitioners, and the National Causes of Death Registry.

The median potential follow-up time was 18 years.

Only first site of BC events recorded.

PT’s PROFILE

• No evidence of DM,
• no prior h/o cancer
• < 70 years.
• unilateral BC,
  ↗ Tumour >5 cm
• High Risk → Positive
  axillary nodes
  ↘ Invasion of skin / Pectoral fascia
Post total mastectomy and partial axillary dissection.
Median of 7 L Nodes removed
Adjuvant Systemic Therapy
  C  Cyclophosphamide  600 mg/m²
  M  Methotrexate     40 mg/m²
  F  Fluorouracil 600 mg/m²
  4 weekly X 8 Cycles → RT arm
  X 9 Cycles → No RT
RT interpolated after 1st Cycle of CMF.
Post-menopausal women received Tamoxifen 30 mg daily for 1 year.
RT → Chest wall + Regional Lymph nodes.
MEDIAN FOLLOW UP TIME - 18 YEARS

1341(87%) megavoltage 50 Gy /25
5#/Week or 48 cg/22#4# /

1538 pts
On RT
Orth voltage 120 (8)
36 cg/20 #, 5# /week

77 (5%) No RT /
Did not complete RT

Information collected by questionnaire
→ Medical records
→ Death Certificate
→ GP;
**Results:** STATISTICAL ANALYSIS Kappllan Meir Method; Log rank test for Compassion B/w treatment group

RR → X2 test used for Comparison of data

<table>
<thead>
<tr>
<th>Site of First LRR</th>
<th>No RT (n = 1,545)</th>
<th>SimLRR-DM*</th>
<th>RT (n = 1,538)</th>
<th>SimLRR-DM*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Chest wall</td>
<td>209</td>
<td>14</td>
<td>48</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>Axilla</td>
<td>143</td>
<td>9</td>
<td>28</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>S/I</td>
<td>34</td>
<td>2</td>
<td>28</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Axilla and chest wall</td>
<td>41</td>
<td>3</td>
<td>7</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>Axilla and S/I</td>
<td>20</td>
<td>1</td>
<td>12</td>
<td>0.8</td>
<td>3</td>
</tr>
<tr>
<td>Chest wall and S/I</td>
<td>8</td>
<td>0.5</td>
<td>5</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Chest wall + axilla + S/I</td>
<td>1</td>
<td>0.1</td>
<td>2</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>All recurrences</td>
<td>456</td>
<td>30</td>
<td>130</td>
<td>8</td>
<td>79</td>
</tr>
</tbody>
</table>

Abbreviations: S/I, supra/infravacular; LRR, locoregional recurrence alone; simLRR-DM, simultaneous locoregional recurrence and distant metastases; no RT, randomized to no radiotherapy; RT, randomized to radiotherapy.

*For simLRR-DM, the localizations of three LRR are absent (n = 203 instead of 206).

†Comparison of site of first LRR between the two randomization groups using the χ² test.

‡Comparison of site of first simLRR-DM between the two randomization groups using the χ² test.
### Table 2. 18-Year Actuarial Probability of Distant Metastases in All Patients

<table>
<thead>
<tr>
<th>Type of First DM</th>
<th>No RT (n = 1,545)</th>
<th>RT (n = 1,538)</th>
<th>Log-Rank P*</th>
<th>RR†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>DM following LRR</td>
<td>35</td>
<td>31 to 38</td>
<td>6</td>
<td>4 to 8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DM first failure</td>
<td>37</td>
<td>34 to 40</td>
<td>47</td>
<td>44 to 49</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SimLRR-DM</td>
<td>12</td>
<td>11 to 15</td>
<td>6</td>
<td>5 to 8</td>
<td>&lt;.001</td>
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<tr>
<td>Any DM</td>
<td>64</td>
<td>61 to 66</td>
<td>53</td>
<td>50 to 56</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: DM, distant metastases; LRR, locoregional recurrence alone; SimLRR-DM, simultaneous locoregional recurrence and distant metastases; no RT, randomly assigned to no radiotherapy; RT, randomly assigned to radiotherapy; RR, relative risk of failure in the RT v no-RT group.

†RR < 1 shows a decreased risk of DM in the RT group.

*Comparison between the no-RT and RT group.
### Table 3. 18-Year Actuarial Probability of Different Sites of DM (only as first DM event) in the Two Randomization Groups

<table>
<thead>
<tr>
<th>Site of DM</th>
<th>No RT (n = 1,545)</th>
<th></th>
<th>RT (n = 1,538)</th>
<th></th>
<th>Log-Rank P*</th>
<th>RR†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>40</td>
<td>36 to 42</td>
<td>32</td>
<td>29 to 34</td>
<td>.003</td>
<td>0.81</td>
<td>0.71 to 0.93</td>
</tr>
<tr>
<td>Lung</td>
<td>17</td>
<td>15 to 20</td>
<td>12</td>
<td>11 to 15</td>
<td>.009</td>
<td>0.75</td>
<td>0.60 to 0.93</td>
</tr>
<tr>
<td>Pleura</td>
<td>15</td>
<td>12 to 17</td>
<td>12</td>
<td>10 to 14</td>
<td>.22</td>
<td>0.86</td>
<td>0.67 to 1.10</td>
</tr>
<tr>
<td>Liver</td>
<td>16</td>
<td>14 to 18</td>
<td>12</td>
<td>10 to 14</td>
<td>.07</td>
<td>0.82</td>
<td>0.66 to 1.02</td>
</tr>
<tr>
<td>CNS</td>
<td>5</td>
<td>4 to 7</td>
<td>3</td>
<td>2 to 4</td>
<td>.03</td>
<td>0.61</td>
<td>0.39 to 0.96</td>
</tr>
<tr>
<td>Skin</td>
<td>9</td>
<td>7 to 11</td>
<td>4</td>
<td>3 to 5</td>
<td>.002</td>
<td>0.57</td>
<td>0.39 to 0.82</td>
</tr>
<tr>
<td>Any DM</td>
<td>64</td>
<td>61 to 66</td>
<td>53</td>
<td>50 to 56</td>
<td>&lt;.001</td>
<td>0.78</td>
<td>0.71 to 0.86</td>
</tr>
</tbody>
</table>

Abbreviations: DM, distant metastases; no RT, randomly assigned to no radiotherapy; RT, randomly assigned to radiotherapy; RR, relative risk of failure in the RT versus no-RT group.

*Comparison between the no-RT and RT group.
†RR < 1 shows a decreased risk of that DM site in the RT group.
### RESULT:

<table>
<thead>
<tr>
<th></th>
<th>No RT</th>
<th>Vs</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 year probability of any first Breast Cancer event</td>
<td>73%</td>
<td></td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>18 year probability of LRR with/without DM</td>
<td>49%</td>
<td>Vs</td>
<td>14%</td>
</tr>
<tr>
<td>18 year probability of DM Subsequent to DM</td>
<td>35%</td>
<td>Vs</td>
<td>6%</td>
</tr>
<tr>
<td>Probability of any dist Met</td>
<td>64%</td>
<td>Vs</td>
<td>53%</td>
</tr>
</tbody>
</table>

### Conclusion

Post Mastectomy RT Changes the disease recurrence pattern in High Risk breast Cancer patients; fewer patients have LRR as first site of recurrence and overall fewer patients have DM.
• Sx + RT → LRR
  • Survival (Benefit less clear).
  • Meta analysis of 8 randomised trials
  • Increased late deaths in women (Sx + RT) compared to (Sx) alone.
  • Meta analysis later: Difference in overall mortality not significant (Large contribution of recent appropriate trials).
  • Harmful effect of radiation on the heart had been reported.
  • As more & more women with BC become long team survivors.
  • ? Morbidity from cardiac disease pertinent
(DBCG) 82b & 82c : Addition of RT lengthens survival in High Risk women.

- **Aim:** To investigate morbidity and mortality from ischemic heart disease in High Risk BC give systemic T+/+ment ± RT after Sx.

- **Methods**
- **Patients:** 1982 to 1990
  Mastectomy + partial axillary clearance.
  No evidence of metastatic disease
  No history of cancer,
  Unilateral breast cancer
  Age younger than <70 years.
  Verbal informed consent
  High Risk for recurrence.

- Node positive
- Tumour size >5cm
- Invasion of skin or pectoral facia.
3083 patients randomized

1598 assigned RT

- 13 excluded because IHD before randomization
  - 756 left breast treated
    - Morbidity IDH 22 & MI 14
    - Mortality IHDS & MI 4
  - Morbidity IHD 24 & MI 12
  - Mortality IHD 7 & MI 1

770 Right breast treated

1545 assigned no RT

- 24 excluded because of IHD before randomization
  - 784 left breast treated
    - Morbidity IHD 27 & IM 13
    - Morbidity IHD 6 & MI 5
  - Morbidity IHD 22 & MI 4
  - Mortality IHDS & MI 4

737 right breast treated
Assessment of Morbidity & Mortality.

Crude survival and cause of death:

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>No RT (n&gt;1525)</th>
<th>RT (n&gt;1521)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>674 (44.2%)</td>
<td>799 (52.5%)</td>
</tr>
<tr>
<td>Other Causes</td>
<td>36 (2.4%)</td>
<td>37 (2.4%)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>12 (0.8%)</td>
<td>13 (0.9%)</td>
</tr>
<tr>
<td>Unknown Causes</td>
<td>5 (0.3%)</td>
<td>4 (0.3%)</td>
</tr>
<tr>
<td>Other Causes</td>
<td>32 (2.1%)</td>
<td>41 (2.7%)</td>
</tr>
</tbody>
</table>

Every women had a unique national identification no.

Patients were linked into the DBCG.

Unique

Linked to

DBCG

National patient register

Supplied

Diagnostic

F/U data.

Therapeutic
### Danish Trial 82b & 82c (Lancet 1999)

<table>
<thead>
<tr>
<th></th>
<th>With RT</th>
<th>Without RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>766 (50%)</td>
<td>627 (41%)</td>
</tr>
<tr>
<td>Died of cancer</td>
<td>710 (47%)</td>
<td>836 (55%)</td>
</tr>
<tr>
<td>Died due to cardiac</td>
<td>12 (0.8%)</td>
<td>13 (0.9%)</td>
</tr>
<tr>
<td>Died due to other causes</td>
<td>37 (2.4%)</td>
<td>45 (3%)</td>
</tr>
</tbody>
</table>
Statistical Analyses.

Morbidity & Mortality = Kaplan Meier method.
Log Rank test: Compare the treatment groups;
Relative Hazard of Ischaemic Heart disease.

SPSS version 8.0 for window.
Analyses was on Intention to treat.

Date of assessment: Dec 31 1996;
Median potential follow up time: 122 mths. (range 81-171).

37 women excluded.
3046 women analysed.
1393 women was alive at analyses.
1393 F/U 117 months (range 81-171)

Median time to death = 45 mths (1-170mths.)
Cumulative survival at 12 years
RT group  no RT group.
46%     36%     p<0.001.
More women of no – radiotherapy group than in radiotherapy group died of BC.
whereas similar proportions of each group died from ischemic Heart disease:
0.9%     vs     0.8%

RH  Morbidity = 0.86 (95% CI 0.6-1.3)
Relative Hazard Death  = 0.84 (0.4-

To cover confounding effect of HD by Subsequent Treatment / RT or Anthracyclines
Data was reanalysed Censoring patients.
To assess whether the risk of ischaemic HD increased with time after treatment with RT.

Hazard Ratio was calculated for 2 year periods. There was no trend for an ↑↑ in HR of Morbidity with time.

Discussion:
Morbidity and mortality from ischaemic HD was not significantly altered by use of adjuvant RT after mastectomy.
Risk of Ischaemic Heart disease was not planned or analysed.
Further F/U necessary to rule out harmful effects on the heart >12 years.
However F/U was long enough to show significant survival benefit from systemic treatment plus RT vs systemic treatment alone.
• Limitation

  Rate of IHD
  Same

  RT + CT (CMF).
  RT + Tamoxifen.

• Further studies with anthracyclines/taxanes with RT needed.
• Only upper 4 inter coastal spaces included in the initial mammary field; dose received by heart will be small.
• Radiotherapy treatment technique: did not use individual three dimensional dose planning.
• Many unanswered question.
High Local recurrence is not associated with large survival reduction after postmastectomy RT in High Risk Breast Cancer a Sub group analysis of DBCG 82 B & C.

**Introduction**

- **Distant Metastasis**
  - Systemic Theory
  - Spectrum Hypothesis

  1000 high-Risk BCP
  \[\downarrow\]
  Systemic Therapy + PMRT
  \[\downarrow\]
  Representative of LR probability (Clinico pathological Markers)
  \[\downarrow\]
  Subsequently Breast Cancer Specific & overall Survival probability

---

included 1000 out of 3083 high-risk breast cancer patients randomly assigned to postmastectomy radiotherapy in the DBCG82 b&c trials
Materials & methods:-

High Risk → Positive Lymph node
Tumour size >5 cm
involvement of skin or pectoral fascia.
Total mastectomy + axillary clearance

Premenopausal → RT + CMF 8 Cycle
▽ CMF Alone 9 Cycle

Postmenopausal → RT + tamoxifen 30
mg daily × 1 Year
▽ Tamoxifen Alone

At least 8 lymph nodes surgically removed
& paraffin Blocks available
1078 Patients selected for extended biological update

Paraffin Blocks
↓ Tissue transferred
Tissue Micro arranged
↓
IHC stained for ER, Progesterone acceptor, and Her 2 neu

• Staging TNM.
• HP Grade – Blood Richardson grade.
• Median potential F/U = 17 years.
• Endpoints → Local Recurrence
  Distant Metastasis
Breast Cancer Morality
Overall Mortality
Statistical Analysis: STATA Version 8.2

Testing relationship between variables Kaplan – Meier Curves

Cox Univariate analyses

Smallest LR Risk
At least 4 out of 5
≤ 3 positive lymph node
Tumour size ≤ 2 cm
Grade 1 Malignant Tumour
Hormonal receptor tumour
Her 2 negative tumour

Intermediate group

Highest LR Risk
- 2 out of 3
> 3 Positive lymph node
Tumour size > 5 cm
Grade 3 malignant tumour

5 Year LR Probability of 50%

5 yr LR Probability of 26%

5 Year LR Probability of 11%

Absolute Reduction in LR Probability after PMRT
Poor prognosis = 36%
Intermediate = 21%
Good prognosis = 11%

Highest Mortality was seen for the poor prognosis group matching 81%.
• The very large absolute reduction in LR Probability was not translated into an absolute reduction in 15 year Breast Cancer Mortality

• A continuously improved Breast Cancer specific and overall survival after PMRT was seen throughout the total period of 15 Years for the “Good” and “Intermediate” prognostic Subgroup.

• For poor prognosis neither breast Cancer Specific nor was Overall Survival significantly improved after PMRT throughout 15 years
Advances in treatment $\rightarrow$ Long term survivors $\downarrow$

Risk

Radiotherapy Induced second malignancies.

**AIM:** Evaluate occurrence of second primary solid non-breast cancer among Danish women treated for early breast cancer with postoperative radiotherapy.

**Patients & Methods:** All women > 20 years with primary invasive Loco regional breast cancer. DBCG database.
Systemic treatment According to DBCA guidelines.

All patients treatment on linear Accelerator. (132 treated on ortho voltage excluded)

46, 176 women:

- Post op RT
- no post op RT

Vital status updated annually

Danish Civil Registration system

RT changed overtime

Majority of patients: with 3-field anterior electron/photon technique.

Election field to chest wall ± IMC photon to Lateral thoracic wall + SCF.

Dose 48-50Gy/24-25 # over 5 weeks.

Breast conserving Sx PORT Remaining breast.

Tangential Photons to the conserved breast + BOOST to Tumour bed with Electrons.

Median Dose 48-50Gy/24-25# over 4.5-5weeks + Boost 10-24Gy 5-12
Second primary cancers were identified

National Danish Cancer Registry:

- Clinical Dept.
- Pathology
- Forensic
- Information from Death Certificates.

High Degree of Completeness and Validity of the Registry.

Solid Cancers → Excluding → Non melanoma skin – 11 defined second breast cancer.

Women censored if C/L BC was first event during clinical F/U

Only 1st, 2nd Primary cancer was counted to avoid influence of other? Treatment.
Second Cancers
Sites potentially associated with RT exposes (RT Associated)*
Sites not associated with RT (non RT – Associated)

*Oesophagus
Bone & Soft tissue sarcomas
Lung
Pleura
Heart / Mediastinum

F/U 1 Years after BC diagnoses (1983-2008)
till second primary malignancy
Recurrence of BC
Date of Death.
Date of emigration.
End of F/U (Dec 31 2008).
- Statistical Methods: Standardised incidence Ratio: \( \text{No of Cancer Case} \) Expected no (Computed).

- Comparison of Cancer Incidence
  - Cox regression Analyses with Estimation of HR.
  - Interaction between Radiotherapy 
    & Treatment with Chemotherapy 
    Endocrine therapy or Combination

- Second Cancers Among women not treated with RT 
- Second cancers among irradiated women 
  \( \rightarrow \) Observed No. of Cancers
• Attributable risk = \( \frac{\text{No of excess cancers}}{\text{Total No of cancer cases}} \)

Excess Absolute Risk (EAR) = \( \frac{\text{No of excess cancers Associated to RT} \times 1000}{\text{Person – years at risk}} \)

• Analysis performed by SAS & strata IC.
RESULTS

Total 46, 176 patients,
- % PORT Younger at BC Diagnosis
- % No PORT,

58 second primary cancer developed

928 second primary cancers developed.

784 cancer were expected.

SIR 1.18; 95% CI (1.11-1.26)

1430 second primary cancer observed

1350 cancer were expected.

Adjusted HR 1.10 (95%CI 1.01-1.21).

Adjusted HR for RT associated sites

1.34 (95%CI 1.11-1.61 P 0.002).

HR for individual sites

Increased for Lung cancer (HR 1.27 95%CI 1.04-1.55)

Not increased for oesophageal cancer (HR 2.96; 95%CI 1.17-6.18)
**Purpose:** To examine the importance of estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER-2), and constructed subtypes to patients receiving ± PMRT.

**Patients and Methods**

1,000 of the 3,083 high-risk BCP (DBCG) protocol 82 trials b and c randomly assigned to ± PMRT. Tissue microarray sections were stained for ER, PgR, and HER-2. Median follow-up time for patients alive was 17 years. End points were locoregional recurrence as isolated first event, distant metastases, and overall survival.
• For statistical analyses four subgroups were constructed from hormonal receptors (Rec).

Rec+ was defined as ER+ and/or PgR+.

Rec− as both ER− and PgR−.

The four subgroups were Rec+/HER-2−,

Rec+/HER-2+,

Rec−/HER-2− (triple negative),

Rec−/HER-2+.
Results

- Improved OS after PMRT: Good prognostic markers: HR+ and HER-2-
  OS improvement after PMRT: poor prognosis,
- HR-negative and HER-2+ patients, and in particular the Rec-/HER-2+
  subtype.
- Hazard ratios and 95% CIs, smaller improvements in LR control after
  PMRT were found for
  ER- & PgR- tumors vs ER+ & PgR+ tumors (P=.003 and .04, respectively),
  and for the triple-negative (P = .02), and the Rec-/HER-2+ subtypes (P =
  .003) compared with the Rec+/HER-2- subtype.
Conclusion:
Hormonal receptor status, HER-2, and the constructed subtypes may be predictive of locoregional recurrence and survival after postmastectomy radiotherapy.
Purpose: To identify genes predicting benefit of radiotherapy in patients with high-risk breast cancer treated with systemic therapy and randomized to receive or not receive postmastectomy radiotherapy (PMRT).

Gene-expression analysis was performed in a training set of frozen tumor tissue from 191 patients.

Genes were identified through the Lasso method with the endpoint being locoregional recurrence (LRR).

A weighted gene-expression index (DBCG-RT profile) was calculated and transferred to quantitative real-time PCR (qRT-PCR) in corresponding formalin-fixed, paraffin-embedded (FFPE) samples, before validation in FFPE from 112 additional patients.
Results: Seven genes were identified, and the derived DBCG-RT profile divided the 191 patients into "high LRR risk" and "low LRR risk" groups. PMRT significantly reduced risk of LRR in "high LRR risk" patients, whereas "low LRR risk" patients showed no additional reduction in LRR rate. Technical transfer of the DBCG-RT profile to FFPE/qRT-PCR was successful, and the predictive impact was successfully validated in another 112 patients.

Conclusions: A DBCG-RT gene profile was identified and validated, identifying patients with very low risk of LRR and no benefit from PMRT. The profile may provide a method to individualize treatment with PMRT.
Additional Achievements

• Abnormal expression of TOP2A as predictive marker for therapeutic effect of anthracycline containing regimen.

• Ongoing trials:
  1) Moderately hypofractionated loco-regional adjuvant radiation therapy of early breast cancer combined with a simultaneous integrated boost in patients with an indication for boost: DBCG HYPO II, a randomised clinically controlled trial.
Quality assurance of diagnostic work-up and treatment regimens. Team work has been accomplished.

Protocolized research activities.

Novel evidence-based treatment modalities are implemented immediately nation-wide.

DBCG activities: improved prognosis: 5-year survival ascending from 60% to roughly 80%.

Indicators for national quality assurance programme and monitoring.

Promotes transitional research.

Improves patient care and education.
Conclusion

High-quality DBCG studies of various designs and scope, nationwide or in international collaboration, have contributed to the current updating of the guidelines, and have been an instrumental resource in the improvement of management and prognosis of breast cancer. Prognosis in breast cancer has continuously improved with a decrease in 5-year mortality from ~37% to 15%.

“The keynote of progress in the 20th century is system and organization in other words, “team-work”.

Dr. Charles H Mayo.
Thanks