Cardiac effects of Radiotherapy for Breast Cancer

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Radiotherapy in Ca Breast

EBRT

• Post BCS
• Post mastectomy
• Palliative–following local recurrence

Brachytherapy

Aim:
• Maximise local control
• Improve survival
• *Minimal complications*
Cardiac effects of Radiotherapy for Breast Cancer

- Basics
- Pathophysiology
- Evidence of RIHD
- Dose volume data
- Ways to improve
- Clinical data
- Future perspective
• **Basics**
  • Pathophysiology
  • Evidence of RIHD
  • Dose volume data
  • Ways to improve
  • Clinical data
  • Future perspective
Radiation Response In Normal Tissues

- Response of tissue or organ to radiation depends on 3 factors viz.
  1. Inherent radiosensitivity of individual cells
  2. Population kinetics of the cells in the tissue
  3. Structural arrangements of the functional subunits (FSUs) in the tissue
     -- serial / parallel

These factors combine to account for the substantial variation in radio-responsiveness of various organs and tissues
RIHD – Radiation Induced Heart Disease

Defn: Clinical and pathological conditions of injuries to the heart and large vessels resulting from therapeutic irradiation of malignancies
Heart Development

- 8th week of gestation – embryonic morphogenesis
- 6 months – full adult number of myocytes
- After this heart growth - myocyte enlargement
- Fajardo & Stewart showed that heart and vasculature are radiosensitive organs

• Basics
• **Pathophysiology**
• Evidence of RIHD
• Dose volume data
• Ways to improve
• Clinical data
• Future perspective
Pathophysiology

- Microangiopathy
- Macroangiopathy
- Atherosclerosis

Fibrosis
Made of a network of collagen fibers that separates the myocytes
Figure 1  Pathology of RIHD.
Heart and its component affected by RT

- Early reactions rare, mostly late effects
- Radiation induced cardiac injuries
  - Pericarditis
  - CCF
  - Restrictive Cardiomyopathy
  - Valvular insufficiency & stenosis
  - CAD: ischemia, infarction

<table>
<thead>
<tr>
<th>Component</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardium</td>
<td>Pericardial thickening</td>
</tr>
<tr>
<td></td>
<td>Pericardial effusion</td>
</tr>
<tr>
<td></td>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td></td>
<td>Constrictive pericarditis</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Obstructive lesion in the anterior descending artery</td>
</tr>
<tr>
<td></td>
<td>Obstructive lesion in the coronary ostia</td>
</tr>
<tr>
<td>Myocardium</td>
<td>Asymptomatic left ventricular diastolic dysfunction</td>
</tr>
<tr>
<td>Valves</td>
<td>Valvular thickening without hemodynamic repercussions</td>
</tr>
<tr>
<td></td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>Cardiac electrical and conduction disorders</td>
<td>Right bundle branch block (more frequent)</td>
</tr>
<tr>
<td></td>
<td>Left bundle branch block</td>
</tr>
<tr>
<td></td>
<td>Complete atrioventricular block</td>
</tr>
<tr>
<td></td>
<td>T-wave flattening or inversion</td>
</tr>
<tr>
<td>Great vessels of the chest</td>
<td>Increased carotid intima-media thickness</td>
</tr>
<tr>
<td></td>
<td>Chronic baroreflex failure: labile hypertension or orthostatic hypotension</td>
</tr>
<tr>
<td></td>
<td>Aortic calcification</td>
</tr>
<tr>
<td></td>
<td>Stenotic lesions of the subclavian arteries</td>
</tr>
</tbody>
</table>
• Basics
• Pathophysiology
• **Evidence of RIHD**
• Dose volume data
• Ways to improve
• Clinical data
• Future perspective
Data Digging
## Cardiac Risk RT vs NO RT

<table>
<thead>
<tr>
<th>Trial</th>
<th>XRT</th>
<th>No XRT</th>
<th>SMR₁</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O₁</td>
<td>E₁*</td>
<td>SMR₁</td>
<td>O₂</td>
<td>E₂*</td>
</tr>
<tr>
<td><strong>Radical ± XRT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manchester Q³</td>
<td>25</td>
<td>16.02</td>
<td>1.56</td>
<td>28</td>
<td>31.28</td>
</tr>
<tr>
<td>Manchester P³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oslo I²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oslo II²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heidelberg¹⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stockholm⁵</td>
<td>8</td>
<td>10.04</td>
<td>0.80</td>
<td>3</td>
<td>9.31</td>
</tr>
<tr>
<td>Subtotal</td>
<td>99</td>
<td>75.68</td>
<td>1.31</td>
<td>67</td>
<td>92.98</td>
</tr>
<tr>
<td><strong>Simple ± XRT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manchester Regional I¹⁵</td>
<td>13</td>
<td>9.82</td>
<td>1.32</td>
<td>10</td>
<td>8.86</td>
</tr>
<tr>
<td>CRC⁴</td>
<td>35</td>
<td>47.62</td>
<td>0.73</td>
<td>26</td>
<td>52.29</td>
</tr>
<tr>
<td>Edinburgh⁶</td>
<td>4</td>
<td>3.13</td>
<td>1.28</td>
<td>5</td>
<td>3.30</td>
</tr>
<tr>
<td>Subtotal</td>
<td>52</td>
<td>60.57</td>
<td>0.86</td>
<td>41</td>
<td>64.45</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>151</td>
<td>136.25</td>
<td>1.11</td>
<td>108</td>
<td>157.43</td>
</tr>
</tbody>
</table>

NOTE. SMRs of <1 favor XRT.

*Expected numbers are based on age- and calendar-specific rates for women in England and Wales.

Trials before 1975, Total – 7941,
Cardiac Mortality for patients surviving 10 years N = 4309

Cuzick et al JCO 1994
### Incidence of IHD SEER data

**N = 27283 (Left and Right side .13000 each)**

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**Giordano et al** Risk of Cardiac Death After Adjuvant Radiotherapy for Breast Cancer : JNCI 2005

### Table 2. Comparison of percent ischemic heart disease mortality (with 95% confidence intervals) at 15 years of follow-up between women with left-sided and right-sided breast cancers, stratified by stage of disease at time of diagnosis

| Cohort by year of diagnosis | All patients | | | | | Patients with in situ/localized disease | | | | | Patients with regional disease | | | |
|-----------------------------|-------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|                             | Left-sided, % | Right-sided, % | P   | Left-sided, % | Right-sided, % | P   | Left-sided, % | Right-sided, % | P   |
| Overall                     | 8.7 (8.0 to 9.3) | 7.5 (6.9 to 8.2) | .07 | 7.6 (6.7 to 8.4) | 6.7 (5.9 to 7.5) | .40 | 10.2 (9.1 to 11.3) | 8.6 (7.6 to 9.6) | .09 |
| 1973–1979                   | 13.1 (11.6 to 14.6) | 10.2 (8.9 to 11.5) | .02 | 12.7 (10.3 to 15.2) | 9.6 (7.5 to 11.8) | .14 | 13.3 (11.5 to 15.1) | 10.6 (8.9 to 12.3) | .06 |
| 1980–1984                   | 9.4 (8.1 to 10.6) | 8.7 (7.4 to 10.0) | .64 | 8.9 (7.2 to 10.5) | 8.7 (7.1 to 10.4) | .87 | 10.0 (7.9 to 12.1) | 8.8 (6.8 to 10.9) | .38 |
| 1985–1989                   | 5.8 (4.8 to 6.7) | 5.2 (4.4 to 5.9) | .98 | 5.7 (4.5 to 6.8) | 4.9 (4.0 to 5.8) | .79 | 6.0 (4.4 to 7.6) | 5.7 (4.1 to 7.2) | .76 |
IHD incidence

Conclusion

Risk of death from ischemic heart disease associated with radiation for breast cancer has substantially decreased over time

Giordano et al. Risk of Cardiac Death After Adjuvant Radiotherapy for Breast Cancer: JNCI 2005
Comparison with historic data

• A review of trials done before 1980 to trials after 1980
• Weighted mean cardiac morbidity and mortality (including myocardial infarction, ischemic heart disease, cardiovascular disease)
  – 1.28 for trials before 1980.
• After 1980,
  – Trials with less than 10 years follow-up had variable or no evidence of increased cardiac morbidity
  – Trials with greater than 10 years follow-up consistently showed increased toxicity

Demirci S et al: Radiation-induced cardiac toxicity after therapy for breast cancer: Interaction between treatment era and follow-up duration. IJROBP 2009
## Long-Term Risk of Cardiovascular Disease in 10-Year Survivors of Breast Cancer

**Table 4.** Multivariable Cox regression analyses for myocardial infarction and congestive heart failure by radiotherapy (RT) field and estimated mean radiation dose to the heart by treatment period*

<table>
<thead>
<tr>
<th>Treatment period</th>
<th>No. of patients</th>
<th>Estimated mean heart dose, Gy</th>
<th>Dose range, Gy</th>
<th>Myocardial infarction</th>
<th>Congestive heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR (95% CI)†</td>
<td>P‡</td>
</tr>
<tr>
<td>1970–1979</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT fields</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No RT/fields not including heart§</td>
<td>431</td>
<td>≈0</td>
<td>≈0</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Chest wall/breast: right-sided</td>
<td>179</td>
<td>≈3</td>
<td>1.2–3.8</td>
<td>1.76 (0.88 to 3.51)</td>
<td>.11</td>
</tr>
<tr>
<td>Chest wall/breast: left-sided</td>
<td>168</td>
<td>≈7</td>
<td>2.5–9.0</td>
<td>2.72 (1.38 to 5.38)</td>
<td>.004</td>
</tr>
<tr>
<td>IMC only: right-sided</td>
<td>348</td>
<td>≈7</td>
<td>0.5–11.6</td>
<td>2.59 (1.46 to 4.61)</td>
<td>.001</td>
</tr>
<tr>
<td>IMC only: left-sided</td>
<td>386</td>
<td>≈9</td>
<td>0.7–15.6</td>
<td>2.00 (1.12 to 3.58)</td>
<td>.02</td>
</tr>
<tr>
<td>IMC + chest wall/breast: right-sided</td>
<td>158</td>
<td>≈11</td>
<td>2.7–15.4</td>
<td>4.77 (2.43 to 9.35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IMC + chest wall/breast: left-sided</td>
<td>166</td>
<td>≈15</td>
<td>4.7–18.3</td>
<td>2.59 (1.29 to 5.18)</td>
<td>.007</td>
</tr>
<tr>
<td>1980–1986</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT fields</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No RT/fields not including heart§</td>
<td>261</td>
<td>≈0</td>
<td>≈0</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Breast/chest wall: right-sided</td>
<td>316</td>
<td>≈1.5</td>
<td>1.2–1.6</td>
<td>0.71 (0.29 to 1.74)</td>
<td>.46</td>
</tr>
<tr>
<td>Breast/chest wall: left-sided</td>
<td>395</td>
<td>≈5</td>
<td>2.5–5.3</td>
<td>0.79 (0.36 to 1.72)</td>
<td>.55</td>
</tr>
<tr>
<td>IMC only: right-sided</td>
<td>399</td>
<td>≈6</td>
<td>0.5–11.6</td>
<td>0.96 (0.46 to 1.93)</td>
<td>.88</td>
</tr>
<tr>
<td>IMC only: left-sided</td>
<td>346</td>
<td>≈7</td>
<td>0.7–15.6</td>
<td>0.94 (0.46 to 1.91)</td>
<td>.86</td>
</tr>
<tr>
<td>IMC + breast/chest wall: right-sided</td>
<td>365</td>
<td>≈9</td>
<td>2.5–14.0</td>
<td>0.80 (0.36 to 1.78)</td>
<td>.58</td>
</tr>
<tr>
<td>IMC + breast/chest wall: left-sided</td>
<td>376</td>
<td>≈13</td>
<td>4.0–19.9</td>
<td>0.67 (0.30 to 1.52)</td>
<td>.34</td>
</tr>
</tbody>
</table>

All 10 year survivors N = 4414
Follow up 18 yrs – 942 cardiac events

Hooning et al JNCI 2007
Conclusion

• Radiotherapy as administered from the 1980s onward is associated with an increased risk of cardiovascular disease. Irradiated breast cancer patients should be advised to refrain from smoking to reduce their risk for cardiovascular disease.

• Patients who underwent radiotherapy plus adjuvant chemotherapy (CMF regimen) after 1979 had a higher risk of congestive heart failure than patients who were treated with radiotherapy only ($P = 0.002$)
**Oxford Overview - Mortality without recurrence in Radiotherapy trials**

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>O-E</th>
<th>Hazard Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulatory disease</td>
<td>1510</td>
<td>77.6</td>
<td>1.25 (0.06)</td>
<td>0.00003</td>
</tr>
<tr>
<td>Heart disease</td>
<td>1106</td>
<td>60.7</td>
<td>1.27 (0.07)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>345</td>
<td>9.1</td>
<td>1.12 (0.12)</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>59</td>
<td>7.8</td>
<td>1.76 (0.36)</td>
<td>0.04</td>
</tr>
<tr>
<td>Other causes</td>
<td>1455</td>
<td>6.4</td>
<td>1.02 (0.06)</td>
<td>NS</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>156</td>
<td>21.7</td>
<td>1.78 (0.22)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Oesophagus cancer</td>
<td>23</td>
<td>4.9</td>
<td>2.40 (0.68)</td>
<td>0.04</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>31</td>
<td>2.4</td>
<td>1.40 (0.45)</td>
<td>NS</td>
</tr>
<tr>
<td>Soft-tissue sarcoma</td>
<td>7</td>
<td>1.3</td>
<td>2.13 (1.14)</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>241</td>
<td>-1.0</td>
<td>0.98 (0.13)</td>
<td>NS</td>
</tr>
<tr>
<td>Other known causes</td>
<td>997</td>
<td>-22.9</td>
<td>0.90 (0.06)</td>
<td>NS</td>
</tr>
<tr>
<td>Unspecified cause</td>
<td>701</td>
<td>7.8</td>
<td>1.05 (0.08)</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>3666</td>
<td>91.8</td>
<td>1.12 (0.04)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

_Slide courtesy – Dr. Ashwini B_
# Cardiac Adverse Events in Hypofractionation Trials

<table>
<thead>
<tr>
<th></th>
<th>START-A</th>
<th></th>
<th>START-B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 Gy (n=749)</td>
<td>41-6 Gy (n=750)</td>
<td>39 Gy (n=737)</td>
<td>Total (n=2236)</td>
</tr>
<tr>
<td><strong>Symptomatic rib fracture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported</td>
<td>5 (0.7%)</td>
<td>8 (1.1%)</td>
<td>9 (1.2%)</td>
<td>22 (1.0%)</td>
</tr>
<tr>
<td>Confirmed†</td>
<td>0</td>
<td>0</td>
<td>1 (0.1%)</td>
<td>1 (&lt;0.1%)</td>
</tr>
<tr>
<td><strong>Symptomatic lung fibrosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported</td>
<td>6 (0.8%)</td>
<td>9 (1.2%)</td>
<td>8 (1.1%)</td>
<td>23 (1.0%)</td>
</tr>
<tr>
<td>Confirmed†</td>
<td>0</td>
<td>2 (0.3%)</td>
<td>1 (0.1%)</td>
<td>3 (0.1%)</td>
</tr>
<tr>
<td><strong>Ischaemic heart disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported</td>
<td>14 (1.9%)</td>
<td>11 (1.5%)</td>
<td>8 (1.1%)</td>
<td>33 (1.5%)</td>
</tr>
<tr>
<td>Confirmed†</td>
<td>0</td>
<td>2 (0.3%)</td>
<td>1 (0.1%)</td>
<td>3 (0.1%)</td>
</tr>
</tbody>
</table>

Data are n (%). *Reported cases include seven after trauma (five in START-A, two in START-B), and ten after metastases (five in START-A and five in START-B). †After imaging and further investigations. ‡26 patients in START-A and 22 in START-B had pre-existing heart disease at enrolment and were excluded.

Table 3: Incidence of other late adverse effects according to fractionation schedule

Joanne S Haviland et al, The Lancet 2013
- Basics
- Pathophysiology
- Evidence of RIHD
- **Dose volume data**
- Ways to improve
- Clinical data
- Future perspective
Normal Tissue Tolerance—Dose volume data

• Summary of historical landmarks to establish the dose-volume parameters and outcomes

<table>
<thead>
<tr>
<th>Report</th>
<th>Key Contributions</th>
<th>Key Shortcomings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubin, 1975</td>
<td>Introduced the concept of TD_{5/5} and TD_{50/5}</td>
<td>Minimal dose–volume data</td>
</tr>
<tr>
<td>Emami, 1991</td>
<td>Concise summary addressing most clinically meaningful endpoints in a uniform manner</td>
<td>Dose–volume relationship based on limited data and, thus, much expert opinion</td>
</tr>
<tr>
<td>QUANTEC, 2010</td>
<td>Based on available data and expert opinion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Driven largely by the available 3D dose/volume/outcome data.</td>
<td>Because dose/volume/outcome data on all meaningful clinical outcomes are not available, the summary is not able to guide all clinical practice</td>
</tr>
<tr>
<td></td>
<td>Systematic review addressing many challenges such as organ delineation and confounding factors such as chemotherapy</td>
<td></td>
</tr>
</tbody>
</table>

• QUANTEC–introduced the concept of evaluation of DVH parameters like V_x (the % of organ receiving ≥ x Gy)

α/β heart is low (about 1 Gy): fractionation results in substantial sparing effect

Source: Eric J. Hall, Seventh Ed. Ch. 20
Radiation Tolerance Doses – Heart

- Data for 2Gy/#
- Variation with
  - Age
  - Individual sensitivity
  - Vascular status
  - Other treatment factors

<table>
<thead>
<tr>
<th>OAR</th>
<th>TD5/5 (Gy)</th>
<th>TD50/5 (Gy)</th>
<th>DVH Vx % or mean dose in Gy</th>
<th>Tolerance dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>1/3 60</td>
<td>70</td>
<td>V40 &lt;30</td>
<td>D_{max} &lt;60</td>
</tr>
<tr>
<td></td>
<td>2/3 45</td>
<td>55</td>
<td>V30 &lt;40-45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/3 40</td>
<td>50</td>
<td>V20 &lt;50</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>1/3 45</td>
<td>65</td>
<td>V30 &lt;10-15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/3 30</td>
<td>40</td>
<td>V20 &lt;25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/3 17.5</td>
<td>24.5</td>
<td>Mean 10</td>
<td></td>
</tr>
</tbody>
</table>
## Radiation Tolerance Doses – Heart

<table>
<thead>
<tr>
<th>Pericardium</th>
<th>3D-CRT</th>
<th>Pericarditis</th>
<th>Mean dose &lt;26</th>
<th>&lt;15</th>
<th>Based on single study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardium</td>
<td>3D-CRT</td>
<td>Pericarditis</td>
<td>V30 &lt;46%</td>
<td>&lt;15</td>
<td></td>
</tr>
<tr>
<td>Whole organ</td>
<td>3D-CRT</td>
<td>Long-term cardiac mortality</td>
<td>V25 &lt;10%</td>
<td>&lt;1</td>
<td>Overly safe risk estimate based on model predictions</td>
</tr>
</tbody>
</table>
Stockholm Breast Cancer Study Group

- Patients: 2168 with major coronary events = 960 (1958 and 2001)
- Matched with population control n = 1205
- Mean dose to Heart
  - Left breast 2.9 Gy
  - Right breast 4.9 Gy
- The percentage increase in risk per gray was similar for women with and those without cardiac risk factors at the time of radiotherapy
- Women irradiated for cancer of the left breast had higher rates of major coronary events than women irradiated for cancer of the right breast (P = 0.002)
- Rate of Major Coronary Events According to Mean Radiation Dose to the Heart with no apparent threshold
- Each 1 Gy increase leads to 7.4% increased risk p < 0.001
Post lumpectomy modern radiotherapy techniques significantly decreased the dose delivered to the heart (mean V25 Gy was 5.7% compared to 25% in Stockholm trial).

Sarah C. Darby et al Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer NEJM 2013
Sifted focus to mean heart dose but the mean dose effect might differ with age

### Table 3. Percentage Increase in the Rate of Major Coronary Events per Gray, According to Time since Radiotherapy.

<table>
<thead>
<tr>
<th>Time since Radiotherapy</th>
<th>No. of Case Patients</th>
<th>No. of Controls</th>
<th>Increase in Rate of Major Coronary Events (95% CI)† % increase/Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 4 yr</td>
<td>206</td>
<td>328</td>
<td>16.3 (3.0 to 64.3)</td>
</tr>
<tr>
<td>5 to 9 yr</td>
<td>216</td>
<td>296</td>
<td>15.5 (2.5 to 63.3)</td>
</tr>
<tr>
<td>10 to 19 yr</td>
<td>323</td>
<td>388</td>
<td>1.2 (−2.2 to 8.5)</td>
</tr>
<tr>
<td>≥20 yr</td>
<td>218</td>
<td>193</td>
<td>8.2 (0.4 to 26.6)</td>
</tr>
<tr>
<td>0 to ≥20 yr</td>
<td>963</td>
<td>1205</td>
<td>7.4 (2.9 to 14.5)</td>
</tr>
</tbody>
</table>
• Basics
• Pathophysiology
• Evidence of RIHD
• Dose volume data
• **Ways to improve**
• Clinical data
• Future perspective
Factors which leads to increase in Heart Dose

**Patient Related**
- Previous co-morbidity
- Large breasts
- Age / Sex
- Lifestyle
- Smoking/alcohol
- Surgical scar

**Treatment Related**

**Radiotherapy**
- Cobalt or MV
- Position
- 2D or 3D
- Technique
- QA

**Chemotherapy**
- Anthracyclins – Type- I cardiotoxicity
- Trastuzumab – Type – II cardiotoxicity
- Hormonal therapy
Technique of Sparing of Heart

- Brest Board
- Prone position
- Heart block
- 3D conformal radiotherapy (3DCRT)
- Intensity modulated Radiotherapy (IMRT)
- Tomotherapy
- Respiratory maneuvers
- APBI
- Proton therapy
Breast Board

- Improves the angle of treatment along the chest wall to spare the anterior heart.
- The tissues of the breast move forward with the slant of the board and higher arm elevation, allowing for less inclusion of tissues deep to the chest wall.  
- Improvements in the position have been shown to reduce the mean cardiac dose by as much as 60% and the maximum dose to the heart by 30% in comparison to treatment with flat positioning and collimation.
- Proper set up and immobilization can decrease cardiac dose.

Breast Board
Importance Of Positioning

A small misalignment of the pt. on the couch will have the same effect as if the couch were angled.
Prone Position

• An alternative to improve cardiac positioning and dose homogeneity throughout the breast.
• Review 200 women simulated with both prone and supine positioning
• Prone positioning decreased the volume of heart in the field for 85% of the patients (with only 15% of women having lower cardiac volume with standard supine treatment).
• The reduction in cardiac volumes was 87% (8.8-1.3cm³).
• Although the benefit in women with < 750 cm³ volume breasts did not reach statistical significance
• Women of all breast volumes had a reduction in cardiac volume with the greatest effect noted in larger breast volumes

Prone Breast Board
Prone Position

Goodman 2002, MSKCC
Heart Block

- Customized blocks
- May be appropriate, particularly in patients with well-visualized surgical beds.
- Average percentage of breast tissue that may be under dosed is 2.8%.
- Overall, local recurrence rates were not significantly different between patients with field heart blocks vs those without blocks.

Raj KA et al: Is there an increased risk of local recurrence under the heart block in patients with left-sided breast cancer? Cancer J 1, 2006
Heart Block

Breast contour

Heart contour

Maximum Heart Distance (MHD)
Heart Block

Left side RT

- Intact Breast
  - Superior tumor
  - Heart Block
- Inferior Tumor
  - Tangent angle
  - DIBH
  - Electron Patch

- Mastectomy
  - Tangent angle
  - DIBH
  - Electron
Newer RT techniques

- Technological advancements in the RT technique has improved over the time
- Shift from orthovoltage cobalt to MV
- 2D to 3D planning
- Improvement in PTV coverage
- Decrease in OAR doses
- Use of 3 DCRT, IMRT, Helical Tomotherapy
Challenges in defining Heart volumes in RT

- Uncertainties to delineate the Heart on CT imaging
  
  - **Anatomical challenge:** Close proximity / intersection of borders with Great Vessels, Liver, Diaphragm and Stomach
  
  - **Physiologic Movements:** Different regions move in different degrees and directions during cardiac cycle and respiration
• n=50
• Approximately half of the patients irradiated with left tangential radiotherapy received doses of ≥ 20 Gy to a small part of the anterior heart, which usually included the LAD coronary artery.
• Most of the heart volume, including the right and circumflex coronary arteries, received scattered irradiation alone, and mean heart dose was approximately 2 Gy for left-sided irradiation.
<table>
<thead>
<tr>
<th>Calendar period</th>
<th>Heart</th>
<th>LAD coronary artery</th>
<th>Right coronary artery</th>
<th>Circumflex coronary artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose (Gy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1970s (Sweden) (4)</td>
<td>13.3</td>
<td>31.8</td>
<td>9.1</td>
<td>6.9</td>
</tr>
<tr>
<td>1990s (Sweden) (4)</td>
<td>4.7</td>
<td>21.9</td>
<td>2.0</td>
<td>2.8</td>
</tr>
<tr>
<td>2006 (United Kingdom)</td>
<td>2.3</td>
<td>7.6</td>
<td>2.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Mean dose (% tumor dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1970s (Sweden) (4)</td>
<td>26.6</td>
<td>63.6</td>
<td>18.2</td>
<td>13.8</td>
</tr>
<tr>
<td>1990s (Sweden) (4)</td>
<td>9.4</td>
<td>43.8</td>
<td>4.0</td>
<td>5.6</td>
</tr>
<tr>
<td>2006 (United Kingdom)</td>
<td>5.8</td>
<td>19.0</td>
<td>5.0</td>
<td>4.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Heart</th>
<th>LAD coronary artery</th>
<th>Right coronary artery</th>
<th>Circumflex coronary artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average mean dose (SD)* (Gy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left-sided irradiation</td>
<td>2.3 (0.7)†</td>
<td>7.6 (4.5)†</td>
<td>2.0 (0.3)</td>
<td>1.8 (0.3)</td>
</tr>
<tr>
<td>Right-sided irradiation</td>
<td>1.5 (0.2)</td>
<td>1.6 (0.2)</td>
<td>2.0 (0.3)</td>
<td>1.2 (0.1)</td>
</tr>
<tr>
<td>Average maximum dose (SD)* (Gy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left-sided irradiation</td>
<td>30.7 (10.8)†</td>
<td>35.2 (8.8)†</td>
<td>2.5 (0.3)</td>
<td>2.4 (0.4)</td>
</tr>
<tr>
<td>Right-sided irradiation</td>
<td>2.6 (0.3)</td>
<td>1.9 (0.2)</td>
<td>2.5 (0.4)</td>
<td>1.5 (0.2)</td>
</tr>
</tbody>
</table>

Taylor et al, Cardiac dose from tangential breast cancer radiotherapy in The year 2006 IJROBP -2007
## Incidence of IHD SEER data

### Table 2. Comparison of percent ischemic heart disease mortality (with 95% confidence intervals) at 15 years of follow-up between women with left-sided and right-sided breast cancers, stratified by stage of disease at time of diagnosis

<table>
<thead>
<tr>
<th>Cohort by year of diagnosis</th>
<th>All patients</th>
<th>Patients with in situ/localized disease</th>
<th>Patients with regional disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left-sided, %</td>
<td>Right-sided, %</td>
<td>( P )</td>
</tr>
<tr>
<td>Overall</td>
<td>8.7 (8.0 to 9.3)</td>
<td>7.5 (6.9 to 8.2)</td>
<td>.07</td>
</tr>
<tr>
<td>1973–1979</td>
<td>13.1 (11.6 to 14.6)</td>
<td>10.2 (8.9 to 11.5)</td>
<td>.02</td>
</tr>
<tr>
<td>1980–1984</td>
<td>9.4 (8.1 to 10.6)</td>
<td>8.7 (7.4 to 10.0)</td>
<td>.64</td>
</tr>
<tr>
<td>1985–1989</td>
<td>5.8 (4.8 to 6.7)</td>
<td>5.2 (4.4 to 5.9)</td>
<td>.98</td>
</tr>
</tbody>
</table>

\( N = 27283 \)

Giordano et al. Risk of Cardiac Death After Adjuvant Radiotherapy for Breast Cancer: JNCI 2005
Modern era shows great promise for reduced cardiac toxicity, although it is likely be decades before we can say this with certainty.
Comparison of different techniques

Comparison of normal tissue dose volume metrics as a function of plan modality.

<table>
<thead>
<tr>
<th>Metric</th>
<th>3DCRT</th>
<th>For. IMRT</th>
<th>Inv. IMRT</th>
<th>Tomotherapy</th>
<th>Topotherapy</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D_{\text{mean}}$ (Gy)</td>
<td>$2.6 \pm 0.9$</td>
<td>$2.3 \pm 0.9$</td>
<td>$1.9 \pm 0.8$</td>
<td>$3.9 \pm 1.3$</td>
<td>$1.9 \pm 0.7$</td>
<td>0.002</td>
</tr>
<tr>
<td>$D_{\text{max}}$ (Gy)</td>
<td>$50.8 \pm 3.5$</td>
<td>$49.1 \pm 5.0$</td>
<td>$44.0 \pm 7.2$</td>
<td>$33.9 \pm 7.7$</td>
<td>$46.1 \pm 5.9$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$V_5$ (%)</td>
<td>$7.6 \pm 3.5$</td>
<td>$6.6 \pm 3.5$</td>
<td>$5.0 \pm 3.1$</td>
<td>$26.5 \pm 18.4$</td>
<td>$4.7 \pm 2.7$</td>
<td>0.003</td>
</tr>
<tr>
<td>$V_{10}$ (%)</td>
<td>$4.2 \pm 2.5$</td>
<td>$3.8 \pm 2.4$</td>
<td>$2.5 \pm 2.0$</td>
<td>$4.8 \pm 4.4$</td>
<td>$3.3 \pm 2.2$</td>
<td>0.354</td>
</tr>
<tr>
<td>$V_{20}$ (%)</td>
<td>$2.0 \pm 1.6$</td>
<td>$2.2 \pm 1.7$</td>
<td>$1.2 \pm 1.4$</td>
<td>$0.5 \pm 0.4$</td>
<td>$1.6 \pm 1.4$</td>
<td>0.010</td>
</tr>
<tr>
<td>$V_{50}$ (%)</td>
<td>$0.3 \pm 0.5$</td>
<td>$0.1 \pm 0.2$</td>
<td>$0.0 \pm 0.0$</td>
<td>$0.0 \pm 0.0$</td>
<td>$0.0 \pm 0.1$</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

10 patients with left breast RT

Leah K. Schubert et al  Dosimetric comparison of left-sided whole breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and topotherapy, radiotherapy & Oncology 2011
**Results:** Target max doses were reduced with for-IMRT compared to 3DCRT, which were further reduced with HT, topotherapy, and inv-IMRT. HT resulted in lowest heart and ipsilateral lung max doses, but had higher mean doses. Inv-IMRT and topotherapy reduced ipsilateral lung mean and max doses compared to 3DCRT and for-IMRT.
IMRT techniques

Reshma Jagsi et al; evaluation of 4 different technique of IMRT; IJROBP 2010
<table>
<thead>
<tr>
<th>Structure</th>
<th>Mean estimate for 9-field technique (SD)</th>
<th>Mean estimate for segmental technique (SD)</th>
<th>Mean estimate for heart blocked segmental technique (SD)</th>
<th>Mean estimate for tangential beamlet technique (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>7.18 (1.21)</td>
<td>4.10 (1.46)</td>
<td>1.91 (0.33)</td>
<td>2.60 (1.33)</td>
</tr>
<tr>
<td>Mean dose (Gy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V2 (%)</td>
<td>99.94 (0.20)</td>
<td>47.76 (14.70)</td>
<td>37.63 (12.71)</td>
<td>51.47 (31.87)</td>
</tr>
<tr>
<td>V5 (%)</td>
<td>80.18 (16.63)</td>
<td>12.47 (6.18)</td>
<td>3.40 (1.33)</td>
<td>10.15 (13.27)</td>
</tr>
<tr>
<td>V10 (%)</td>
<td>11.49 (7.32)</td>
<td>7.11 (4.10)</td>
<td>0.55 (0.39)</td>
<td>2.46 (3.32)</td>
</tr>
<tr>
<td>V20 (%)</td>
<td>0.31 (0.36)</td>
<td>4.84 (3.11)</td>
<td>0.03 (0.06)</td>
<td>0.40 (0.79)</td>
</tr>
<tr>
<td>V30 (%)</td>
<td>0.01 (0.02)</td>
<td>3.34 (2.38)</td>
<td>0.005 (0.01)</td>
<td>0.05 (0.17)</td>
</tr>
<tr>
<td>LAD artery</td>
<td>11.23 (1.53)</td>
<td>20.59 (8.46)</td>
<td>6.00 (1.63)</td>
<td>5.44 (2.38)</td>
</tr>
<tr>
<td>Mean dose (Gy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose to 1% volume (Gy)</td>
<td>19.32 (4.29)</td>
<td>46.60 (14.50)</td>
<td>14.22 (5.34)</td>
<td>9.81 (5.17)</td>
</tr>
</tbody>
</table>

Dosimetric comparision
Gating and Deep Inspiration Breathing Techniques

DIBH

Active Breathing

Normal Breathing

Breath Holding
Gating and Deep Inspiration Breathing Techniques

• Deep inspiration breath hold (DIBH) involves gating radiation to deliver treatment when the least volume of heart is in the field
• Inferior and posterior displacement of the cardiac silhouette caused by near maximal inspiration (Fig. 1)
• ~50% cases Heart could be entirely removed from the field and that cardiac volumes were reduced by approximately 80% \(^1\)
• Comparisons of techniques found that median heart volume receiving greater than 50% of the dose was decreased from 19% to \(\leq 3\)% with either inspiratory gating or DIBH \(^2\)

---

2. Korreman SS et al: Breathing adapted radiotherapy for breast cancer Comparison of free breathing gating with the breath-hold technique. Radiother Oncol 2005
Gating and Deep Inspiration Breathing Techniques

- Active breathing may be combined with treatment modalities such as fixed gantry IMRT as well. The reduction in V30 using DIBH for deep tangent IMRT plans was on average 13% - 3%.

- With active breathing techniques, there is an average reduction of 5% to the volume near the left anterior descending (LAD) receiving 20Gy or more when using fixed gantry angle IMRT over 3D-conformal radiation therapy (CRT).

References:
1. Remouchamps VM et al: Significant reductions in heart and lung doses using deep inspiration breath hold with active breathing control and intensity-modulated radiation therapy for patients treated with locoregional breast IJROBP 2003
2. Mast ME et al: Left-sided breast cancer radiotherapy with and without breath-hold: Does IMRT reduce the cardiac dose even further? Radiother Oncol 2013
VBH (Voluntary Breath Hold) vs Prone

Estimated breast volume of >750 cm³
VBH (Voluntary Breath Hold) vs Prone

- All cardiac dose parameters (Gy) were statistically significantly lower with VBH than prone treatment
  
  - Heart NTDmean 0.44 [0.38–0.51] vs. 0.66 [0.61–0.71] (p < 0.001)
  
  - LAD NTDmean 2.9 [1.8–3.9] vs. 7.8 [6.4–9.2] (p < 0.001)
  
  - LADmax 21.0 [15.8–26.2] vs. 36.8 [35.2–38.4] (p < 0.001)
Proton Therapy

PTV1 scenario—Whole Breast only

3D-CRT  IMRT  IMPT
Proton Therapy

PTV3 scenario – Whole Breast, MSC, LSC, AxIII and IMC

3D-CRT

IMRT

IMPT

Carmen Ares, Proton Therapy, IJROBP - 2010
APBI

- Accelerated Partial breast irradiation
- As the dose is limited to tumor bed cavity and rapid dose fall off
- The cardiac morbidity and risk is very low
• Basics
• Pathophysiology
• Evidence of RIHD
• Dose volume data
• Ways to improve
• Clinical data
• Future perspective
Future perspective

- Incorporation of specialties such as cardio-oncology in the patient management and long-term follow-up are opportunities to identify high-risk patients earlier.
- Biomarkers of cardiotoxicity – cardiac troponins, natriuretic peptides, and proposed early markers of cardiac injury markers, such as heart-type fatty acid-binding proteins and glycogen phosphorylase isoenzyme BB.
- Cardiac Stem cell
Conclusion

- RIHD is known toxicity of breast RT
- Data clearly states the adverse effects of RT on heart
- Recent advanced techniques of RT has reduced the cardiac doses significantly
- Further long term follow up data will be needed to analyze effect of newer techniques
- Use proper techniques and doses to spare the heart as much as possible
- All patients should be treated with CT simulation plans
- For centers doing 2D plans minimize MHD to <1cm
Thank you