Cardiovascular disease after radiation therapy

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Radiation induced long-term health effects after medical exposure
The principles of Radiation Therapy

• The ideal radiation source: the "infinitron" - 100% of the energy delivered to the tumour, zero energy outside.

• Brachytherapy comes close (source of short-range radiation inside the tumour).

• Real (external) beams deliver energy from the patient skin all the way to the tumour and beyond and also laterally (due to scatter). Therefore irradiation of non-tumour tissue is unavoidable.

• The aim of radiotherapy treatment planning is to find the best compromise between tumour elimination (= ’control’) and complication avoidance.
When irradiating the thorax:

- Heart
- Lung
- Esophagus
- Ribs
- Chest wall pain
- Liver

From Kong et al, 2010
Dose distribution (example)

Breast ca, left lung, heart

Typical treatment prescription:

46 Gy, 2 Gy/fr
Tool to summarize 3D information in a 2D picture

Dose-Volume Histograms (DVH)

Each point represents the percentage of the volume of the structure receiving at least that dose

V20
Radiation induced heart disease

• Spectrum of clinical syndromes: pericardial disease, myocardial disease, valvular defects, coronary artery disease

• Clinical data come from population of radiotherapy patients - breast cancer, lymphoma, seminoma, lung cancer

• Studies from the 1960s demonstrated the radiosensitivity of the heart and of the vascular structure

• Not many dose-volume response relationships have been quantified
<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis, # patients, years of treatment</th>
<th>OAR</th>
<th>Fractionation schedule Dose data</th>
<th>Predictive parameters</th>
<th>NTCP parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Carmel and Kaplan 1976</td>
<td>Hodgkin’s 377 pts 1964-1972</td>
<td>Pericardium</td>
<td></td>
<td>(D_{\text{pericardium}} &gt; 30) Gy (50%) pericarditis, (36%) requiring treatment</td>
<td></td>
</tr>
<tr>
<td>Cosset et al 1991</td>
<td>Hodgkin’s 499 pts 1971-1984</td>
<td>Pericardium</td>
<td>35-43 Gy/2.5-3.3 Gy/fr pre-3D dose data</td>
<td>(D_{\text{mediastinum}} \geq 41) Gy d/ fraction (\geq 3) Gy (marginal significance)</td>
<td></td>
</tr>
<tr>
<td>Burman et al 1991</td>
<td>Historical data</td>
<td>Pericardium</td>
<td></td>
<td>LKB (TD50=48) Gy (m=0.10) (n=0.35)</td>
<td></td>
</tr>
<tr>
<td>Martel et al 1998</td>
<td>Esophagus 57 pts 1985-1991</td>
<td>Pericardium</td>
<td>37.5-49 Gy/1.5-3.5 Gy/fr 3D data</td>
<td>(D_{\text{mean}} \geq 27.1) Gy (D_{\text{max}} &gt; 47) Gy d/ fraction 3.5 Gy LKB (CI 95%) (TD50=50.6) Gy (-9; 23.1) (m=0.13) (-0.07; 0.13) (n=0.64) (-0.58; 3)</td>
<td></td>
</tr>
<tr>
<td>Wei et al 2008</td>
<td>Esophagus 101 pts 2000-2003</td>
<td>Pericardium</td>
<td>45-50.4 Gy/1.8-2.0 Gy/fr 3D data</td>
<td>(D_{\text{mean, pericardium}} &gt; 26.1) Gy (V_{30} &lt; 46%)</td>
<td></td>
</tr>
</tbody>
</table>
Pericarditis - acute effect

- 101 pts, esophagus ca, (2000-03), 27% crude incidence pericardium DVH better than heart DVH $V_{30} < 46\%, \text{ MD } < 26 \text{ Gy}$  
  (Wei X et al, IJROBP 2008)

- 377 Hodgkin’s pts (1964-72), $D_{\text{mean pericardium}} > 30 \text{ Gy}$ 
  50% pericarditis, 36% requiring treatment  
  (Carmel Kaplan 1976)

- 140 Hodgkin’s pts (1964-81) $D_{\text{mediastinum}} \geq 41 \text{ Gy}$  
  (Cosset 1991)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis. # patients, years of treatment</th>
<th>OAR</th>
<th>Dose data</th>
<th>Predictive parameters</th>
<th>NTCP parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hancock et al. 1993</td>
<td>Hodgkin’s 2232 pts 1960-1990</td>
<td>heart</td>
<td>dose up to 44 Gy pre-3D dose data</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D&lt;sub&gt;mediastinum&lt;/sub&gt; &gt; 30 Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gagliardi et al 1996</td>
<td>Breast 809 pts 1964-1976</td>
<td>heart*</td>
<td>45-50 Gy 1.8-2.5 Gy/fr treatments reconstructed in 3D on average patients</td>
<td></td>
<td>RS (CI 68%) D&lt;sub&gt;50&lt;/sub&gt;=52.3 Gy (49;57)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>γ=1.28 (1.04;1.64) s=1 (0.63;at limit)</td>
</tr>
<tr>
<td>Eriksson et al 2000***</td>
<td>Hodgkin’s 157 pts 1972-1985</td>
<td>heart</td>
<td>≈ 40 Gy 2 Gy/fr individual treatments reconstructed in 3D on phantom</td>
<td></td>
<td>RS: Hodgkin’s D&lt;sub&gt;50&lt;/sub&gt;=70.3 Gy γ=0.96 s=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RS: Hodgkin’s + breast D&lt;sub&gt;50&lt;/sub&gt;=63 Gy γ=0.94 s=1</td>
</tr>
<tr>
<td>Carr et al 2005</td>
<td>Peptic ulcer 1859 pts 1936-65</td>
<td>heart</td>
<td>1.5 Gy/fr 250-kVp X-rays treatment simulated on phantom</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D&lt;sub&gt;mean&lt;/sub&gt; to 5% &gt;12 Gy heart volume within the beam D&lt;sub&gt;mean&lt;/sub&gt; &gt;2.5 Gy whole heart volume</td>
<td></td>
</tr>
</tbody>
</table>
**Long-term cardiac mortality**

- **Breast cancer data (Oslo and Stockholm randomized trials)**
- **NTCP - RS model, 3D reconstruction of treatment techniques**
- **weak volume effect**
- **heart definition, comparison with myocardium DVH**

*Gagliardi et al, Br J Rad. 1996*

**Normal Tissue Complication Probability Modelling (NTCP)**

**The data behind the modelling:**
CLINICAL DATA (NTCP)

• Oslo breast cancer trial: 1968-72
• endpoint: death from myocardial infarction (FU > 11 ys)
• ant. field to the sternal nodes, $^{60}$Co; 50 Gy, 2.5 Gy/f

**excess cardiac mortality:** $7.9\% \pm 3.7\%$ (left); $3.3\% \pm 2.7\%$ (right)

• Stockholm breast cancer trial: 1971-76
• endpoint: death from ischemic heart disease (FU > 13 ys)
• tang. fields to the chest wall and IMC $^{60}$Co; 45 Gy, 1.8 Gy/f

**excess cardiac mortality:** $6.8\% \pm 3.5\%$ (left)
$0\%$ (right)

• oblique e-field:
$0\%$ (left)
Hodgkin’s data and breast data:

1) different parts of heart irradiated (almost complementary)

2) breast dose-response curve: steeper-safer (think of LDA location in tangential fields irradiation)


Cardiac mortality modeling problems:
• Clinical data: low number of events (registers are needed)
• Long-term complications
• Dosimetrical data (retrospective studies; lack of 3D information)

by courtesy of C.Taylor,Oxford
Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

- Population based case-control study of major coronary events (i.e. myocardial infarction, coronary revascularization, death from ischemic heart disease)
- 2168 breast cancer pts, RT (963 cases, 1205 controls) treated between 1958 and 2001
- Mean dose to the whole heart and to left descendent artery (from hospital charts)
• Mean dose to heart = 4.9 Gy (range: 0.03-27.72) left sided: 6.6 Gy, right sided: 2.9 Gy
• Rates of major coronary events increase linearly with mean dose to heart by 7.4% per Gray, no threshold (compared to the non irradiated population)
• Debut within the first 5 yrs after RT, continuing into the third decade after RT
• Women with pre-existing cardiac risk factors: greater absolute increase in risk, than other women

Major coronary events:

- Myocardial infarction
- Coronary revascularization
- Death from ischemic heart disease

compared to non irradiated women
not corrected for fractionation (but this does not change the picture)

Darby et al, 2013
Mortality ratios, by laterality of breast ca, were estimated for >500,000 women recorded with breast ca during 1973-2008 in the Surveillance, Epidemiology and End Results (SEER) cancer registries and followed until Jan 2009.
• For women diagnosed with breast cancer and treated with RT, the cardiac mortality ratios, left-sided vs right-sided

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;10years</th>
<th>10-14 yrs</th>
<th>15-19 yrs</th>
<th>20+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973-1982</td>
<td>1.19</td>
<td>1.35</td>
<td>1.64</td>
<td>1.90</td>
</tr>
<tr>
<td>1983-1992</td>
<td>0.99</td>
<td>1.02</td>
<td>1.11</td>
<td>1.21</td>
</tr>
<tr>
<td>1993-</td>
<td>0.97</td>
<td>0.9</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
• For women receiving RT after 1982, almost no evidence of any radiation related increase in heart disease mortality compared to earlier treatments

• Points to note - new treatment guidelines? too short follow-up? Quality of dose-volume data (no individual radiation dose available)

• Decline in the use of internal mammary nodes
  → Change of target and treatment techniques, not of dose prescriptions

Henson KE et al, BJC2013
• Left breast ca pts, with internal mammary chain mean heart dose: 13-17 Gy - ”earlier”

• Left breast ca pts, (decreased irradiation of IMC) mean heart dose: 2-7Gy  - ”currently”

**risks for women irradiated today are likely to be lower**


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**Example from the clinic:**

<table>
<thead>
<tr>
<th>Current treatments</th>
<th>Mean dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>stage I (50 pts)</td>
<td>2.8 Gy (0.0-8.2)</td>
</tr>
<tr>
<td>stageII (50 pts)</td>
<td>3.4 Gy (1.3, 6.4)</td>
</tr>
</tbody>
</table>
Quantitative Estimates of Normal Tissue Effects in Clinic

Summary of the knowledge

• Each constraint is associated with the incidence of a particular complication or toxicity.

• The choice of the constraint is a choice of the toxicity rate.

This choice is left to the responsibility of the user.
QUANTEC group was formed from a loose network of researchers with a longstanding interest in dose–volume modeling. The Steering Committee defined three aims for QUANTEC.

1. To provide a critical overview of the current state of knowledge on quantitative dose–response and dose–volume relationships for clinically relevant normal-tissue endpoints
2. To produce practical guidance allowing the clinician to reasonably (though not necessarily precisely) categorize toxicity risk based on dose–volume parameters or model results
3. To identify future research avenues that would help improve risk estimation or mitigation of early and late side effects of radiation therapy
Cardiovascular disease following radiation therapy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Radiation Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericarditis</td>
<td>Mean Dose &lt; 26 Gy V30&lt;46%</td>
</tr>
<tr>
<td>Long-term cardiac mortality</td>
<td>V25&lt;10%</td>
</tr>
</tbody>
</table>

QUANTEC summary of data, 2010
### Example from the clinic - Breast-stage I

<table>
<thead>
<tr>
<th></th>
<th>V25 (%)</th>
<th>NTCP (%)</th>
<th>Mean dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>2.9</td>
<td>0.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Std</td>
<td>1.9</td>
<td>0.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Min</td>
<td>0.0</td>
<td>0.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Max</td>
<td>8.2</td>
<td>0.9</td>
<td>6.6</td>
</tr>
</tbody>
</table>
Example from the clinic - Breast-stage II

<table>
<thead>
<tr>
<th></th>
<th>V25 (%)</th>
<th>NTCP (%)</th>
<th>Mean dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>3,2</td>
<td>0,3</td>
<td>3,4</td>
</tr>
<tr>
<td>SD</td>
<td>2,2</td>
<td>0,3</td>
<td>1,3</td>
</tr>
<tr>
<td>Min</td>
<td>0,0</td>
<td>0,0</td>
<td>1,3</td>
</tr>
<tr>
<td>Max</td>
<td>7,9</td>
<td>0,9</td>
<td>6,4</td>
</tr>
</tbody>
</table>
Cardiovascular disease following radiation therapy

Still open issues

• Quantification of dose-volume response for relevant substructures, e.g. left descendent artery/delineation
• More specific dose-volume predictors?
• How to identify women at risk?
• ….What to say and how to say it?
From Feng et al, 2011

Delineation of subvolumes within the heart
• Acknowledgments:
Jakob Öden, Medical Physics Department, Karolinska University Hospital, Stockholm