Radiation-Related Cardiac Effects
Rebecca Howell, PhD, DABR

Overview

• Background and Significance
• Challenges of studying radiation related cardiac effects
• Effects at High Doses
• Effects at Low Doses
  – Childhood Cancer Survivors
  – Breast Cancer survivors
• Clinical Relevance

Will include overview of dose reconstruction techniques used in these studies.

Significance
10 Million Cancer Survivors

• Number of cancer survivors in the U.S. has increased every year since 1971 and is now estimated to be 10 million+.

• This increase in cancer survivors due to improved treatments, more frequent screening, greater life expectancy, and in some cases, increased cancer incidence rates.

Radiation Related Late Effects

• Second Cancers
• Cardiovascular Toxicity
  • Most commonly reported late effect in Cancer Survivors
  • Cardiovascular events are the leading non-malignant cause of death among survivors of childhood cancers
  • Responsible for a 7-fold increase of risk of death compared with age matched peers.
• Cognitive impairments
• Sexual development
• Reproduction/fertility
• Endocrine abnormalities
• Growth/development delays
It is difficult to study radiation related cardiac effects. Why?

- Long latency
- Broad spectrum of cardiac diseases, including:
  - Coronary artery disease, congestive heart failure, myocardial infarction, pericardial disease, valvular dysfunction
- Each type of disease may be associated with damage to particular parts of the heart.
- Medical record validation of cardiac events is challenging:
  - Difficult to obtain and ensure accuracy of records for all events and deaths.

Evidence of Radiation Related Cardiac Effects at High Doses

- Until recently, there was a general belief that radiation related cardiac effects were only associated with high doses, i.e., >30 Gy.
  - Evidence in the literature was for patients treated for Hodgkin Lymphoma (Hancock, Tucker, and Hopp 1993).
  - Older treatment techniques, i.e., mantle field → heart in field.
  - Higher doses than current standard of care for HL.

Evidence of Radiation Related Cardiac Effects at Low Doses

- More recently, evidence is emerging that cardiac toxicity can occur at much lower doses.
  - A bomb survivors (Preston et al. 2003)
  - Childhood cancer survivors (Mulroony et al. 2009, Tukenova et al 2010)
  - Breast cancer survivors (Taylor et al. 2007, EBCTCG, 2005, Darby et al. 2010)
  - Patients treated for peptic ulcers (Carr et al. 2005)

Cardiac Outcomes

Childhood Cancer Survivors
Largest analysis to date of INCIDENCE of cardiovascular disease among adult survivors of childhood/adolescent cancers.
- Design: Retrospective cohort study
- Setting: 26 Institutions that participated in CCSS
- Participants: 14,358 5-year survivors of 8 different types of cancer treated between 1970 and 1986.
- Comparison group: 3899 siblings of cancer survivors.
- Dose Reconstruction - Mean radiation dose to the heart was estimated on the basis of detailed dosimetry calculations by Stovall (Methodology described in Stovall et al., 2006).

Major Finding: Radiation significantly increased risk for (compared with a sibling control group):
1. congestive heart failure,
2. myocardial infarction,
3. pericardial disease,
4. valvular dysfunction

Increased risk was significantly associated with specific therapeutic exposures to
- Anthracyclines or
- cardiac radiation dose of more than 15 Gy.

An important finding of this study was that it provided some insight into the dose-response relationship for cardiac outcomes.

For all 4 outcomes incidence was found to increase with increasing dose.

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>Dose (Gy)</th>
<th>0</th>
<th>&lt;5</th>
<th>5</th>
<th>15</th>
<th>&gt;35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1.0</td>
<td>0.8</td>
<td>1.3</td>
<td>2.2</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Valvular Abnormalities</td>
<td>1.0</td>
<td>0.6</td>
<td>1.4</td>
<td>3.3</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1.0</td>
<td>0.7</td>
<td>0.6</td>
<td>2.4</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Pericardial Disease</td>
<td>1.0</td>
<td>0.7</td>
<td>1.9</td>
<td>2.2</td>
<td>4.8</td>
<td></td>
</tr>
</tbody>
</table>
Incidence of Cardiovascular Disease
Mulrooney et al. BMJ 2009

- Congestive Heart Failure
- Myocardial Infarction
- Pericardial Disease
- Valvular Disease

This finding suggests that the long-term impact of on the health of cancer survivors will be substantial.

Study Strengths and Limitations
Mulrooney et al. BMJ 2009

Limitation
- Self-report outcomes, i.e., cardiac complications were evaluated by having survivors fill out a questionnaire.

Strength
- Dose Reconstruction.

Dose Reconstruction – Cardiac Dose
Mulrooney et al. BMJ 2009

Patient Data
- Abstract radiotherapy records for individual patients.

Dose Reconstruction
- Analytical dose model + mathematical phantoms used to reconstruct the heart dose

Dose Reconstruction
- Cardiac Dose

- Therapeutic dose and treatment field details were obtained from Rx records, but individual organ doses were not available, patients were treated in pre-CT era.

Analytical Model of Out-of-Field Dose

- Photon dose inside and outside the treatment beam was measured in large water phantom.
  - Various beam energies and field sizes.

Data were fit to analytical models to derive doses at specified distances from the field.

Figure from: Stovall et al. Radiat Res 166:141-157, 2006
Total Absorbed Dose from Treatment Beams
6 MV Photon - 10x10 cm² Field Size - Various Energies

Distance (cm) from Field Edge

<table>
<thead>
<tr>
<th>Energy</th>
<th>Dose at D_max on Central Axis (cGy/1000 cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 MV</td>
<td></td>
</tr>
<tr>
<td>6 MV</td>
<td></td>
</tr>
<tr>
<td>10 MV</td>
<td></td>
</tr>
<tr>
<td>18 MV</td>
<td></td>
</tr>
<tr>
<td>25 MV</td>
<td></td>
</tr>
<tr>
<td>Co-60</td>
<td></td>
</tr>
</tbody>
</table>

Mathematical Phantom

- Organs represented by a grid of points.
  - Grid can moved.
  - Grid resolution can be 0 or 0.
- Field can be placed in any position.
- Field geometry can be varied

Mathematical Phantom(s) Advantages

- Phantom size can be modified to represent patient of any age.
- Models representing 7 age groups are shown in figure.
- Mathematical phantoms are also inexpensive to use.

Cardiac and Cardiovascular Mortality
Tukenova et al. JCO 2010

- Analysis of Mortality from cardiovascular disease among adult survivors of childhood/adolescent cancers.
  - Design: Retrospective cohort study
  - Setting: French-British cohort
  - Participants: 4,122 5-year survivors of childhood cancer (excluding leukemia) treated between 1942 and 1986.
  - Comparison group: Compared cardiac mortality in cohort with that of general populations of France and United Kingdom.
  - Dose Reconstruction: Mean radiation dose to the heart was estimated on the basis of detailed dosimetry calculations by using Dos_EG software, Gustave-Roussy Institute (Diallo et al 1996)
Cardiac and Cardiovascular Mortality
Tukenova et al. JCO 2010

- Individuals in this cohort were 5x more likely to die as a result of cardiovascular disease (compared to the general populations of France and Great Britain).
- Cumulative death rate increased with time since diagnosis.

- The adjusted RR of death as a result of cardiac disease was significantly higher among patients treated with radiotherapy (RR 7.4%; 95% CI 1.0 to 56.5).

- RR increased with increasing average radiation dose received by the heart and with cumulative exposure to anthracyclines.

Cardiac and Cardiovascular Mortality
Tukenova et al. JCO 2010

- RR increased with increasing heart dose
  
  - A linear fit dose response model, with ERR = 60% (95% CI, 20% to 250%)

Study Strengths and Limitations
Tukenova et al. JCO 2010

**Strength**
- Cause of death determined from death certificate.
  - more definitive than self-reported incidence (information).
- Dose Reconstruction.

**Limitation**
- Cause of death determined from death certificates.
  - only considered principal cause of death as result of cardiovascular disease probably underreported.
- No information regarding tobacco consumption, weight, or genetic factors → can introduce bias.
Cardiac Outcomes
Breast Cancer Survivors

Radiation Associated Cardiac Events (RACE)

Radiation Associated Cardiac Events (RACE)
- An Initiative in Denmark and Sweden to evaluate the risk of developing cardiovascular disorders in women who were treated for breast cancer.
- Project is dedicating substantial effort in establishing accurate heart doses
- http://www.race.ki.se/

Incidence of Cardiovascular Disease
Darby et al. 2010

- Analysis of INCIDENCE of cardiovascular disease among breast cancer survivors in Sweden and Denmark.
  - **Design:** Retrospective cohort study
  - **Setting:** used the population-based disease registries in Denmark and Sweden
  - **Participants:** 1118 breast RT patients with of heart disease (cases)
  - **Comparison group:** 1436 breast RT patients, matched for age to the cases, but who had not yet developed heart disease.
  - **Dose Reconstruction:** Mean cardiac doses were estimated using dose-volume histograms (Methodology described in Taylor et al., 2007)
For both cases and controls, radiotherapy treatment charts were obtained and categorized according to regimen and laterality.

Each regimen was reconstructed using a 3D treatment planning + contouring of the heart and three main coronary arteries.

Commonly used RT techniques were reconstructed for CT data set for representative patient.

Reconstructions based on RT details from >60 trials of early breast cancer.

Risk of heart disease was 27% higher in left-sided than in right-sided breast cancer (95% CI, 7-50%).

Risk of heart disease increased with dose (linear response)

On average, there was a 4% increase in heart disease risk per 1 Gy increase in mean heart dose (95% CI, 2-6%).

These data are very interesting. When the full manuscript is published, it will fill an important gap in our present knowledge regarding the details of the dose response relationship for breast cancer patients.
Study Strengths and Limitations
Darby et al. IJORB P 2010

• Strength: Heart disease was defined using hospital discharge codes.
  – Scandinavian countries have detailed medical records that follow individuals for entire lifespan.
  – More definitive than self-reported incidence information.

• Strength: Dose reconstruction was completed for both cases and for controls.
  – Limitations: commercial TPSs underestimate low doses.

Summary
Cardiac Outcome Studies

Summary and Applications to Clinical Practice

• There remains uncertainty in the exact details of the dose response models for radiation related cardiac effects,
  – but as discussed today, there is increasing evidence that points toward a linear dose response model.

• While more research is needed in this area, efforts should be made to keep the cardiac dose as low as possible for individual patients.

How can we incorporate information on cardiac effects in clinical practice?

Pediatric CSI Example
Reducing Cardiac Dose in Clinical Practice

• Two different 6MV FIF CSI treatment plans, appear identical in sagittal view.

However……

Reducing Cardiac Dose in Clinical Practice

• Proton CSI treatment plan, very low exit dose.

- Low heart dose.

However……
How can we incorporate information on cardiac effects in clinical practice?

**Breast Cancer Example**

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**Reducing Cardiac Dose in Clinical Practice**

Add sagittal images from breast treatment plan comparison of breath hold versus free breathing.

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**Concluding Remarks… Important Questions Remain**

- **What are the effects of non-uniform irradiation?**
  - Such effects are particularly important in the era on contemporary radiotherapy where IMRT is often the standard of care.

- **What are the effects associated with dose to various parts of heart?**
  - Evidence exists that certain parts of the heart are more radiosensitive than others. (Adams *et al.*, 2003; Stewart *et al.*, 1995, but more research is needed.)
Question Set for Radiation-Related Cardiac Effects

Radiation Related Late Effects

- Second Cancers
- Cardiovascular Toxicity
  - Cognitive impairments
  - Sexual development
  - Reproduction/fertility
  - Endocrine abnormalities
  - Growth/development delays

It is difficult to study radiation related cardiac events for all of the following except:

1. Long latency
2. Broad spectrum of cardiac diseases.
3. Medical record validation is challenging.
4. Cardiac events are rare in cancer survivors.
5. Each type of disease may be associated with damage to particular parts of the heart.

Cardiovascular events are the leading non-malignant cause of death among survivors of childhood cancers.

- 1. Cardiovascular events.
- 2. Reproduction/fertility events.
- 3. Endocrine abnormalities.
- 5. Skin cancers.

- Most commonly reported late effect in Cancer Survivors
- Cardiovascular events are the leading non-malignant cause of death among survivors of childhood cancers
- Responsible for a 7-fold increase of risk of death compared with age matched peers.
It is difficult to study radiation related cardiac effects. Why?

- Long latency
- Broad spectrum of cardiac diseases, including:
  - Coronary artery disease, congestive heart failure, myocardial infarction, pericardial disease, valvular dysfunction
- Each type of disease may be associated with damage to particular parts of the heart.
- Medical record validation of cardiac events is challenging:
  - Difficult to obtain and ensure accuracy of records for all events and deaths.

Analytic calculation methods for dose reconstruction (in epidemiological studies) using generic phantoms typically include organ doses from:

0% 1. Leakage/Scatter photon radiation.
0% 2. Primary (in-field) radiation.
0% 3. Scatter photon radiation
0% 4. Neutron contamination.
0% 5. All of these are included.

Analytical Model of Out-of-Field Dose

- Photon dose outside the treatment beam was measured in large water phantom.
  - Various beam energies and field sizes.

Out-of-field data includes leakage and scatter, but for high energy does not include stray neutrons

Data were fit to analytical models to derive doses at specified distances from the field.

In the studies of incidence and mortality of radiation related cardiac events in survivors of childhood cancer, cardiac events were found to:

0% 1. Increase with doses > 30 Gy.
0% 2. Increase with increasing dose.
0% 3. Follow a linear plateau dose response model.
0% 4. No pattern was observed.
0% 5. Increase only if chemotherapy was also part of the patient’s therapy.
Incidence of Cardiovascular Disease
Mulrooney et al. BMJ 2009

- Major Finding: Radiation significantly increased risk for (compared with a sibling control group):
  1. congestive heart failure,
  2. myocardial infarction,
  3. pericardial disease,
  4. valvular dysfunction

- Increased risk was significantly associated with specific therapeutic exposures to
  - Anthracyclines or
  - cardiac radiation dose of more than 15 Gy.

Cardiac and Cardiovascular Mortality
Tukenova et al. JCO 2010

- The adjusted RR of death as a result of cardiac disease was significantly higher among patients treated with radiotherapy (RR 7.4%; 95% CI 1.0 to 56.5).

- RR increased with increasing average radiation dose received by the heart and with cumulative exposure to anthracyclines.

The mortality ratio from heart disease in patients who received radiotherapy for left verses right breast was approximately ___ at 15 years after treatment.

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<thead>
<tr>
<th></th>
<th>No radiotherapy</th>
<th>Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart disease death</td>
<td>left versus right &amp; 95% CI</td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>2164/14572</td>
<td>1.02 (0.97-1.09)</td>
</tr>
<tr>
<td>5 - 9</td>
<td>1633/14779</td>
<td>1.05 (0.98-1.13)</td>
</tr>
<tr>
<td>10 - 14</td>
<td>806/759</td>
<td>1.01 (0.91-1.11)</td>
</tr>
<tr>
<td>15+</td>
<td>585/524</td>
<td>1.02 (0.91-1.15)</td>
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Cardiac Mortality Left vs Right Breast RT
Darby et al. IJROBP 2010

- Compared mortality ratio from heart disease in 300,000 women from SEER cancer registry that received radiation for left and right breast cancers.

<table>
<thead>
<tr>
<th>Years since breast cancer diagnosis</th>
<th>No radiotherapy</th>
<th>Radiotherapy</th>
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</tr>
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</table>

All other known causes

The incidence of cardiac events in patients who received radiation therapy for breast cancer was found to

- 0% 1. To have a linear dose response, 4%/Gy
- 0% 2. To have a linear dose response, 14%/Gy
- 0% 3. Increase with dose above 30 Gy.
- 0% 4. No pattern was observed
- 0% 5. Dosimetry data was insufficient to establish a dose response model

Incidence of Cardiovascular Disease
Darby et al. 2010

- Risk of heart disease was 27% higher in left-sided than in right-sided breast cancer (95% CI, 7-50%).
- Risk of heart disease increased with dose (linear response)
- On average, there was a 4% increase in heart disease risk per 1 Gy increase in mean heart dose (95% CI, 2-6%).

These data are very interesting. When the full manuscript is published, it will fill an important gap in our present knowledge regarding the details of the dose response relationship for breast cancer patients.

References (1)


References (2)

Thank you.

Questions?

References (1)


References (2)


Reformat references to consistent format.