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
• Test Questions

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 is 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
  - Cognitive impairments
  - Sexual development
  - Reproduction/fertility
  - Endocrine abnormalities
  - Growth/development delays

Cardiovascular events are the leading non-malignant cause of death among survivors of childhood cancers.
- Responsible for a 7-fold increase in risk of death compared with age matched peers.

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

It 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 part 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 (Mulrooney et al. 2009, Tukenova et al 2010)
  – Patients treated for peptic ulcers (Carr et al. 2005)

Cardiac Outcomes
Childhood Cancer Survivors

Incidence of Cardiovascular Disease
Mulrooney et al. BMJ 2009

• 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
  – 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.
The incidence of each cardiovascular outcome increased with time from diagnosis.

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

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

Study Strengths and Limitations

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

**Strength**
- Dose Reconstruction.

Dose Reconstruction – Cardiac Dose

**Patient Data**
- Abstract radiotherapy records for individual patients.

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.

**Dose Reconstruction**
- Analytical dose model + mathematical phantoms used to reconstruct the heart dose
Analytical Model of Out-of-Field Dose
Stovall et al. Radiat Res, 2006

• Dose 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.

Mathematical Phantom
Stovall et al. Radiat Res, 2006

• Organs represented by a grid of points.
  – Grid can be moved.
  – Grid resolution can be 5 or 0.

• Field can be placed in any position.
• Field geometry can be varied.

Mathematical Phantom(s)
Stovall et al. Radiat Res, 2006

• 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)

- 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 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.

Study Strengths and Limitations
Tukenova et al. JCO 2010

Strengths
• Cause of death determined from death certificate. – more definitive than self-reported incidence information.
• Dose Reconstruction.

Limitations
• 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
Cardiac Mortality Left vs Right Breast RT
Darby et al. Lancet Oncology 2005

- 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 after breast cancer diagnosis</th>
<th>No radiotherapy</th>
<th>Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of deaths</td>
<td>Mortality ratio</td>
</tr>
<tr>
<td>Left breast cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5 years</td>
<td>24641875</td>
<td>1.03 (0.97-1.09)</td>
</tr>
<tr>
<td>5-9</td>
<td>10321747</td>
<td>1.02 (0.96-1.08)</td>
</tr>
<tr>
<td>10-14</td>
<td>809768</td>
<td>1.07 (0.91-1.14)</td>
</tr>
<tr>
<td>15+</td>
<td>566505</td>
<td>1.02 (0.96-1.08)</td>
</tr>
</tbody>
</table>

All other known causes
- 1 years                           | 147750522     | 1.04 (0.94-1.05) | 6914018      | 1.01 (0.96-1.05) |
- 5-9                               | 8300792       | 0.97 (0.85-1.09) | 5712380      | 1.01 (0.96-1.02) |
- 10-14                             | 3072034       | 0.90 (0.82-1.00) | 1195366      | 1.01 (0.93-1.08) |
- 15+                               | 2100584       | 0.98 (0.89-1.06) | 617150       | 1.04 (0.93-1.17) |

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/](http://www.race.ki.se/)

Incidence of Cardiovascular Disease
McGale et al. Radiother Oncol 2011

- 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, included 34,828 patients that had received RT
  - Study design: Radiation-related risk was evaluated by comparing patients treated with left verses right sided breast cancer.
  - Dose Reconstruction: Mean cardiac doses were estimated using dose-volume histograms (Methodology described in Taylor et al., 2007 and 2011).
Radiotherapy treatment charts were obtained and categorized according to regimen:
- laterality, target dose(s), dose/fx, and ± supraclav or axillary RT.

Dose Reconstruction – Cardiac Dose

- 22 different RT regimens (11 left & 11 right) were reconstructed on a CT scan of typical patient of average build.
- Heart and Coronary arteries were contoured
- DVH were used to determine mean heart dose for each regimen.
Dose Reconstruction – Cardiac Dose

McGale et al. Radiother Oncol 2011 (Taylor et al 2011)

- Low doses dominated by RIGHT breast patients
- High Doses dominated by LEFT Breast Patients

Results
- Left and right sided breast tumors: mean heart dose = 6.3 Gy and 2.7 Gy, respectively
- Incidence ratios for cardiac effects were higher in patients treated left verses right:
  - Myocardial infarction: 1.22
  - Angina: 1.25
  - Pericarditis: 1.61
  - Valvular heart disease: 1.54

Incidence of Cardiovascular Disease

McGale et al. . Radiother Oncol 2011

Study Strengths and Limitations

McGale et al. . Radiother Oncol 2011

- 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: Unbiased compared to studies that use unirradiated patients as control group.
  - Such studies often underestimate cardiac effects as patients with left sided disease are frequently selected for therapy without radiation due to concerns regarding cardiac effects.
**Study Strengths and Limitations**  
*McGale et al. . Radiother Oncol 2011*

- **Strength:** Dose reconstruction was completed using real patient anatomy for 22 different treatment regimes and TPS.

- **Limitations:**
  - All data are for a single “typical” patient, study does not take anatomical variations between patients into account.
  - All MV photon plans were for 6 MV (actual was 6-25 MV).
  - All electron plans were calculated for 10 MeV (actual 6-18 MeV).
  - Commercial TPSs underestimate stray photon doses.
  - Stray dose from neutrons not considered.

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**Incidence of Cardiovascular Disease**  
*McGale et al. . Radiother Oncol 2011*

- The work by McGale et al. did not report dose response model…
- However such data will likely be published in future manuscript…
- Until then, we have glimpse of results from 2010 ASTRO presentation by Darby et al.
  - In case control study of patients that received breast radiation therapy, compared:
    - those who developed heart disease
    - those who had not developed heart disease

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**Incidence of Cardiovascular Disease**  
*Darby et al. IJORBP 2010*

- Risk of heart disease increased linearly with dose.

- 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.*
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 to 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.

Isodose (%)

110
105
100
90
80
70
60
50
40
30

photon without mlc blocking, mean = 59.7%
photon with mlc blocking added, mean = 51.8%

mean heart dose ~ 8%

Percent Heart Volume (%) vs Percent Dose (%)
How can we incorporate information on cardiac effects into clinical practice?

Breast Cancer Example

Free Breath verses Breath Hold
**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.
References (1)


References (2)


Question Set for Radiation-Related Cardiac Effects
are the leading non-malignant cause of death among survivors of childhood cancers

Correct answer: 1

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

Correct answer: 4
It is difficult to study radiation related cardiac events for all of the following reasons 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.

Correct answer: 4

Analytic calculation methods for dose reconstruction (in epidemiological studies) using generic phantoms typically include all of the following EXCEPT:

1. Leakage photon radiation.
2. Primary (in-field) photon radiation.
3. Patient (photon) scatter radiation.
5. Collimator scatter radiation.

Correct answer: 4
In the studies of incidence and mortality of radiation related cardiac events in survivors of childhood cancer, cardiac events were found to:

1. Increase with doses > 30 Gy.  
2. Increase with increasing dose.  
3. Follow a linear plateau dose response model. 
4. No pattern was observed. 
5. Increase only if chemotherapy was also part of the patient’s therapy.

Correct answer: 2


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

1. 1.0  
2. 0.5  
3. 3.5  
4. 2  
5. 1.5

Correct answer: 5

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

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

Correct answer: 1
Thank you.

Questions?