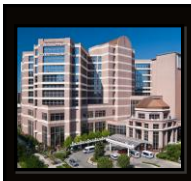

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Evidence of Radiation Related Cardiac Effects

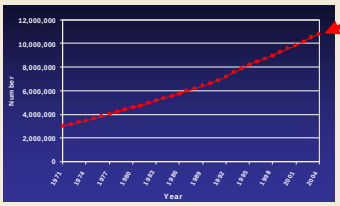
Rebecca Howell, PhD, DABR

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



10 million+

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

Source: Ries et al. (eds). SEER Cancer Statistics Review, 1975-2004, NCI. Bethesda, MD.http://seer.cancer.gov/1975_2004/, based on November 2006 SEER data submission, posted to the SEER website, 2007.

- **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 → Most commonly reported late effect in Cancer Survivors.
- Cardiovascular Toxicity → 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.
- Cognitive impairments
- Sexual development
- Reproduction/fertility
- Endocrine abnormalities
- Growth/development delays

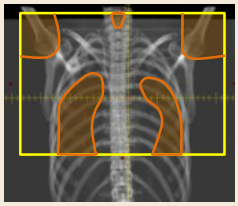
It difficult to study radiation related cardiac effects.

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 (*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

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
  - **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).

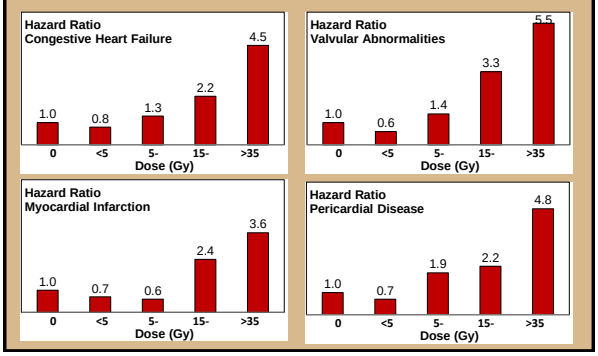
Incidence of Cardiovascular Disease
Mulrooney *et al*. BMJ 2009

- **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.**

Incidence of Cardiovascular Disease
Mulrooney *et al.* BMJ 2009

- 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.

Incidence of Cardiovascular Disease
Mulrooney *et al.* BMJ 2009



Incidence of Cardiovascular Disease

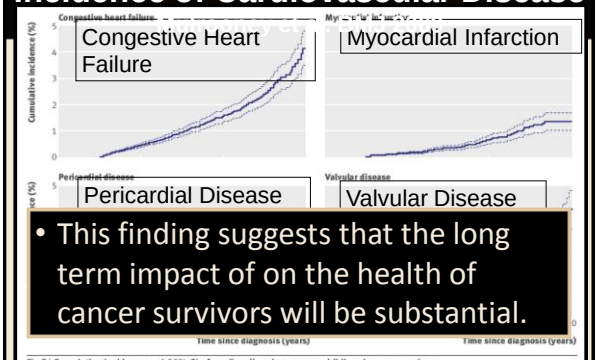


Fig 2 | Cumulative incidence and 95% CI of cardiac disorders among childhood cancer survivors

- 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 reported 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.

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.**

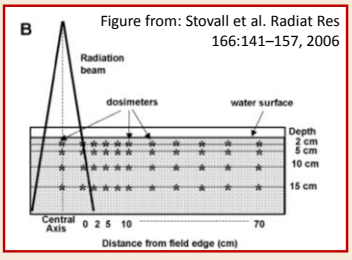
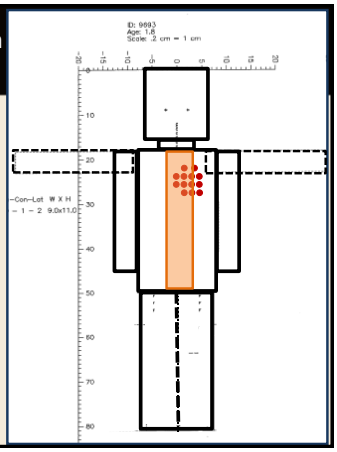


Figure from: Stovall et al. Radiat Res 166:141–157, 2006

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

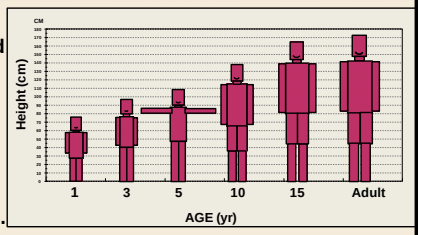
Mathematical Phantom
Stovall et al. Radiat Res, 2006

- **Organs represented by a grid of points.**
  - **Grid can moved.**
  - **Grid resolution can be ⇧ or ⇩.**
- 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.

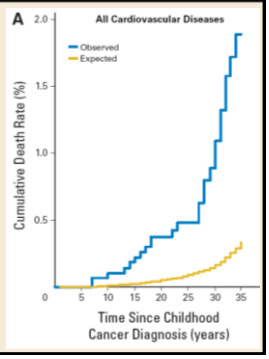
Figure from: Stovall et al. Radiat Res 166:141–157, 2006

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 Britian).
- Cumulative death rate increased with time since diagnosis.



Cardiac and Cardiovascular Mortality
Tukenova et al. JCO 2010

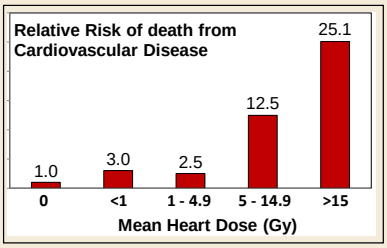
- The adjusted RR of death as a result of cardiac disease was significantly higher among patients treated with radiotherapy (RR 7.4%; 95% CI 1.0 to 56.5).

and

- **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

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 → 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.**

Years since breast cancer diagnosis	No radiotherapy: No. of deaths left/right	No radiotherapy: Mortality ratio left versus right & 95% CI	Radiotherapy: No. of deaths left/right	Radiotherapy: Mortality ratio left versus right & 95% CI
Heart disease death				
< 5 years	2164/1972	1.03 (0.97-1.09)	700/633	1.04 (0.93-1.15)
5 - 9	1632/1479	1.05 (0.98-1.13)	521/442	1.10 (0.97-1.25)
10 - 14	806/758	1.01 (0.91-1.11)	281/197	1.37 (1.14-1.64)
15+	568/524	1.02 (0.91-1.15)	254/162	1.53 (1.25-1.86)
All other known causes				
< 5 years	14775/13522	1.04 (1.01-1.06)	6911/6516	1.01 (0.98-1.05)
5 - 9	8009/7863	0.97 (0.94-1.00)	3178/2990	1.01 (0.96-1.06)
10- 14	3472/3343	0.99 (0.94-1.04)	1165/1095	1.01 (0.93-1.10)
15+	2106/2040	0.98 (0.92-1.04)	611/560	1.04 (0.93-1.17)

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

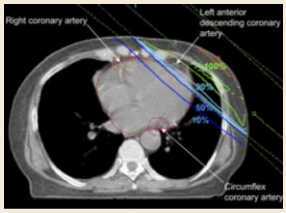
- Analysis of **INCIDENCE** of cardiovascular disease among breast cancer survivors in Sweden and Denmark.
  - **Design:** Retrospective cohort study
  - **Setting:** used the population-based disease registries in Denmark and Sweden
  - **Participants:** 1118 breast RT patients with of heart disease (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**).

Dose Reconstruction – Cardiac Dose
Darby *et al.* IJORBP 2010

- 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.

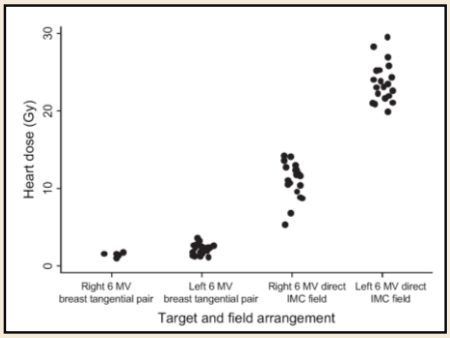
Cardiac Dose for Different Treatment Techniques
Taylor *et al.* IJORBP 2007

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



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

Cardiac Dose for Different Treatment Techniques
Taylor *et al.* IJORBP 2007



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.

Study Strengths and Limitations
Darby *et al*. IJORBP 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.
  - Limitation: commercial TPSs underestimate dow doses.

Summary

Cardiac Outcome Studies

Summary and Applications to Clinical Practice

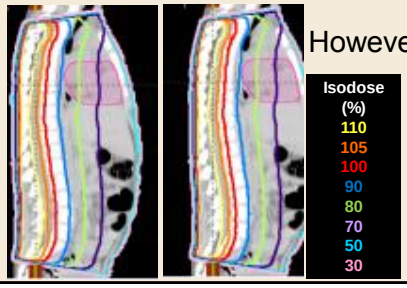
- There remains uncertainty in the exact details of the dose response models for radiation related cardiac effects,
  - but as discussed today, there is increasing evidence that points toward a linear dose response model.
- While more research is needed in this area, efforts should be made to keep the cardiac dose as low as possible for individual patients.

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

Pediatric CSI Example

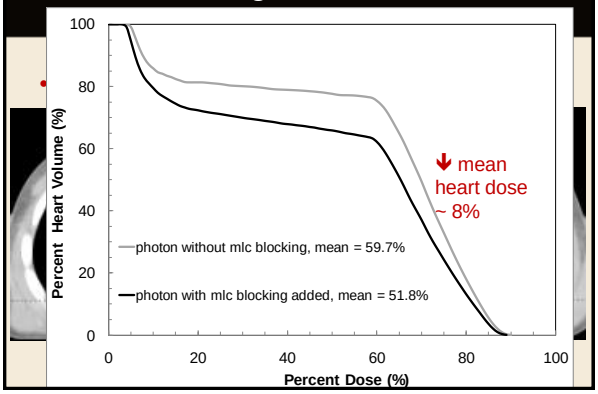
Reducing Cardiac Dose in Clinical Practice

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

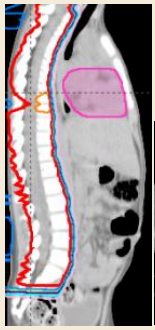


However, …

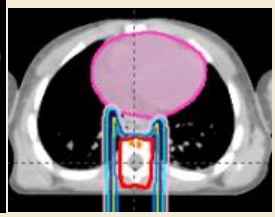
Reducing Cardiac Dose

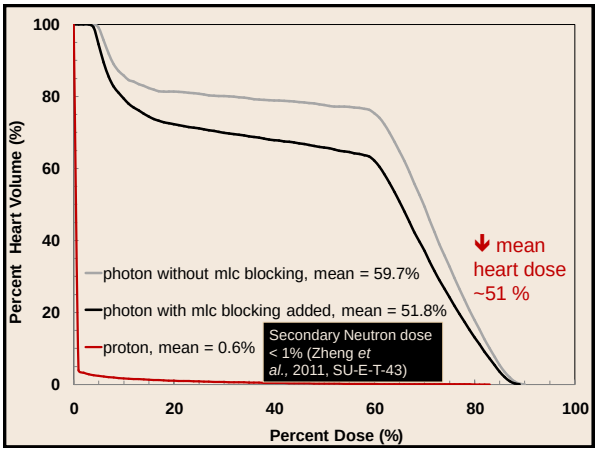


Reducing Cardiac Dose in Clinical Practice



- Proton CSI treatment plan, very low exit dose.
- **Low heart dose.**





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.

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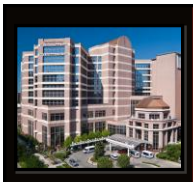

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Thank you.

Questions?