The Spectrum of Late Effects of Radiation Fibrosis
Moving from Risk to Risk Reduction
1st Annual Cancer Rehabilitation Symposium
May 31, 2013

Kevin C. Oeffinger, MD
Director, Adult Long-Term Follow-Up Program
Member, Departments of Medicine and Pediatrics

Outline

• Moving from risk to risk reduction
• Two models for research and clinical care of post radiation sequelae
  – Breast cancer (younger age at exposure)
  – Coronary artery disease (any age at exposure)
• Future directions
  ❖ Remember: radiation is critically important in curing the primary cancer

Cumulative incidence of chronic physical health conditions among 10,397 young adult survivors of childhood cancer
Childhood Cancer Survivor Study

73.4% with at least one chronic condition
42.4% with a severe or life-threatening condition or death

Cumulative incidence of chronic physical health conditions among 10,397 young adult survivors of childhood cancer
Childhood Cancer Survivor Study


Morbidity following Adult Cancer

- To date, some studies looking at specific outcomes (SMN, cardiac) in specific cancer populations (Hodgkin lymphoma, testicular cancer)
- No overall estimates of morbidity
- U-shaped curve by age?
  - Younger age: developing organs
  - Mid-age: interaction of therapy with comorbid health conditions
  - Older age: senescent organs

Breast Cancer After Treatment of Hodgkin’s Disease
Steven L. Hancock, Margaret A. Tucker, Richard T. Hoppe
Journal of the National Cancer Institute, Vol. 85, No. 1, January 6, 1993
Mantle Field

Hodgkin’s lymphoma
2500 – 4500 cGy

Involved Field, Mediastinum

• Hodgkin’s lymphoma
• Non-Hodgkin
• Neuroblastoma
1500 – 3500 cGy

Cumulative incidence of breast cancer among women treated for a childhood cancer with chest radiation and BRCA mutation carriers

Childhood Cancer Survivor Study and WECARE Study

Moskowitz CS, unpublished, 2013
Breast cancer risk decreases with concurrent radiation to the ovary
Childhood Cancer Survivor Study

Younger age at radiation exposure is associated with increased risk of breast cancer

32,591 HL patients in 16 population-based registries

<table>
<thead>
<tr>
<th>Age at HL</th>
<th>RR</th>
<th>AER</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 21 yrs</td>
<td>14.2</td>
<td>18.6</td>
</tr>
<tr>
<td>21-30</td>
<td>3.7</td>
<td>12.9</td>
</tr>
<tr>
<td>31-40</td>
<td>1.2</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Characteristics of Breast Tumors

- Median age is young
- Interval from radiation to breast cancer is often short (10-20 yrs)
- Upper outer quadrant (inner quadrant)
- Updated CCSS data
  - 26% bilateral: 12% synchronous, 14% asynchronous
  - 55% w/ bilateral mastectomy at time of 1st diagnosis

Outcomes of Breast Cancer

- 5-yr survival strongly associated with stage at diagnosis (women with early stage disease have good outcomes)
- Limitations in therapy
  - Further radiation?
  - Anthracyclines (doxorubicin)

1. Incidence and excess risk of breast cancer following chest radiation
2. Clinical characteristics and the outcomes following breast cancer
3. Harms and benefits associated with breast cancer surveillance
Annual mammogram and breast MRI
Starting at the age of 25 or 8 yrs after the RT

Long-Term Follow-Up Guidelines
for Survivors of Childhood, Adolescent,
and Young Adult Cancers
Version 3.0 – October 2008

International Harmonization of Guidelines
Proportion of women with at least ONE screening mammogram within the preceding TWO years
Childhood Cancer Survivor Study

Proportion of women with at least TWO screening mammogram within the preceding FOUR years
Childhood Cancer Survivor Study

R01 CA134722
Research Team
Kevin Oeffinger
Greg Armstrong
Aaron McDonald
Jennifer Ford
Chaya Moskowitz
Al Marcus
Elena Elkin
Melissa Hudson
Tara Henderson
Lisa Diller

Co-Investigators
St. Jude / CCSS
University of Colorado
Dana-Farber
U Chicago
Predicting Risk
Chaya Moskowitz, PhD

Breast Cancer Risk Prediction Model

Gene-Radiation Interaction

Identified two variants at chromosome 6q21 associated with radiation-induced SMN in Hodgkin's lymphoma survivors

Identified a genetic profile for breast cancer following Hodgkin’s Lymphoma
Hodgson DC, et al. Semin Radiat Oncol 2007

24 Gy Irradiation to 11 year-old with Hodgkin lymphoma

Mantle/Mediastinal RT

- 20 yrs post moderate dose RT (37.2 Gy), actuarial risk of symptomatic CAD = 21.2%
- By 30 yrs, incidence of MI = 12.9%
- Standardized Mortality Ratio with MI = 3.2
Cumulative incidence of CVD in 1474 survivors of Hodgkin lymphoma diagnosed prior to age 41 (1965-1995)*

*Death from any cause as competing risk


Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

The risk assessment tool below uses recent data from the Framingham Heart Study to estimate 10-year risk for "hard" coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes. Use the calculator below to estimate 10-year risk.

Age:
Gender:
Total Cholesterol:
HDL Cholesterol:
Smoker:
Systolic Blood Pressure:
Currently on any medication to treat high blood pressure:

Calculate 10-Year Risk

Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

The risk assessment tool below uses recent data from the Framingham Heart Study to estimate 10-year risk for "hard" coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes. Use the calculator below to estimate 10-year risk.

Age:
Gender:
Total Cholesterol:
HDL Cholesterol:
Smoker:
Systolic Blood Pressure:
Currently on any medication to treat high blood pressure:

Calculate 10-Year Risk

40-year-old female Hodgkin lymphoma survivor
20 yrs from treatment with 30 Gy mediastinal RT + non-anthracycline chemotherapy

© 2013 Memorial Sloan-Kettering Cancer Center, All Rights Reserved.
40-year-old female Hodgkin lymphoma survivor
20 yrs from treatment with 30 Gy mediastinal RT
+ non-anthracycline chemotherapy

**Risk score results:**

- **Age:** 40
- **Gender:** female
- **Total Cholesterol:** 222 mg/dL
- **HDL Cholesterol:** 38 mg/dL
- **Systolic:** 130
- **Diastolic:** 80

**Risk Score**

- **Low Risk:** 1% 10-year risk

- **OR=28.2**

**Interaction between Chest RT and CVD Risk Factors**

**Childhood Cancer Survivor Study**

Risk of Coronary Artery Disease

CAD post Chest Radiation

- Risk is modified by traditional risk factors
  - Tobacco avoidance/cessation
  - Evaluation for HTN and insulin resistance
  - Aggressive management of dyslipidemia with LDL target < 100
  - ASA 81 mg/day
  - Physical activity, low fat diet
- Detection of pre-obstructive disease?

Screening for CAD in HL survivors

- Stress echo or radionucleotide perfusion
  - 294 asymptomatic HL survivors
  - 21% with abnormal testing
  - False negative rates:
    - 61% - stress echo
    - 35% - nuclear scintigraphy
    - 62% - stress EKG
  - CT coronary angiogram
    - Role? Radiation exposure?

Novel Tools to Screen for CAD in HL survivors

- Calcium score (CAC)
  - Risk stratify?
- CMR tissue characterization to detect regional cardiac injury

Many questions remain: who to screen with what test initiating at what age and how frequently

Future Directions

• Risk estimates are established; being refined as population ages
• High risk groups (partially) identified
• Early work showing genetic predictors and potential pathways in small studies
• No studies with ample power to investigate the interaction of treatment, genetic factors, lifestyle behaviors, and comorbid conditions
• Era of large collaborations

Future Directions (2)

• Study of harms / benefits of surveillance with limitations of small samples
• Development of risk prediction models
• Use of models in assessing / determining surveillance strategies
• Testing of patient or clinician education aids and knowledge translation/transfer incorporating risk prediction

Acknowledgements

<table>
<thead>
<tr>
<th>MSKCC</th>
<th>CCSS Investigators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaya Moskowitz, PhD</td>
<td>Greg Armstrong, MD</td>
</tr>
<tr>
<td>Jennifer Ford, PhD</td>
<td>Lisa Diller, MD</td>
</tr>
<tr>
<td>Richard Steingart, MD</td>
<td>Melissa Hudson, MD</td>
</tr>
<tr>
<td>Jennifer Liu, MD</td>
<td>Tara Henderson, MD</td>
</tr>
<tr>
<td>Jonathan Weinsaft, MD</td>
<td>Wendy Leisenring, PhD</td>
</tr>
<tr>
<td>Matthew Matasar, MD, MS</td>
<td>Leslie Robison, PhD</td>
</tr>
<tr>
<td>Emily Tomorozos, MD, MPH</td>
<td></td>
</tr>
<tr>
<td>Charles Sklar, MD</td>
<td></td>
</tr>
<tr>
<td>Talya Salz, PhD</td>
<td></td>
</tr>
<tr>
<td>Elena Eskin, PhD</td>
<td></td>
</tr>
<tr>
<td>Suzanne Wolfen, MD</td>
<td></td>
</tr>
<tr>
<td>Elizabeth Morris, MD</td>
<td></td>
</tr>
<tr>
<td>Joanna Chou, MPH</td>
<td></td>
</tr>
<tr>
<td>Nidha Mubdi, MPH</td>
<td></td>
</tr>
</tbody>
</table>

Grants

NCI: R01CA106972, R01CA134722, R21CA55723, K05CA168724
LiveStrong, Centers for Disease Control and Prevention, and the Meg Berté Owen Foundation