Cardiovascular Health After Cancer:

Common and Overlooked
Issues for Post-Cancer Care

Barbara Natterson Horowitz, M.D.
UCLA Division of Cardiology
David Geffen School of Medicine at UCLA
UCLA-LIVESTRONG™ Survivorship Center of Excellence

- One in three individuals will receive a cancer diagnosis in their lifetime.
- 10.6 million Americans are living past their cancer diagnosis.
- These cancer survivors will now be challenged by some of the long-term effects of their cancer therapies.
Risk Benefit Ratio of Cancer Treatment

- At the time of cancer diagnosis a risk/benefit analysis must be made by the patient and the family.

- The known risks of a cancer therapy must be “weighed” against the benefits of the treatment.

- Patients often have no choice but to accept the risks up front and plan to deal with them in the future should they occur.
Late Effects of Cancer Therapy

- Many therapies for cancer are associated with long-term cardiovascular issues
- All parts of the cardiovascular system can be affected by chemotherapy, radiation and surgery
  - Ventricles
  - Conduction System
  - Valves
  - Pericardium
  - Autonomic Nervous System
Pericardium
Conduction (Electrical) System
Coronary Arteries

left main stem

circumflex artery

right coronary artery

left anterior descending artery
Atherosclerosis Timeline

- Foam Cells
- Fatty Streak
- Intermediate Lesion
- Atheroma
- Fibrous Plaque
- Complicated Lesion/Rupture

From first decade: Growth mainly by lipid accumulation
From third decade: Smooth muscle and collagen
From fourth decade: Thrombosis, hematoma

What Are We Worrying About?

- Heart Failure
- Heart Attack
- Conduction Abnormality (need for a pacemaker)
- Pericardial Disease
- Autonomic Nervous System Problems
Heart Failure

- A terrible term.
- It doesn’t mean your heart has failed.
- It means it has been weakened
- ....And can be strengthened
Risks for Heart Failure in Cancer Patients

- Treatment with Anthracyclines:
  - Potent and effective drugs used in treatment of many pediatric and adult hematologic and solid organ cancers
  - May cause overt CHF (congestive heart failure) or a reduction in LVEF without symptoms

*Anthracyclines: Doxorubicin (Adriamycin), Daunorubicine, Epirubicin etc etc.*
Risk of heart failure is related to dose. Risk increases proportionally to the total accumulated dose.

Notably combination of radiation therapy and anthracycline agents increases risk of heart failure (breast cancer R vs. L debate).

May present with systolic dysfunction or diastolic dysfunction.
Risk Factors for Anthracycline Cardiomyopathy

<table>
<thead>
<tr>
<th>Table 1. Risk Factors for Anthracycline Cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Characteristic</strong></td>
</tr>
<tr>
<td>Young age (&lt; 18 years) at treatment initiation</td>
</tr>
<tr>
<td>Age &gt; 65 years at treatment initiation</td>
</tr>
<tr>
<td>Associated hypertension, pre-existing cardiac disease (coronary artery disease, left ventricular dysfunction)</td>
</tr>
<tr>
<td>Pregnant or contemplating pregnancy</td>
</tr>
<tr>
<td>Engaging in extreme/competitive athletics</td>
</tr>
<tr>
<td><strong>Treatment Characteristic</strong></td>
</tr>
<tr>
<td>Higher cumulative dose equal to ( \geq 300 \text{ mg/m}^2 ) of doxorubicin or ( \geq 600 \text{ mg/m}^2 ) of epirubicin</td>
</tr>
<tr>
<td>Associated mediastinal radiation therapy</td>
</tr>
<tr>
<td>Combination chemotherapy (trastuzumab, cyclophosphamide, etoposide, melphalan, paclitaxel, mitoxantrone, idarubicin)</td>
</tr>
<tr>
<td>Longer duration of survival</td>
</tr>
</tbody>
</table>
Herceptin (Trastuzumab) Related Cardiac Dysfunction

- Occurs in up to 14% of patients
- Increased when anthracyclines have been given
- Improved with prior heart disease
- Does not usually cause death, not dose related and often improves with discontinuation of the drug. *May be reversible in some cases*
Normal
Left Ventricular Ejection Fraction
(60-65%)
Reduced Ejection Fraction
Estimated 25%
EF: Systolic Dysfunction
Diastolic Dysfunction
Pressure Increases in the Left Atrium.....Leads to Shortness of Breath
Shortness of Breath and Fatigue

The Doctor and His Patient by Jan Steen, c. 1665. The Rijksmuseum, Amsterdam
Diastolic Dysfunction:

Just because the “EF” is normal doesn’t mean the dyspnea isn’t cardiac
Echocardiographic Dx of Diastolic Dysfunction
Pressure Increases in the Left Atrium.....Leads to Shortness of Breath
Shortness of Breath and Fatigue
Radiation Therapy
Radiation Therapy

- 10-30% patients have heart effects by 5 to 10 years post treatment
- 88% have asymptomatic damage to the ventricles, valves, pericardium, conduction system and the vascular system
- Special notice should be taken about the effect of XRT on the autonomic nervous system
Radiation Injury
Chest, Mantle, or Left Breast Radiation Therapy (XRT)

- XRT had a surge in the mid 1980s
  - Increased risk with young age so adult survivors of pediatric cancers (many Hodkins pts) have an increased risk
  - Trend towards less cardiotoxicity as modern techniques including lower doses, image-guided therapy and decreased radiation field
Status Post Mediastinal Radiation

- RR of Myocardial Infarction s/p XRT 4.2
- RR of Sudden Cardiac Death s/p XRT 6.7
# Radiation Therapy

## Table 4. Spectrum of Radiation Damage to the Heart

<table>
<thead>
<tr>
<th>Structure</th>
<th>Abnormality</th>
<th>Natural History</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardium</td>
<td>Pericarditis</td>
<td>Chronic asymptomatic effusion and/or pericarditis with symptoms: hemodynamic compromise with either constriction or tamponade</td>
<td>Fibrous thickening and fluid production</td>
</tr>
<tr>
<td>Myocardium</td>
<td>Myocarditis</td>
<td>Progressive diastolic dysfunction and restrictive hemodynamics with symptoms: CHF</td>
<td>Diffuse interstitial fibrosis/microcirculatory damage leading to capillary obstruction/extensive fibrosis</td>
</tr>
<tr>
<td>Endocardium</td>
<td>Valvular damage</td>
<td>Over time, progressive stenosis and regurgitation</td>
<td>Cusp and/or leaflet fibrosis</td>
</tr>
<tr>
<td>Vascular System</td>
<td>Arteritis</td>
<td>Premature CAD/accelerated atherosclerosis</td>
<td>Ostial and proximal stenosis; LAD, RCA, and left main more than left circumflex</td>
</tr>
<tr>
<td>Conduction System</td>
<td></td>
<td>Pulmonary hypertension</td>
<td>Pathology similar to atherosclerosis</td>
</tr>
<tr>
<td>Autonomic Dysfunction</td>
<td></td>
<td>All forms of heart block and conduction delay</td>
<td>Fibrosis of the conduction system</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supraventricular tachycardia; heart rate variability</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; CAD, coronary artery disease; LAD, left anterior descending coronary artery; RCA, right coronary artery.
<table>
<thead>
<tr>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three-dimensional treatment planning</td>
</tr>
<tr>
<td>Intensity-modulated radiation therapy in selected cases</td>
</tr>
<tr>
<td>Positron emission tomography-computed tomography fusion planning in</td>
</tr>
<tr>
<td>selected cases</td>
</tr>
<tr>
<td>Reducing total dose (being tested in randomized trials)*</td>
</tr>
<tr>
<td>Reducing treatment field size (ongoing trials testing further reducing</td>
</tr>
<tr>
<td>involved-field radiation therapy to involved-node radiation therapy using</td>
</tr>
<tr>
<td>conformal techniques)*</td>
</tr>
<tr>
<td>Daily fraction size $\leq 2$ Gy</td>
</tr>
</tbody>
</table>

*Pertains to the lymphoma patient population, in which MR is often employed.
<table>
<thead>
<tr>
<th><strong>Table 5. Factors Increasing the Risk of Cardiac Sequelae After Mediastinal Radiation Therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors</strong></td>
</tr>
<tr>
<td>Associated anthracycline chemotherapy</td>
</tr>
<tr>
<td>Location of tumor close to heart border*</td>
</tr>
<tr>
<td>Age &lt; 18 years</td>
</tr>
<tr>
<td>Associated cardiac risk factors</td>
</tr>
<tr>
<td>Baseline cardiac disease*</td>
</tr>
<tr>
<td>&gt; 10 year post-radiation therapy</td>
</tr>
<tr>
<td><strong>Radiation factors</strong></td>
</tr>
<tr>
<td>Orthovoltage radiation (rarely used since the 1970s)</td>
</tr>
<tr>
<td>Volume of irradiated heart*</td>
</tr>
<tr>
<td>Total dose to the heart &gt; 30 Gy</td>
</tr>
<tr>
<td>Daily dose fraction &gt; 2 Gy/day</td>
</tr>
<tr>
<td>Absence of subcarinal blocking</td>
</tr>
</tbody>
</table>

*These factors are consensus based and not individually validated.*
Pacemaker

Schematic of pacemaker system.
In an important study published in 2003, frequent abnormalities in valvular function, left aortic regurgitation, were found. The most common valvular abnormality was aortic regurgitation.
Pericardium and Radiation Therapy
Pericardial Disorders

- Pericardial Effusion
- Constrictive Pericarditis
Pericardial Effusion and Thickening
CT of Constrictive Pericarditis
Pressure Increases in the Left Atrium.....Leads to Shortness of Breath
“Cookie”
19 Year Old Lioness with Cardiac Tamponade: *Tired and Short of Breath*
700 cc Serosanguinious Fluid Removed
Comparative Cardiology and Cancer
“Cookie”
Post-Op
Heart Attacks and Atherosclerosis of the Carotid Arteries

- Radiation Therapy-
- Cisplatin-Based Chemotherapy-
Atherosclerosis Timeline

Endothelial Dysfunction

- Foam Cells
- Fatty Streak
- Intermediate Lesion
- Atheroma
- Fibrous Plaque
- Complicated Lesion/Rupture

- From first decade
- From third decade
- From fourth decade

Growth mainly by lipid accumulation
Smooth muscle and collagen
Thrombosis, hematoma

MYOCARDIAL INFARCTION

RIGHT CORONARY ARTERY

LEFT CORONARY ARTERY

CLOT

AREA DEPRIVED OF BLOOD
Autonomic Nervous System (ANS)

Master Control for the Body and Brain

- Parasympathetic: Rest and Digest
- Sympathetic: Fight or Flight

Diagram showing the functions of the parasympathetic and sympathetic nervous systems, including stimulation of saliva flow, slowing of heartbeat, constriction of bronchi, stimulation of peristalsis and secretion, and contraction of the bladder.
Dysautonomomias

- **Dysautonomia** literally means dysregulation of the autonomic nervous system.
  
  – *Chemotherapy and Radiation Therapy Have Been Shown to Injure the Autonomic Nervous System in Some Cancer Patients*
Cancer Treatment Induced Dysautonomias

- Under-recognized and under-diagnosed
- Profoundly disabling in some cases
How to Diagnose

- **History**
- Tilt Table
- Holter Monitor
- Catecholamine Test
- Sweat Test
- Fluid/Salt Challenge
- Medication Challenge
- In some cases imaging (MRI/CT)
What Can Help

- Proper Diagnosis
- Information for patient *and physician*
- Medications may be useful:
  - Beta blockers
  - Clonidine
  - Florinef
  - Prednisone
  - Erythropoietin
  - NSAIDS
  - Benzodiazepines
  - SSRIs
Non-Pharmacologic Therapy

- Countermeasures
- Regular walking exercise
- Cooling Devices
- Compression Devices
- Heart Rate Watches
- Leg Weights
- Scheduling Afternoon Activities
Heart Recommendations for Post Cancer Care

- Awareness of treatments and associated toxicities
- Enhanced awareness of *diastolic dysfunction* as early presenting feature of chemotherapy cardiotoxicity.
- Enhanced awareness of dyslipidemias and accelerated atherosclerosis in some cases
- Consideration of pericardial injury
- Recognition of autonomic dysfunction as an etiology for unexplained symptoms
Routine Screening of Adults Post Cancer

Insist on screening measures depending upon your exposures:
- Echocardiogram (assessing for more than EF!)
- Fasting lipids
- TG
- Glycosylated Hg
General Recommendations to Patients

- Regular walking exercise
- American Heart Association Diet
- No smoking
- No substances
- Very moderate alcohol
- Positive outlook
Multi-Species Medicine and Heart Health...We Aren’t Alone in This
Thank you for your attention!