RADIATION ASSOCIATED CARDIAC DISEASE (RACD)

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Objectives

- Prevalence of Risk Factors of RACD
- Evolution of Radiotherapy
- Pathophysiology of RACD
- Cardiac and Vascular Manifestations
- Multimodality Risk Stratification, Screening, and Diagnosis
- Management
- Cardiac Surgery Implications
- Surgical Procedures for RCAD and Outcomes
- Percutaneous CV interventions and TAVR
Radiation therapy is used in ~50% of patients diagnosed with cancer. X-rays, gamma rays, electron beams, photons and protons are used to “break or damage” tumor cells and cause their death. Surrounding normal tissues are also affected by XRT. Guiding Principle: Delivering a therapeutic dose to the tumor AND minimize unwanted exposure to the surrounding tissue. Cardiac Radiation is usually “stray”, not intended for the heart. Thoracic malignancies: Lymphoma, breast, lung, esophageal cancer. RACD, a heterogeneous disease that can manifest years or decades following radiation exposure to the chest, is associated with high morbidity and mortality.
Evolution of Radiotherapy

- Decreasing the XRT field to involved tumor/lymph node
- Start with chemo then irradiate residual tumor (rather than XRT first)
- Deep Inspiratory Breath Hold (DIBH)- pulls heart inferiorly
- 2D Conformational Radiotherapy (CRT) to 3D CRT
- IMRT (Intensity Modulated Radiotherapy)- XRT fits the shape of tumor
- Prone (vs. supine) positioning for left breast cancer (for large breasts)
- Proton Therapy
Figure 2. Mantle field radiation versus involved node radiation therapy for Hodgkin disease. (A) Mantle field radiation for large mediastinal tumor, (B) Involved node radiation for large mediastinal tumor, (C) Mantle field radiation for small mediastinal tumor, (D) Involved node radiation for small mediastinal tumor. Involved node radiotherapy reduces the amount of the cardiac volume within the treatment field. Reprinted with permission from Maraldo MV et al.53
In a patient with lymphoma, significantly higher cardiac exposure occurred with mantle radiation (A and C) versus involved node XRT (B suggests large and D suggests smaller nodal involvement). In a patient with left breast cancer, comparison plans suggest a significantly higher amount of cardiac involvement with partially wide tangent field (E) and (F) photons/electrons versus proton therapy (G). Adapted with permission from Maraldo et al. (20) and MacDonald et al. (32). XRT = radiotherapy.
Planning CT scanning prior to radiation of the left breast. Light blue=heart, Green=left anterior descending artery, Red= 74Gy, Blue= 0 Gy. Treatment restricted to inspiration to maximize distance of heart from radiation field.

Typical PTV and OAR contouring and field setup in the supine (a) and prone (b) positions. The shortest distance between the anterior surface of the LAD and the chest wall (d median) and the surface area of the heart in the radiation field (A heart) are measured at the middle of the LAD in the supine position (insert).
Figure 1

Example of (A) free breathing and (B) deep inspiration breath hold plans for a single patient.
Figure 2: Evolution of XRT Dosage

(A) Mean heart dose (Gy) from whole left breast XRT by year:
- 2014: 4.6 Gy
- 2015: 3.9 Gy
- 2016: 3.4 Gy
- 2017: 2.6 Gy

(B) Mean heart dose (Gy) from whole left breast XRT by technique:
- No Breath Control
  - No Breath: 4.5 Gy
  - Yes Breath: 1.7 Gy
- Supine Breath Control
  - No Breath: 4.7 Gy
  - Yes Breath: 1.7 Gy
- Supine, Prone, Lateral
  - Supine: 3.7 Gy
  - Prone: 2.3 Gy
  - Lateral: 1 Gy

Reduction in mean heart radiation doses for left breast cancer by (A) year and (B) different techniques. Adapted with permission from Drost et al. (25).

XRT = radiotherapy.
CENTRAL ILLUSTRATION: Cardiac Radiation Dose and Lung Cancer Mortality

A Total Population

B No Pre-Existing Coronary Heart Disease

C Pre-Existing Coronary Heart Disease

Pathophysiology of RCAD

Fibroblasts $\rightarrow$ Activated Myofibroblasts $\rightarrow$ Collagenous extracellular matrix $\rightarrow$ increased tissue stiffness/decreased elasticity
CENTRAL ILLUSTRATION: Various Manifestations of Radiation-Associated Cardiac Disease

- **Vasculopathy**
  - Microvascular disease
  - Coronary artery disease
  - Macrovascular disease including calcification of the ascending thoracic aorta

- **Valvular Heart Disease**
  - Valve leaflet thickening, calcification and restriction
  - Calcification and thickening of the aorto-mitral curtain and mitral annulus
  - Valvular stenosis and regurgitation

- **Pericardial Disease**
  - Inappropriate sinus tachycardia
  - High degree atrioventricular block

- **Conduction System Disease**
  - Inappropriate sinus tachycardia
  - High degree atrioventricular block

- **Myocardial Disease**
  - Ischemic myocardial scar
  - Non-ischemic myocardial scar
  - Restrictive cardiomyopathy

Manifestations of RACD

- **Myocardial disease and Heart Failure**
  - Diastolic dysfunction more common with XRT damage than systolic
  - Can have decrease in functional capacity without heart failure symptoms
  - Bi-ventricular fibrosis, non-ischemic and ischemic
  - Can be compounded by chemotherapy: Anthracyclines, Trastuzumab

- **Valvular Heart Disease**
  - Left sided valves > Right, Aortic > Mitral
  - Mitral-aortic intervalvular fibrosa calcification (hallmark of previous heart irradiation)
  - Symptomatic later than CAD (>10 years post XRT)
  - Regurgitation and stenosis
Figure 2 Echocardiogram from a patient who received mediastinal radiotherapy 24 years ago. Grossly thickened and calcified anterior mitral valve leaflet (white arrow). The calcification extends to non-coronary aortic valve cusp and sinus of Valsalva (red arrow). Ao, aorta; LV, left ventricle.

Published in Heart 2016

**Radiation-induced valvular heart disease.**

Dorothy M. Gujral, Guy Lloyd, Sanjeev Bhattacharyya
Manifestations of RACD

- **Pericardial Disease**
  - Most common, can be clinically unrecognized
  - Early acute pericarditis $\rightarrow$ Chronic pericardial inflammation
  - Thickened, calcified pericardial sac
  - Ventricular interdependence $\rightarrow$ Constriction

- **Vasculopathy/Coronary Artery Disease**
  - Micro and macro vascular disease
  - Usually affects ostia and proximal coronaries
  - LM and RCA
  - Long Tubular lesions, concentric, often non-calcified
  - Large vessel atherosclerosis $\rightarrow$ Embolic CVA
  - IVUS/OCT
Cardiac CT of the pericardium: Normal pericardium (A), thickened pericardium (B), pericardial effusion and hyper-enhanced pericardial layers (C), and pericardial calcification (D).
Radiation-Associated Coronary Artery Disease Severe right coronary ostial stenosis (arrows) after radiotherapy for Hodgkin lymphoma (surgical clips from splenectomy).
Manifestations of RACD

- **Conduction system dysfunction**
  - AVB, SSS, Atrial fibrillation, VT
  - Autonomic dysfunction (IST)
  - Infranodal and Right bundle more susceptible due to anterior location

- **Pulmonary Disease**
  - Particularly important when considering cardiac surgery
  - Major source of peri-op morbidity/mortality
  - Recurrent pleural effusions
  - Severely reduced lung volumes, ventilation impairment
Multimodality Risk Stratification

- Echocardiography
- Strain imaging
- Cardiac MRI
- Cardiac Cath (right and left)
- Cardiac CT
- EKG
- Stress Echo/Nuclear Stress Testing
Listed clockwise 1 to 9: 1) coronary angiography demonstrating severe circumflex stenosis; 2) ‘porcelain’ ascending aortic calcification on cardiac computed tomography (CT); 3) severe mitral annular, aorto-mitral curtain, and aortic valve calcification on cardiac CT and 4) transthoracic echocardiography; 5) near-transmural inferior wall ischemic scar on cardiac magnetic resonance (CMR) in short-axis and 6) vertical long-axis planes; 7) complete heart block on electrocardiography; 8) severe pericardial calcification on noncontrast CT, and 9) strain ‘bullseye’ plot demonstrating reduced left ventricular anterolateral wall deformation due to tethering.
## Screening and Diagnosis

### TABLE 2 Risk Factors and Long-Term Manifestations of Chest and Mediastinal Radiotherapy

<table>
<thead>
<tr>
<th>Risk factors for developing RACD and RAPD</th>
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<tbody>
<tr>
<td>Younger age at the time of XRT (&lt;50 yrs)</td>
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<tr>
<td>Presence of cardiovascular risk factors or established cardiopulmonary disease</td>
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<tr>
<td>Lack of shielding or cobalt as a source of radiation</td>
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<td>High cumulative dose (&gt;30 Gy) or high dose of radiation fractions (&gt;2 Gy/day)</td>
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<td>Tumor in or next to the heart</td>
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<td>Anterior or left chest radiation</td>
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<td>Concomitant chemotherapy (e.g., anthracyclines)</td>
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Screening and Diagnosis

**FIGURE 4 Imaging in RACD**

- **? Baseline pre-XRT echocardiography** → **Prior chest XRT**
- **Annual history and physical examination**
- **Screen for and correct modifiable risk factors**
- **Search for symptoms and signs suggestive of RACD:**
  - Pericardial disease
  - Valvular heart disease
  - LV/RV dysfunction
  - Coronary artery disease
  - Extracardiac vascular disease
  - Conduction system disease
- **Present** → **EKG/arrhythmia monitoring**
  - Comprehensive echocardiography
  - CT chest to evaluate lungs, heart and aorta
  - PFTs with DLCO
  - CMR (if constriction/restriction suspected)
  - Left/right heart catheterization
  - Carotid ultrasound
- **None present and asymptomatic**
- **Screening echocardiography** (5 years after exposure in high risk patients)
  (10 years after exposure in the others)
- **Functional non-invasive stress test for CAD detection**
  (5 to 10 years after exposure in high risk patients)
- **Re-assess every 5 years**

Suggested screening and diagnostic algorithm for RACD. CAD = coronary artery disease; CMR = cardiac magnetic resonance; CT = computed tomography; DLCO = diffusion lung capacity; PFT = pulmonary function test; RV = right ventricular; other abbreviations as in Figure 3.
Drugs to Prevent RACD

- Primary Prevention- Before exposure to XRT and the presence of disease
- Secondary Prevention- After XRT and the presence of fibrosis
- Mostly animal models and small size human studies
- Anti-inflammatory medications for constrictive pericarditis
- Statins may reduce radiation induced fibrosis
- ACEi/ARBs may reduce cardiac fibrosis
- Intraperitoneal melatonin injections, recombinant human neuregulin-1β
## Medical Management of RACD

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
<th>Target</th>
<th>Observations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Atorvastatin</td>
<td>Atorvastatin reduced the expression of TGF-β1, Smad3/P-Smad3, ROCK I and p-Akt</td>
<td>Atorvastatin Ameliorate radiation-induced cardiac fibrosis in Sprague-Dawley rats.</td>
<td>Zhang et al. [70]</td>
</tr>
<tr>
<td>ACEIs</td>
<td>Captopril</td>
<td>Captopril inhibits the renin-angiotensin system and scavenges free radical</td>
<td>Captopril improves breathing rate and cardiopulmonary density/structure</td>
<td>van der Veen et al. [71]</td>
</tr>
<tr>
<td>Anti-inflammation and Anti-OS compounds</td>
<td>Tocotrienol-rich mix</td>
<td>Tocotrienol-rich mix protects mitochondrial dysfunction</td>
<td>Tocotrienol-rich mix relieves mitochondrial changes and achieves anti-OS and anti-apoptosis in hearts.</td>
<td>Sridharan et al. [89]</td>
</tr>
<tr>
<td></td>
<td>Pentoxifylline + α-tocopherol</td>
<td>Pentoxifylline and α-tocopherol inhibits expression of intracellular TGF-β and CTGF and defends endothelial function</td>
<td>Pentoxifylline and α-tocopherol inhibit myocardial fibrosis</td>
<td>Boerma et al. [90]</td>
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<tr>
<td></td>
<td>caffeic acid phenethyl ester (CAPE)</td>
<td>No description</td>
<td>CAPE suppresses acute immune system, inflammatory response and induces antioxidant properties</td>
<td>Mansour et al. [44]</td>
</tr>
<tr>
<td></td>
<td>L-carnitine</td>
<td>L-carnitine administration activated p38MAPK/Nrf2 signaling</td>
<td>L-carnitine attenuates cardiac function loss</td>
<td>Fan et al. [91]</td>
</tr>
<tr>
<td></td>
<td>Melatonin</td>
<td>Melatonin scavenges free radical</td>
<td>Melatonin prevents vasculitis and decreases fibrosis and necrosis</td>
<td>Gurses et al. [92]</td>
</tr>
<tr>
<td></td>
<td>Amifostine</td>
<td>No description</td>
<td>Amifostine prevents vascular damage and vasculitis</td>
<td>Kruse et al. [93]</td>
</tr>
<tr>
<td>TGF-β1 inhibitors</td>
<td>IPW-5371</td>
<td>IPW-5371 antagonizes TGF-βR1</td>
<td>IPW-5371 reduces collagen deposition in the heart and lungs and significantly improve the cardiopulmonary function of mice after irradiation</td>
<td>Rabender et al. [95]</td>
</tr>
<tr>
<td>Recombinant human neuregulin-1</td>
<td>rhNRG-1β</td>
<td>rhNRG-1β activates ErbB2-ERK-SIRT1 signaling transduction</td>
<td>rhNRG-1β reduces myocardial damage and protects heart function</td>
<td>Gu et al. [96]</td>
</tr>
</tbody>
</table>
Cardiac Surgery in RACD

- **Pre-Op evaluation/planning**
  - Echo, Coronary Angiography, MDCT, PFTs, strong consideration for cMR or RHC/LHC
  - Severe MAC: consider pre-planning for aggressive resection with anterior annular debridement and reconstruction of intervalvular fibrosa (COMMANDO operation)
  - What to do if aorta is heavily calcified

- **Timing of Surgery**
  - Surgery should be considered later in the course of disease than normal
  - High risk of complications related to radiation lung disease/pleural effusions
  - Re-do surgery VERY HIGH risk and should be avoided

- **Surgical Procedures**
  - CABG, quality of the LIMA
  - Usually targets are diffusely calcified but still amenable to bypass
Cardiac Surgery in RACD

- **Valve Surgery**
  - If one severe and one moderate, consider replacing both valves
  - Repairs usually do not hold up, replacement recommended
  - Heavy MAIVF calcification limits suture placement
  - Extensive debridement can leave no adequate tissue remaining to fix and seal valve
  - Smaller annular size as XRT damage sets in early while heart not yet fully developed

- **Choice of Prosthesis**
  - Mechanical (younger, no problems with taking AC)
  - Bioprosthetic, valve in valve

- **Post-Op Considerations**
  - Conduction system disturbances (permanent epicardial LV lead placement)
  - Avoid overuse/high dose of BB (rate dependent on cardiac out-pt)
Surgical Management
TAVR and RACD

- Attractive option in RACD patients with high surgical risk
- However, there are several important considerations
  - Calcified aorta increases risk of injury, Ca embolization
  - Coronary ostia can be more susceptible to occlusion
  - Annular rupture
  - Increased risk for pacemakers
  - Low flow, low gradient physiology
- Femoral Approach should be default
- 15% pacemaker rates, lower survival than those without XRT
- Annular Rupture increased in
  - Extensive aortic calcifications with extension to aortomitral curtain
  - Avoid predilatation and use self-expanding or mechanically expanding valves over balloon- expandable valves
Conclusions

- With increased awareness, RACD from prior XRT likely to increase over the next decade
- Challenging management in terms of morbidity and mortality
- Timing of intervention is key especially if surgery is planned
- Percutaneous interventions with aortic and mitral disease are promising although increased risks of peri-procedural complications but probably less than surgical (however not been directly studied, evolving field)
- Thankfully, newer techniques of XRT limits cardiac exposure and thus future risk for RACD
Thank You