Radiation Fibrosis Syndrome

Definition

• Radiation Fibrosis (RF) describes the insidious pathologic fibrotic tissue sclerosis that often occurs in response to radiation exposure.

• The term radiation fibrosis syndrome (RFS) describes the myriad clinical manifestations of progressive fibrotic tissue sclerosis that result from radiation treatment.
Radiation Fibrosis Syndrome

What is Radiation?

• Radiation is composed of packets of energy
  – Photons and particles (protons, neutrons, electrons)
• These packets penetrate human tissue and ionize to cause direct and indirect tissue damage via the production of hydroxyl radicals.
• Therapeutic effect derived from ability to kill fast dividing cancer cells with relative sparing of more slowly dividing somatic cells.

Radiation Fibrosis Syndrome

Role of Radiation in Cancer Treatment?

• Intent to Cure
• Palliate
  – Prolong life
  – Improve or maintain function
  – Reduce pain
• Approximately half of cancer patients receive radiation during the course of their disease
• Not all radiation patients develop RFS

Radiation Fibrosis Syndrome

Modes of Delivery

• Basic Strategies
  – Brachytherapy
  – External Beam Radiation
Radiation Fibrosis Syndrome
Dose and Fractionation

• Conventional
• Hyperfractionated
• Hypofractionated
• Single fraction

• Dose usually expressed in Gy or cGy
• Gy = 100cGy = 100rads

Radiation Fibrosis Syndrome
Dose Sculpting Techniques

• Intensity-modulated radiotherapy (IMRT)
  – Intensity of radiation is modulated across the treatment field using a multileaf collimator to subdivide the radiation beams into beamlets and aim them at the tumor from multiple directions
  – Allows shaping of the beam to closely approximate the three dimensional configuration of the tumor and spare the normal surrounding tissue.
  – IMRT is usually combined with image guidance.

Radiation Fibrosis Syndrome
Dose Sculpting Techniques

• Image-guided radiotherapy (IGRT)
  – This is a more sophisticated and accurate technique which uses imaging such as computed tomography (CT) to compensate for variables such as tumor movement or shrinkage between sessions, organ filling with perfusion or respiration, etc.
  – IGRT is often combined with intensity modulation
  – Radiation can be controlled to a very high degree of precision such that tumors around critical structures such as the spinal cord can be treated with only a few millimeter margin.
Radiation Fibrosis Syndrome

Multileaf Collimator

Single Fraction Radiation

- Dose Map demonstrating dose distribution
- IMRT/IGRT
- 2400 cGy to tumor
- <1400 cGy to spinal cord only a few milliliters away

Standard 3-field for supraclavicular nodes and chest wall vs. IMRT for Breast Cancer
Radiation Fibrosis Syndrome
Biologic Effects of Radiation

- Induction of apoptosis
  - Free radical-mediated DNA damage

- Other overlapping factors
  - Mediated by cytokines, chemokines, growth factors
    - Activation of coagulation system
    - Inflammation
    - Epithelial regeneration
    - Tissue remodeling

Radiation Fibrosis Syndrome
Biologic Effects of Radiation

- Vascular endothelial dysfunction
  - Loss of vascular thrombo-resistance
    - Decreased fibrinolysis
    - Increased expression tissue factor, von Willebrand factor
    - Decreased prostacyclin, thrombomodulin
  - Presence of local fibrin formation
    - Intravascularly
    - Perivascular area
    - Extracellular matrix

Radiation Fibrosis Syndrome
Temporal Classification of Sequelae

- **Acute**
  - During or immediately after treatment
- **Early-delayed**
  - Up to 3 months after treatment completion
- **Late/Chronic**
  - > 3 months – several years post-treatment
  - Poor prognosis, irreversible

Radiation Fibrosis Syndrome
Histopathological Phases

- **Prefibrotic Phase**
  - Often asymptomatic
  - Signs of chronic inflammation
  - Endothelial cell dysfunction important
- **Organized Fibrosis Phase**
  - Patchy areas of active fibrosis containing a high density of myofibroblasts
  - In an unorganized matrix adjacent to poorly cellularized fibrotic areas
  - Consisting of senescent fibrocytes in a dense sclerotic matrix
- **Late Fibroatrophic Phase**
  - Retractile fibrosis
  - Gradual loss of parenchymal cells

Radiation Fibrosis Syndrome
Illustrated Changes
Radiation Fibrosis Syndrome
Determinates of Risk and Severity

- Treatment-related Factors
  - Radiotherapy
    - Dose
    - Fractions
    - Time
    - Tissue treated (radiation field)
  - Surgery
  - Chemotherapy

- Patient-related Factors ("protoplasm")
  - Physiological status
  - Age
  - Comorbidities
    - Cardiovascular disease
    - Collagen vascular disease
    - Degenerative disease


Radiation Fibrosis Syndrome
Radiation Fields: Dermal Changes

Radiation Fibrosis Syndrome
Breast Fibrosis and Contraction
Radiation Fibrosis Syndrome
Severe Radiation Dermatitis

Radiation Fibrosis Syndrome
Dermatitis from XRT for Treatment of Breast Cancer Mets of Left Chest Wall

Radiation Fibrosis Syndrome
Radiation Fields: Skeletal Changes
Radiation Fibrosis Syndrome
Key Determinants of Severity of RFS

Radiation-induced Brachial Plexopathy with Adjuvant Breast Cancer Radiation

<table>
<thead>
<tr>
<th>Dose/Fraction</th>
<th>Total Dose</th>
<th>Brachial Plexopathy Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Gy</td>
<td>50 Gy</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>2.2 Gy – 2.5 Gy</td>
<td>34 Gy – 40 Gy</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>2.2 Gy – 4.58 Gy</td>
<td>43.5 Gy – 60 Gy</td>
<td>1.7% – 73%</td>
</tr>
</tbody>
</table>


Radiation Fibrosis Syndrome
Select Non-neuromuscular Sequelae

- Cardiovascular
  - Coronary artery disease
  - Carotid occlusion
  - Cardioembolism
  - Valvular heart disease
  - Conduction abnormalities
  - Pericardial disease
  - Baroreceptor failure

- Pulmonary
  - Pulmonary fibrosis
  - Pulmonary hypertension
  - Restrictive lung disease

- Gastrointestinal
  - Dysphagia
  - Esophageal dysmotility

- Urinary
  - Cystitis
  - Prostatitis

- Reproductive
  - Vaginal atrophy

- Immunomodulatory
  - Anemia
  - Leukopenia
  - Lymphopenia

- Lymphatic
  - Lymphedema

- Endocrine
  - Fatigue
  - Hypothyroidism
  - Xerostomia

© 2013 Memorial Sloan-Kettering Cancer Center, All Rights Reserved.
Radiation Fibrosis Syndrome
Head and Neck Cancer: Late Swallowing Dysfunction

- Symptomatic Late Swallowing Disturbance as high as 50%
- Aggressive chemoradiation for H&N Cancer has improved disease control but with higher treatment-related toxicity
- IMRT allows sparing of parotid gland function and decreased xerostomia but dysphagia and aspiration are increased.
- Acute dysphagia starts and progressively increases during radio(chemo)therapy and usually resolves shortly after treatment.
- Late dysphagia and aspiration start months to years later and may decrease in 32%, remain unchanged in 48%, and worsen in 20% even with therapy.


Radiation Fibrosis Syndrome
Head and Neck Cancer: Carotid Stenosis

<table>
<thead>
<tr>
<th>Control</th>
<th>Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild → Moderate</td>
<td>6/37 (16%)</td>
</tr>
<tr>
<td>Severe</td>
<td>1/34 (3%)</td>
</tr>
<tr>
<td>Worsened</td>
<td>9/54 (17%)</td>
</tr>
</tbody>
</table>

2 groups of head and neck cancer patients:
- Radiotherapy (surgery & adjuvant radiation)
- Control (surgery only)

Carotid stenosis as evaluated by Doppler imaging 1 week before and 36 months surgery

Carotid stenosis classification: low (0-30%), moderate (31-49%), or severe (>50%)


Cancer Rehabilitation
Facial Lymphedema

© 2013 Memorial Sloan-Kettering Cancer Center, All Rights Reserved.
### Radiation Fibrosis Syndrome

**Prevalence of Lymphedema in Head and Neck Cancer**

<table>
<thead>
<tr>
<th>Type of Lymphedema</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lymphedema</td>
<td>20 (24.7)</td>
</tr>
<tr>
<td>Some form of lymphedema</td>
<td>61 (75.3)</td>
</tr>
<tr>
<td>Total</td>
<td>81 (100)</td>
</tr>
</tbody>
</table>

**Distribution of Lymphedema type**

<table>
<thead>
<tr>
<th>Lymphedema type</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>External lymphedema only</td>
<td>6 (9.8)</td>
</tr>
<tr>
<td>Internal lymphedema only</td>
<td>24 (39.4)</td>
</tr>
<tr>
<td>Combined lymphedema</td>
<td>31 (50.8)</td>
</tr>
<tr>
<td>Total</td>
<td>61 (100)</td>
</tr>
</tbody>
</table>

### Radiation Fibrosis Syndrome

**External Lymphedema in Head and Neck Cancer**

<table>
<thead>
<tr>
<th>Lymphedema Grade</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>44 (54.3)</td>
</tr>
<tr>
<td>Stage I</td>
<td>15 (18.5)</td>
</tr>
<tr>
<td>Stage II</td>
<td>22 (27.2)</td>
</tr>
<tr>
<td>Total</td>
<td>81 (100)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymphedema distribution (n=37)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>One site (e.g., neck only)</td>
<td>24 (64.9)</td>
</tr>
<tr>
<td>Two sites (e.g., face and neck)</td>
<td>10 (27.0)</td>
</tr>
<tr>
<td>Three sites (e.g., face, neck, and eyes)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Total</td>
<td>37 (100)</td>
</tr>
</tbody>
</table>

### Radiation Fibrosis Syndrome

**Neuromuscular and Musculoskeletal Sequelae**

- Skeletal growth arrest
- Scoliosis
- Osteoporosis
- Osteoradionecrosis
- Dysphagia
- Dysarthria
- Cerebropathy
  - Cerebral necrosis
  - Leukoencephalopathy
  - Neuropsychologic dysfunction
- Myelopathy
- Radiculopathy
- Plexopathy
- Mononeuropathy
- Myopathy
- Tendin-ligamentous dysfunction
- Enthesopathy
- Shoulder dysfunction

© 2013 Memorial Sloan-Kettering Cancer Center, All Rights Reserved.
Radiation Fibrosis Syndrome
Neuromuscular and Musculoskeletal Sequelae

Radiation Fibrosis Syndrome
Hodgkin Lymphoma and H&N Cancer

Thank You