The Radiation Fibrosis Syndrome

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Radiation Fibrosis Syndrome
Disclosures

None

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.

Stubblefield MD. Radiation fibrosis syndrome: neuromuscular and musculoskeletal complications in cancer survivors. PM R 2011;3(11):1041-54.

Radiation Fibrosis Syndrome
What is Radiation?

- Radiation is composed of packet 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 radicles.
- Therapeutic effect derived from ability to kill fast dividing cancer cells with relative sparing of more slowly dividing somatic cells.

Stubblefield MD. Radiation fibrosis syndrome: neuromuscular and musculoskeletal complications in cancer survivors. PM R 2011;3(11):1041-54.

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

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Hauer-Jensen M, et al. Radiation injury and the protein C pathway. Crit Care Med 2004;32:S325-30.

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

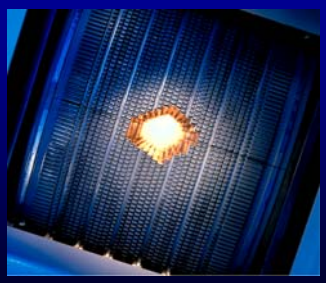
Radiation Fibrosis Syndrome
Dose Sculpting Techniques

- 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



Yamada Y. Principles of Radiotherapy. In: Stubblefield MD and O'Dell MW, editors. Cancer Rehabilitation: Principles and Practice. New York, NY: Demos Medical Publishing; 2009.

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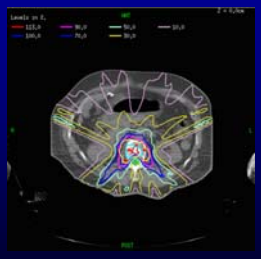
Radiation Fibrosis Syndrome
Single Fraction Radiation

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



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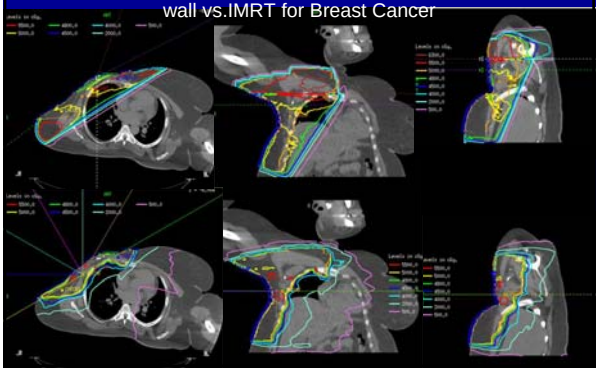
Radiation Fibrosis Syndrome
Standard 3-field for supraclavicular nodes and chest wall vs.IMRT for Breast Cancer



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

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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

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Radiation Fibrosis Syndrome
Temporal Classification of Sequelae

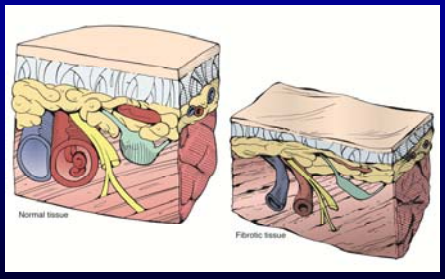
- Acute
  - During or immediately after treatment
- Early-delayed
  - Up to 3 months after treatment completion
- Late/Chronic
  - > 3 months – several years post-treatment
  - Poor prognosis, irreversible

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

Delanian S, Lefaix JL. Current management of late normal tissue injury: radiation-induced fibrosis and necrosis. Semin Radiat Oncol 2007;17:99-107.

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

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Radiation Fibrosis Syndrome
Radiation Fields: Dermal Changes

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Radiation Fibrosis Syndrome
Breast Fibrosis and Contraction

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Radiation Fibrosis Syndrome

Severe Radiation Dermatitis

Radiation Fibrosis Syndrome

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

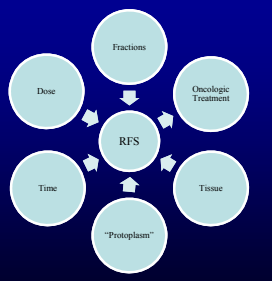
Radiation Fibrosis Syndrome

Radiation Fields: Skeletal Changes

Pre RT

Post RT

Radiation Fibrosis Syndrome
Key Determinants of Severity of RFS



Radiation Fibrosis Syndrome
Radiation-induced Brachial Plexopathy with Adjuvant Breast Cancer Radiation

Dose/Fraction	Total Dose	Brachial Plexopathy Risk
2 Gy	50 Gy	<1%
2.2 Gy – 2.5 Gy	34 Gy – 40 Gy	<1%
2.2 Gy – 4.58 Gy	43.5 Gy – 60 Gy	1.7% – 73%

Galecki J, Hicer-Grzenkowicz J, Grudzien-Kowalska M, Michalska T, Zalucki W. Radiation-induced brachial plexopathy and hypofractionated regimens in adjuvant irradiation of patients with breast cancer--a review. Acta Oncol 2006;45(3):280-4.

Radiation Fibrosis Syndrome
Select Non-neuromuscular Sequelae

- Cardiovascular
  - Coronary artery disease
  - Carotid stenosis
  - Cardiomyopathy
  - Valvular heart disease
  - Conduction abnormalities
  - Pericardial disease
  - Baroreceptor failure
- Pulmonary
  - Pulmonary fibrosis
  - Pulmonary hypertension
  - Restrictive lung disease
- Gastrointestinal
  - Dysphagia
  - Esophageal dysmotility
- Urinary
  - Cystitis
  - Proctitis
- Reproductive
  - Vaginal stenosis
- Integumentary
  - Alopecia
  - Dermatitis
  - Skin atrophy
- Lymphatic
  - Lymphedema
- Endocrine
  - Fatigue
  - Hypothyroidism
  - Xerostomia

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.

Duprez F, Madani I, De Potter B, Boterberg T, De Neve W. Systematic Review of Dose-Volume Correlates for Structures Related to Late Swallowing Disturbances After Radiotherapy for Head and Neck Cancer. Dysphagia 2013.

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Radiation Fibrosis Syndrome

Head and Neck Cancer: Carotid Stenosis

	Control	Radiotherapy	
Mild → Moderate	6/37 (16%)	15/25 (60%)	p = 0.004
Severe	3/54 (6%)	9/39 (23%)	p = 0.029
Worsened	9/54 (17%)	24/32 (62%)	p < 0.0001

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%)

Greco A, Gallo A, De Virgilio A, Marinelli C, Macrì GF, Fusconi M et al. Carotid stenosis after adjuvant cervical radiotherapy in patients with head and neck cancers: a prospective controlled study. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2012;37(5):376-81.

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Cancer Rehabilitation

Facial Lymphedema

Radiation Fibrosis Syndrome
Prevalence of Lymphedema in Head and Neck Cancer

Type of Lymphedema	Frequency (%)
No lymphedema	20 (24.7)
Some form of lymphedema	61 (75.3)
Total	81 (100)
Distribution of lymphedema type	
External lymphedema only	6 (9.8)
Internal lymphedema only	24 (39.4)
Combined lymphedema	31 (50.8)
Total	61 (100)

Deng J, Ridner SH, Dietrich MS, Wells N, Wallston KA, Sinard RJ et al. Prevalence of secondary lymphedema in patients with head and neck cancer. J Pain Symptom Manage 2012;43(2):244-52.

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Radiation Fibrosis Syndrome
External Lymphedema in Head and Neck Cancer

Lymphedema Grade	Frequency (%)
External lymphedema	
Stage 0	44 (54.3)
Stage I	15 (18.5)
Stage II	22 (27.2)
Stage III	0 (0.0)
Total	81 (100)
External lymphedema distribution (n=37)	
One site (e.g., neck only)	24 (64.9)
Two sites (e.g., face and neck)	10 (27.0)
Three sites (e.g., face, neck, and eyes)	3 (8.1)
Total	37 (100)

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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

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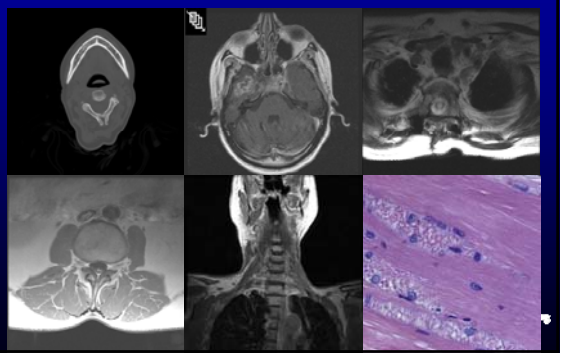
Radiation Fibrosis Syndrome

Neuromuscular and Musculoskeletal Sequelae



Radiation Fibrosis Syndrome

Hodgkin Lymphoma and H&N Cancer

Thank You