Radiation Induced Lung Injury (RILI): Distinguishing New Patterns of Toxicity From Recurrent Malignancy

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Disclosure

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Objectives

1. Describe the principles of modern radiotherapy techniques.
2. Illustrate and discuss newer patterns of radiation induced lung injury (RILI).
3. Discuss radiosensitizing and radioprotective agents.
4. Discuss methods of detecting disease recurrence.
Radiation Delivery Techniques

- Conventional Radiation Therapy.
- 3D Conformal Radiation Therapy (CRT)
  - CT or MRI for planning.
  - 4D respiratory gated.
- Stereotactic body radiation therapy (SBRT)
  - Hypofractionated 3-5 fractions of 10-20 Gy/fraction.
- Intensity modulated radiotherapy (IMRT)
  - Tomotherapy = CT guided IMRT.
Principles of Modern Radiotherapy Techniques

- Fractionation reduces the biologic impact of radiation.
- Stereotactic techniques reduce planning target volume margins.
- High cumulative doses to the tumor improves local control.
- Reduced dose related toxicity by minimizing exposure to organs at risk.
Pathophysiology of RILI

- Ionizing radiation $\Rightarrow$ oxygen free radicals.
- Oxygen free radicals $\Rightarrow$ oxidative stress.
- Oxidative stress $\Rightarrow$ cell structure, DNA damage
- Endothelial cell damage $\Rightarrow$ intraalveolar proteinaceous exudate impairs gas exchange.
- Inflammatory cell infiltrate results.
- Activated alveolar macrophages consume oxygen $\Rightarrow$ local hypoxia producing additional oxygen free radicals and cytokine production.
- Cytokine profibrogenic and angiogenic cascade.
Risk Factors for RILI

- Treated lung volume (rare <25%, ↑ w/ volume)¹
- Total dose, fractionation, dose rate – rare <20 Gy, common > 20-40 Gy, almost always > 40 Gy¹
- Type: 3DCRT 13-37%, SBRT 4%.
- Individual susceptibility (pre-existing ILD, DM, ↓ PFT’s).
- Prior or simultaneous therapy
  - Overlapping XRT.
  - Potentiating agents (actinomycin D, adriamycin, bleomycin, busulfan, cyclophosphamide).
- Cytoprotectant: amifostine, ACE inhibitors².
Acute Radiation Pneumonitis

- **Classic**
  - Whole lung radiation.
  - Single dose.
  - Threshold of 6 Gy, uniformly fatal for doses > 12 Gy.

- **Sporadic**
  - Fractionated radiation.
  - Whole or partial lung irradiation.
  - Unpredictable, occurs in 5-10%.
  - Volume of lung receiving >20 Gy corresponds with clinical pneumonitis.
  - Dyspnea disproportionate to volume of lung radiated (corollary: radiographic change not predictive of symptoms).
  - Evidence suggests a hypersensitivity pneumonia (lymphocyte predominant alveolitis).
Sporadic RILI: CT

- **Acute**
  - Ground glass and consolidation most severe in radiation portal although also outside the field.
  - Small pleural & pericardial effusions, within 6 months self-limited.

- **Chronic**
  - Progressive fibrosis with parenchymal distortion.
  - Decreased peripheral vascularity reflecting radiation induced vascular sclerosis.
  - Bronchiectasis within the radiation induced consolidation.
Sporadic RILI Timeline

Latent
1-4 wk

Acute Exudative
4 wk – 6 mo

Fibrosis
6 mo – 1 yr

\( T_0 \) - Date of XRT Completion\(^3\)
CT Classification of Acute Radiation Pneumonitis

- Clinical symptoms: cough (nonproductive or productive of clear sputum), low-grade fever, dyspnea, fatigue, and pleuritic chest pain.
- Abnormalities partially or completely fill the high dose region.
- Differential diagnosis: infectious pneumonia, pulmonary embolism, and tumor recurrence. 

- Diffuse consolidation
- Patchy consolidation
- Diffuse ground glass
- Patchy GGO
Acute Radiation Pneumonitis

Pneumonectomy 34 years prior s/p 30 Gy IMRT in 10 fractions to RLL lung cancer. Diffuse consolidation in distribution of high dose (see isodose lines) requiring 3L O2 and steroids.
Evolving Sporadic RILI Change

4 months

9 months

Acute: consolidation and ground glass with OP appearance (arrows).

Chronic: fibrosis, parenchymal distortion, sharp margins (arrowheads).

Acute: consolidation and ground glass with OP appearance (arrows).

Chronic: fibrosis, parenchymal distortion, sharp margins (arrowheads).
Note progressive volume loss, well defined margins, decreased vascularity and failure to respect anatomic boundaries (fissure).
SBRT Lung Injury Timeline

Latent (1-8 wk)

Acute Exudative (3 mo – 9 mo)

Fibrosis (12 mo – >2 yr)

$T_0$ - Date of SBRT Completion$^5,6$
SBRT Changes for Stage I Lung Cancer

- CT scans of 61 patients.
- 68 lesions.
- Median f/u of 2.5 years.
- Radiologic abnormalities
  - 54% at 6 months.
  - 99% at 36 months.
  - Acute.
  - Late.
  - Changes peaked at 1-2 yr.
- Note: 25% appeared > 1 year post SBRT.
- Change in morphology or severity >2 yr post SBRT.

Key point: CT Changes were dynamic over long periods of time.\(^6\)
SBRT Dynamic Changes Over > 3 years

RLL 50 Gy in 5 fractions - GGO evolves to scar-like pattern. Note late changes.

50 Gy in 5 fractions to LLL adenocarcinoma - evolving mass-like area of consolidation.
Radiation-induced Pulmonary Fibrosis

- Independent of acute pneumonitis.
- Severity related to V20 (volume of lung receiving > 20 Gy) and dose per fraction (>2.67 Gy/fraction).
- Cytokine mediated:
  - TGFβ (transforming growth factor β)
  - PDGF (platelet-derived growth factor)
  - Fibronectins
  - TNFα (tumor necrosis factor)
- Sx: dyspnea, fever, cough, clubbing.
- PFTs: ↓DLco, FVC, FEV₁.
SBRT RILI: Late Change

Modified Conventional
- Well-defined consolidation.
- Volume loss.
- Traction bronchiectasis.

Masslike
- Focal consolidation confined to 2 cm margin around the original tumor.

Scarlike
- Linear.
- Less than 1 cm wide.
- Moderate volume loss.

Conventional
- Volume loss.
- Traction bronchiectasis.
Potentiated Radiation Pneumonitis

- Radiosensitizing agents: ↑ risk of pneumonitis esp. given as concurrent therapy w/ XRT compared to sequential therapy: Actinomycin D, adriamycin, bleomycin, busulfan, cyclophosphamide, doxorubicin, taxanes, vincristine, mitomycin, gemcitabine, bevacizumab.
- Newer immunotherapies including CTLA-4 inhibitors (ipilimumab) and PD-1 inhibitors (pembrolizumab, nivolumab) have been shown to cause pneumonitis.
- PD-1 inhibitors now FDA approved in recurrent or metastatic NSCLC. Their risk of pneumonitis in combination with XRT is unknown and being investigated.
Radioprotective agents

- Protective agents studied include amifostine, pentoxifylline and angiotensin converting enzyme inhibitors.

- Although a RCT* of XRT + amifostine compared to XRT alone showed that amifostine reduces the incidence of pneumonitis and lung fibrosis, these results have not been replicated. Current guidelines do not advise the use of amifostine for prevention of radiation-induced pneumonitis\(^9\).

- Pentoxifylline may prevent radiation-induced fibrosis but it has not been fully studied\(^10\).

*RTC: Randomized Controlled Trial
Radiation Recall Pneumonitis

- Rare.
- Diagnosis:
  - History of chemotherapy after thoracic XRT (time interval 2 days to 15 years). May occur upon initiation of treatment or after several cycles (?dose threshold).
  - Radiographic findings in treatment port.
  - Clinical symptoms: low grade fever, dry cough, CP, SOB.
- Cytotoxic agents: bleomycin, cyclophosphamide, mitomycin, vincristine, taxanes, anthracyclines, gemcitabine and erlotinib\textsuperscript{11}.
RILI: Organizing Pneumonia

- Criteria:
  - XRT within 12 months.
  - Symptoms >2 weeks.
  - Opacities outside the XRT fields.
  - Exclusion of other causes.

- Reported after treatment for: lung cancer\textsuperscript{12}, thymoma and breast cancer.

- Incidence: breast cancer (2.5%), lung cancer (4.8%).
70 y.o. man with stage 4 lung cancer s/p chest wall radiation for recurrence with evanescent.

Ground glass opacity and consolidation. Note the atoll signs (arrow) characteristic of organizing pneumonia.
CT Findings of Local Recurrence Following XRT

- Convex/bulging margins.
- Change in contours (loss of linear margins).
- Enlarging opacity/sequential enlargement (especially > 12 months).
- Obliteration of air bronchograms.
- Craniocaudal growth.
- New unilateral pleural effusion\textsuperscript{13}. 
Recurrence: Convex Margins

60 Gy SBRT for stage IA NSCLC in a nonsurgical candidate. Note increased nodular change posteriorly (arrow) over serial CT scans in region of previously stable fibrosis. Focal metabolic activity at PET/CT is consistent with local recurrence.
Recurrence: Sequential Enlargement

50 Gy in 5 fractions for RUL adenocarcinoma. Note expected volume loss and cystic spaces through 19 mos. Loss of bronchogram (arrow) and increased density and convex margins at 39 months, metabolically active at PET/CT.
Recurrence: Loss of Linear Margin and Bronchiectatic Segment Obliteration

S/p chemotherapy and XRT for stage III NSCLC. Stable radiation fibrosis at 15 months. New suspicious opacity in the azygoesophageal recess with convex margins at 22 months (arrow). Bronchial obstruction (arrowhead) and increased density at 28 months with positive PET/CT is consistent with recurrence.
PET in RILI

- More accurate than CT for persistent or recurrent tumor.
- Acute radiation pneumonitis may cause increased FDG activity and persists for up to 18 months resulting in false positives for tumor recurrence.
- High negative predictive value of a normal FDG-PET.
- SUVmax > 5 high predictive value of recurrence\(^{14}\).
Acute Radiation Pneumonitis: PET

Metabolically active ground glass and consolidation 4 mo s/p SBRT 45 Gy in 25 fractions for LUL NSCLC. These regions progressively improved on follow-up imaging confirming radiation pneumonitis.
64 y.o. man with stage IIIA NSCLC treated with 66 Gy sequential SBRT to the right middle lobe and mediastinum with residual stable nodular radiation fibrosis. PET/CT performed for other reasons confirms no metabolic activity. This has a high negative predictive value.
Future Directions: Texture Analysis and Radiomics

- **Predicting RILI**
  - Combining mean lung density quantification changes with the standard deviation of the density (second order statistics) improves sensitivity and specificity over mean density alone in predicting radiation-induced lung damage\(^\text{15}\).

- **Predicting Lung Cancer Recurrence**
  - 2nd-order entropy texture features calculated within manually delineated ground-glass opacity (GGO) regions may predict recurrence within six months post-SBRT with 76% accuracy\(^\text{16}\).
  - Quantitative radiomic CT analysis on CT imaging ultimately may distinguish fibrotic change from local recurrence earlier than gross morphologic features.
Recurrent lung cancer in the superior segment of the right lower lobe after radiation. Note the subtle increase in the 1st order statistic (mass) over serial exams (arrow). Texture analysis reveals earlier change in 2nd order statistics. There is more heterogeneity (blue) in the region of recurrent malignancy while radiation fibrosis and vessels remain more homogeneous (red).

Texture Analysis courtesy of HealthMyne, Inc.
Summary

- Severity of RILI related to the V20.
- CRT and SBRT have changed the appearance of RILI – modified conventional, masslike or linear.
- CT changes do not correlate well with clinical pneumonitis.
- Correlation with treatment plans can be very useful in predicting the appearance of RILI vs local recurrence.
- Advanced quantitative radiomics analysis is being heavily studied and may be a valuable tool in the future to help distinguish between early recurrence and evolving RILI.
Suggested Reading


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