Radiation Induced Lung Toxicity

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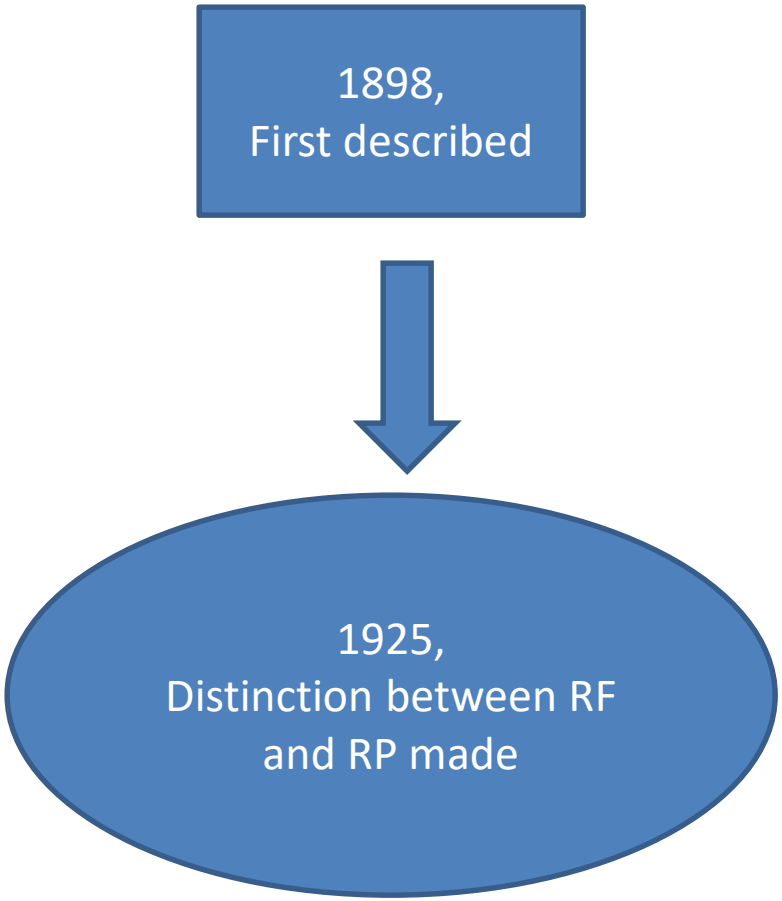
Pulmonary Medicine
13/10/17

1. Introduction
2. Pathogenesis and Pathology
3. Risk factors and Epidemiology
4. Clinical features
5. Diagnosis including Differential diagnosis
6. Treatment
7. Prevention

Introduction



Arch Electr Med 1898
AJR 1925; 13:203

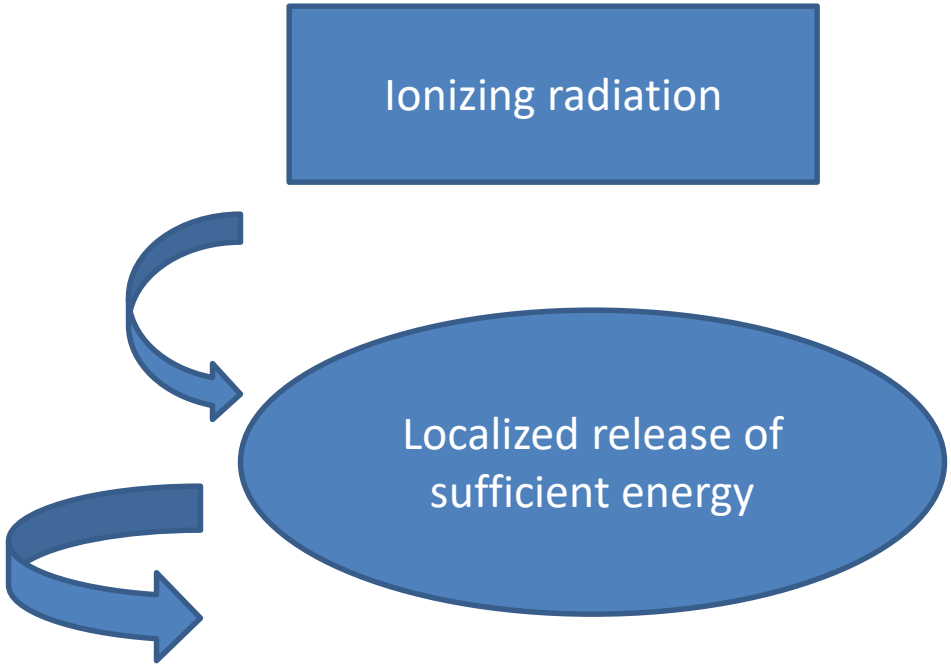
- Radiation-induced damage to normal lung parenchyma remains the dose-limiting factor in chest radiotherapy,
- involves other structures within the thorax in addition to the lungs.
- clinical diagnosis of RILI is often complicated by the presence of other conditions

CPE
Malignancy
infection

Recent Results Cancer Res 1993; 130:109.
Chest 1997; 111:1061
Int J Radiat Oncol Biol Phys 2005; 62:635

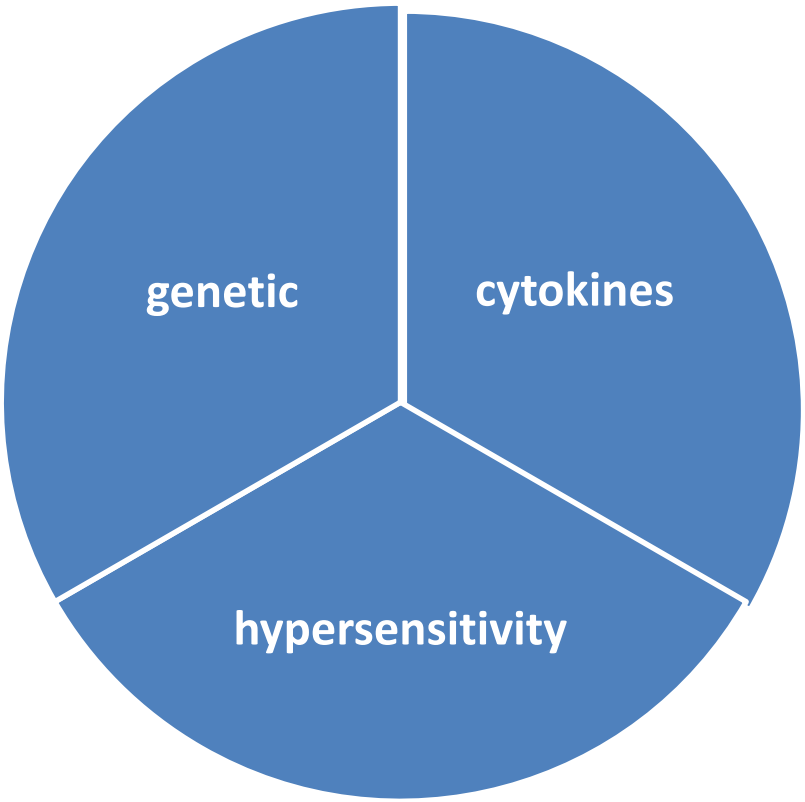
Thoracic effects of radiation
Radiation dermatitis Rib fractures
Bronchitis
Pleural effusion
Haemoptysis
Airway obstruction
Pulmonary fibrosis
Pulmonary vascular damage
Esophagitis
Pericarditis
Pneumothorax

Pathogenesis and pathology



reactive free radical species disrupting cellular molecules and cytotoxic effect is largely a consequence of **DNA damage that causes clonogenic** death in normal lung epithelial cells

Cancer 2012; 118:3450


genetic
cytokines
hypersensitivity

GENETIC BACKGROUND:

Breast cancer-association between irradiation and fibrosis/telangiectasia found.

Lung cancer-*both small/non small cell*

- single nucleotide polymorphism in the methylene tetrahydrofolate reductase gene **(MTHFR; rs1801133)** and RP
- polymorphisms of the ataxia telangiectasia mutated **(ATM)** gene and RP

Int J Radiat Oncol Biol Phys 2007; 69:685
Cancer 2012; 118:3654
int J Radiat Oncol Biol Phys 2010; 77:1360

ROLE OF CYTOKINES:

Upregulated

Transforming growth factor beta 1 [TGF-beta1]-

- Most extensively studied
- Induces fibroblast collagen deposition
- Plasma level at the end of therapy can predict RP
- No predictable pattern.

Int J Radiat Oncol Biol Phys 1998; 41:1029
Int J Radiat Oncol Biol Phys 2003; 56:988
Int J Radiat Oncol Biol Phys 2010; 77:38

Anscher MS etal, **1998**	**N-73** lung cancer treated with curative intent were recruited TGFbeta1 level at the end of RT was considered "**normal" if it was both < or = 7.5 ng/ml**	Fifteen of the 73 patients (21%) developed symptomatic pneumonitis A normal plasma TGFbeta1 by the end of RT was more common in patients who did not develop pneumonitis	monitoring of plasma TGFbeta1 levels may identify candidates for dose escalation studies in the treatment of lung cancer

Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 1, pp. 38–43, 2010

0360-3016/10/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.04.019

CLINICAL INVESTIGATION **Lung**

PREDICTIVE FACTORS OF LATE RADIATION FIBROSIS: A PROSPECTIVE STUDY IN NON–SMALL CELL LUNG CANCER

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Purpose: To determine predictive factors of late radiation fibrosis (RF) after conformal radiotherapy (3D-RT) in non–small cell lung cancer (NSCLC).

Methods and Materials: Ninety-six patients with Stage IA–IIIB NSCLC were included in a prospective trial. Clinical evaluation, chest X-ray, and pulmonary functional tests including diffusion parameters were performed before and 6 months after radiotherapy. An independent panel of experts prospectively analyzed RF, using Late Effects in Normal Tissues—Subjective, Objective, Management and Analytic scales classification. Logistic regression analysis was performed to identify relationships between clinical, functional, or treatment parameters and incidence of RF. Variations of circulating serum levels of pro-inflammatory (interleukin-6, tumor necrosis factor α, tumor growth factor β1) and anti-inflammatory (interleukin-10) cytokines during 3D-RT were examined to identify correlations with RF.

Results: Of the 96 patients included, 72 were evaluable for RF at 6 months. Thirty-seven (51.4%) developed RF (Grade $\geq$1), including six severe RF (Grades 2–3; 8.3%). In univariate analysis, only poor Karnofsky Performance Status and previous acute radiation pneumonitis were associated with RF ($p < 0.05$). Dosimetric factors (mean lung dose, percentage of lung volume receiving more than 10, 20, 30, 40, and 50 Gy) were highly correlated with RF ($p < 0.001$). In multivariate analysis, previous acute radiation pneumonitis and dosimetric parameters were significantly correlated with RF occurrence. It was not significantly correlated either with cytokines at baseline or with their variation during 3D-RT.

Conclusions: This study confirms the importance of dosimetric parameters to limit the risk of RF. Contrary to acute radiation pneumonitis, RF was not correlated to cytokine variations during 3D-RT. © 2010 Elsevier Inc.

Non–small cell lung cancer, Radiotherapy, Fibrosis, Predictive factors, Cytokines.

Tumor necrosis factor-alpha (TNFa) and Interleukin 1-alpha (IL-1a)-

upregulated immediately

IL 6-

elevated pretreatment plasma IL-6 concentrations correlate with an increased risk of developing RILI

Radiat Oncol 2002; 12:26
Int J Radiat Oncol Biol Phys 2001; 49:641

PDGF/bFGF-

- fibroblast mitogens
- reduce RILI and apoptosis in mice by the intravenous administration of bFGF

Basic fibroblast growth factor inhibits radiation-induced apoptosis in endothelial cells via activation of protein kinase C

Int J Radiat Oncol Biol Phys 1995; 33:99
Cancer Res 1994; 54:2582

The role of inflammation in the pathogenesis of RILI is supported by the observation that anti-CD40 ligand antibodies significantly reduce the influx of inflammatory cells, collagen deposition, and septal thickening in a murine model of RILI.

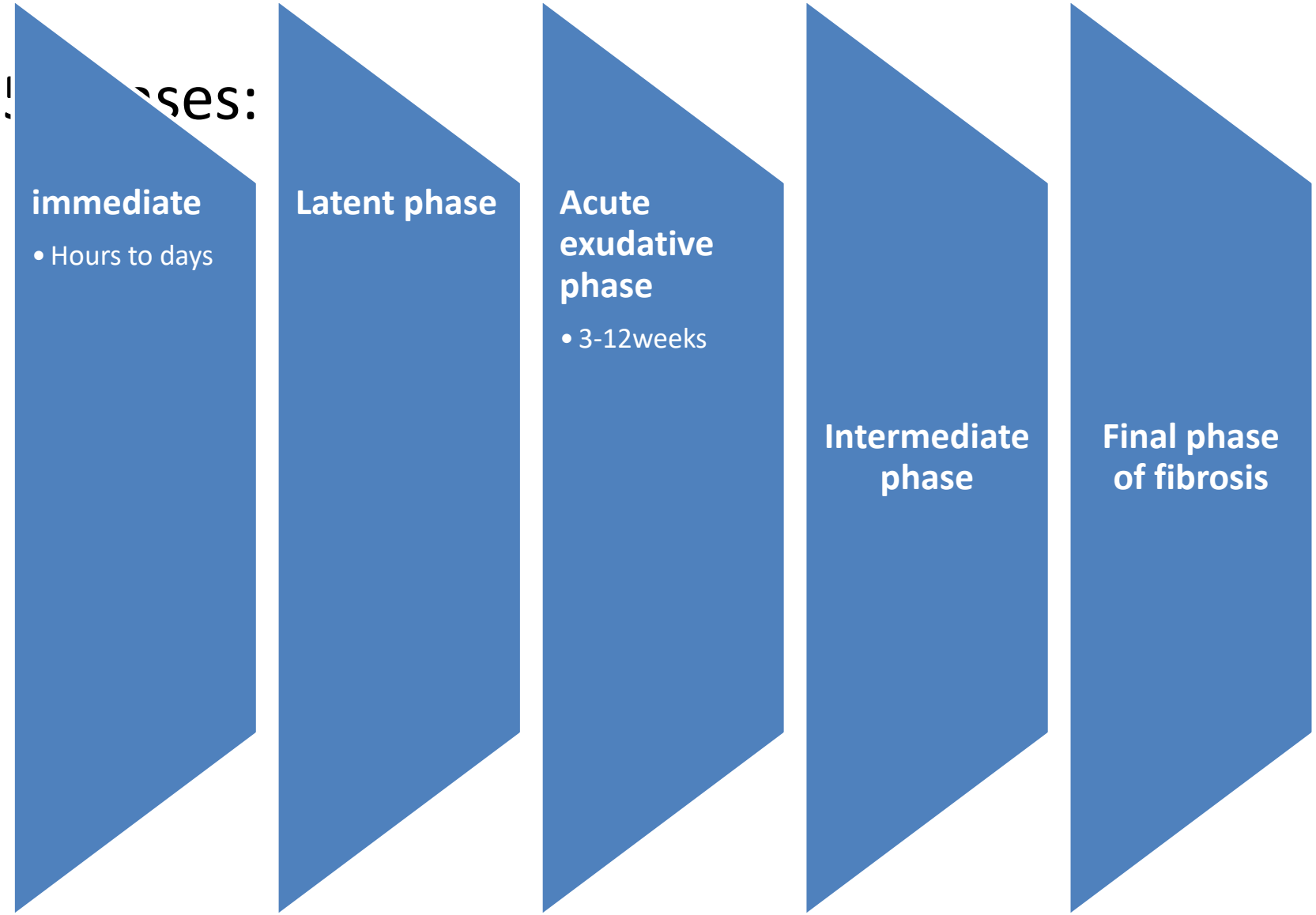
Clin Immunol Immunopathol 1998; 89:222

Hypersensitivity reaction:

- less common and unpredictable lung injury
- involves areas of the lung outside the radiation port
- bilateral hypersensitivity reaction following unilateral chest radiotherapy
- CD4+ lymphocytic alveolitis

Eur Respir J 1999; 13:727

PATHOLOGY:


sses:
immediate
• Hours to days
Latent phase
Acute exudative phase
• 3-12weeks
Intermediate phase
Final phase of fibrosis

Immediate phase

- hyperemic, congested mucosa with leukocytic infiltration an increased capillary permeability-pulmonary edema
- tracheal bronchial hypersecretion and degenerative changes in the alveolar epithelium and endothelium

Latent phase

- thick secretions accumulate
- increase in the number of goblet cells

Acute exudative phase

- Hyaline membranes form
- fibrin-rich exudate in alveoli
- pneumocytes become hyperplastic with marked atypia.

Int J Radiat Oncol Biol Phys 1995; 31:1187
Int J Radiat Oncol Biol Phys 2003; 56:988
Semin Radiat Oncol 2002; 12:26

Intermediate phase

- Dissolution of the hyaline membranes
- collagen deposition by fibroblasts

Final phase

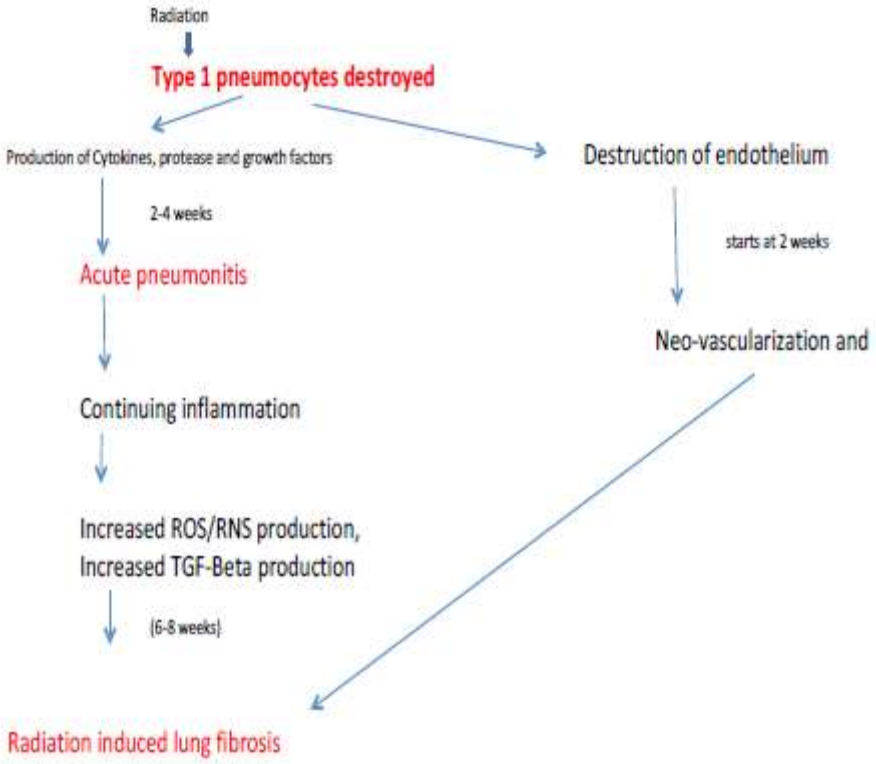
- early as six months
- myofibroblasts within the interstitium and alveolar spaces
- anatomic narrowing of alveolar spaces which results in diminishing lung volume; vascular sub-intimal fibrosis

Int J Radiat Oncol Biol Phys 2003; 56:988
Semin Radiat Oncol 2002; 12:26

Organizing pneumonia:

- 3-17 months after radiotherapy
- Also in areas outside radiation port including contralateral lung

Int J Radiat Oncol Biol Phys 2009; 73:1049
Mayo Clin Proc 1999; 74:27
Can Respir J 1998; 5:211



Asian Pac J Cancer Prev. 2015;16(7):2613-7

RISK FACTORS:

- Method of irradiation
- Volume of lung irradiated
- Dose of radiation
- Time-dose factor
- Induction chemotherapy
- Concurrent chemotherapy
- Radiation recall
- Others-
  - Smoking
  - Copd
  - ILD

Method of irradiation:

- conformal radiation therapy [CRT] is the approach used to
  - shape the distribution of therapeutic radiation dose within the patient to match as well as possible to the intended target volume

➢ intensity modulated radiation therapy (IMRT)

➢ stereotactic body radiation therapy (SBRT)

The use of protons rather than photons decreases the incidence of radiation pneumonitis as the mass of protons limits tissue penetration and allows more precise dosing

Int J Radiat Oncol Biol Phys 2007; 69:985
J Clin Oncol 2017; 35:56
Int J Radiat Oncol Biol Phys 2013; 85:1332

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ORIGINAL REPORT

Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non–Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial

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Author affiliations appear at the end of this article.

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Clinical trial information: NCT00533949.

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0732-183X/17/3501w-66w/$20.00

ABSTRACT

Purpose

Although intensity-modulated radiation therapy (IMRT) is increasingly used to treat locally advanced non–small-cell lung cancer (NSCLC), IMRT and three-dimensional conformal external beam radiation therapy (3D-CRT) have not been compared prospectively. This study compares 3D-CRT and IMRT outcomes for locally advanced NSCLC in a large prospective clinical trial.

Patients and Methods

A secondary analysis was performed to compare IMRT with 3D-CRT in NRG Oncology clinical trial RTOG 0617, in which patients received concurrent chemotherapy of carboplatin and paclitaxel with or without cetuximab, and 60- versus 74-Gy radiation doses. Comparisons included 2-year overall survival (OS), progression-free survival, local failure, distant metastasis, and selected Common Terminology Criteria for Adverse Events (version 3) ≥ grade 3 toxicities.

Results

The median follow-up was 21.3 months. Of 482 patients, 53% were treated with 3D-CRT and 47% with IMRT. The IMRT group had larger planning treatment volumes (median, 427 *v* 486 mL; $P = .005$); a larger planning treatment volume/volume of lung ratio (median, 0.13 *v* 0.15; $P = .013$); and more stage IIIB disease (30.3% *v* 38.6%, $P = .056$). Two-year OS, progression-free survival, local failure, and distant metastasis–free survival were not different between IMRT and 3D-CRT. IMRT was associated with less ≥ grade 3 pneumonitis (7.9% *v* 3.5%, $P = .039$) and a reduced risk in adjusted analyses (odds ratio, 0.41; 95% CI, 0.171 to 0.986; $P = .046$). IMRT also produced lower heart doses ($P < .05$), and the volume of heart receiving 40 Gy (V40) was significantly associated with OS on adjusted analysis ($P < .05$). The lung V5 was not associated with any ≥ grade 3 toxicity, whereas the lung V20 was associated with increased ≥ grade 3 pneumonitis risk on multivariable analysis ($P = .026$).

Conclusion

IMRT was associated with lower rates of severe pneumonitis and cardiac doses in NRG Oncology clinical trial RTOG 0617, which supports routine use of IMRT for locally advanced NSCLC.

J Clin Oncol 35:56-62. © 2016 by American Society of Clinical Oncology

- Clinically significant radiation pneumonitis develops in fewer patients treated with SBRT compared with conventional radiation therapy.
  - attributable to lower irradiated lung volumes and a lower mean lung dose

Int J Radiat Oncol Biol Phys 2017; 97:778

Volume of lung irradiated:

- Directly related
- This risk is higher with increasing lung volume in the tangential fields, treatment to the regional lymph nodes (supraclavicular, axillary apex, and internal mammary regions).

Int J Radiat Oncol Biol Phys 2010; 76:S10
Int J Radiat Oncol Biol Phys 2010; 76:S70

Induction chemotherapy

- Induction chemotherapy prior to chemoradiotherapy may increase the risk of radiation pneumonitis
- In a retrospective review of 96 patients treated for esophageal cancer,
  - the incidence of moderate to severe pneumonitis at one year was higher among those who received induction chemotherapy prior to chemoradiotherapy, compared with those who did not (49 versus 14 percent)

Int J RadiatOncol Biol Phys 2007; 67:1360.

DOSE OF IRRADIATION:

Mean lung dose[MLD]-

- Average dose received by the normal lung

V20-

- defined as the volume of normal lung (total lung volume minus planning target volume for radiotherapy) that receives more than 20 G

MLD and V20 are the best supported for routine clinical practice and its recommended to keep the V20 to <30 to 35 percent and MLD <20 to 23 Gy to decrease the risk of pneumonitis <20 percent.

Int J Radiat Oncol Biol Phys 2010; 76:S70

Published in final edited form as:

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Radiation Dose Volume Effects in the Lung

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Recommending dose/volume limits is challenging since there are no clear/consistent "thresholds" for candidate metrics (i.e., the response function is often gradual), and the "acceptable" risk level varies with the clinic scenario. RT fields for lung cancer may be appropriately-large for target coverage; physicians and patients often need to accept the significant pulmonary risks. Further, there are marked inter-patient variations in pre-RT lung function that may impact symptom development, and tumor-related dysfunction may improve after RT.

Despite these caveats, it is prudent to limit V20 to ≤30–35 %, and MLD to ≤20–23 Gy (with conventional fractionation), if one wants to limit the risk of RP to ≤20%, in definitively treated patients with non-small cell lung cancer. Similar guidelines for other parameters can be extracted from the figures. Limiting the dose to the central airways to ≤80 Gy may reduce the risk of bronchial stricture (26). In patients treated post-pneumonectomy for mesothelioma, it is prudent to limit the V5 <60%, the V20 <4–10%, and the MLD to <8 Gy (see Miles [31] for detailed review).

TIME DOSE FACTOR:

- the use of twice daily fractionation appeared to reduce the risk of RILI compared with administration of the same total daily dose as a single fraction.
- Due to lack of clear benefit and the increase in logistical difficulties, twice daily dose fractionation is rarely used.

Jpn J Clin Oncol 2010; 40:464

Concurrent chemotherapy

Sensitizers to radiotherapy- higher risk of developing RILI.

- doxorubicin, taxanes, dactinomycin, bleomycin, cyclophosphamide, vincristine, mitomycin, gemcitabine,
- recombinant interferon-alpha, and bevacizumab

Clin Chest Med 2017; 38:201

- A 2012 meta-analysis of eight studies and 1607 patients demonstrated an increased odds ratio (OR) of 1.6 (1.11 to 2.32) of radiation pneumonitis in patients receiving concurrent compared with sequential chemotherapy.
- Other risk factors identified included older age, pulmonary comorbidities and mid- to lower lung tumor location

Acta Oncol. 2012;51(8):975

Radiation recall:

when certain antineoplastic agents are administered to a patient who has received prior radiation therapy to the lung.

Doxorubicin
Erlotinib
Etoposide
Gemcitabine
Pemetrexed
paclitaxel

Chemotherapy 2012; 58:84

Other factors:

Prior thoracic irradiation
volume loss due to lung collapse
Younger age
Copd
IId
Smoking
Poor pretreatment lung function

EPIDEMIOLOGY:

Incidence of radiation pneumonitis varies depending upon the particular regimen used and upon the radiation field

Lung cancer-

7%-V20 22 to 31%

13%-V20 32 to 40%

Int J Radiat Oncol Biol Phys 2009; 45:323

A DOSE–VOLUME ANALYSIS OF RADIATION PNEUMONITIS IN NON–SMALL CELL LUNG CANCER PATIENTS TREATED WITH STEREOTACTIC BODY RADIATION THERAPY

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Purpose: To examine the rates and risk factors of radiation pneumonitis (RP) in non–small cell lung cancer (NSCLC) patients treated with stereotactic body radiotherapy (SBRT).

Methods and Materials: Dosimetry records for 251 patients with lymph node-negative Stage I–IIB NSCLC and no prior chest radiation therapy (RT) treated with SBRT were reviewed. Patients were coded on the basis of the presence of at least Grade (G) 2 RP using the Common Toxicity Criteria version 2 criteria. Radiation doses, V5, V10, V20, and mean lung dose (MLD) data points were extracted from the dose–volume histogram (DVH).

Results: Median PTV volume was 48 cc. Median prescribed radiation dose was 60 Gy delivered in three fractions to the 80% isodose line. Median age at treatment was 74 years. Median follow-up was 17 months. RP was reported after treatment of 42 lesions: G1 in 19 (8%), G2 in 17 (7%), G3 in 5 (2%), and G4 in 1 (0.4%). Total lung DVHs were available for 143 patients. For evaluable patients, median MLD, V5, V10, and V20 were 4.1 Gy, 20%, 12%, and 4%, respectively. Median MLDs were 4 Gy and 5 Gy for G0–1 and G2–4 groups, respectively ($p = 0.14$); median V5 was 20% for G0–1 and 24% for G2–4 ($p = 0.70$); median V10 was 12% in G0–1 and 16% in G2–4 ($p = 0.08$), and median V20 was 4% in G0–1 and 6.6% in G2–4 ($p = 0.05$). G2–4 RP was noted in 4.3% of patients with MLD ≤4 Gy compared with 17.6% of patients with MLD >4 Gy ($p = 0.02$), and in 4.3% of patients with V20 ≤4% compared with 16.4% of patients with V20 >4% ($p = 0.03$).

Conclusion: Overall rate of G2–4 RP in our population treated with SBRT was 9.4%. Development of symptomatic RP in this series correlated with MLD and V20.

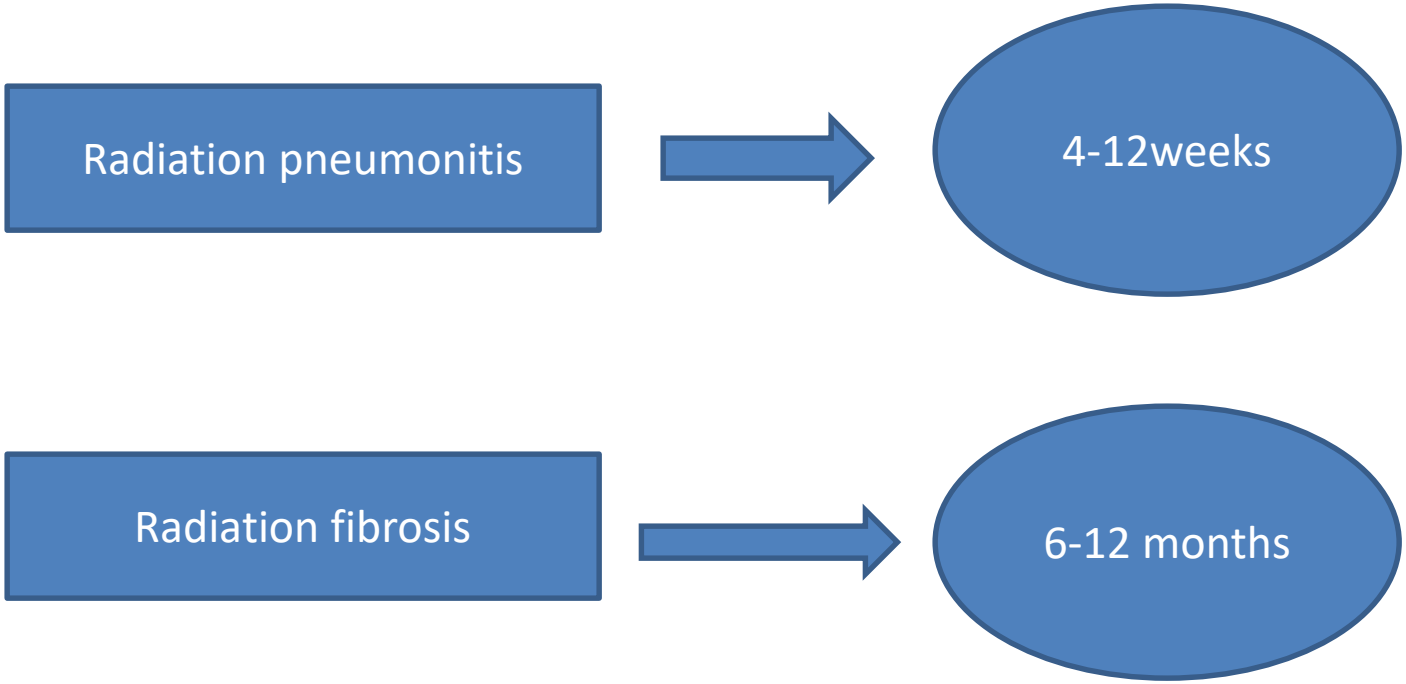
Breast cancer:

1-3%-organizing pneumonia

1-9%-grade 2 or higher radiation pneumonitis

J Thorac Oncol 2012; 7:709

CLINICAL FEATURES:



symptoms and signs of the two phases are similar
fever is less likely to occur in the fibrotic phase

Clin Chest Med 2004; 25:167

Symptoms:

- nonproductive cough,
- Dyspnea
- Low grade fever
- Chest pain → Esophageal, Rib, pleuritis
- Malaise
- Weight loss

Signs:

- Crackles
- Dullness → Pleural effusion:10%,does not increase in size
- Skin erythema
- Cyanosis, pulmonary hypertension-advanced

Toxicity Criteria for Pneumonitis					
	Grade				
Scoring System	1	2	3	4	5
CTCAE	Asymptomatic; radiographic findings only	Symptomatic; not interfering with ADL	Symptomatic; interfering with ADL; O_2 indicated	Life-threatening ventilatory support indicated	Death
RTOG/EORTIC (LENT-SOMA)	Asymptomatic or mild symptoms (dry cough), with radiographic findings	Moderately symptomatic (severe cough fever)	Severely symptomatic	Severe respiratory insufficiency; continuous oxygen/assisted ventilation	Death
SWOG (33)	Asymptomatic or symptoms not requiring steroids with radiographic findings	Initiation of or increase in steroids required	O_2 required	Assisted ventilation necessary	Death

CTCAE-common terminology criteria for adverse effects

RTOG-radiation therapy oncology group

SWOG-south west oncology group

Fishman's pulmonary diseases and disorders, 5e

DIAGNOSTIC EVALUATION

a patient who has undergone thoracic irradiation

develops dyspnea, cough, fever, malaise, auscultatory crackles, or a pleural rub, in the weeks to months after radiation therapy

RILI should be suspected

The evaluation aims at

- Assess the severity of respiratory impairment,
- exclude other possible causes
  - infection,
  - thromboembolic disease,
  - drug induced pneumonitis,
  - spread of the underlying malignancy,
  - tracheoesophageal fistula, or
  - exacerbation of underlying chronic obstructive pulmonary disease (COPD),
  - interstitial lung disease, or
  - heart failure

Int J Radiat Oncol Biol Phys. 2005;62(3):635

Laboratory studies

- No commonly employed laboratory test identifies the development of radiation pneumonitis.
- low-grade peripheral blood polymorphonuclear leukocytosis is often present
- sedimentation rate
- serum lactic dehydrogenase (LDH)
- C-reactive protein

} may be modestly elevated,

but these findings are nonspecific.

- Most patients are evaluated with a complete blood count and differential.
- Clotting studies
- blood cultures
- brain natriuretic peptide
- Appropriate tests for
  - infection,
  - heart failure, and
  - bleeding.

Serum KL-6

- Serum KL-6, a sialylated carbohydrate epitope
- Highly expressed in bronchial epithelial cells and type II pneumocytes
- Associated with interstitial lung disease and irradiation-induced lung injury for over 20 years.

Serum KL-6

- In a study of 117 patients undergoing radiation therapy for lung cancer,
  - raised serum levels of KL-6 and surfactant protein-D (SP-D) prior to therapy identified patients with evidence of interstitial lung disease on preradiation-therapy chest computed tomography (CT) and
  - high risk of severe worsening of this disease after radiation therapy

Radiat Oncol. 2010;5:32. Epub 2010

Imaging studies

- Chest radiographic abnormalities following thoracic irradiation need to be distinguished from other pulmonary diseases, such as

Infection,
Lymphangitic or direct extension of tumor,
Drug-induced pneumonitis,
Thromboembolism,
Hemorrhage,
Cardiogenic edema

- Chest computed tomography (CT) is preferred over conventional chest radiography,
  - CT provides greater sensitivity for more subtle changes
  - Improved detail regarding the type of opacity
  - More complete delineation of the radiation therapy ports.

Chest radiograph

- Chest radiographs *may be normal in symptomatic subjects during the subacute phase* of radiation pneumonitis,

or

- may show *evolving radiographic patterns* depending on the phase of lung injury (eg, *acute exudative, organizing, and fibrotic*).

Chest radiograph

- Perivascular haziness is an early radiation-induced abnormality on chest radiograph, often progressing to patchy alveolar filling densities.

- Radiographs taken during the chronic phase of radiation pneumonitis may show volume loss with coarse reticular or dense opacities.

Chest radiograph

- A straight line effect, which does not conform to anatomical units but rather to the confines of the radiation port, is **virtually diagnostic of RILI**.
- conformal and stereotactic treatment strategies, such as three-dimensional conformal radiation therapy (3D-CRT), stereotactic body radiation therapy (SBRT), **do not cause this "straight line" radiographic finding** due to the complex distribution of the radiation therapy.
  - With these techniques, a focal area of opacity with ill-defined margins is seen in the irradiated region.
  - Better delineation of the radiation fields is possible with chest CT

- Small pleural effusions and rib fractures may be seen, but *lymphadenopathy does not occur.*
- A few cases have been reported of radiographic abnormalities attributed to radiation pneumonitis outside of the irradiation port, and even in the contralateral lung

Mayo Clin Proc. 1999;74(1):27.
Cancer. 1998;82(5):842.

- This may be due to radiation scatter, lymphatic obstruction, or immunologic (hypersensitivity-like) mechanisms.

Chest computed tomography

- More sensitive in detecting subtle lung injury following radiation treatment
- The CT scan may take the form of a CT pulmonary angiogram (CTPA) to exclude pulmonary thromboembolism.

- The key step in the evaluation of radiation pneumonitis is *comparison of pretreatment CT images, containing irradiation dosimetric information*, with diagnostic CT images obtained at the time of symptom presentation by the radiation oncologist.
- Lung involvement in CT images of radiation pneumonitis typically aligns closely with the irradiated area.
- Comparisons between pre- and posttreatment images may be difficult due to tumor growth or shrinkage, changes in depth of respiration, and the complexity of the radiation port, but use of specialized software may help

Int J Radiat Oncol Biol Phys. 2011;80(2):506. Epub 2010

- Similar to the plain chest radiograph, the CT scan appearance of radiation pneumonitis correlates with the phase of lung injury, although a given patient may present at any one of the phases

Radiographics. 2000;20(1):83
Radiographics. 2004;24(4):985.

- The *initial phase,*
  - occurs three to five months after completion of radiation therapy,
  - typically shows ground-glass attenuation within the area of irradiated lung.
- The *organizing phase*
  - is typically associated with patchy areas of consolidation that coalesce to form a relatively sharp edge that conforms to the radiation therapy portals rather than anatomic structures.
  - These patchy areas sometimes appear nodular.

- The opacities associated with the organizing phase may resolve with minimal scarring or may evolve into *a fibrotic phase*,
  - characterized on CT by linear opacities (scarring) or an area of dense consolidation and volume loss.
  - The area of consolidation typically corresponds to the radiation port, although conformal and stereotactic treatment strategies do not yield the classic "straight line" radiographic finding

Table 1. Radiological Grading Scale of Radiation Induced Pneumonitis (RP) (Kouloulias et al., 2013)

Grade	CT Findings
0	No f indings.
1	Ground glass opacities without fuzziness of the subjacent pulmonary vessels.
2	The findings may vary from ground glass opacities, extending beyond the radiation field, to consolidation
3	Clear focal consolidation ± elements of fibrosis.
4	Dense consolidation, cicatrisation atelectasis, (traction bronchiectasis), significant pulmonary volume loss and thickening.

Asian Pac J Cancer Prev. 2015;16(7):2613-7

Nuclear medicine studies

- Standard nuclear medicine scans add little to the diagnosis of radiation pneumonitis.
- there is growing interest in single photon emission tomography (SPECT), functional magnetic resonance (MR) spectroscopy, and positron emission tomography (PET) scanning to better define and perhaps predict outcome.
- These concepts are under active investigation

Radiat Res. 2012 Apr;177(4):449-66. Epub 2012

Pulmonary function tests

- PFTs may help in differentiating whether symptoms are due to a flare of COPD or an interstitial process and to determine the severity of respiratory impairment.
  - Spirometry (before and after broncho
  - lung volumes,
  - diffusing capacity for carbon monoxi
  - six-minute walk test with oximetry

are *obtained as a baseline prior to radiation therapy* and *repeated in response to symptoms*.

Pulmonary function tests

- Demonstrate
  - Reduction in lung volumes (total lung capacity [TLC],forced vital capacity [FVC], residual volume [RV]), diffusing capacity, and lung compliance
  - Tidal volumes are also decreased
  - Respiratory rate may be elevated.
  - Resting and ambulatory pulse oxygen saturation (SpO2) may be reduced

Clin Chest Med. 2017;38(2):201. Epub 2017
Int J Radiat Oncol Biol Phys. 2005;62(3):639
J Thorac Oncol. 2015;10(12):1762.

Pulmonary function tests

- The diffusing capacity for carbon monoxide (DLCO or transfer factor) is usually depressed in patients with radiation-induced lung damage, but this finding is nonspecific, as it can also be reduced in emphysema and interstitial lung disease.

Int J Radiat Oncol Biol Phys. 2012Aug;83(5):1573-9.

Pulmonary function tests

- One trial suggested that failure of the DLCO to increase from the nadir value following myeloablative chemotherapy was more closely associated with the risk of progressive pulmonary dysfunction during subsequent irradiation than other parameters of lung function

Cancer 2002;94:2821.

Bronchoscopy

- The main role for flexible fiberoptic bronchoscopy is to evaluate for
  - infection,
  - bleeding,
  - drug hypersensitivity, or
  - spread of the underlying malignancy.
- Bronchoscopy with bronchoalveolar lavage is performed in the majority of patients.
- Transbronchial biopsy specimens may be useful for assessment of
  - infection or
  - lymphangitic spread of tumor in cases that are clinically atypical for RILI,
    - but the size of the specimens is usually too small to establish a diagnosis of radiation pneumonitis.

Bronchoalveolar lavage fluid (BALF)

- BALF findings in radiation pneumonitis are not specific
  - Usually showing an increased number of leukocytes (predominantly lymphocytes)
  - majority are CD4+

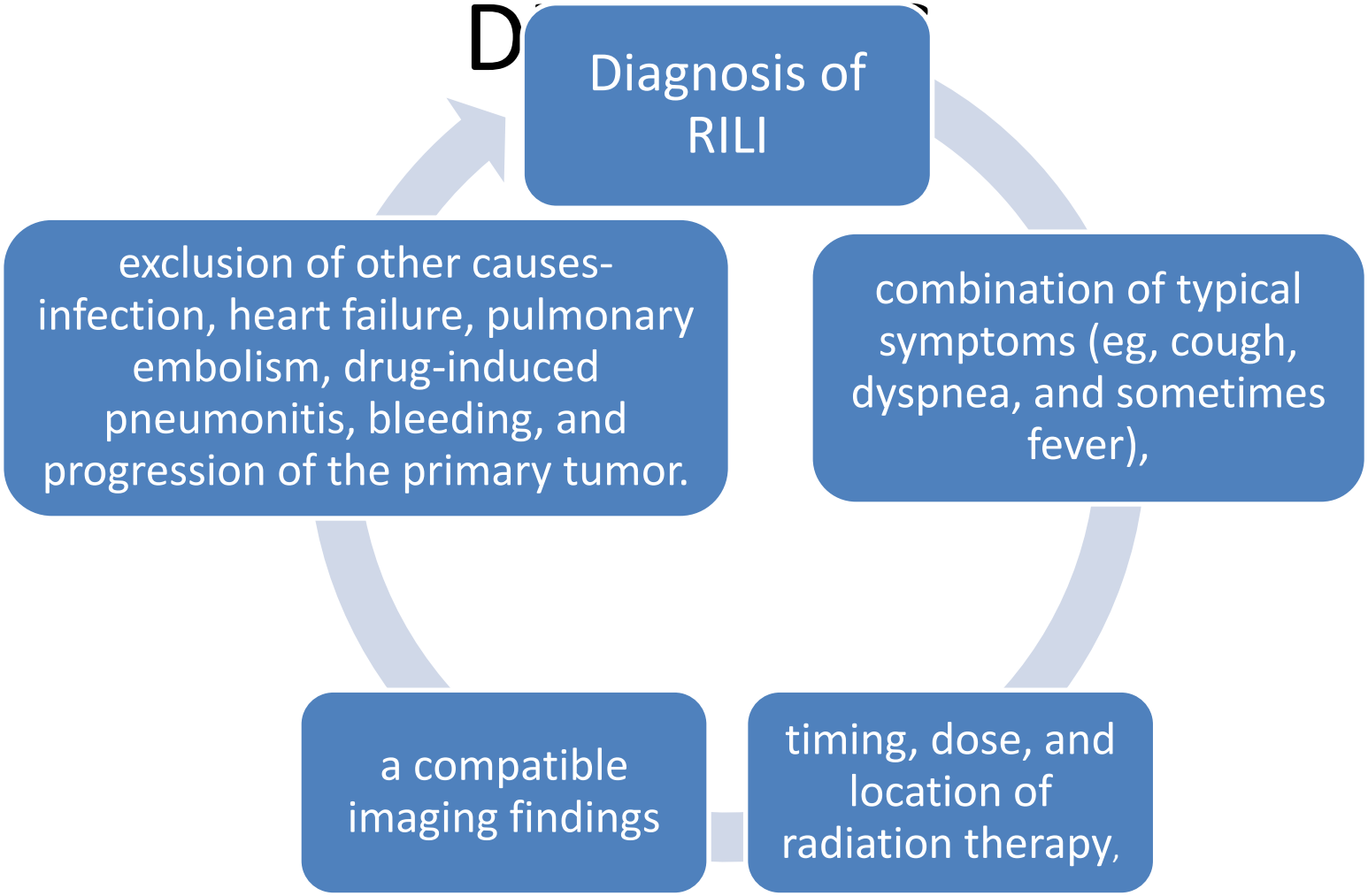
Lymphocyte numbers are increased in both the irradiated and nonirradiated lung

- The number of neutrophils, eosinophils, and macrophages may also be increased.

Int J Radiat Oncol Biol Phys. 1996;34(2):459

- Tissue specimens are only occasionally required in the evaluation of patients suspected to have radiation pneumonitis.
- Transbronchial and transthoracic needle biopsy specimens are too small to establish a diagnosis, but may be useful for ruling out infection or lymphangitic spread of tumor in cases that are clinically atypical for RILI.

D


Diagnosis of RILI
combination of typical symptoms (eg, cough, dyspnea, and sometimes fever),
timing, dose, and location of radiation therapy,
a compatible imaging findings
exclusion of other causes- infection, heart failure, pulmonary embolism, drug-induced pneumonitis, bleeding, and progression of the primary tumor.

DIFFERENTIAL DIAGNOSIS

- Infection;
- thromboembolic disease;
- drug-induced pneumonitis;
- spread of the underlying malignancy; and
- exacerbation of chronic obstructive pulmonary disease (COPD),
- interstitial lung disease, or
- heart failure.
  - For patients with chest discomfort, but without new lung parenchymal changes on chest imaging, potential causes include pericarditis and esophagitis.

TREATMENT:

No prospective controlled studies have evaluated the efficacy of therapies for radiation pneumonitis in humans

- Most widely used therapy-Glucocorticoids
- Established fibrosis-steroids less useful

Supportive care:

- ✓ antitussive therapy,
- ✓ supplemental oxygen
- ✓ treatment of comorbid diseases
- ➢ chronic obstructive pulmonary disease (COPD)
- ➢ heart failure.

Patients with minimal or no symptoms:

May have spontaneous resolution

Monitor at regular intervals-clinically, chest radiograpg and PFTs.

Inhaled glucocorticoids may help

single center study-

24 patients with pneumonitis[grade2] following irradiation for lung cancer were initially treated with high dose inhaled glucocorticoids (budesonide 800 micrograms twice a day) for 14 days.

- 18-responded
- Median duration-8months.

Radiat Oncol 2016; 11:12

Symptomatic patients with subacute radiation pneumonitis:

- Moderate to severe symptoms
- Evidence of impaired respiratory function

Glucocorticoids:

Prednisolone 60mg/day
2-4 weeks
Taper over 3-12 weeks

If relapses-
return to full dose for two weeks
Taper slowly

Clin Chest Med 2017; 38:201

Other immunosuppressive drugs:

Only case reports

- Cyclosporine
- Azathioprine

In those who don’t tolerate or steroid resistant.

Radiation-associated organizing pneumonia:

approach used for cryptogenic organizing pneumonia (COP) followed

- Minimal symptoms-monitor
- Moderately/ severely symptomatic-

Prednisolone-

0.75-1mg/kg-4-8weeks –once improves 0.5-0.75mg/kg next 4-6weeks-gradual taper

Radiation-induced pulmonary fibrosis:

- no established guidelines
- Inflammation not prominent-steroids wont help
- Best treatment-supportive care.

Int J Radiat Oncol Biol Phys. 2004 Jan 1;58(1):213-9

EXPERIMENTAL AGENTS:

Ozturk B etal, 2004	40 patients with lung or breast cancer were randomized to receive **Ptx (400 mg) or a placebo**, 3 times daily, during the entire period of radiotherapy	grade 2 or 3 pulmonary toxicity- **20 vs 50%** pentoxifylline group had a **significantly better diffusing capacity** for carbon monoxide at both three and six months following therapy (73 versus 58, and 72 versus 57 percent at three and six months, respectively)	significant protective effect of Ptx for both early and late lung radiotoxicity

Int J Radiat Oncol Biol Phys. 2004 Jan 1;58(1):213-9

Amifostine:

- prodrug that is dephosphorylated by alkaline phosphatase in tissues to a pharmacologically-active free thiol metabolite
- acts as a scavenger of free radicals generated in tissues exposed to radiation

- might decrease RILI without diminishing the therapeutic effect of radiation

Semin Radiat Oncol 2002; 12:50
Semin Oncol 2005; 32:S55

Antonadou D etal, 2001	**n-146** Radiotherapy (XRT) patients (n = 146) received a daily fraction of 2 Gy/5 days/week to a total of 55-60 Gy +/- amifostine 340 mg/m(2) administered daily 15 min before irradiation	**2m-** **43% (23/53) of patients in the XRT arm and 9%** (4/44) in the A + XRT arm experienced > or = Grade 2 pneumonitis ($p < 0.001$) **6m-** At 6 months, fibrosis was present in **53% (19/36) receiving XRT vs. 28%** (9/32) receiving A+XRT ($p < 0.05$)	Amifostine reduces the incidence of pneumonitis, lung fibrosis, and esophagitis in radiotherapy patients with lung cancer without compromising antitumor efficacy

Int J Radiat Oncol Biol Phys 2001; 51:915

Angiotensin converting enzyme inhibitors:

- shown to reduce radiation-induced lung fibrosis in rats
- In a retrospective study of patients who underwent radiation therapy for lung cancer, those taking an ACEI demonstrated less clinically significant RILI.

Kharofa J etal, 2012	Patients with Stage I through III small-cell and non-small-cell lung cancer treated definitively with radiation from 2004-2009 were retrospectively reviewed N-162	**38%(62) were using ACEI** The rate of Grade 2 or higher pneumonitis was lower in ACE inhibitor users vs. nonusers **(2% vs. 11%, p = 0.032)**	ACE inhibitors may decrease the incidence of radiation pneumonitis in patients receiving thoracic radiation for lung cancer

Aidi-

Aidi (Z52020236, China Food and Drug Administration [CFDA]) is an injectable agent composed of the extracts from Astragalus, Eleutherococcus senticosus, Ginseng, and cantharidin

Traditional chinese medicines

Systematic Review and Meta-Analysis

Medicine®

OPEN

Can Aidi injection alleviate the toxicity and improve the clinical efficacy of radiotherapy in lung cancer?

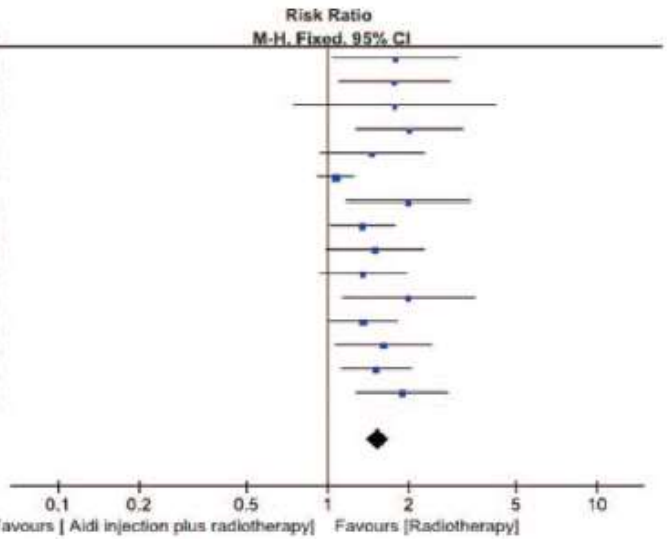
A meta-analysis of 16 randomized controlled trials following the PRISMA guidelines

Zheng Xiao, MD, MS[a,b,*], Rui Liang, BS[c], Cheng-qiong Wang, BS[a,b], Shaofeng Xu, BS[c], Nana Li, MS[a,b], Yuejuan He, MS[a,b], Fushan Tang, MD, MS[a,d], Ling Chen, MD, MS[a,b], Hu Ma, MD, MS[e]

Study or Subgroup	Aidi injection plus radiotherapy Events	Total	Radiotherapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Wu.J2003	18	25	10	25	3.9%	1.80 [1.05, 3.08]	2003
Wen.XX2005	23	32	13	32	5.0%	1.77 [1.10, 2.84]	2005
Wang.Y,et.al2006	12	37	6	33	2.4%	1.78 [0.75, 4.22]	2006
Tian.YP,et.al2007	29	38	14	37	5.5%	2.02 [1.29, 3.16]	2007
Han.Q,et.al2007	16	20	12	22	4.4%	1.47 [0.94, 2.28]	2007
Qian.YH,et.al2007	41	45	38	45	14.6%	1.08 [0.92, 1.26]	2007
Wang.QC,et.al2008	23	30	10	26	4.1%	1.99 [1.18, 3.37]	2008
Huang.ZG,et.al2008	31	35	21	32	8.4%	1.35 [1.02, 1.78]	2008
Jia.YS,et.al2010	24	33	15	31	6.0%	1.50 [0.99, 2.29]	2010
Wang.CY,et.al2012	22	27	15	25	6.0%	1.36 [0.94, 1.96]	2012
Liu.XH,et.al2012	20	30	10	30	3.9%	2.00 [1.14, 3.52]	2012
Li.ZY,et.al2013	42	60	31	60	11.9%	1.35 [1.01, 1.82]	2013
Zhao.YJ,et.al2013	24	40	23	62	6.9%	1.62 [1.07, 2.44]	2013
Yang.Z.2013	38	46	25	46	9.6%	1.52 [1.13, 2.04]	2013
Song.LL,et.al2013	36	49	19	49	7.3%	1.89 [1.28, 2.80]	2013
Total (95% CI)		**547**		**555**	**100.0%**	**1.54 [1.39, 1.70]**	
Total events	399		262				

Heterogeneity: $Chi^2 = 27.19$, $df = 14$ ($P = 0.02$); $I^2 = 49\%$

Test for overall effect: $Z = 8.57$ ($P < 0.00001$)



PREVENTION:

best known strategies for reducing RILI are those that limit the radiation dose and volume of normal lung tissue irradiated

- mean lung dose (MLD)-<20Gy
- V20-<35% to keep risk of Rpn <20%

TAKE HOME MESSAGE:

- Many factors affect the risk for RILI including the method of irradiation, the volume of irradiated lung, the total dosage and frequency of irradiation, associated chemotherapy, and possibly the genetic background of the patient.

- optimal treatment for RILI is not known
- Those with established fibrosis due to prior irradiation are unlikely to benefit from glucocorticoid therapy
- The best known strategies for reducing RILI are those that limit the radiation dose and volume of normal lung tissue irradiated.
- RCTs required to establish the role of drugs for prevention of RILI.