Case Report

# Fatal Radiation Pneumonitis in Patients With Subclinical Interstitial Lung Disease

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## Clinical Practice Points

- We report 2 cases of fatal radiation pneumonitis (RP) in lung cancer patients with asymptomatic interstitial lung disease (ILD) found incidentally on pretreatment imaging.
- Symptomatic ILD appears to be a risk factor for RP.
- Asymptomatic ILD found incidentally on imaging may be an underreported and underrecognized risk factor for RP.
- Additional research is needed in patients with any degree of ILD so that providers can better counsel patients and minimize the risks of thoracic radiotherapy.

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## Introduction

Interstitial lung disease (ILD) is a heterogeneous group of conditions characterized by restrictive physiology, impaired gas exchange, and progressive irreversible fibrosis over the course of years. The most common type of ILD is idiopathic pulmonary fibrosis (IPF), which carries a median overall survival of 2 to 5 years and has been identified in 7.5% of patients with surgically resected lung cancer.[1] The diagnosis of IPF is based on the absence of a known cause of lung fibrosis and findings of usual interstitial pneumonia (UIP) on high-resolution computed tomography (CT) or surgical lung biopsy. Diagnostic criteria for UIP on CT include predominantly basilar and subpleural reticular abnormalities and honeycombing in the absence of any features "inconsistent with UIP pattern."[2]

Radiation pneumonitis (RP) is an important toxicity of thoracic radiotherapy (TRT). It is a clinical diagnosis characterized by cough, fever, and dyspnea on exertion between 1 and 6 months after TRT in the absence of an alternative diagnosis. In patients who undergo thoracic chemoradiotherapy (CRT), symptomatic RP occurs in about 30% and fatal RP in 2%.[3] In patients who undergo thoracic stereotactic body radiotherapy (SBRT), symptomatic RP occurs in about 20% and fatal RP in 1%.[4]

Clinical ILD has been reported as a potential risk factor for RP.[5,6] However, up to 10% of smokers[7] and up to 18% of patients who have undergone TRT[5] have asymptomatic subclinical ILD as an incidental finding on CT. The risk of RP among these patients has been poorly characterized. Yamaguchi et al[5,6] suggest that patients with extensive subclinical ILD should be treated with caution owing to potential increased risk for fatal RP. However, limited subclinical ILD has not yet been associated with fatal RP. We present 2 cases of fatal RP in patients with limited subclinical IPF found incidentally on pretreatment CT.

### *Patient 1*

A 74-year-old woman with prior 40-pack-year smoking history was diagnosed with right lower lobe squamous cell carcinoma (T2bN0M0). Pulmonary history included asthma, obstructive sleep apnea, and prior pulmonary coccidioidomycosis. Baseline chest CT had incidental classic findings for UIP. She had no known cause of lung fibrosis. She was diagnosed with limited IPF but was asymptomatic. Pulmonary function tests showed forced vital capacity 1.66 L or 67% predicted, forced expiratory volume in the first second of expiration (FEV1) 1.35 L or 73% predicted, and diffusion capacity of the lungs for carbon monoxide 10.18 mL/min/mm Hg or 54% predicted. She was treated with SBRT, 50 Gy in 5 consecutive daily fractions. Planning target volume (PTV) measured 80.7 $cm^3$. Dose-volume histogram of the lungs showed V20 of 11% (the percentage

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of the lungs receiving > 20 Gy). Mean lung dose (MLD) was 13.8 Gy. Two months after SBRT, she developed severe RP. Alternative etiologies for her symptoms were ruled out. Treatment included oral dexamethasone (4.0 mg daily), tapered over 1 month. Symptoms progressed. Oral dexamethasone taper was repeated over 2 months, and she started tiotropium inhaler (18 mcg capsule daily). She required supplemental oxygen. Eight months after SBRT, she died of respiratory failure attributed to RP. Figure 1 shows pre-radiotherapy (RT) imaging, RT treatment plan, and post-RT imaging 7 months after SBRT completion.

### *Patient 2*

An 80-year-old man with prior 25-pack-year smoking history was diagnosed with right-sided, limited-stage small-cell lung cancer (SCLC). Baseline chest CT had incidental classic findings for UIP. He had no known cause of lung fibrosis. He was diagnosed with limited IPF but was asymptomatic. Pulmonary function tests showed forced vital capacity 2.93 L or 75% predicted, FEV1 2.27 L or 82% predicted, and diffusion capacity of the lungs for carbon monoxide 18.58 mL/min/mm Hg or 87% predicted. He was treated with TRT, 45 Gy in 30 fractions twice daily, with concurrent cisplatin-etoposide (60 mg/m$^2$-120 mg/m$^2$) for 4 cycles. PTV measured 191.3 cm$^3$. Dose-volume histogram of the lungs showed V20 of 17% and MLD of 10.33 Gy. Four months after TRT completion, he developed severe RP. Alternative etiologies for his symptoms were ruled out. Treatment included oral methylprednisolone (6 day taper, starting at 24 mg). Symptoms progressed. He was given oral prednisone (60 mg daily for 2 weeks, followed by 40 mg daily). He required supplemental oxygen. Six months after RT completion, he died of respiratory failure attributed to RP. Figure 2 shows pre-RT imaging, RT treatment plan, and post-RT imaging 6 months after CRT completion.

## Discussion

Fatal RP has been reported in 2% of TRT[3] and 5% of thoracic CRT.[8] Classically, V20 $\leq$ 30% to 35% and MLD $\leq$ 20 to 23 Gy have been associated with a risk of symptomatic RP $\leq$ 20%.[9] For medically inoperable non–small-cell lung cancer (NSCLC) treated with definitive TRT, Graham et al[10] found symptomatic RP to be associated with V20 and MLD. V20 < 22% resulted in no

**Figure 1** Pre-Radiation Therapy (RT) Chest Computed Tomography. A, Coronal, B, Axial, and C, Sagittal Images With Limited Interstitial Changes. RT Treatment Plan Dose-Color-Wash. D, Coronal, E, Axial, and F, Sagittal Images (Red = Greater than 55 Gy; Green = 25-40 Gy; Blue = 5-15 Gy). Seven Months Post-RT Chest Computed Tomography. G, Coronal, H, Axial, and I, Sagittal Images With Extensive Interstitial Changes