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Radiation-Induced Lung Injury
Assessment and Management

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Radiation-induced lung injury (RILI) encompasses any lung toxicity induced by radiation therapy (RT) and manifests acutely as radiation pneumonitis and chronically as radiation pulmonary fibrosis. Because most patients with thoracic and breast malignancies are expected to undergo RT in their lifetime, many with curative intent, the population at risk is significant. Furthermore, indications for thoracic RT are expanding given the advent of stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR) for early-stage lung cancer in nonsurgical candidates as well as oligometastatic pulmonary disease from any solid tumor. Fortunately, the incidence of serious pulmonary complications from RT has decreased secondary to advances in radiation delivery techniques. Understanding the temporal relationship between RT and injury as well as the patient, disease, and radiation factors that help distinguish RILI from other etiologies is necessary to prevent misdiagnosis. Although treatment of acute pneumonitis is dependent on clinical severity and typically responds completely to corticosteroids, accurately diagnosing and identifying patients who may progress to fibrosis is challenging. Current research advances include high-precision radiation techniques, an improved understanding of the molecular basis of RILI, the development of small and large animal models, and the identification of candidate drugs for prevention and treatment.
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First discovered as treatment for breast tumors at the beginning of the 1900s, radiation therapy (RT) remains a cornerstone of treatment in both the definitive (ie, curative) and palliative settings for many malignancies. Patients undergoing definitive RT typically have locally advanced, surgically unresectable, or medically inoperable malignancies. For patients in whom surgery or chemotherapy are the definitive treatment modalities, RT is commonly used in the adjuvant/consolidative setting. The goal of RT is to eliminate or reduce tumor growth/burden while sparing normal tissues, a feat facilitated by improvements in imaging techniques, stereotactic RT, and treatment planning. However, the benefits of RT are occasionally complicated by off-target adverse effects.

Radiation-induced lung injury (RILI) is an important dose-limiting factor in radiation

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directed to the thorax and may primarily affect patients treated for lung cancer, breast cancer, lymphoma, or those who receive total body irradiation as part of a bone marrow transplant.[1,2] In lung cancer, about 200,000 new cases were reported in the US alone in 2017 and up to 80% of these patients had unresectable disease.[3,4] For early-stage disease, stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR) has emerged as a standard treatment regimen for nonsurgical candidates.[5] In patients with locally advanced disease, thoracic radiotherapy with concurrent chemotherapy remains the standard of care for definitive management.[6] Furthermore, > 50% of patients with breast or other thoracic malignancies receive RT, and improvements in systemic therapy are likely to only increase the number of patients receiving thoracic RT in the palliative or oligometastatic setting.[7,8] Thus, the overall number of patients at risk of RILI is significant and not limited to lung cancer.

The estimated incidence of RILI varies widely across studies, likely due to varying definitions of clinically significant lung injury and the citation of data prior to modern radiotherapy planning (two-dimensional era). More recent data suggest RILI incidence is highest for lung cancer (5%-25%) followed by mediastinal lymphoma (5%-10%) and breast cancer (1%-5%).[9-14] It is imperative for clinicians to recognize and distinguish RILI from other lung pathologies when evaluating respiratory symptoms in a patient with cancer and a history of thoracic RT. This distinction proves particularly difficult in patients with cancer, whose clinical presentation is often complicated by the presence of other underlying conditions, such as the tumor itself (atelectasis, obstruction, and lymphangitis), drugs (ie, chemotherapy), or infection. In clinical practice, clinicians are often not familiar with the modality of radiation, the differences in dose, delivery technique, and the associated biological effect of RT, factors which may directly correlate with toxicity.

The present review offers current knowledge about the risk factors associated with RILI, outlines the molecular and cellular mechanisms of RILI, and highlights clinically relevant perspectives on the approach to its diagnosis and management.

Pathophysiology

The effect of radiation on the lung was originally described in 1925 by Evans and Leucutia,[15] who categorized RILI into an acute injury stage, radiation pneumonitis (RP), and the ensuing chronic injury stage, radiation pulmonary fibrosis (RPF). Although the two stages are interdependent, they can be clearly separated in time: RP occurs within 6 months of therapy (most often within 12 weeks), whereas RPF occurs > 1 year following therapy.[2,16,17] A temporal biological phenomenon exists, with events proceeding at a molecular level until the development of histopathological abnormalities that define lung injury. The majority of patients will never reach the level of clinically significant RPF; however, fibrosis is believed to be the end point of a continuous progression of events, whereby each phase contributes to the eventual development of irreversible damage.[10,18]

The pathophysiology of RP can be described as two distinct mechanisms, "classic" or "sporadic." Classic RP is well described and historically has been used to describe damage following radiation to large lung volumes.[19] The injury occurs "in-field" (eg, within the treatment volume), likely due to the direct cytotoxic action of ionizing radiation on lung cells and can progress to pulmonary fibrosis. A proposed sequence of histologic changes leading to classic pneumonitis was first described in 1968 by Rubin and Casarett[20] and later detailed by others.[21-23] This sequence divides the clinical picture into three main phases of radiation response: an early phase, an intermediate phase (acute pneumonitis), and a late phase (pulmonary fibrosis). Immediately following radiation exposure, increased capillary permeability contributes to pulmonary edema. Damage to type I and II pneumocytes leads to loss of surfactant and transudation of serum proteins into the alveoli.

These changes are not visible by light microscopy, and there are no radiographic or clinical signs of damage; thus, the first sequence is known as the "latent phase." However, electron microscopy has allowed visualization of the degenerative changes to pneumocytes, thickened secretions of mucus from goblet cells, basement membrane swelling, and endothelial cell changes that occur during this phase. Cytokines released from damaged lung cells (eg, tumor necrosis factor alpha) attract inflammatory cells to the alveoli and pulmonary interstitium, inducing the acute-phase pneumonitis.[19] Injury in the acute phase seems to be radiation dose-dependent in that higher doses are associated with more severe pneumonitis.[24-26] The late phase constitutes pulmonary fibrosis, which stems from pathological repair following classical RP. Cytokines, growth factors, and reactive oxygen species released by macrophages and other resident lung cells stimulate collagen

production by fibroblasts, leading to reductions in lung elasticity and scarring seen on imaging studies. Transforming growth factor beta (TGF-β) is particularly important in stimulating collagen synthesis,[27] and thoracic irradiation has been associated with persistently elevated TGF-β levels upon therapy completion.[28]

Simply, the summarized sequence of classic RP is as follows: cellular injury leads to cytokine release, cytokine recruitment of the inflammatory infiltrate causes acute pneumonitis, and the body's attempt to repair the injury results in pulmonary fibrosis (Fig 1). However, several questions about the progression of the disease remain, as some investigators note many cases of RP cannot be explained entirely by this process. For example, if there is a dose-dependent response to radiation in the lungs, why is the occurrence and onset of RP unpredictable?

Furthermore, in many cases, the severity of dyspnea or radiologically evident lung damage appears out of proportion to the radiation dose or lung volume irradiated. Finally, it is unclear why most patients have complete resolution of symptoms without progression to pulmonary fibrosis. The mechanism for "sporadic" RP was developed to account for cases unexplained through the "classic" mechanism. The most accepted model, proposed by Morgan et al,[29] suggests that "sporadic" RP mimics hypersensitivity pneumonitis. BAL from such patients receiving unilateral radiotherapy showed significant lymphocytosis in both lungs composed primarily of CD4+ T cells.[30,31] This effect is more pronounced in patients who develop clinically significant RP. This model of pneumonitis, comparable to hypersensitivity pneumonitis, helps explain cases that fall outside the classic presentation. The recognition of
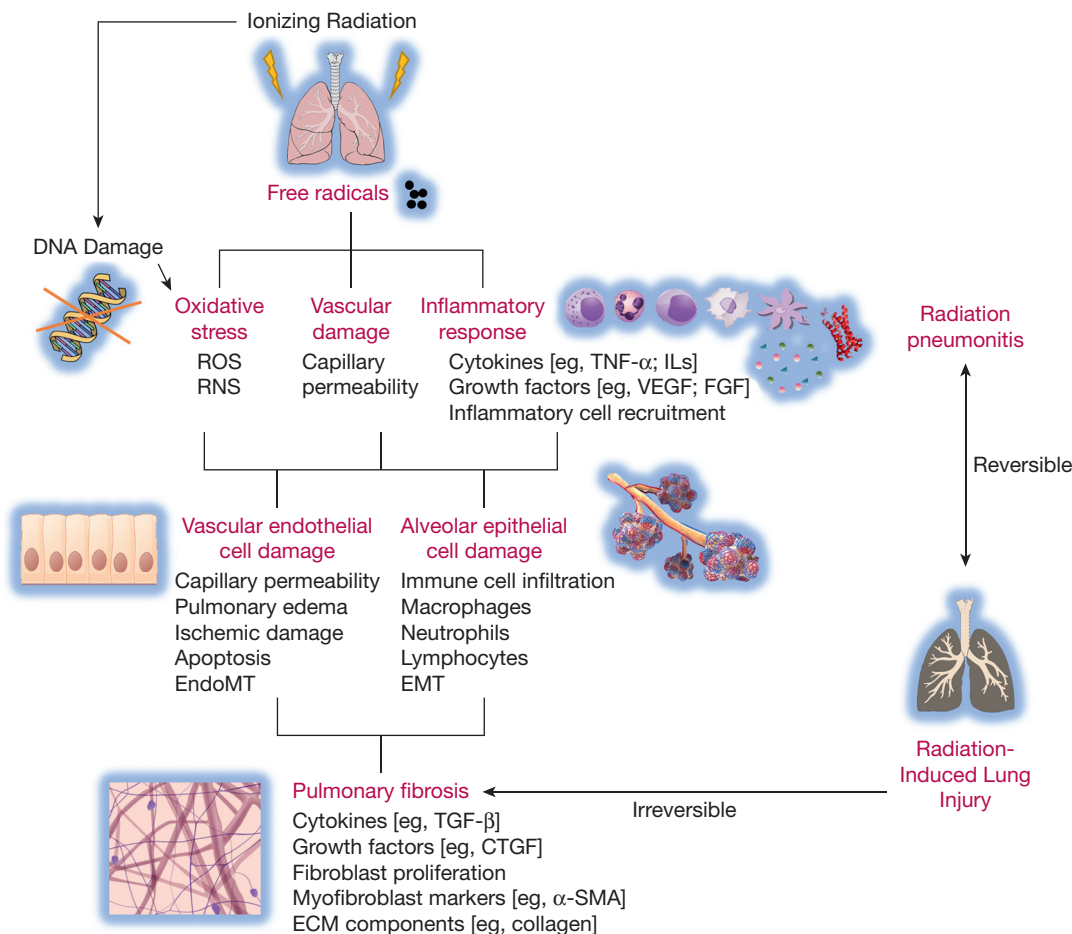

Figure 1 – *The pathobiology of radiation pneumonitis and radiation-induced lung injury. Ionizing radiation induces free radicals and DNA damage to promote oxidative stress, vascular damage, and inflammation that manifest during radiation pneumonitis. Persistent inflammation sustains alveolar epithelial and vascular endothelial cell damage and contributes to pathologic changes, including immune cell infiltration, capillary permeability, and pulmonary edema. Prolonged alveolar and vascular damage leads to EMT and/or EndoMT and eventually culminates in fibrotic changes. α-SMA = alpha smooth muscle actin; CTGF = connective tissue growth factor; ECM = extracellular matrix; EMT = epithelial-to-mesenchymal transition; EndoMT = endothelial-to-mesenchymal transition; FGF = fibroblast growth factor; ILs = interleukins; ROS = reactive oxygen species; RNS = reactive nitrogen species; TGF-β = transforming growth factor beta; TNF-α = tumor necrosis factor alpha; VEGF = vascular endothelial growth factor.*

sporadic RP can be particularly difficult for clinicians because it is rare (approximately 10% of cases[29]), and patients often present with severe dyspnea and/or "out-of-field" radiographic findings that may raise the possibility of other disease processes.

Risk Factors

Although most patients receiving thoracic irradiation are at risk for RILI, the presence or absence of several factors may modify their risk (Table 1). For all patients, history of smoking, COPD, and interstitial lung disease are all associated with increased risk.[32-38] In patients with breast cancer, concurrent use of chemotherapy or tamoxifen, older age, chest wall irradiation with electrons, and supraclavicular field treatment are correlated with increased risk.[39,40] In patients with lymphoma, risk of pneumonitis is increased in those treated for relapsed or refractory disease vs those who received consolidation therapy.[14] Both induction and concurrent chemotherapy increase the risk of RILI, particularly in chemotherapeutic agents known to cause lung injury.[41] In addition, systemic agents, including chemotherapy, immunotherapy, and targeted therapies, have all been implicated in cases of radiation recall pneumonitis. Radiation recall is a poorly understood, unpredictable, acute inflammatory phenomenon in the irradiated field, and in the case of thoracic RT, the patient develops or redevelops RP at a time interval

TABLE 1] Risk Factors for Radiation-Induced Lung Injury

Radiation risk factors
% Total lung volume receiving $\geq$ 20 Gy (V20), $\geq$ 30%
% Total lung volume receiving $\geq$ 5 Gy (V5), $\geq$ 65%
Mean lung dose, > 20 Gy
Absolute volume lung spared >5 Gy (AVS5), < 500 cc
Target location, lower lobe
Disease risk factors
Refractory or relapsed disease (lymphoma)
Supraclavicular field (breast cancer)
Bulky disease
Chemotherapy
Re-irradiation
Host risk factors
Age $\geq$ 50 y
Autoimmune disease
Interstitial lung disease
Former or current smoker
COPD

significantly later than expected and secondary to drug administration.[42-44] Historically, doxorubicin, docetaxel/paclitaxel, gemcitabine, and capecitabine are known offenders.[45]

In general (but particularly for patients with lung cancer), radiation oncologists attempt to limit RILI by minimizing the volume of lung receiving $\geq$ 20 Gy or 30 Gy (V20 and V30, respectively), as a higher V20 in particular has been shown to be predictive of RP.[9,46-49] Higher mean lung doses and irradiation of the lower lung fields also correlate with increased incidence of pneumonitis.[24,48,50] Given this understanding, the radiation oncologist must balance dose between toxicity and target, the latter of which, if compromised, can yield inferior local tumor control and overall survival in thoracic malignancies.[51] Recently, even low doses of radiation, given to a large volume of lung, have been associated with increased risk of acute lung toxicity. One increasingly used metric is the volume of lung receiving > 5 Gy (V5).[52] Inversely, the absolute volume of lung spared 5 Gy is labeled AVS5, and higher AVS5 values have been associated with reduced incidence of RILI.[46,53] As radiation dose constraints are defined from clinical end points and the dosimetric data of every patient are maintained by their radiation oncologist, it would be prudent to inquire on these when assessing pretest probability for RILI.

More sophisticated techniques of conformal RT technologies such as intensity-modulated RT (IMRT), volumetric arc radiotherapy (VMAT), SBRT, and stereotactic radiosurgery (SRS) are associated with a lower incidence of RILI compared with standard, three-dimensional conformal RT.[54-59] This finding is likely due to increased precision of radiation delivery to a tumor while sparing surrounding normal tissue (Fig 2). In addition, the versatility of these techniques helps account for patients' anatomy, breathing pattern, and organ motion to guide the beams' intensity and direction. All of these modalities are expected to lower the volume and dose of lung irradiated (both associated with risk of RILI[9,24,60-63]) while maintaining millimeter range accuracy. Furthermore, many centers use daily-image guidance as well as deep inspiratory breath hold or respiratory-gating. In patients with early-stage lung cancer undergoing SBRT, fiducial-based tracking (ie, CyberKnife; Accuray Incorporated) of the tumor may be used to reduce the total treatment volume given increased precision. In theory, charged particle therapy (ie, protons) provides superior dose distributions vs photon therapy, as energy is primarily deposited over
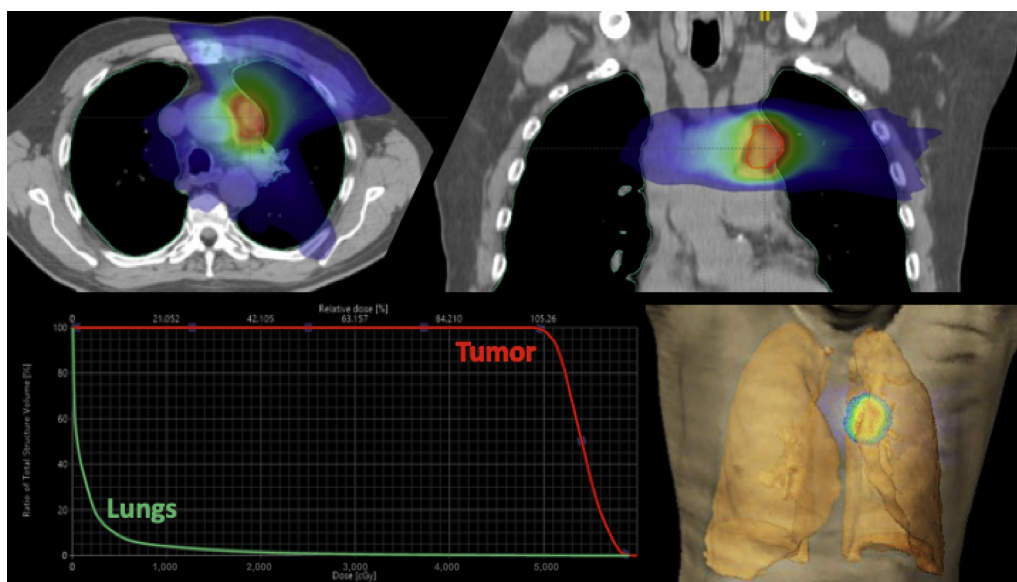
Figure 2 – *Stereotactic body radiation therapy (SBRT) for a mediastinal lymph node. SBRT allows for high doses of radiation to small volumes of disease. The example presented demonstrates the use of SBRT to treat a site of oligometastatic disease in the mediastinum of a patient with otherwise controlled metastatic lung cancer. A dose-volume histogram (DVH) is also presented that shows the volume by dose of the target and organ at risk (in this case, the lungs). When radiation oncologists evaluate a DVH, the target should span to the upper right corner. Ideally, organs at risk will be to the bottom left corner. A pulmonologist can request the DVH or treatment plan for any patient from the radiation oncologist. SBRT is often used for early-stage lung cancer in patients medically ineligible for surgery and can spare normal tissue by distributing dose to numerous individual beamlets, which converge to an ablative dose at a specified target. The most common mode of delivery is volumetric modulated arc therapy, in which there exists a coplanar arc-beam arrangement. Essentially, as the gantry head rotates around the patient, beams from a complete spectrum of angles and with varying intensity deliver highly conformal dose to the target.*

a specific depth with essentially no exit dose (Fig 3).[64] However, a significant clinical benefit in reducing RP was not seen in a recent clinical trial compared with IMRT.[65]

Clinical Assessment

The severity of RP varies from radiographic findings with no clinical symptoms to life-threatening disease requiring hospitalization.[18] Two widely used radiation toxicity grading systems, the Radiation Therapy Oncology Group and the Common Terminology Criteria for Adverse Events, categorize patients based on the severity of their pneumonitis (Table 2).[66] The most common symptoms are dyspnea, which can be mild to severe, and a dry, nonproductive cough. Low-grade fevers present in < 10% of cases, but high fevers can occur in some patients. Hemoptysis is also a rare symptom and is sometimes reflective of other disease. The physical examination of a patient with RP may be normal; in other cases, evidence of consolidation, a pleural rub, or adventitious lung sounds may indicate disease progression. Dullness to percussion may be detected in patients who develop pleural effusions, but these are typically small, often cause no symptoms, and are distinguishable from malignant effusions as they

remain stable in size over time. Clinically significant radiation-induced pulmonary fibrosis typically occurs months to years following therapy and is described as progressive dyspnea associated with lung scarring. Tachypnea and cyanosis are both signs of advanced disease. In both RP and PF, chronic pulmonary insufficiency can occur if the volume of lung damaged is large enough. This insufficiency can result in pulmonary hypertension and may progress to cor pulmonale.[18]

The differential for the vague symptoms presented here is broad and includes infection, sequela from malignancy, COPD, chemotherapy-induced pneumonitis, disease recurrence in the lung, and cardiac disease.[67] However, if a patient presents with these symptoms weeks or months following completion of RT, physicians should also be suspicious for RILI and promptly begin a diagnostic evaluation (Fig 4). Generally, RP develops at 4 weeks following conventionally fractionated therapy. Signs of pulmonary infection include a unilateral or bilateral lung opacity appearing prior to completion of radiation, tree-in-bud opacities, and cavitation. RT-related necrosis and local recurrence can also manifest as cavitation; however, these generally occur at a later interval following completion of therapy.[68]
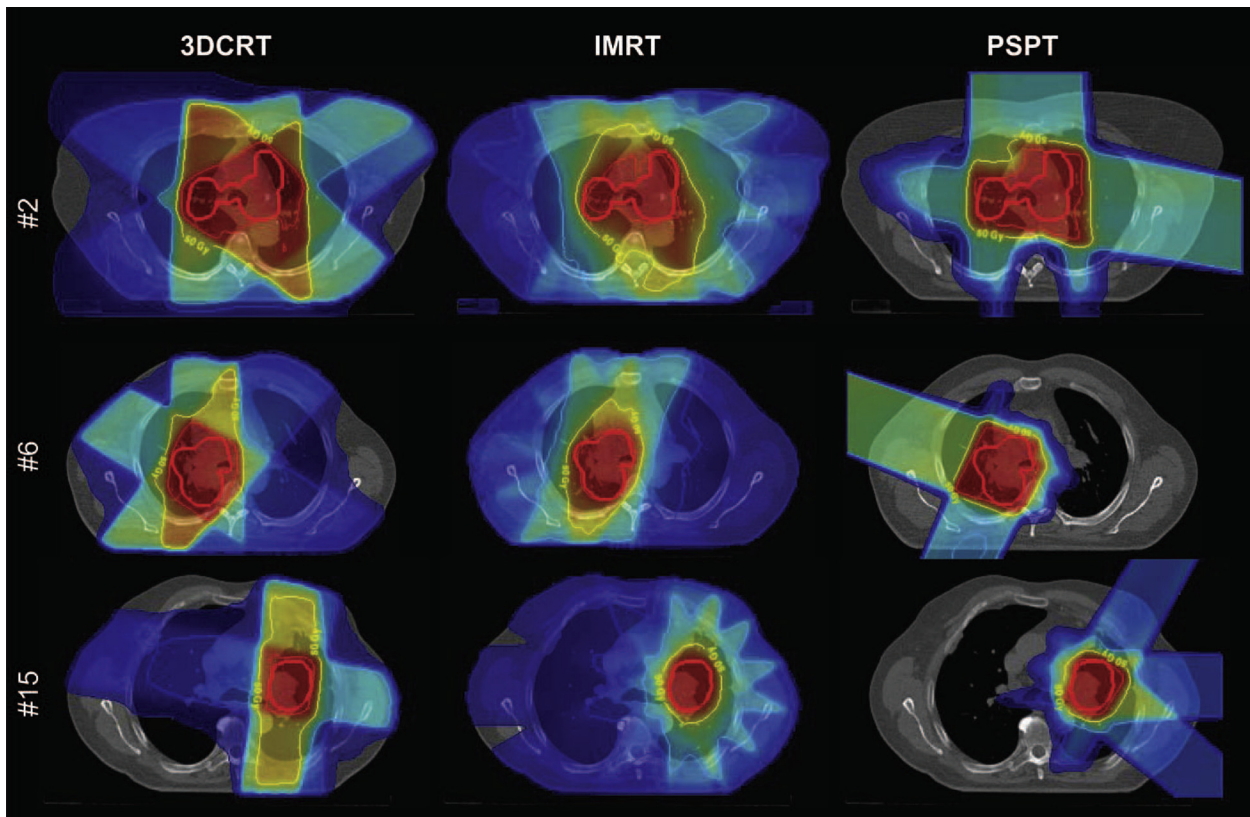
Figure 3 – *Conformal radiation techniques (3DCRT vs IMRT vs PSPT). Three cases are demonstrated with respective dose (color wash) utilizing the differing techniques. 3DCRT was the initial form of conformal radiotherapy, which requires beams to be manually arranged with custom blocks using multileaf collimators. IMRT is currently the most utilized technique for modern treatment planning. IMRT allows for an inverse planning computer optimization algorithm to select the optimum configuration of beam arrangements and multileaf collimator positions to produce ideal target dose and organ-sparing based on preset dosimetric goals. PSPT represents the most commonly used form of proton therapy and takes advantage of the lack of exit dose in a proton beam. Of note, IMRT tends to limit higher doses of radiation to normal structures vs 3DCRT, although it can increase low-dose spillage to a high volume of lung if V5 (percent lung volume receiving ≥ 5 Gy) constraint is not accounted for. PSPT in certain cases can completely spare contralateral lung. 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiation therapy; PSPT = passively scattered proton therapy. (Reprinted from Roelofs et al.[64] Copyright [2012], with permission from Elsevier.)*

No commonly used laboratory or imaging tests can definitively identify RP, as it is a clinical diagnosis. Some patients may have an elevated WBC count, erythrocyte sedimentation rate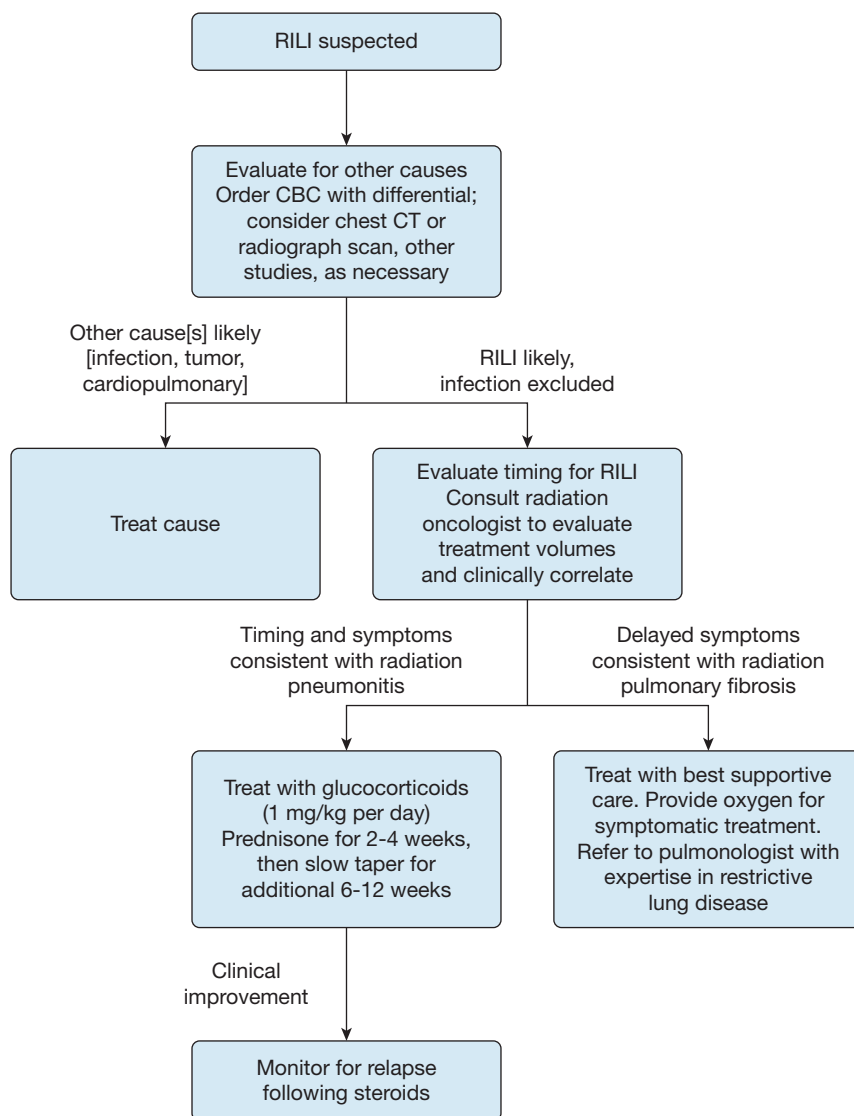, or C-reactive protein, but these findings are nonspecific. A complete blood count with differential is used to evaluate most patients, whereas further laboratory studies may be obtained as needed to evaluate for alternate etiologies. Chest radiograph may

TABLE 2] Radiation Pneumonitis Grading Systems

Grading System	RTOG	CTCAE
Grade 1	Asymptomatic or mild symptoms (dry cough). Slight radiographic appearances	Mild; asymptomatic. Clinical and diagnostic observations only. Intervention not indicated
Grade 2	Moderate symptomatic fibrosis or pneumonitis (severe cough). Low-grade fever. Patchy radiographic appearances	Moderate. Minimal, local, or noninvasive intervention indicated. Limiting age-appropriate instrumental ADL
Grade 3	Severe symptomatic fibrosis or pneumonitis. Dense radiographic changes	Severe or medically significant but not immediately life-threatening. Hospitalization or prolongation of hospitalization indicated. Disabling. Limiting self-care ADL
Grade 4	Severe respiratory insufficiency/continuous oxygen/assisted ventilation	Life-threatening consequences. Urgent intervention indicated
Grade 5	Death related to adverse events	Death related to adverse events

ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events; RTOG = Radiation Therapy Oncology Group.

Figure 4 – *Clinical algorithm outlining the assessment and management of RILI. Suspicion of RILI should be initiated when a patient's physical examination findings correlate temporally (typically within 3 months) with completion of thoracic radiation. RILI = radiation-induced lung injury.*

RILI suspected

Evaluate for other causes Order CBC with differential; consider chest CT or radiograph scan, other studies, as necessary

Other cause[s] likely [infection, tumor, cardiopulmonary]

RILI likely, infection excluded

Treat cause

Evaluate timing for RILI Consult radiation oncologist to evaluate treatment volumes and clinically correlate

Timing and symptoms consistent with radiation pneumonitis

Delayed symptoms consistent with radiation pulmonary fibrosis

Treat with glucocorticoids (1 mg/kg per day) Prednisone for 2-4 weeks, then slow taper for additional 6-12 weeks

Treat with best supportive care. Provide oxygen for symptomatic treatment. Refer to pulmonologist with expertise in restrictive lung disease

Clinical improvement

Monitor for relapse following steroids

be normal in the latent phase of RP, but ground-glass opacities or consolidations in the radiation treatment field reflect later stages of lung injury (Figs 5, 6). Generally, pulmonary opacities develop in areas receiving > 40 Gy and thus correlation can be made with the patient's radiation treatment plan.[68] As the disease progresses to RPF, the chest radiograph may show a defined area of volume loss, scarring, and consolidation.[69]

In general, chest CT imaging is the preferred imaging technique over chest radiography, as it is more sensitive in detecting RILI. Homogeneous ground-glass attenuation representing early RP can be detected on CT imaging a few weeks following completion of therapy, even when there are no findings on chest radiograph.[25,70,71] The appearance of RP on CT imaging often correlates with the phase of lung injury, progressing from ground-glass attenuation in the initial phase, patchy areas of consolidation in later phases, and linear scarring with consolidation and volume loss as pulmonary fibrosis develops.[69] For both radiographic modalities, opacities on imaging frequently conform to the radiation treatment field, although this finding is not universal. Additional diagnostic techniques such as bronchoscopy, thoracentesis, and lung biopsy allow differentiation of RP from underlying tumor or infectious pneumonitis and are occasionally necessary to make a more accurate diagnosis of RP. Pulmonary function tests are often used to distinguish RILI from other lung diseases such as COPD. Lung dysfunction from RILI is typically associated with a restrictive pattern with decreased lung volumes, compliance, FVC, and diffusing capacity.[72-74] Bronchoscopy is typically
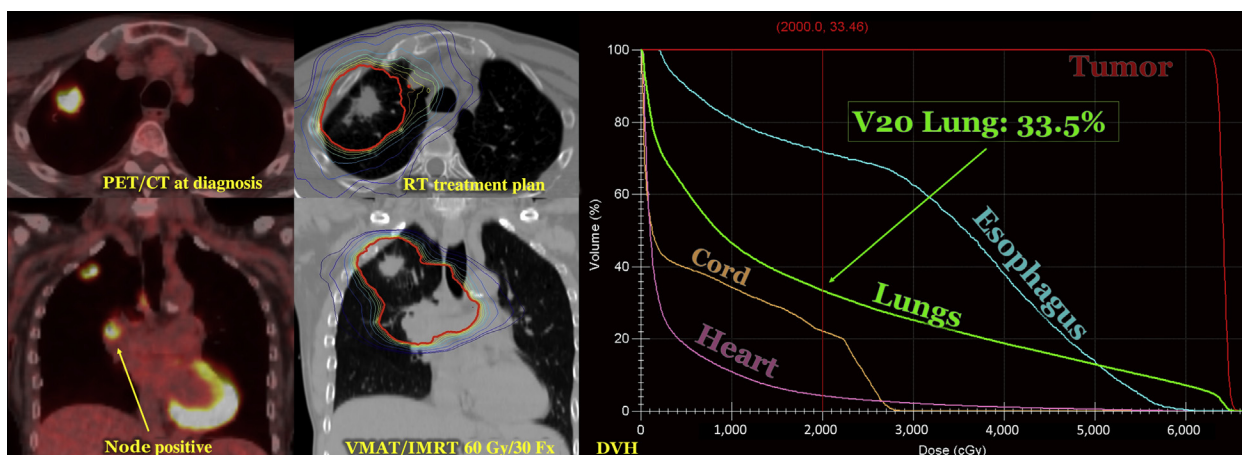
Figure 5 – *Locally advanced lung cancer treated with definitive chemoradiation. We present a case of locally advanced non-small cell lung cancer in a patient who underwent chemoradiation. The patient had node-positive disease as illustrated by staging PET/CT scan. He received 60 Gy/30 Fx utilizing VMAT/IMRT with daily image guidance. The RT plan with isodose lines (IDLs) is displayed. IDLs are generated to describe where the radiation dose is distributed. The bolded, red IDL represents the prescription line (6,000 cGy). The patient's DVH is also displayed, which identifies organs-at-risk by displaying dose vs organ volume. In this patient's case, the lung V20 or volume of lung receiving ≥ 20 Gy is above the 30% constraint. DVH = dose volume histogram; RT = radiation therapy; VMAT = volumetric modulated arc therapy. See Figure 3 legend for expansion of other abbreviation.*

used to evaluate for spread of malignancy, infection, bleeding, or drug hypersensitivity. As described earlier, bronchoscopy with BAL can reveal nonspecific findings such as increased leukocytes and primary CD4$^+$ lymphocytes.[75]

Evolving postradiation treatment changes may also be mistaken for local disease recurrence or progression months or years later. In fact, it is possible to observe a reduction in the size of a lung nodule/mass followed by radiographic stability, only for it to later enlarge radiographically, secondary to postradiation change. This phenomenon is demonstrated by the case in Figure 6 in which a suspicious enlarging opacity at 48 months was biopsied and revealed notable fibrotic and degenerative lung tissue with chronic focal inflammation but no evidence of malignancy. In these situations, PET/CT imaging is helpful in evaluating for metabolic activity in the treated field prior to biopsy and yields a sensitivity of 98% and specificity of 82% for identifying disease recurrence.[76] An endobronchial ultrasound approach is appropriate for central and mediastinal lesions, whereas peripheral lesions generally require CT scan-guided biopsy.[77] PET/CT imaging for surveillance and/or biopsy sooner than 6 weeks following definitive radiotherapy may be difficult to interpret because patients may continue to have treatment response in this period.

SBRT/SABR provides a nonsurgical treatment option with excellent local control (approximately 90% at 3 years) and has become standard for patients who are not

candidates for or refuse surgery for early-stage lung cancer.[5] Clinicians managing these patients should be aware of unique radiographic scar properties that generally form after 3 months and do not necessarily suggest recurrence. This scenario varies from conventionally fractionated radiation in which RT-related radiographic findings generally appear after 4 weeks.[68] Several studies have defined these high-risk radiologic features (HRFs) (Table 3), including one recent study evaluating 88 patients without local recurrence for a minimum of 2 years.[78] The investigators found that one HRF developed in > 50% and ≥ 3 HRFs developed in nearly 25% of patients undergoing SBRT/SABR. Furthermore, a diagnosis of clinically significant RILI should be avoided in patients with only a radiographic appearance of an SBRT/SABR scar, specifically when clinical correlation to patients' pulmonary symptoms cannot be established anatomically or temporally. Ultimately, these high-precision techniques target a small volume to an ablative dose while generally sparing the majority of lung tissue from significant radiation; thus, the incidence of symptomatic RILI is low (approximately 10%).[79]

Diagnosis, ultimately, is based on history of RT with consideration of target, dose, and technique as well as a combination of symptoms, timing, imaging findings, laboratory studies, and exclusion of other causes of lung disease. Evaluation should be started immediately to appropriately treat any underlying pathology responsible for the patient's symptoms.
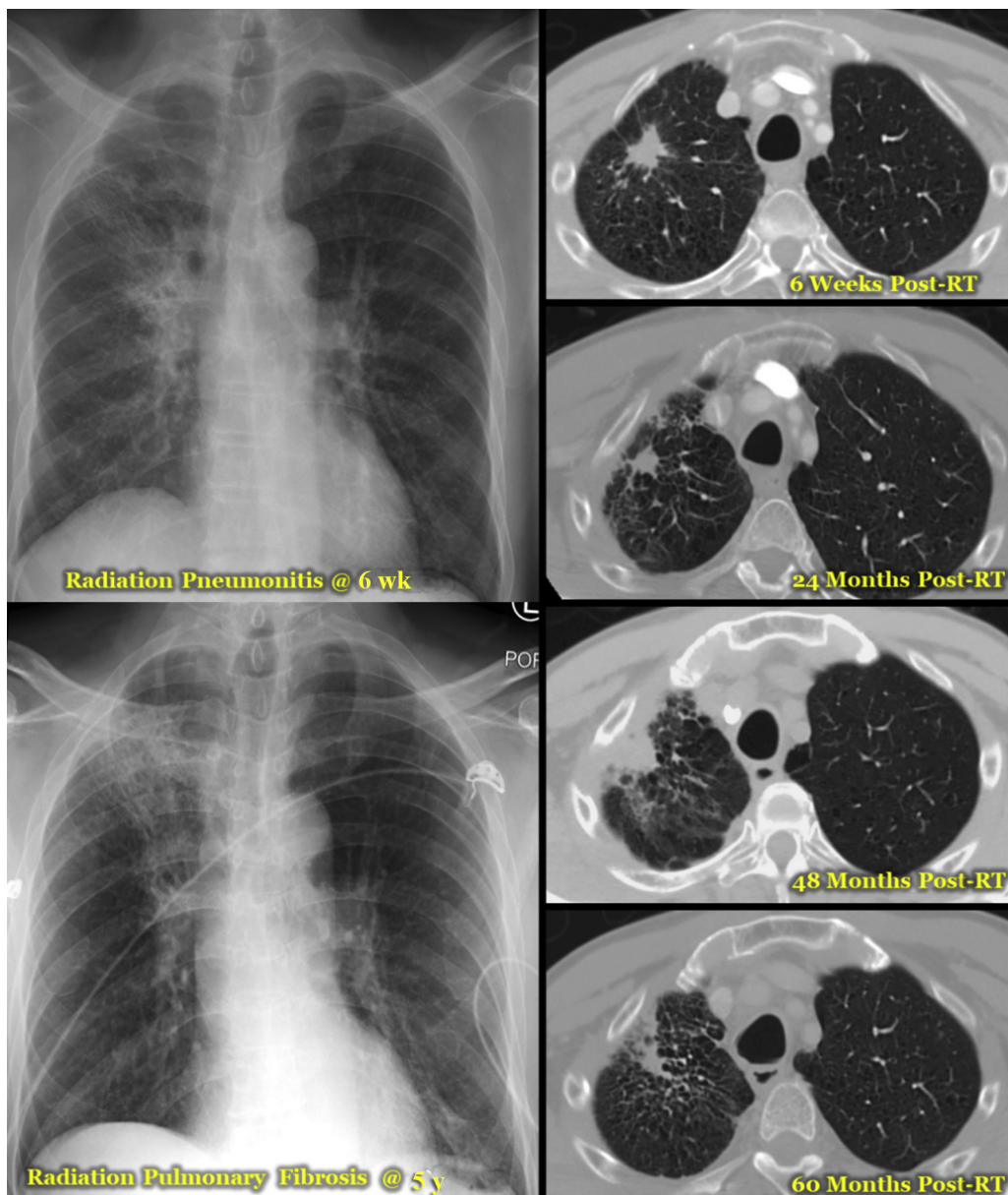
Figure 6 – *Radiographic appearance of RILI. The previously described patient (Fig 5) developed clinically significant radiation pneumonitis in the form of cough and required a short course of steroids at 6 weeks from the end of radiation (Grade 2). The radiographic findings of radiation pneumonitis at 6 weeks are illustrated on CT imaging (homogeneous ground-glass attenuation) and chest radiograph (linear, reticular stranding). The patient improved clinically following initiation of steroids, with stable radiographic findings. On follow-up, the patient's mass initially decreased in size (24 months); however, at 48 months, there was significant concern for local recurrence given enlarging soft tissue density arising from the nodule on CT imaging. Results of biopsy and PET/CT imaging were negative for pathologic or metabolic evidence of malignancy. Ultimately, following continued observation, the lung findings improved, and the patient remains without evidence of disease at 5 years. Radiographic findings of progressive fibrosis are displayed over time on CT imaging (right upper lobe traction bronchiectasis, volume loss, and thickened interstitium). A chest radiograph represents radiographic fibrosis (linear fibrosis, scarring, and volume loss). Of note, the radiographic findings in this patient correspond anatomically to the original radiation fields, which is a key finding when making a diagnosis of RILI in the clinically symptomatic patient. At last follow-up, this patient was doing well and has no clinically significant fibrosis. See Figure 4 legend for expansion of abbreviation.*

Management Strategies

No controlled studies have been conducted to evaluate the role of various therapies in treating RILI in humans. For very mild symptoms, clinical observation can be considered. However, most experts recommend systemic glucocorticoids to treat significantly symptomatic RP,[72]

provided that lung infection has been ruled out. For example, a treatment course of 1 mg/kg per day of prednisone can be given for 2 to 4 weeks, followed by a slow tapering of the medication for an additional 6 to 12 weeks. Patients may experience marked symptomatic relief, with reduction in cough, chest tightness, dyspnea,

TABLE 3] SBRT/SABR High-Risk Radiologic Features and Frequency in Patients Without Local Recurrence

SBRT/SABR High-Risk Radiologic Features	% Observed[a]
Enlarging opacity at primary site	65
Sequential enlarging opacity	50
Enlarging opacity after 12 mo	14
Loss of air bronchograms	4
Loss of linear margins	2
Cranio-caudal growth	2
Bulging margin	2

SABR = stereotactic ablative radiotherapy; SBRT = stereotactic body radiation therapy.
[a]Frequency of high-risk radiologic features observed in a retrospective study of 88 patients undergoing SBRT/SABR without local recurrence.[78]

and fever, along with resolution of radiographic changes. However, relapse is possible following response to steroids. Single case studies have also reported effectiveness for both azathioprine and cyclosporine.[80,81] However, the only two drugs that have shown efficacy in reducing rates of pneumonitis in humans are amifostine and pentoxifylline in combination with tocopherol. Amifostine, a free radical scavenger, was shown to significantly reduce rates of grade 2 or higher pneumonitis in patients receiving radiation for advanced-stage lung cancer.[82] Furthermore, amifostine is currently the only radioprotective agent approved by the US Food and Drug Administration for clinical use. Unfortunately, due to its significant side-effect profile (ie, hypotension and severe nausea) and poor tolerability (especially when administered intravenously), its use is limited in modern practice. Studies involving the subcutaneous use of amifostine in patients with head and neck cancer suggest feasibility and less hypotension, although nausea remains problematic.[83] Pentoxifylline inhibits proinflammatory molecules such as tumor necrosis factor alpha and leukotriene and has been shown to significantly prevent pneumonitis in both lung and breast cancer patients.[84,85]

There are no established guidelines for the treatment of RPF. The mechanism of pulmonary fibrosis (primarily driven by TGF-β and collagen overproduction, as described earlier) is different from pneumonitis and does not necessarily derive from inflammation; therefore, glucocorticoids and other antiinflammatory agents are not effective and should be avoided to reduce unwanted side effects. For example, clinical studies that evaluated the efficacy of "triple therapy," which combined the antiinflammatory drugs prednisone and

azathioprine, found that these drugs increased the risk of hospitalization and death in patients with established lung fibrosis.[86] Unfortunately, there is no effective therapy for established lung fibrosis, and treatment is primarily supportive: supplemental oxygen should be provided for symptomatic relief, and patients should be referred to a pulmonologist with experience treating restrictive lung disease. Several agents are hypothesized to be effective in treating radiation fibrosis but have not been tested in prospective randomized controlled clinical trials. In preclinical studies, angiotensin-converting enzyme inhibitors were shown to reduce fibrosis in irradiated rat lungs,[87] and drugs that inhibit collagen synthesis, such as colchicine and interferon-γ, may have efficacy in preventing lung fibrosis or reducing its progression rather than reversing it. Antiinflammatory agents such as corticosteroids and azithromycin have failed to show efficacy clinically in the prevention of RILI despite encouraging outcomes in animal models.[88,89] Recently, interest has surfaced for the multi-kinase inhibitor nintedanib, which targets vascular endothelial growth factor among other growth factors and has been identified as a possible treatment to prevent RP and reduce the incidence of lung fibrosis. Preclinical results have been promising; however, several phase II trials are ongoing.[90-92] Pirfenidone, which downregulates procollagens and growth factors, is another emerging medication, and an early pilot study has suggested subjective improvement in RPF; however, this requires validation in a large, randomized trial.[93] Evidence continues to emerge on the efficacy of new chemical entities to prevent and/or treat RP and RPF.[94]

Future Directions

Irradiated volumes continue to decrease as external beam radiation planning becomes increasingly conformal and spares healthy tissue while maximizing dose delivery to target. In addition, emerging clinical, serologic, and radiographic predictors of lung injury may lead to further personalized and risk-adaptive radiation planning.[11] Several promising immunomodulating agents targeting interleukins such as IL-1β, IL-13, and IL-17α and the transcription factor STAT3 have shown promising efficacy in suppressing TGF-β-mediated fibrosis in animal models.[95-98] Other agents such as nebulized synthetic lamellar lipids have also shown promise in preventing RILI in large animal models.[99]

Well-designed, randomized controlled trials are needed, as RILI remains a significant toxicity in patients

undergoing thoracic irradiation in the setting of significant risk factors. Development of objective measures is also needed to properly quantify RILI, as opposed to relying on physician- and patient-reported outcomes. In this regard, several studies have evaluated the use of advanced imaging techniques, which may assist in determining the efficacy of pharmacotherapy in future clinical trials.[100–102] Ideally, radioprotective agents developed for RILI should carry minimal adverse effects and not impair the ability of radiation to kill underlying cancer cells. In addition, such therapeutic agents should be easy to administer (eg, aerosolized or subcutaneous delivery) in a period immediately preceding radiation treatment.

Conclusions

Although it is important to recognize RILI as a possible etiology in the appropriate patient, it should only be considered after other possibilities have been fully exhausted. With modern treatment techniques, the incidence of adverse effects from radiation have declined immensely,[103] and it is important to realize that the vast majority of patients receiving thoracic RT may not have significant pulmonary toxicity requiring medical intervention. Furthermore, patients undergoing RT outside the thorax are not at risk for RILI. Benefits of consultation with the treating radiation oncologist to obtain precise details regarding lung volumes irradiated and perceived clinical risk cannot be understated.

Acknowledgments

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