RADIATION-INDUCED PULMONARY DISEASE

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Abstract
This article discusses the natural history, clinical epidemiology, diagnosis, and treatment of radiation-induced lung diseases (RILDs). Furthermore, we review current experimental developments and assess potential areas for future investigation. Radiation therapy (RT) is a key component of the approach to the treatment of thoracic neoplasms. The use of radiation for the treatment of cancer exploits the preferential cytotoxicity of radiation to cells with high mitotic index. By the same principle, non-neoplastic cells with high mitotic index are also vulnerable to the deleterious effects of radiation. As a consequence, RT to the lung culminates in significant injury to normal cells with high mitotic index such as vascular endothelial cells and alveolar type II pneumocytes. The clinical manifestations of radiation-induced lung injury fall into two categories, acute radiation pneumonitis (RP) and radiation-induced lung fibrosis (RIF) which is a late sequela of RT. Epidemiological analyses reveal that radiation-mediated lung injury is amplified by many factors, such as radiation dose–lung volume relationships, concomitant use of chemotherapy, and the abrupt withdrawal of previously instituted steroid therapy. The cornerstone of the management of RILDs is prevention that is accomplished through surveillance of lung function, prompt evaluation of respiratory symptoms, and the early institution of steroids upon making a diagnosis of RP.

Introduction
The discovery of X-rays by Wilhelm Roentgen in 1895 heralded the origin of radiation oncology. Shortly after the discovery of X-ray radiation, the first use of radiation for the treatment of cancer was reported. The development of the cathode ray tube and subsequently cobalt-60 teletherapy and linear accelerators revolutionized the generation of X-rays for cancer treatment. Groover and co-workers first reported in 1922 that side effects of radiation therapy (RT) were radiation pneumonitis (RP) and pulmonary fibrosis (see Pulmonary Fibrosis). In 1928, Antoine Lacassagne observed that a short duration of the interval between radiation treatments, high radiation doses, low voltage, and opposing fields were associated with radiation injury.

A rise in the number of cases of radiation-induced lung diseases (RILDs) can result from several factors: (1) an increase in the incidence and prevalence of neoplasms as a result of the growing number of elderly patients; (2) use of RT as part of the conditioning regimen prior to bone marrow transplantation; and (3) increase in the number of immunocompromised hosts, in whom malignancies are more prevalent (see Table 1 for a list of RILDs). Both, the demand to improve the efficacy of RT and the need to limit lung injury, have spurred technical modifications in the delivery of RT. At present, the use of RT is preceded by rigorous planning that encompasses accurate tumor localization through the use of ultrasound (US), magnetic resonance imaging (MRI), and computer tomography (CT) (see Lung Imaging). The future of RT will, in part, focus on the reduction of side effects through targeting of RT to tumor but not normal cells and enhancing cytotoxic effects of lower doses of RT through the use of radio-sensitizers and genetic engineering as well as the antagonism of endogenous mediators of RILDs.

Etiology

Genetic Factors
The lack of stereotyped uniformity in the incidence of RILD among recipients of RT suggests that genetic factors may be crucial to the development of radiation lung injury. Investigators have identified that the loss of heterozygosity at the mannose 6-phosphate insulin-like growth factor-2 receptor (M6P/IGF2R) leads to elevated transforming growth factor beta (TGF-β) levels (see Transforming Growth Factor Beta (TGF-β) Family of Molecules). They proposed that the elevated TGF-β levels enhance the susceptibility of the surrounding tissues toward the development of RP. The repertoire of potential genes that are likely to be involved in the immune response to radiation injury is immense. Moreover, the interaction of potential genes is likely to be very complex but at present the precise role of genetic factors is not well understood.

Host Factors
A variety of patient factors – age, sex, tobacco use, tumor site, and pre-RT pulmonary function tests
(PFTs) as well as the Karnofsky performance status (Table 2) – have been proposed to impact the emergence of RP. The role of each factor alone is unclear because some of the studies exploring their significance reveal different dosing regimens which is the most important factor in the development of RP. It is clear that underlying pretreatment patient conditions that reduce total lung volume favor the development of RP. A retrospective study of 84 patients with small or non-small cell lung cancer (NSCLC) evaluated the role of gender, age, surgery, chemotherapy, chronic obstructive pulmonary disease (COPD), and performance status. The study found only COPD and the concomitant use of mitomycin as independent risk factors which are associated with the emergence of RP. Another study that assessed the influence of patient-specific factors on RT-induced reduction in pulmonary perfusion employed a multivariate analysis to analyze the effect of tobacco history, pre-RT diffusion capacity, TGF-β, chemotherapy exposure, disease type, and mean lung dose. The study found a trend but it was not statistically significant toward increased radiation sensitivity among patients who were nonsmokers and receiving radiation doses greater than 40 Gy. The authors concluded that patient-specific factors have a minimal effect on RT-induced reduction in regional lung perfusion. A study using CT scans among patients with limited small cell lung cancer (SCLC) that was designed to evaluate the magnitude of individual variation in the severity of lung fibrosis following treatment with chemoradiation, found significant patient-to-patient heterogeneity in patients at risk for developing radiation-induced fibrosis. The role of age in the development of RP is conflicting: some studies have failed to identify an association between age and the emergence of RP while others have reported an association. As alluded to previously, the propensity to develop RT may be more related to pretreatment lung volume than age.

### Dosimetric Factors

Several investigators have shown that dosimetric factors are the best predictors of clinically manifest RP following external-beam RT for a variety of neoplasms (see Table 2 and Radiotherapy). The dosimetric factors that have been evaluated include mean lung dose (MLD), V20, V30 (defined as the percentage of the total lung volume receiving greater than 20 or 30 Gy of radiation, respectively), and radiation dose per fraction. A prospective study of 96 patients who underwent three-dimensional conformal radiotherapy (3D-CRT) for NSCLC observed a threshold effect for the emergence of RP at radiation doses of 20–40 Gy. The study also noted that the MLD, V20, V30, and age were predictive of RP following RT.
A univariate and multivariate analysis of patient- and treatment-related factors among lung cancer patients treated with conventional fractionated radiotherapy and concurrent chemoradiation identified V20 as the best predictor of the incidence and grade of the ensuing RP post-RT. The study also demonstrated that concurrent use of chemotherapy increases the incidence of RP (Figure 1). A study designed to correlate dose–volume histogram factors to clinically manifest RP reported that all dosimetric factors (V30, MLD, normal tissue complication probability (NTCD)) correlated with the emergence of RP. However, an analysis of factors such as age, irradiation of the lower lung field, and low pre-RT pulmonary function demonstrated no correlation with the emergence of RP. An intriguing observation is that the incidence of RP may be lower among smokers.

**Chemotherapy**

The concurrent use of chemotherapy with radiation in regimes that exploit the radiosensitizing effects of drugs such as taxanes has been associated with the potentiation of the pneumotoxic effects of radiation. The compounding effects of chemotherapy on pneumonitis appear to be independent of the mechanisms of action of individual chemotherapeutic agents although some agents such as bleomycin are known to be radiosensitziers. Moreover, there is no clear dose–effect relationship between chemotherapy and the emergence and extent of RP. A study of 13 SCLC cases treated with bleomycin, adriamycin, cyclophosphamide, and vincristine in addition to radiotherapy noted severe pulmonary fibrosis in five cases, two of which were fatal. In a study of 41 patients with breast cancer who were treated with RT concurrently with chemotherapy, the regimes that included paclitaxel showed that RP developed at a rate of 14.6%. In comparison, patients treated with RT and chemotherapy without paclitaxel developed RP at the rate of 1.1% (95% confidence interval = 0.2–2.3%, \( p < 0.0001 \)). Additional chemotherapeutic drugs that have been associated with RP are shown in Table 3.

**Pathology**

Murine models of RP strongly suggest that injury to pulmonary capillary endothelial cells and type II pneumocytes mediates the pathogenesis of RP (Figure 2) (see **Endothelial Cells and Endothelium**). Within an hour of RT, quantitative and qualitative
changes are observed in type II pneumocytes that include reduced intracytoplasmic lamellar bodies followed by the release of surfactant. These changes are followed by a loss of type II cells and the synthesis of less viscous surfactant. A compensatory lamellar body repletion and type II pneumocyte proliferation are observed 4–12 weeks after RT. These changes occur simultaneously with a florid inflammatory cellular infiltrate into the alveolar septae. Inflammatory cells such as mast cells, plasma cells, fibroblasts, macrophages, and polymorphonuclear cells populate the infiltrating cells. Overall, the inflammatory picture usually resolves by 6–9 months although continued type II pneumocyte and arterial smooth muscle proliferation, and free-radical-induced endothelial and type II pneumocyte damage can lead to extensive collagen deposition, that is, radiation-induced lung fibrosis (RIF). The histopathological features of RP and RIF are shown in Figure 2.


Clinical Features
Incidence and Prevalence
The observation that not all radiologically evident RP is associated with symptomatic disease leads to higher prevalence and survival statistics when radiological criteria are used in isolation to diagnose RP. In contrast, clinical criteria for diagnosing RP yield lower prevalence rates. The incidence of RP following external-beam RT varies from 1% to 34%. The incidence of RP depends on the type of tumor owing to technical variation in irradiation strategies, but the variability in dosimetry is still the largest factor that determines the risk of developing RP (Table 3). RP is uncommon in breast cancer when RT is restricted to the thoracic wall following mastectomy or after breast-conserving surgery. However, the inclusion of the supraclavicular fossa, axilla, and lung apex increases the incidence of pneumonitis from 1.4% to 3.9%. Incorporation of all
lymph nodes above the diaphragm, lung apices, and axilla bilaterally in the irradiation field for the treatment of Hodgkin’s lymphoma is associated with less than 5% risk of RP. Compared with RT for lung cancer, smaller areas of lung are irradiated in Hodgkin’s lymphoma. As a result, long-term follow-up of patients treated with RT for lymphoma shows only clinically insignificant pulmonary function changes in differing capacity of the lung for carbon monoxide (DLCO) and total lung capacity. In a study of 590 patients with stage 1A-IIIB Hodgkin’s disease, RP was observed in 3% of the patients receiving radiation alone while whole lung irradiation was associated with a 15% risk; the concurrent use of chemotherapy elevated the risk to 11%.

A prospective evaluation of 96 patients with NSCLC who were treated with 3D-CRT reported an incidence of grade 1 RP to be 44% at 6 weeks while grade 2 or greater RP was evident in 7.8%. Mean lung dose, V20, V40, and age greater than 60 were predictive of RP. As we discussed previously, estimates of the prevalence of RIF are challenging owing to the variability in the diagnostic criteria, diagnostic methods, and the difficulty in excluding pre-existing lung injury. A prospective study, using CT scans, of 24 patients with advanced NSCLC treated with chemoradiation was undertaken to evaluate the incidence of RIF. Using the European Organization for Research and Treatment of Cancer-Radiation Therapy Oncology Group Scale, the investigators found the prevalence of RIF grades 1, 2, and 3 to be 14%, 33%, and 19%, respectively. Japanese Clinical Oncology Group trials for lung cancer observed 29 deaths out of 1176 (2.5%) that resulted from RT after a follow-up of four and a half years.

Clinical Features of Radiation Pneumonitis

An inconstant relationship has been reported between radiological RILDs and clinically manifest RP. On occasion, clinically evident RP may precede radiographic changes. The spectrum of RP ranges from self-limiting radiological disease or evanescent dyspnea to respiratory failure that culminates in mechanical ventilatory support or rapid demise. RP manifests itself clinically 4–12 weeks after lung irradiation. Dyspnea is the most prominent and frequently the initial manifestation of RP and can be quantified using dyspnea scores (DSs) such as the Abratt or Borg scale. The Abratt scale defines a DS of 1 as dyspnea during brisk ambulation on a flat surface or while walking up an incline. A DS of 2 is dyspnea on ambulating distances greater than 100 m while a DS of 3 denotes failure to ambulate distances greater than 100 m. Patients with a DS of 4 are dyspneic at rest. A prospective evaluation of lung function among patients irradiated for lung cancer observed a DS of 1 in 50% of the cases, while the remaining cases had a score of 2. At a 6-month follow-up, the DS increased from 1 to 2 in half of the cases. A DS of 3 was observed in approximately 5% of the cases.

Cough is the second commonest manifestation of RP. Characteristically, the cough is nonproductive. In some cases, the cough becomes productive with pink frothy sputum but frank hemoptysis is rare in RP. Occasionally, systemic symptoms with ill-defined global malaise and fever occur together with dyspnea. A study of 29 patients with RP revealed the prevalence of symptoms to be dyspnea (93%), cough (58%), and fever (7%).

Physical evaluation may be unrevealing. Classic auscultatory findings of RP include rales in the irradiated zone. However, RP has been reported in pulmonary locations outside the zone of irradiation and these findings may thus exist outside the irradiated lung zones. Regional RP may manifest as a focal consolidation. Also, pleural rubs may be evident in cases of radiation-induced pleuritis. A variety of conditions with a similar temporal appearance to RIP may mimic pneumonitis in the peri-irradiation period and include infectious pneumonitis, drug-induced pneumonitis, pulmonary alveolar hemorrhage, and less commonly, residual tumor. Also, underlying lung disease may confound an accurate diagnosis of RP.

Clinical Features of Radiation-Induced Lung Fibrosis

RIF is characterized by an incipient pleuroparenchymal interstitial injury that ensues 6–24 months after RT. All patients who have received RT are at risk for developing RIF irrespective of whether they had evidence of RP. The clinical manifestations of RIF are diverse and patients with mild focal fibrosis may be asymptomatic. In contrast, patients with large areas of lung irradiation may present with a DS greater than 2 that can evolve into dyspnea at rest. Late cardiovascular and pulmonary complications accrue from the effects of RT on the vasculature. Advanced cases of RIF have been associated with delayed effects on the vasculature including thrombo-embolic disease, superior vena cava syndrome, and secondary pulmonary hypertension and cor pulmonale.

The physical evaluation often reveals varying degrees of dyspnea and cutaneous effects of RT on the thoracic cavity may be evident on visual inspection. For example, the patient may show a deviated trachea and radiation-induced skeletal deformities. Chest excursion may be diminished along with inspiratory rales which is associated with a restrictive
process. Regional air flow may also be diminished in some settings so PFTs may reveal a mixed obstructive and restrictive picture. Pulmonary hypertension is characterized by a loud pulmonic heart sound, pulmonic and tricuspid regurgitation, elevated jugular venous pressure, engorged liver, and bilateral leg edema. Superimposed complications accruing from fibrosis and the altered lung function and anatomy include bronchiectasis and recurrent pneumonia.

**Diagnostic Evaluation**

**Chest X-Rays**

The chest X-ray (CXR) is useful in the surveillance of patients following RT. It also allows the speedy diagnosis of RP, in addition to assisting in the establishment of alternative diagnoses. The clinical utility is enhanced by the fact that it is inexpensive and can be deployed rapidly. Classic radiographic features of RP include a diffuse hazy opacification that evolves into a patchy appearance. In some settings, the abnormalities coalesce over time into a uniformly radiodense appearance that mirrors the configuration of the irradiated field. More frequently, these changes are transient but in other cases they progress to frank RIF. RIF may be detected by serial radiographs beginning at 6 months after RT and initial manifestations include patchy and linear opacities. These changes culminate in reticular parenchymal opacities, the progression of which leads to lung-volume reduction. Pleural adhesions to the thoracic wall, pericardium, or the diaphragm can occur. Radiographic appearances vary depending on the method and location of irradiation. The employment of oblique radiation beams in the treatment of breast cancer, for example, is associated with atypical distribution of interstitial opacities. Apical opacities are encountered with the use of supraclavicular portals. Peripheral reticular opacities result from tangential beam portals (as observed in breast cancer) and paramediastinal opacities are encountered following irradiation of a mediastinal tumor.

**Computer Tomography**

CT permits the early detection of subtle parenchymal changes that may not be evident on routine chest radiographs. Moreover, the superior parenchymal definition seen with high-resolution computer tomography (HRCT) enables the earlier detection of consolidation, subtle pulmonary parenchymal changes, and endobronchial occlusion that may herald tumor recrudescence. Characteristic CT appearances of RP include nonhomogeneous opacities and alveolar filling defects. Homogeneous reticular ground glass opacities are encountered more often in RIF. Ground glass opacities are observed in both RP and RIF and can progress into reticular opacities. Over time there is associated volume loss, and pleural and diaphragmatic thickening. In three-dimensional confocal radiotherapy, lung injury may adopt unusual radiographic configuration which reflects the field and mode of radiation delivery. A study looking at 87 CT scans in 17 patients noted CT abnormalities in 15 of the 17 cases within 16 weeks of RT. In three out of the 15 cases, there were no changes indicative of RP evident at 16 weeks. In three cases, CXR changes became apparent much later than 1, 5, and 8 weeks respectively. In nine cases, the radiological features of lung injury were detected simultaneously by either CT or CXR. This same study reported air bronchograms (25%), loss of lung volume (15%), and pleural thickening as changes complicating RT. Adjuncts to CT scans have included gallium scintigraphy but its value is limited by low specificity and sensitivity.

**Bronchoscopy**

The use of bronchoscopy in the evaluation of RP is limited. Most patients receiving RT are also immunocompromised; consequently, the emergence of parenchymal opacities on CXR necessitates bronchoscopy to exclude alternative etiologies such as infections, or diffuse alveolar damage. In RP, inspection of the airways may show hyperemia and mucosal engorgement. Bronchoalveolar lavage fluid (BALF) from irradiated patients compared to that of nonirradiated patients with lung cancer showed that total lymphocyte and eosinophil counts were higher in irradiated lungs. Moreover, human leukocyte antigen DR (HLADR)-positive CD4\(^+\) T cells and HLADR-positive CD8\(^+\) T cells as well as intercellular adhesion molecule (ICAM)-1-positive T cells are markedly increased. An interesting observation from this study was that the emergence of ICAM-1 positive cells correlated with the interval between initiation of RT and emergence of RP. However, other investigators have found no difference in the lymphocytic content between irradiated breast cancer cases that develop RP and those that do not.

**Pulmonary Function Tests**

PFTs in lung cancer patients treated with RT and followed for a mean of 38 months noted that RT caused a decline of forced vital capacity (FVC) (89% of subjects), forced expiratory volume in 1 s (FEV\(_1\)) (89%), and DLCO (90%). These variables returned to baseline at 1 year (105%, 100%, and 90% of subjects, respectively). Nevertheless, the study further observed that a progressive decline
followed the initial improvement phase. The study was however limited by its size. De Jaeger and co-workers evaluated the effect of RT on pulmonary function post-RT in 82 cases of NSCLC and correlated it to radiation dose, tumor regression, and changes in lung perfusion as measured by single photon emission CT (SPECT) lung perfusion scan. They estimated the post-RT perfusion using dose distribution and a dose–effect relation for loco-regional lung perfusion to calculate a predicted perfusion reduction (PPR). Reperfusion was defined as the difference between the baseline perfusion and the PPR. Tumor regression was associated with an improvement in FEV₁ but a decline in DLCO, while the PPR did not correlate with improvement of FEV₁ and FVC. Overall, RT causes restrictive ventilatory defects with diminution in FVC and FEV₁ due to reduced compliance caused by fibrosis. The changes in FVC and FEV₁ are variable and rather limited in their utility to follow the effects of RT. In contrast, the assessment of the alveolar functional integrity by DLCO is more sensitive for detecting RILDs.

Serological Markers

No single serologic marker is a consistent predictor of risk for development of RP. Consequently, a search for a reliable marker for RP is ongoing. Markers that have been described as showing a positive correlation with RP include TGF-β, interleukin (IL)-1α and IL-6. The clinical significance of these findings has, however, been questioned by others. The cytokeratin 19 fragment, a marker of epithelial cell damage, mucin-like high molecular weight glycoprotein (KL-6/MUC-1), intercellular adhesion molecule-1 (ICAM-1), type III procollagen N-terminal peptide (P-III-P), laminin P1, and surfactant protein A and D have been shown to significantly correlate with RF. However, the clinical utility of these markers remains to be validated.

Pathogenesis

The leading theories of the mechanism of RILDs invoke the role of free radicals and cytokines. Figure 3 shows a schematic representation of the putative mechanisms of RP and RIF.

Free Radicals

Radiation causes structural modification of DNA, lipids, and proteins through peroxidation, aldehyde reactions, reactive oxygen species, and activates cytokine cascades that mediate processes that impair the structural integrity of pneumocytes and endothelial cells. Also, Cottier and co-workers showed that desferroxamine levels are elevated in patients who are likely to develop RP following RT. One group of investigators has observed that smokers undergoing RT for esophageal and breast cancer are less prone to RP possibly because glutathione (GSH) levels are known to be elevated in smokers compared to non-smokers. Since GSH functions as a scavenger for singlet oxygen and superoxides, it may abrogate the proinflammatory effects of RT (76). Hashimura and co-workers have observed that LTC₄ and LTD₄ as

![Figure 3](image-url) Hypothetical mechanisms of radiation-induced pneumonitis.
well as glutathione peroxidase are acutely upregulated in the irradiated mouse lung and remain persistently elevated 24 h postradiation and that the second generation antihistamine, azelastine, and coenzyme – Q, both free radical scavengers ameliorated these changes. Further evidence supporting the theory that antioxidants protect against RP has been provided by experiments that demonstrate that the overexpression of manganese superoxide dismutase (MnSOD) in a transgenic murine model or the exogenous administration of the iNOS inhibitor L-NAME ameliorates the deleterious effects of RT.

**Cytokines**

Both *in vitro* and clinical observations of the irradiated lung support the immunological basis of RILDs. As reviewed above, RT induces the generation of reactive oxygen species that is thought to initiate and propagate the pathological manifestations of RP. It has been shown that irradiated mice upregulate the chemokine macrophage chemoattractant protein 1 (CCL2), macrophage-derived chemokines (CCL22), thymus-derived and activation-derived chemokines (CCL17), and the CCR-4 receptors on alveolar lymphocytes and macrophages (see Chemokines, CC: MCP-1 (CCL2)–MCP-5 (CCL12)) (Figure 4). Both CCL22 and CCL17 are the natural ligands for CCR-4 and assist in the recruitment of proinflammatory cells and also regulate the proportion of Th2/Th1 lymphocytes. An analysis of the BAL from irradiated lungs reveals elevated TGF-β, IL-6, and IL-1 whose levels appear to correlate with the extent of RP (see Interleukins: IL-1 and IL-18; IL-6). TGF-β plays a pivotal role in the pathogenesis of other fibrotic lung diseases such as idiopathic pulmonary fibrosis where TGF-β mediates the differentiation of lung fibroblasts into myofibroblasts (see Transforming Growth Factor Beta (TGF-β) Family of Molecules. Interstitial Lung Disease: Idiopathic Pulmonary Fibrosis) (Figure 5). The myofibroblast elaborates cellular matrix, for example, elastin and collagen, and produces TGF-β. IL-6 is pleiotropic cytokine that regulates multiple pro-inflammatory cytokines and is crucial for lymphocyte development. The role of TGF-β in RP is supported by the observation that the administration of a recombinant TGF-β1 type II receptor (TGF-βRII) gene, which inhibits TGF-β activation, in a mouse model of RP attenuates histological evidence of radiation-induced lung injury. The administration of halofuginone, an inhibitor of TGF-β, was shown to reduce the colocalization of TGF-β with the tight junction protein Zo-1 and also reduces radiation-induced lung injury. This is interesting because the localization of TGF-β to Zo-1 is essential for the epithelial to mesenchymal transition suggesting that TGF-β-mediated epithelial–mesenchymal transition may play a role in radiation-induced lung injury.

In summary, radiation induces chemokines and cytokines which promote the expression of proinflammatory and profibrotic mediators in RP.

**Management and Current Therapy**

**Steroids**

Steroids are the mainstay for the treatment of RP (see Corticosteroids: Therapy). Up to 80% of RP cases have a dramatic clinical and radiological response to steroids. Supportive evidence for the use of steroids
accrues from clinical experience and in vitro data. The employment of steroids in the treatment of experimental mouse models of RP demonstrates that steroids delay the emergence of RP, attenuate the endothelial damage, and reduce the inflammatory cellular infiltrate. Notably, the effects of steroids on RP do not affect the emergence of RIF but the discontinuation of steroids in mice with experimental RP leads to accelerated mortality.

Human data supporting the use of steroids are lacking. On the whole, the discontinuation of steroids in human subjects leads to worsening of RP but there is no data to support the prophylactic use of corticosteroids to prevent the disease. The duration of steroid therapy is subjective but is on the order of several weeks accompanied by a slow taper. There are also sporadic reports showing cyclosporine is of benefit in steroid-refractory radiation pneumonitis. Angiotensin converting enzyme (ACE) inhibition has been suggested as a protective strategy against RP based on limited animal data. However, there is no sufficient human data to support the use of ACE inhibitors for protection against RP. In summary, these observations support the use of steroids in clinically symptomatic RP, although the empiric use of steroids in asymptomatic patients’ post-RT is not recommended.

**Novel Therapeutic Targets**

Ongoing research to identify novel methods to mitigate the adverse effects of RT focuses on reducing total radiation doses and blocking molecular mediators of RP. Technological innovations have dominated the impetus to reduce the unintended lung injury. However, there is promise that targeting RT specifically to the tumor may be improved with DNA-based technology to activate proapoptotic genes such as tumor necrosis factor-related apoptosis-inducing ligand (Apo-2L) (TRAIL), which preferentially activates apoptotic pathways in tumor versus normal cells. Additional strategies are focusing on limiting damage from RT-induced free radicals by increasing scavenger activity through activation of manganese superoxide dismutase or administration of antioxidants (see Oxidants and Antioxidants: Antioxidants, Enzymatic; Antioxidants, Nonenzymatic; Oxidants. Pulmonary Fibrosis. Radiotherapy. Transforming Growth Factor Beta (TGF-β) Family of Molecules).

**Further Reading**


