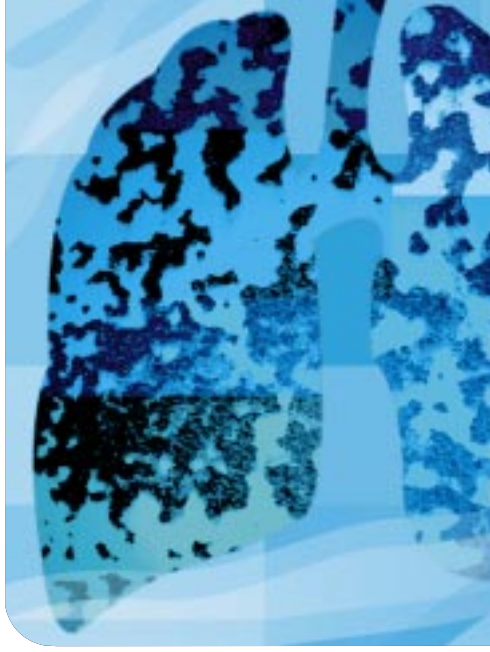

RADIATION-INDUCED LUNG INJURY

Strategies for reducing damage while optimizing therapeutic dosage

Ericka Wiebe, MSc and George Rodrigues MD, FRCPC, MSc

Top-line summary

Therapeutic radiation aims to achieve locoregional control of malignancy while minimizing acute and long-term adverse effects of radiation therapy. Safe administration of therapeutic radiation demands knowledge of both tumour and normal tissue response to radiation. Normal tissue tolerance depends on the tissue's intrinsic radiosensitivity, the dose-volume relationship (i.e. the percentage of organ volume receiving a specified dose) and modifying factors such as radiosensitizing chemotherapy. Use of tumour and/or patient immobilization, 3-dimensional computerized tomography (3D CT) planning and advanced radiation delivery techniques have all contributed to reductions in the dose administered to nontumour critical structures. Here, *Oncology Exchange* reviews the pathology and incidence of radiation damage to the lungs associated with thoracic radiation, describes new technologies that are continually improving the therapeutic ratio by maximizing dose to the target while minimizing treatment toxicity, and discusses treatments available and/or under investigation to treat radiation damage when it does occur.

Thoracic radiation is commonly employed to treat lung, esophageal, breast and lymphoma cancers. Lung inflammation caused by radiation therapy, called radiation pneumonitis (RP), is the most common dose-limiting complication of thoracic radiation.

RP can considerably affect patient morbidity — chiefly respiratory function and quality-of-life — and, infrequently, mortality. Persistent inflammation can lead to scarring of the lungs, or radiation fibrosis (RF), which irreversibly impairs oxygen exchange and is a cause of late morbidity and mortality in lung cancer patients. Therefore, the prevention, clinical identification and treatment of RP and RF are vital for optimally managing thoracic malignancies requiring radiation therapy.

RADIOBIOLOGY AND RADIOPATHOLOGY[1]

The lungs' primary function is to provide an interface for gas exchange between the blood vessels and the outside environment. This is accomplished by numerous branchings of the airways, eventually terminating in alveoli that provide a large surface area for diffusion. A dense network of capillaries exists within the walls of the alveoli. Capillaries consist of a single layer of endothelial cells upon a basement membrane, and are just wide enough to allow the passage of red blood cells, one cell at a time.

The alveoli are lined with specialized epithelial cells termed Type I pneumocytes. Interspersed among these cells are surfactant-producing Type II pneumocytes. Within the alveolar wall, pneumocytes are separated from endothelial cells by their associated basement membranes and a potential stromal space. Where present, the stromal space may contain smooth muscle cells, pericytes, fibroblasts and collagen. In some areas the alveolar wall is reduced to thin extensions of Type I pneumocytes in close approximation with the capillaries, resulting in a very thin blood-air barrier.

Capillary endothelial cells are highly sensitive to ionizing radiation and thus are critical for the development of radiation pneumonitis. Damage to endothelial cells is manifested by detachment of cells from their basement membrane, obstruction of the capillary lumen by thrombi, and interruption of the continuity of

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the capillary. Following endothelial cell injury, fibrinous exudate leaks into the stromal space and alveolar lumen. Intraseptal edema and formation of a fibrinous hyaline membrane then impair gas exchange. Ionizing radiation can also damage alveolar cells, particularly Type II pneumocytes, resulting in release of surfactant into the alveolar space and detachment of the pneumocytes from their basement membrane.

Inflammatory processes such as radiation pneumonitis activate cytokines and growth factors including transforming growth factor beta (TGFβ) and interleukin-1 (IL1). Acute pneumonitis may be followed by restoration of alveolar-capillary integrity or may evolve into fibrosis, an irreversible process of collagen deposition leading to obstruction of the capillary lumen. Collagen, along with the formation of elastic fibers, also thickens the alveolar septae. The pneumocytes become less prominent and may disappear. Eventually the alveoli collapse and become obliterated by connective tissue. Vascular changes consisting of myointimal hyperplasia and fibrin deposition may also occur in the arterioles during the progression from acute pneumonitis to fibrosis.

EPIDEMIOLOGY AND RISK FACTORS

The incidence of RP depends on the tumour site. Past estimates of RP incidence have ranged from 5% to 37% of patients receiving high-dose external-beam radiation treatment of lung cancer, varying with the population studied and the endpoint definition used.[2-4] With better radiation therapy delivery, however, the incidence of RP in lung cancer may be decreasing. Use of a mantle technique (radiation of lymph nodes in the neck, center of the chest and armpits) in Hodgkin's disease patients has been shown to decrease RP to less than 5%.[5] The probability of inducing RP in breast radiotherapy is too low (< 1%) to be statistically analyzed with high accuracy.[6]

The literature reports investigations of multiple patient, tumour, and treatment risk factors associated with the development of RP, primarily in the setting of lung cancer radiation (**Table 1**).[3,7-10] There is considerable variability among the studies in the strength of the association with RP for many of these risk factors. For example, initial studies of TGFβ1 indicated promise for this cytokine as a predictor of RP development;[11,12] but more recent studies have contradicted that view.[13,14]

CLINICAL AND RADIOGRAPHIC FINDINGS

RP encompasses a spectrum of clinical signs and symptoms. Manifestations range from incidental radiographic findings in asymptomatic patients to severe symptomatic illness. Symptoms of radiation pneumonitis usually become apparent 2 to 3 months after radiation therapy, but the onset can be as early as 1 month or as late as 6 months after the treatment. Dyspnea is the cardinal symptom of RP. The progression of dyspnea is usually self-limited, but may advance to severe respiratory distress. Additional symptoms of radiation pneumonitis may include low-grade fever, cough, pleuritic chest pain and hemoptysis. Radiographic findings in RP generally show diffuse infiltrates corresponding to the confines of the treatment field.

RP is an inflammatory process that may resolve entirely or progress to irreversible fibrosis. As RF develops, results of pulmonary function tests may deteriorate. When small lung volumes are irradiated, however, adjacent lung regions may be able to compensate and prevent significant clinical changes.[15] Diffusion capacity studies are considered the most accurate assessment method for radiation-induced injury as they evaluate damage at the capillary-alveolar level.[16] Predominant radiologic findings include lung infiltrate, retraction of the involved lung and elevation of the ipsilateral hemidiaphragm (**Figure 1**). The scarring process of RF evolves over 6 to 24 months, usually stabilizing after this time. Patients with RF may be asymptomatic or may have varying degrees of disability, depending mainly on the lung volume involved and the compensatory ability of the nonirradiated lung parenchyma. Lung tissue becomes noncompliant, with the potential to cause shortness of breath and possibly leading to pulmonary hypertension and congestive heart failure.

LUNG RADIATION TOXICITY CRITERIA

Several RP scoring systems have been developed and published in the literature to aid in recognizing and reporting RP and RF endpoints. Two of the most frequently used scales include the Radiation Therapy Oncology Group/European Organization for the Research and Treatment of Cancer (RTOG/EORTC) scale,[17] and the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3) scale.[18] Another modified scale is the LENT SOMA scoring system.[19] Grading of symptoms generally ranges from 0 (no RP) to 5 (death from RP). RP requiring steroid administration is assigned to either Grade 2 or 3 depending on the scale used. Use of oxygen generally denotes Grade 3 RP, and life-threatening RP is usually considered to be Grade 4.

A prospective study recently assessed the level of uncertainty in determining RP in patients under treatment for non-small cell lung cancer (NSCLC).[20] In 28% of cases, issues such as lung infection, COPD exacerbation, tumour

TABLE 1. Risk factors for development of radiation pneumonitis

patient-specific	treatment-specific
• age > 60 years	• high radiation dose
• smoking history	• large radiation treatment volume
• lower lobe location of tumour	• elevated dose rate
• poor performance status	• chemotherapy agents including: cisplatin, paclitaxel, docetaxel, mitomycin C, gemcitabine, irinotecan
• pulmonary dysfunction (e.g., PaO2 < 80)	
• post-RT elevation of TGF-β1 levels	

progression, and cardiac disease confounded the diagnosis of RP. The authors suggest that this uncertainty in RP determination may limit the investigation, prediction and prevention of this important toxicity endpoint.

DOSE-VOLUME HISTOGRAM PARAMETERS

The Photon Treatment Planning Collaborative Working Group Consensus initially compiled pulmonary tolerance doses.[21] Minimal and maximal radiation tolerance doses reflect, respectively, a 5% and 50% incidence of radiation pneumonitis within 5 years of RT completion (**Table 2**). With the advent of 3D CT planning, lung dose-volume histograms (DVHs) have been generated that provide both graphic and mathematic representation of the cumulative lung dose-volume relationship either as an individual or paired organ. DVH is a graphic tool that summarizes the 3D dose to tumours and critical structures in a 2-dimensional format, allowing easier identification of normal tissue areas that are receiving a dose of radiation above a specified threshold (**Figure 2,** page 32).

Several DVH parameters, defined in **Table 3**, have been developed in order to reduce the complex nature of the DVH into a single parameter that can then be used to predict RP risk. Both the Vdose and mean lung dose (MLD) parameters have been assessed frequently for their predictive value in regards to RP.[4,22] Several mathematic models of normal tissue complication probability (NTCP) have also been developed to calculate the RP risk from lung DVH and estimates of single and paired lung tolerance.[23,24] As the accuracy and positive predictive values with these methods are low, the ideal DVH parameter either alone or in conjunction with other variables has not yet been discovered.

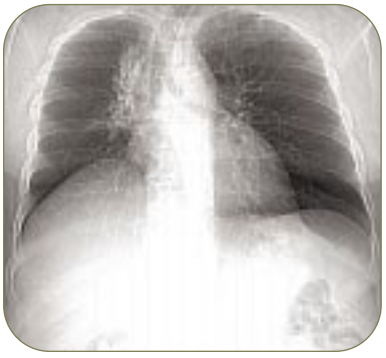
V20Gy is the most common currently used DVH parameter to attempt to predict for — and modify — moderate to severe pneumonitis risk in lung cancer irradiation. A generally accepted V20Gy parameter in clinical use is V20Gy < 35% for both lungs. Manipulation of DVH parameters by alteration of treatment technique, beam arrangement and weighting, inclusion and exclusion of elective nodal volumes, and introduction of advanced radiation delivery technologies (e.g. intensity modulated radiation therapy and stereotactic lung radiation) plays a significant role in contemporary attempts to reduce radiation-induced lung injury risk. Other technologies such as metabolic imaging, respiratory treatment gating, and automated breathing control are currently under evaluation as potential methods to improve the therapeutic ratio by reducing RP and RF risk.

TABLE 2. Tolerance doses (TD) for lung

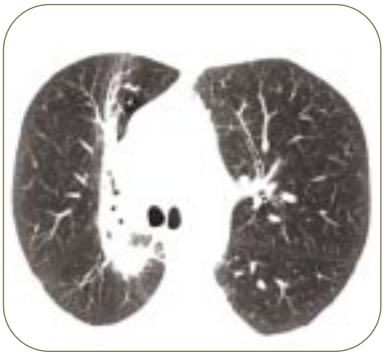
Lung volume irradiated	TD 5/5 (Gy)*	TD 50/5 (Gy)†
1/3	45	65
2/3	30	40
3/3	17.5	24.5

*TD 5/5: tolerance dose reflecting a cumulative incidence of radiation pneumonitis of 5% within 5 years of RT completion
†TD 50/5: tolerance dose reflecting a cumulative incidence of radiation pneumonitis of 50% within 5 years of RT completion

FIGURE 1. Radiation fibrosis



Chest radiograph
This patient completed treatment for NSCLC with concurrent radiochemotherapy 14 months earlier. The radiograph indicates changes consistent with radiation fibrosis in the right parahiliar region, including increased lung density and retraction of the affected lung volume. Note shift of the mediastinum toward the damaged side and tenting of the right hemidiaphragm.

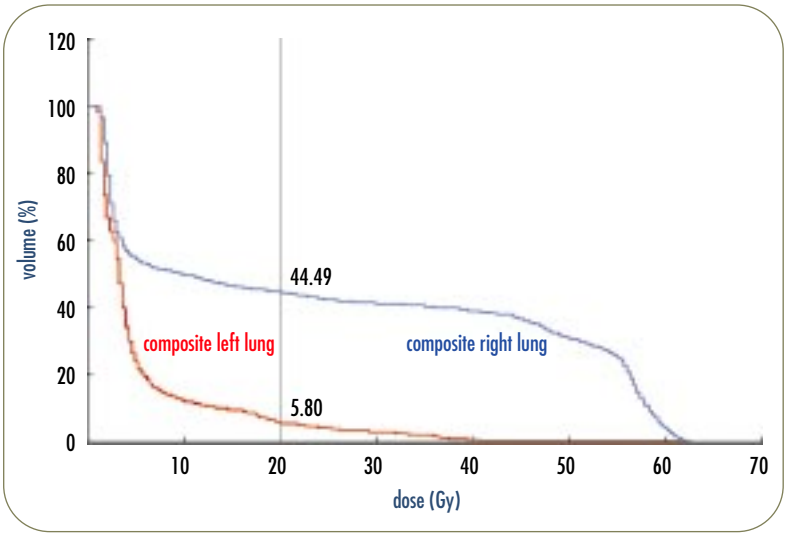


Lung CT scan
This lung CT of the same patient treated for NSCLC with radiochemotherapy shows linear opacities extending through the right parahilar region, corresponding to the treatment field and consistent with radiation fibrosis.

RP CHEMOPREVENTION STRATEGIES

Administration of agents that protect normal tissue from the effects of radiation is an emerging area of study. Amifostine is a pro-drug that dephosphorylates to become an active radioprotective agent. It is thought to protect normal tissue from radiation-induced damage by scavenging resulting free radicals, thereby providing an alternate target for reactive free radical species that would otherwise target DNA. It also protects normal tissue against cytotoxic agents, particularly useful in the setting of concurrent radiochemotherapy. **Table 4**, page 34, shows a series of randomized controlled clinical trials that evaluated the ability of amifostine to reduce the incidence of radiation pneumonitis arising from radiation therapy for NSCLC given concurrently with radiochemotherapy.[25-27] These trials sup-

FIGURE 2. Lung DVH



Dose-volume histogram of radiation treatment for NSCLC of the right lung. Here, the volume of bilateral lung receiving a dose ≥ 20Gy, i.e. V20Gy, is estimated to be 25.1%.

port the hypothesis that amifostine reduces the incidence of pulmonary toxicity. The theoretical consideration that amifostine could protect tumour tissue as well as normal tissue has not been validated. While these trials showed no reduction in locoregional control or reduced survival, they were underpowered to detect small differences in these outcomes. Giving amifostine carries drawbacks of intravenous administration and potential side effects, mainly hypotension and nausea, and more study is needed to establish the most effective and best-tolerated dose.

Additional agents found to have cytoprotective properties in preliminary studies include pentoxifylline, ACE inhibitors and carvedilol. A randomized trial of 40 patients indicated that pentoxifylline reduces acute side effects of lung radiotherapy compared to placebo.[28] Although ACE inhibitors conferred a benefit in reducing radiation-induced lung injury in animal studies, it did not reduce risk of RP in a retrospective analysis of lung cancer patients.[29] Carvedilol also showed promising cytoprotective effects in animal trials.[30] These agents do not have well-defined safety and efficacy profiles in the setting of radioprotection, so further study is required to delineate these properties. Gene therapy has also been investigated as an approach to radioprotection: in an animal model, intratracheal application of manganese superoxide dismutase-plasmid/liposome given prior to irradiation was selectively protective of normal lung tissue.[31]

TABLE 3. Dose-volume histogram parameter definitions

Vdose *example:* **V20Gy**	Percentage of the CT-defined total lung volume that receives a radiation dose greater or equal to the threshold dose. Percentage of the CT-defined total lung volume receiving a radiation dose ≥ 20 Gy.
MLD	Mean lung dose delivered to the total lung volume, calculated from dose-volume histogram data.
NTCP	Normal tissue complication probability: reflects a dose-response relationship of the probability of experiencing normal-tissue complications. The probability of pulmonary damage is calculated from tolerance doses and lung dose-volume histogram curves.

TREATING RP AND RF

In many cases RP is reversible. Corticosteroids can reduce inflammation and promote recovery. Generally accepted dosing is 0.5–1.0 mg/kg² for 2–3 weeks, with gradual tapering over 3–12 weeks depending on the severity of the RP and local institutional practice, but there is no universally accepted tapering schedule. Dose reductions should be done cautiously and in view of pneumonitis symptom resolution. Some patients may need supplemental oxygen, and antibiotics are indicated for suspected and proven infections.

The scarring involved in the process of radiation-induced pulmonary fibrosis is considered irreversible. However, preliminary studies have shown that combining pentoxifylline and vitamin E promotes regression of clinical radiation-induced fibrosis.[32] Conventional management of radiation fibrosis involves supportive measures including supplemental oxygen and bronchodilators. Counselling patients regarding the risks of smoking and guidance in smoking cessation is imperative to minimize further lung tissue damage.

FURTHER PROGRESS

Radiation therapy confers locoregional control and improved survival in the treatment of malignancy, but can also affect surrounding normal tissue, leading to adverse effects. Advances in the delivery of radiation treatments are limiting acute and late toxicity and improving overall outcomes. Appropriate identification and management of RP and RF as well as further study into prevention strategies will very likely continue to optimize the therapeutic ratio with respect to thoracic malignancies. OE

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Rodrigues, continued from page 32

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TABLE 4. Amifostine clinical trials

Randomized clinical trials of amifostine in patients receiving radiation therapy for NSCLC

reference	setting	effect on pneumonitis
Antonadou et al, 2001[25]	XRT in patients with advanced-stage NSCLC	XRT plus amifostine vs XRT alone reduced the incidence of both RP and RF
Antonadou et al, 2003[26]	RCT for locally-advanced NSCLC	Significant reduction in the incidence of both acute and late ($\geq$ 3 months) Grade $\geq$ 3 pulmonary toxicity in patients receiving RCT plus amifostine vs RCT alone
Komaki et al, 2004[27]	RCT for inoperable NSCLC	Lower rates of severe pneumonitis in patients receiving RCT plus amifostine vs RCT alone

NSCLC: Non-small-cell lung cancer; RCT: radiochemotherapy; XRT: external beam radiation therapy