Pulmonary toxicity generated from radiotherapeutic treatment of thoracic malignancies (Review)

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Abstract. Radiation-induced lung injury (RILI) remains a major obstacle for thoracic radiotherapy for the treatment of lung cancer, esophageal cancer and lymphoma. It is the principal dose-limiting complication, and can markedly impair the therapeutic ratio as well as a patient's quality of life. The current review presents the relevant concepts associated with RILI, including the pathogenic mechanisms and the potential treatment strategies, so as to achieve a general understanding of this issue. RILI comprises an acute radiation pneumonitis phase and subsequent late lung fibrosis. The established assessment criteria are clinical manifestations, imaging changes and the necessity for medical assistance. Risk factors are also considered in order to optimize treatment planning. Due to the underlying molecular mechanisms of RILI, the present review also discusses several targeted pharmacological approaches for its treatment, as well as corticosteroid therapy.

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1. Introduction

Radiotherapy (RT) is one of the main therapies for lung malignancies. As an organ that is sensitive to ionizing radiation, the lung tends to be easily damaged by radiation beams (1). Radiation-induced lung injury (RILI) is a major dose-limiting complication that develops in 7-37% of patients who undergo definitive RT for lung cancer (1-5). Although the application of modern radiation techniques has allowed for more accurate determination of target volume and a reduction of the dose administered to the normal lung tissues, acute radiation pneumonitis (RP) and late lung fibrosis have not been eradicated (6-8). Advanced non-invasive imaging techniques have provided a visual understanding of the disease, which has improved the rates of diagnosis and cure of RILI (9-11). In addition, various factors predictive of RILI, particularly dosimetric parameters, can contribute to the optimization of treatment planning (12). Classical countermeasures consisting of corticosteroids have demonstrated only an ameliorating effect on RILI, but not prevention of disease progression (1). Fortunately, with advances in research into its pathogenic mechanisms, several promising pharmacological interventions for RILI have been developed (13-15). Nevertheless, these novel agents have only been studied pre-clinically or in early clinical trials thus far. Therefore, further research is still required.

2. Pathogenic mechanisms

RILI includes an acute inflammatory phase, presenting as RP (1-3 months after RT), and a chronic fibrotic phase, presenting as radiation fibrosis (6-24 months after RT) (1). The pathological modifications associated with RILI in these two phases comprise a dynamic sequential process: Inflammation-induced depletion of alveolar surface cells, infiltration of inflammatory cells into the interstitial space, exudative response, and fibrotic changes (16).

The alveolar epithelium in humans is composed of two types of cells. Type I pneumocytes, which are squamous epithelial cells covering >90% of the alveolar surface, are the

first to be damaged by radiation beams. Following irradiation, type I cells undergo apoptosis, which promotes the proliferation of type II pneumocytes and leads to repopulation of the alveolar epithelium. Type II pneumocytes are cuboidal cells that are specialized in synthesizing and secreting pulmonary surfactants; this substance covers the alveolar surface and adjusts the surface tension. Thus, hyperplasia of type II cells resulting from radiation, and the associated surfactant overproduction, can be a non-specific indicator of pulmonary damage and reconstruction (17,18). Recent studies on animal models demonstrated that irradiated alveolar epithelial cells play an important role in pulmonary fibrosis (19,20).

Following RT, various cytokines are released. Activated alveolar macrophages can produce chemotactic and mitogenic cytokines, which act on immunocytes, fibroblasts and endothelial cells. These cytokines lead to the local recruitment of inflammatory leukocytes, including macrophages. Subsequently, leukocytes adhere to the endothelial cells of microvasculature and transmigrate to the interstitium; these cells further secret cytokines to recruit and activate additional immunocytes to trigger the inflammatory process (17). Tumor necrosis factor-α (TNF-α) is a type of proinflammatory and profibrotic cytokine that is synthesized by activated macrophages (21). During the course of fibrosis, TNF-α plays an important role in the secretion of proinflammatory cytokines, such as interleukin (IL)-1 and IL-6, in the proliferation of fibroblasts, and in the production of extracellular matrix (ECM) proteins. Under the hypoxic conditions in lung tissue following radiation, the macrophages will also persistently produce reactive oxygen species (ROS), which promote pulmonary injury and fibrosis (17).

Pulmonary fibrosis results from the accumulation of fibroblasts, myofibroblasts, fibrin and ECM proteins in the interstitium, followed by the pathological changes of scar formation (22). However, the molecular mechanism remains unclear, and numerous studies have been conducted to investigate related factors (17,22-31). Myofibroblasts are recognized as crucial factors in pulmonary fibrosis. Commonly, myofibroblasts are considered to be generated from resident fibroblasts, but recent evidence has indicated that damaged epithelial cells may directly provide myofibroblasts by means of epithelial-mesenchymal transition (EMT) (23). Nagarajan *et al* (24) revealed that a related pathway mediates EMT in irradiated alveolar type II epithelial cells. In a study by Phillips *et al* (25), it was demonstrated that circulating fibrocytes are associated with the pathogenesis of lung fibrosis.

Transforming growth factor-β (TGF-β) is a key cytokine in the fibrotic process; it is derived mainly from inflammatory cells, and also from pneumocytes and fibroblasts to some degree (17). In epithelial cells, upregulated TGF-β stimulates the expression of Smad proteins, which induce the activation of other transcription factors. TGF-β/Smad signaling plays an important role in promoting pulmonary fibrosis in various ways, including ROS production, activation of myofibroblasts and fibrocytes, and ECM synthesis (31). In a study by Yano *et al* (26), the Smad pathway was shown to contribute to radiation-induced lung fibrosis via the production of type I collagen, and not mitogen-activated protein kinase (MAPK). TGF-β can act as a powerful stimulator of collagen synthesis through modulating the transition from a human lung fibroblast to a myofibroblast phenotype, which facilitates lung fibrosis (27,28).

In addition to TGF-β, inflammatory cytokines derived from T helper (Th) cells also contribute to lung fibrosis. Han *et al* (29) noted that, in mice, Th2 immune response-associated factors, including IL-13, GATA-binding protein 3 and arginase 1, may be crucial in the fibrotic process. ECM remodeling, which involves collagen-degrading matrix metalloproteinases (MMPs) and tissue-inhibitors of MMPs, also augments the fibrotic process (30). Yang *et al* (30) suggested that MMP-2 and MMP-9, which degrade collagen IV in the basement membrane, were overexpressed in mice post-radiation during the inflammatory response, and destroyed the normal structure of the lung tissue.

3. Clinical manifestations

In the acute phase of RILI, typical clinical symptoms including dyspnea, ranging from mild to serious, and dry cough, which is observed in ~60% of patients with RP. Low-grade temporal fever is uncommon, and occurs in ~10% of cases. Upon physical examination in cases of suspected RILI, there may be no apparent abnormalities. However, rare signs such as pleural friction rub, moist rales, and consolidation may be heard occasionally in some cases, in addition to the common presentations (1). These manifestations may be complicated by pre-existing lung disease, such as chronic obstructive pulmonary disease (32). The incidence of fatal RP is low; in a study by Palma *et al* (33), it appeared in only 1.9% of cases in all patients who accepted concurrent chemoradiation therapy for non-small cell lung cancer (NSCLC).

Radiation fibrosis, which develops in the later phase of RILI, is a scarring disease that can markedly reduce the pulmonary function (32). It may be developed without the patient having suffered the acute phase. Different degrees of respiratory difficulty can occur in fibrotic patients. Chronic pulmonary insufficiency commonly evolves in patients with a large volume of irradiated lung tissue, and this facilitates the development of pulmonary hypertension or even cor pulmonale (pulmonary heart disease) (1). As a restrictive disease, pulmonary function test outcomes in RP patients, including the first expiratory volume in 1 sec (measuring gas movement) and the forced vital capacity (indicating lung capacity), are reduced (16). Carbon monoxide diffusion capacity (DLCO), an essential test that evaluates the gas diffusion condition of RILI patients, decreases significantly when the local radiation dose in normal lung tissue totals ≥13 Gy (34). DLCO loss tends to increase according to radiation dose (~72% in patients who received 10-20 Gy, and ~90% in patients who received >20 Gy) (34). However, the severity of lung injury is usually defined by the presentation of clinical symptoms and the corresponding treatment strategies, not pulmonary function indexes (16,34).

4. Imaging findings

In cases of suspected RILI, non-invasive radiological imaging, including chest radiography, computed tomography (CT), single-photon emission CT (SPECT), magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron

emission tomography (FDG-PET), may be applied to evaluate the damaged region and potentially predict the corresponding clinical features (6). Various radiological abnormalities associated with RILI may be observed in the different phases of lung pathological injury. An increased density on areas of CT images is associated with inflammatory reactions during the acute phase (7). Not all radiological appearances of RILI are accompanied by clinical symptoms; 50-100% of lung cancer patients who have undergone RT tend to present with radiological signs of RILI, whereas only 5-35% develop clinical symptoms (35-37). Thus, imaging examinations are important for patients who have undergone thoracic irradiation. The frequency of imaging examinations is determined on the basis of the sensitivity of the specific radiographic assessment; it is reported that CT is more sensitive and reveals RP-associated changes earlier compared with chest radiography, as it provides 3D visualization of the lung (6).

CT findings. For conventional thoracic RT, Libshitz and Shuman (38) classified the lung injury-associated CT findings into four types: i) Ground-glass attenuation or homogeneous consolidation; ii) patch-like increased density in the irradiated area that is not consistent with the portal shape; iii) scattered consolidation that is consistent with the portal shape but has a poorly-defined border; and iv) solid consolidation that involves the entire region of irradiated lung tissue. The former patterns correspond to the acute phase of inflammatory exudation, while the latter patterns correspond to the late phase of lung fibrosis.

With the improvement of radiation methods, certain advanced techniques, including 3D conformal RT (3DCRT), intensity-modulated RT (IMRT), and stereotactic body RT (SBRT), which are able to deliver a maximized tumoricidal dose to tumors while minimizing the irradiation of normal lung tissues, have been developed.

3DCRT is a modern and sophisticated technique that applies multiple radiation beams to form a conformal radiation field properly fitted to target volumes. This method greatly reduces the rate of RILI and has an improved curative effect compared with conventional 2-dimensional radiotherapy. In patients with NSCLC undergoing 3DCRT, CT images for lung areas with RILI can develop into altered conventional fibrosis (increased density, volume loss, and bronchiectasis in a shrunken extent compared with conventional radiotherapy), scar-like patterns (an opacity change in tumor tissues) or mass-like patterns (7).

In IMRT, intensity-modulated radiation is delivered to irregularly shaped tumor volumes by means of the dynamic multileaf collimators on the basis of 3DCRT. Given that tumor location, size and disease entity determine the radiation portal and beam angles, RILI may differ in shape and distribution depending on tumor features (39).

SBRT is a novel RT technique in which multiple radiation portals are applied from different directions, allowing good treatment effects for medically inoperable early-stage NSCLC patients. Radiation lesions in normal tissue are limited to the periphery of the tumor and have a complex shape. In patients who have undergone SBRT, the CT findings associated with RILI conform more closely to the shape of the tumor, and there is no distinct boundary dividing the irradiated and non-irradiated lung, in contrast to conventional RT (8).

Figs. 1 and 2 show the typical CT imaging findings of RP.

SPECT findings. CT scans depict density modifications of lung tissue in RILI patients that are consistent with the 3D dose distribution map. However, SPECT has been demonstrated to be a more sensitive examination than CT imaging for assessing lung injury, by evaluating regional lung perfusion and ventilation functions (6,40). Physiologically, lungs tend to adjust blood flow according to ventilation changes rather than adjust ventilation according to blood flow changes. Therefore, perfusion is a more sensitive factor than ventilation for predicting RILI (6). Zhang *et al* (41) conducted a study of 20 patients with locally advanced NSCLC who received radical- or non-radical-dose IMRT, in order to quantitatively evaluate early abnormalities in lung perfusion using SPECT imaging. SPECT was conducted prior to and immediately subsequent to IMRT. The study calculated lung perfusion index (LPI) with regard to blood flow through radioactive count. The results revealed no statistically significant difference between the LPIs pre- and post-IMRT (P=0.135). In the radical-dose group, LPI difference was not statistically significant (P=0.993); by contrast, the difference was significant in non-radical-dose group (P=0.025). Thus, SPECT scanning is useful in evaluating early alterations in perfusion in patients undergoing non-radical-dose IMRT. Currently, SPECT scanning in assessing perfusion is primarily judged by visual inspection by physicians; therefore, it is inevitably biased and it is challenging to identify early subtle changes in perfusion (9). Thus, radioactive counts in qualifying SPECT images are required.

MRI findings. In previous studies, MRI findings have been described for RILI lesions in animal models and human patients (10,11). In a Japanese study conducted by Shioya *et al* (10), MRI was used to measure the extent of lung injury in rats that had undergone hemithoracic radiation, indicating that MRI may be a sensitive technique for detecting early RILI. Ireland *et al* (11) compared helium-3 MRI (^{3}He-MRI) acquired from patient with NSCLC pre- and post-external-beam RT. In their study, all 5 patients with pathologically confirmed NSCLC received CT and ^{3}He-MRI ventilation imaging. Post-irradiation, 3 patients developed pneumonitis that was apparent on CT images. Concurrently, a significant reduction of ^{3}He-MRI ventilation was observed in these 3 patients on post-irradiation imaging compared with pre-irradiation imaging (P=0.02). This indicates that ^{3}He-MRI is a potential method for describing RP by means of expressing the reduction in ventilation.

PET findings. FDG-PET is a type of metabolic imaging technology that can present regional functional information, and which has the potential to evaluate RILI. In a study by Hart *et al* (42), pulmonary metabolic radiation response, a parameter generated from FDG-PET analysis, was found to be associated with an increased probability of developing RILI (P=0.033). McCurdy *et al* (9) also demonstrated that the FDG-uptake dose-response was associated with symptomatic RP in patients with lung cancer treated with thoracic RT. Additionally, combined PET-CT and PET-MRI, which can present anatomical and metabolic information, are promising techniques (43). Studies indicated that ventilation/perfusion

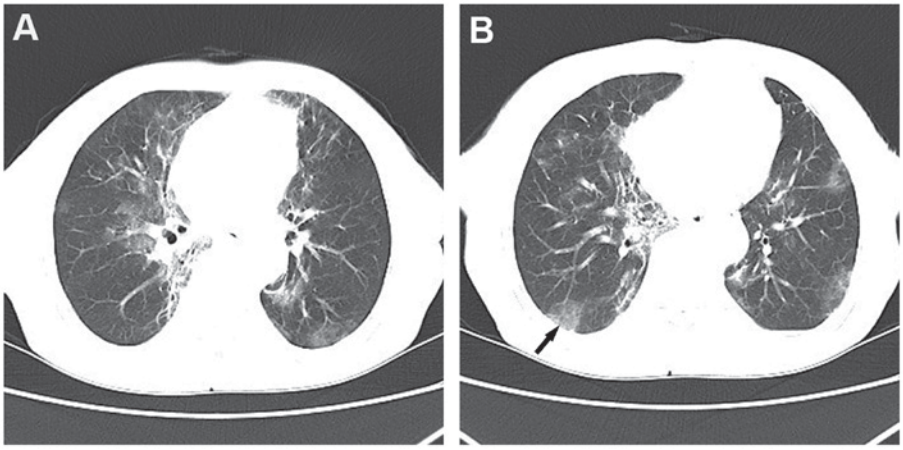

Figure 1. Computed tomography images (A, before radiotherapy; B, post radiotherapy) of a 63-year-old woman with esophageal cancer. Following radiation of ≤59.4 Gy, certain imaging changes were apparent in panel B, including scattered areas of patchy density in the lung (noted by the black arrow in panel B). The clinical manifestations of this patient were mild, with only a dry cough reported.

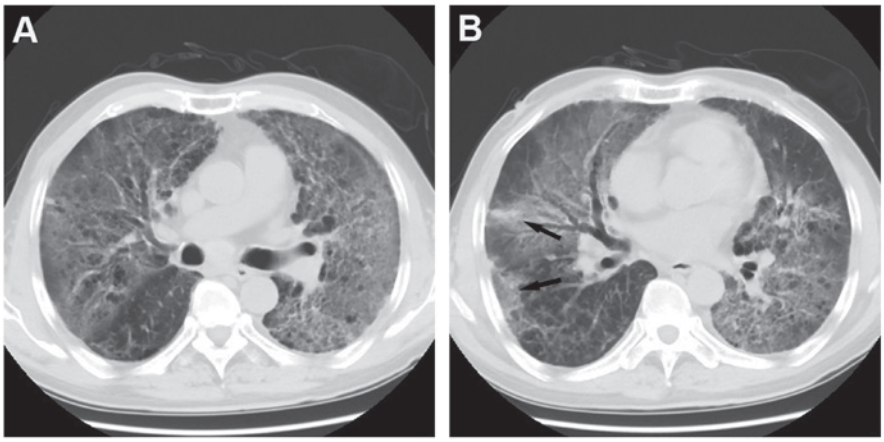

Figure 2. Computed tomography images of a 58-year-old man with lung cancer (A, before radiotherapy; B, post radiotherapy). Although the V_{20} (% volume of lung that received ≥20 Gy radiation) for the whole lung was 23%, typical imaging findings of RP were visible, including patchy infiltration and density (noted by the black arrows in panel B). This patient presented with severe symptoms, including a prolonged high fever with yellow mucus production, which were insensitive to standard antibacterial agents.

index of PET-CT imaging was able to predict the occurrence rate of RILI and PET-CT could be recommended to differentiate RILI from cancer recurrence (44,45).

5. Predictive factors

Parameters from dose-volume histograms (DVHs). DVHs generated from 3DCRT planning have been investigated in numerous studies, and have revealed the dosimetric parameters that are able to predict RILI caused by external-beam RT. V_{dose}, mean lung dose (MLD) and normal tissue complication probability (NTCP), which are described below, are three dosimetric parameters with high predictive value for RILI that have been studied extensively (2). These parameters may assist clinicians with optimizing radiation treatment planning.

V_{dose} and MLD. The definition for V_{dose} (e.g., V_5, V_{10}, V_{20}, V_{30} or V_{40}) is described as the percentage of the whole CT-measured volume of the irradiated lung that received equal to or more than the threshold dose (5, 10, 20, 30 or 40 Gy, respectively). MLD represents the mean dose applied over the whole lung volume measured by CT imaging. Among the dosimetric factors, V_{20} and MLD are the most frequently used parameters for predicting RILI (33).

Hernando *et al* (3) conducted a study of 201 patients with lung cancer, all of whom received RT utilizing 3D planning tools, and investigated the correlation between DVH-based factors and RP rates. In total, 39 (19%) of the 201 patients developed RP. Univariate and multivariate analyses indicated that V_{30} and MLD were the only factors significantly associated with RP rates. An increasing rate of RP was observed with increasing V_{30} (RP rates: 6 and 24% in patients with V_{30} of ≤18 and >18%, respectively) and MLD values (RP rates: 10, 16, 27 and 44% in patients who received an MLD of <10, 11-20, 21-30 and >30 Gy, respectively). The authors concluded that dosimetric factors were the best predictors of RP, superior to clinical factors (age, gender, tumor location, chemotherapy application, smoking, pre-RT forced expiratory volume in 1 sec and performance status) for lung cancer patients treated with 3DCRT (3). Barriger *et al* (4) reviewed dosimetric data

from 243 patients with stage III NSCLC treated with concurrent cisplatin/etoposide chemoradiotherapy to examine the rates and predictive factors for RP. In that study, 17 (7%) of the patients developed grade ≥2 RP according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The median MLD, V_5, V_{20} and V_{30} values were 18 Gy, 52, 35 and 29%, respectively. An increasing rate of RP was associated with increasing MLD (MLD <18 Gy, 2.2% RP rate; MLD >18 Gy, 19% RP rate; P=0.015) and V_{20} (V_{20} <35%, 4.8% RP rate; V_{20} >35%, 17% RP rate; P=0.097). Thus, the results revealed that an MLD >18 Gy was a predictive factor for RP, and that V_{20} was possibly associated with RP. Furthermore, a recent meta-analysis performed on 836 patients who received concurrent chemoradiotherapy obtained a similar outcome; the results suggested that 29.8% of patients developed symptomatic RP, and that V_{20} was a significant factor in predicting symptomatic RP (P=0.008) (33).

In previous studies, most of the V_{dose} and MLD values used standardly refer to the bilateral lungs, which means that each dosimetric parameter represents the average value of the total lung parenchyma, rather than that of the unilateral lung with the primary tumor (2-5). Therefore, it is necessary to establish new parameters for use in treatment planning to aid in concentrating the radiation beams on a single lung. Ramella *et al* (5) analyzed 97 patients with locally advanced NSCLC who received complete 3DCRT with V_{20}, V_{30} and MLD limits of 31%, 18% and 20 Gy, respectively. The authors investigated novel parameters V_{20}ipsi and V_{30}ipsi (percentages of ipsilateral lung volume receiving >20 and >30 Gy, respectively), which were indicated to be significant predictors of RP. The cutoff points for V_{20}ipsi and V_{30}ipsi were 52 and 39%, respectively: The risk of RP was 9% if V_{20}ipsi was ≤52% vs. 46% if V_{20}ipsi was >52%; and the risk of RP was 8% if V_{30}ipsi was ≤39% vs. 38% if V_{30}ipsi was >39%. The differences in V_{20}ipsi and V_{30}ipsi between the RP group and the non-RP group were statistically significant (P=0.010 and P=0.001, respectively). Furthermore, in their clinical practice, RP incidence was reduced from 14.4 to 6.8% when adding the ipsilateral constraints to standard lung dosimetric parameters. Thus, this may be an accessible way to improve treatment planning.

Despite the numerous studies confirming the predictive value of dosimetric factors, certain studies have presented contrasting findings. Rodrigues *et al* (2) conducted a review of 12 studies to assess the association between DVH parameters and RP rates. The study showed a negative result, and the overall accuracy, sensitivity, specificity and positive predictive value of DVH parameters were found to be undesirable. Each DVH parameter in that study failed to predict RP alone or in a model with additional variables. Another meta-analysis also suggested that dose-volume metrics should be explored further to evaluate the RP risk (12).

NTCP. NTCP is another parameter that can be calculated as a function of the normal tissue DVH by different algorithms. Various studies have demonstrated that NTCP is a strong predictor of RILI (46). The Lyman model (47) is the most widely applied NTCP model, and is characterized by the binary (yes/no) toxicity evaluation endpoint (48). Although it is successful in estimating RP rates, there remains potential to improve the standard Lyman model. Recent studies have attempted to incorporate clinical risk factors in the model to better predict RILI. Tucker *et al* (48) introduced a generalized model accounting for censored time-to-toxicity data and smoking status, and the results demonstrated a higher predictive value of NTCP model compared with the model developed on DVH alone. Adding single-nucleotide polymorphisms to the standard Lyman model also enhanced its predictive value for RP (43).

Serum markers. The pathogenesis of RP remains unclear; it is known to be a complex inflammatory process that involves the cellular interactions between lung parenchymal cells and circulating immune cells, mediated through a series of cytokines (49). Thus, the plasma levels of distinct cytokines may be of significance in identifying patients at risk of developing RILI. However, these cytokines are derived from the irradiated normal lung tissues as well as the tumor tissues, including the tumor cells themselves, the immune cells of the tumor microenvironment and the host stroma of NSCLC specimens, influencing the circulating plasma cytokine concentrations (50,51). This indicates that further investigation is necessary to confirm the ability of cytokines in predicting RILI. IL-6 and TGF-β are pro-inflammatory and profibrogenic cytokines, which have been extensively investigated in numerous studies, including human clinical reports and animal trials. The fluctuating IL-6 and TGF-β plasma levels measured before and during RT may be associated with the development of RILI (49).

Rübe *et al* (49) analyzed the TGF-β1, TNF-α, IL-1β and IL-6 circulating plasma levels in 52 patients with NSCLC (stage I-III) to explore the prognostic values for the development of RP. The Late Effects in Normal Tissue-Subjective Objective Management Analysis (LENT-SOMA) system (Table I) was used in the study, and the cytokine data was obtained before RT, weekly during RT, every 3 months during follow-up, and at the beginning of RP. In the study, 40% of patients developed RP, with 10 cases exhibiting RP of grade II or higher (grade II/III/IV, 3/6/1 patients). The study failed to confirm any correlation between TGF-β1 or IL-6 plasma levels and the probability of RP occurrence. However, it appeared to be possible to predict RILI when cytokines were combined with dosimetric factors. In a study by Stenmark *et al* (52), five cytokines (IL-1β, IL-6, IL-8, TNF-α and TGF-β1), in 58 NSCLC patients treated with definitive RT, were analyzed to ascertain their value as predictive factors for RILI. All cytokines were evaluated individually and in combination with physical dosimetric parameters. The results indicated that a low level of pre-treatment IL-8 was a significant predictor for RILI, while elevated TGF-β1 resulting from radiation was mildly correlated with the development of RILI. The other three cytokines demonstrated no predictive value. However, the combined model, utilizing IL-8, TGF-β1 and MLD, yielded an advanced capacity for predicting RILI compared with any variable alone (P<0.001). Therefore, the authors concluded that a model based on inflammatory cytokines and dosimetric parameters may estimate RILI accurately (52).

A number of studies have indicated that surfactant protein (SP) levels in the serum may be meaningful in predicting RILI. Takahashi *et al* (53) reported that SP-A and SP-D concentrations in RP patients were higher than those of non-RP patients

Table I. Summary of generally used grading systems.

	Grade				
Criteria	1	2	3	4	5
CTCAE 4.0					
Pneumonitis	Asymptomatic; observations only	Symptomatic; requires medical intervention; limited ADL	Severe symptoms; oxygen indicated; impair patient self-care ADL	Life-threatening respiratory dysfunction; urgent intervention indicated	Mortality
Pulmonary fibrosis	Mild hypoxemia; pulmonary fibrosis <25%	Moderate hypoxemia; pulmonary hypertension; pulmonary fibrosis 25-50%	Severe hypoxemia; right-sided heart failure; pulmonary fibrosis 50-75%	Life-threatening consequences; assisted ventilation indicated; pulmonary fibrosis >75%	Mortality
RTOG: Pneumonitis	Mild symptoms	Persistent symptoms requiring symptomatic treatment	Severe symptoms, possibly requiring intermittent O_2 or steroids; evidence of acute pneumonitis	Severe symptoms requiring continuous O_2 or assisted ventilation	-
RTOG/EORTC: Fibrosis (LENT-SOMA)	Asymptomatic or mild symptoms; slight imaging changes	Moderate symptoms; patchy imaging changes	Severe symptoms; increased density imaging changes	Severe symptoms requiring continuous O_2 or assisted ventilation	Mortality
SWOG					
Pneumonitis	Imaging changes; mild symptoms without steroids	Symptoms requiring steroids or tap for effusion	Symptoms requiring oxygen	Symptoms requiring assisted ventilation	Mortality
Fibrosis	Asymptomatic; imaging changes	-	Imaging changes with symptoms (also code symptoms)	-	-

CTCAE 4.0, common terminology criteria for adverse events, version 4.0; RTOG, radiation therapy oncology group; EORTC, European organization for research and treatment of cancer; LENT-SOMA, late effects in normal tissue-subjective objective management analysis; SWOG, southwest oncology group; ADL, activities of daily living.

(P=0.0065 and P=0.0011, respectively), which suggested an RP-diagnostic value of these two variables. In an article analyzing the Radiation Therapy Oncology Group (RTOG) 91-03 trial, an elevated serum level of SP at 20 Gy and increased IL-6 serum density after 10 Gy radiation were considered predictive factors of grade ≥2 acute lung toxicity (54).

Clinical risk factors for the development of RILI. Prediction of RILI is not only dependent on dosimetric factors or plasma cytokine levels, but may also be influenced by clinical risk factors. Patient characteristics, including age, gender, comorbidity, tumor location, performance status and smoking status, combined with treatment-related factors, such as chemotherapy schedule and surgery, comprise the clinical factors associated with RP. These factors have been widely investigated in previous studies: Pre-treatment Karnofsky performance status was associated with late lung toxicity (54), and chemotherapy (P<0.0001) and advanced age (61-70 years) were notable predictive factors for RP (55), whereas pre-RT surgery demonstrated no effect on the development of RP (56). However, few reports of RILI to date have systematically elucidated these risk factors.

In order to study the clinical factors professionally, Vogelius *et al* (57) conducted a meta-analysis synthesizing data from 31 independent studies with available odds ratio (OR) data for RP, and provided a framework for this large amount of information. The results indicated that advanced age (OR, 1.7; P<0.0001), disease located in middle or lower lobe (OR, 1.9; P=0.002) and the presence of comorbidities (OR, 2.3; P=0.007) were significantly associated with RP. Sequential chemotherapy scheduling was also associated with a higher risk of developing RP (OR, 1.6; P=0.01) than concomitant chemotherapy scheduling. Smoking status, which showed contrasting effects, was analyzed in two parts: Ongoing smoking could prevent lung cancer patients from developing RP (OR, 0.6; P=0.008); and a history of smoking indicated a

non-significant protective effect against RP (OR, 0.7; P=0.06). No association of gender or surgery with RP development was confirmed in the study. This research demonstrated a method of synthesizing published clinical risk factor data across various studies, facilitating its analysis with regard to RP. Depending on the method, it may be beneficial to combine these factors with dosimetric factors in a multivariate model in future research to better understand the development of RP, and generate guidelines for clinical research.

6. Grading systems

Several toxicity scoring systems evaluating the clinical, functional and imaging changes of acute and late RILI have been used in various studies. CTCAE version 4.0 (58) is currently the most recommended set of guidelines by the National Cancer Institute. In addition, the RTOG and European Organization for Research and Treatment of Cancer (RTOG/EORTC) scoring system (designated as RTOG for brevity) (59), as well as the Southwest Oncology Group (SWOG) scoring system (60) are also generally applied (Table I). Other criteria from the Eastern Cooperative Oncology Group (61) and the World Health Organization (62) are also in use (63). In generally used systems, toxicity grades of 1, 4 and 5 similarly represent mild symptoms, lethal conditions, and mortality, respectively. However, the criteria vary for definitions of grades 2 and 3. RTOG grade 2 is described as a persistent cough requiring narcotic antitussive agents, while the grade 3 patients present with severe cough requiring steroid treatment. By contrast, in SWOG grade 2, steroid treatment is required. However, the CTCAE 4.0 system does not involve the utility of steroid agents. For late lung toxicity, RTOG criteria appear to be the easiest to follow among the scoring systems, as they depicts lung fibrosis together with pneumonitis in detail (64).

7. Treatments

In order to reduce the probability or mitigate the severity of RILI, a variety of strategies have been investigated, ranging from radiation techniques to pharmacological methods (1). As standard, modern radiation treatment planning techniques should be implemented to minimize the dose to normal lung tissues. Age, sex, tumor location, smoking status, pulmonary function, performance status and a number of other patient characteristics should also be considered (1,16). Given the high rate of infection in these patients, antibiotics are used prophylactically (16). For established RILI, multiple agents are used empirically, and corticosteroids are a mainstay due to their anti-inflammatory effects; the common dose is 60-100 mg/day for 2 weeks, followed by an extended taper over 3-12 weeks (1). Although steroids are widely used in patients with RILI, there appears to be no evidence confirming its possible influence on long-standing fibrosis. Due to advances in understanding the molecular pathology of RILI, several promising prophylactic and therapeutic approaches for this disease have been proposed.

Cytoprotective agents. Amifostine, an analog of cysteamine, is the first broad-spectrum cytoprotectant to have been approved in various countries for clinical use (65). It is an organic thio-phosphate molecule. Following its dephosphorylation by vascular endothelial cell alkaline phosphatase, amifostine transforms into its biologically active metabolite. The metabolite exerts its biological actions via two approaches: Scavenging ROS generated following radiation, and protecting nucleic acids from alkylating or platinum-based drugs (65-67). Several clinical trials have reported that amifostine could significantly reduce the incidence of RILI without compromising the anti-tumor efficacy of radiation in lung cancer patients (13,66,67). Komaki *et al* (13) reported that no severe RP was observed in patients with lung cancer in the amifostine treatment group, compared with 16% of patients not treated with amifostine (P=0.02). Furthermore, amifostine did not exhibit any apparent effects on survival in these patients. The authors thus concluded that amifostine had no tumor-protective effect. Recently, Koukourakis *et al* (68) demonstrated that a moderate dose of amifostine administered subcutaneously to irradiated postmastectomy patients had a significant effect in preventing fibrosis in lung and soft tissue.

Superoxide dismutases (SODs) are natural enzymes in mammals that converting superoxide radicals into oxygen and hydrogen peroxide (H_2O_2) prior to further metabolism. In humans, three forms of SOD exist: Mn SOD, Cu/Zn SOD and extracellular (EC) SOD (17). EC SOD is the major extracellular antioxidant enzyme and is highly produced in type II pneumocytes. Therefore, in the lungs, type II pneumocytes may play a critical role in cytoprotection via EC SOD (69). Numerous studies have successfully demonstrated the effects of SOD administration on radiation-induced fibrosis (RIF). Delanian *et al* (70) showed for the first time that liposomal-form SOD (Lip-SOD) reversed RIF in a clinical trial. They treated 42 distinct zones of RIF, involving the skin and underlying tissues, with Lip-SOD in 34 patients. Regression was observed in 79% of the fibrotic zones, and treatment was well-tolerated. The stability of the response at 3 and 5 years was 95 and 70%, respectively. Lefaix *et al* (71) suggested that two agents, Mn SOD and Cu/Zn SOD, exerted curative effects on RIF in animal models. Epperly *et al* (72) demonstrated that overexpression of Mn SOD in the lungs of transgenic mice pre-radiation could decrease the occurrence of irradiated lung alveolitis and fibrosis.

The anti-fibrotic properties of SODs may act via mediating TGF-β1 repression and inducing the reversion of myofibroblasts into normal fibroblasts (73). In previous studies, SOD-mimetic agents were shown to alleviate RILI. For example, Gao *et al* (74) administered EUK-207, a SOD/catalase mimetic agent, to rats via subcutaneous injection, starting at 7 days after total-body irradiation and stopping prior to the development of pneumonitis. The results indicated that EUK-207 may act as a mitigator of RP and fibrosis. EUK-207 was also shown to diminish multiple vascular injuries in irradiated lungs *in vivo* for the first time (74). Pan *et al* (75) suggested that pretreatment with the recombinant protein SOD-TAT in mice demonstrated an advantage over amifostine in reducing RIF and improving quality of life.

Suppressors of the renin-angiotensin (RAS) system. Classically, in the RAS, biological effects are initiated by the interplay between kidney mesangial cell-generated renin (substrate) and liver-generated angiotensinogen (enzyme)

in circulation, followed by the production of angiotensin (Ang) I, an inactive decapeptide. After being cleaved by angiotensin-converting enzyme (ACE), Ang I transforms into the effective Ang II, which binds to Ang II receptor type 1 (AT_1) or type 2 (AT_2) to exert its functions (including vasoconstrictor activity to regulate blood pressure) (76). Furthermore, mounting evidence indicates that Ang II is associated with the development of fibrosis via TGF-β upregulation (77) and ECM protein synthesis (78). Ang II also contributes to the injury process as a powerful proinflammatory substance (79). Thus, ACE inhibitor (ACEI), which blocks Ang II synthesis, may play a significant role in alleviating RILI. Ghosh *et al* (14) indicated that the ACEI captopril could increase survival and ameliorate RILI, including increased breath rate, vascular reactive changes and histopathological evidence, in irradiated mice. In a randomized controlled trial, application of captopril in 55 patients demonstrated a favorable efficacy in reducing pulmonary-related mortality resulting from total-body irradiation (80). However, captopril is a special type of ACEI, as the sulfhydryl group in its molecular structure was shown to be capable of scavenging radicals (81), which suggested another mechanism by which captopril could attenuate RILI. Wang *et al* (82) retrospectively analyzed 413 irradiated NSCLC patients, of whom 65 were given ACEIs during RT (only 1 received captopril), and the results suggested lower symptomatic RP rates in ACEI-treated patients compared with the non-ACEI-treated group. This outcome indicated that ACEI agents other than captopril could also reduce RILI. From another perspective, Molteni *et al* (83) showed that Ang II receptor inhibitors were helpful in palliating RILI. Additionally, certain researchers suggested renin as a profibrotic mediator independent from the angiotensin system, in the lung and other organs, which may provide another approach to mitigating lung fibrosis (84,85).

Statins. HMG-CoA-reductase inhibitors (statins) are pleiotropic drugs mainly used as interventions for hypercholesterolemia. Other than lowering blood lipid levels, they have functions in reducing radiation-related proinflammatory and profibrotic responses as well as apoptosis, *in vitro* and *in vivo* (86,87). A pharmacological use of statins involves inhibition of the radiation-induced activation of the transcription factor nuclear factor κB, and of the resulting overproduction of cytokines (including IL-6 and TNF-α) (88). Pre-treatment with lovastatin in irradiated murine models achieved a reduction of endothelial selectin and intercellular adhesion molecule 1, which are important mediators in the inflammatory process (87). On the genetic level, simvastatin reversed the radiation-induced dysregulation of gene expression (such as p53, NRF2, and sphingolipid metabolic pathway genes) in rat lungs (89). In addition, statins showed an improved repair capacity for radiation-induced DNA double-strand breaks (88). Clinically, Wedlake *et al* (90) indicated that, among 308 patients who received pelvic RT for cancer, statin (P=0.04) and statin + ACEI (P=0.008) treatment regimens significantly relived radiation-induced acute gastrointestinal symptoms and exhibited long-term protective effects. Given the well-established clinical use of statins for lipid-lowering purposes, it is desirable to assess their application as radioprotectants in humans.

Growth factor-related protocols. TGF-β/Smad signaling is important in the development of radiation-induced damage, and has been investigated as a treatment target in numerous studies. Pentoxifylline (PTX), a xanthine derivative, appears to mitigate fibrosis by blocking Smad3/4-activated transcription (91). In a clinical trial by Ozturk *et al* (15), 40 patients with thoracic malignancies were randomly assigned to receive PTX (400 mg) or a placebo three times per day during the entire RT period. The results showed a statistically significant protective effect of PTX against acute and late lung radiotoxicity. In that study, the initial curative mechanism of PTX was suggested to be platelet reaggregation and TNF inhibition. Furthermore, Misirlioglu *et al* (92) used a combined therapy of PTX and α-tocopherol (vitamin E) for lung cancer patients during and for 3 months after RT, which considerably ameliorated RILI. SB203580 and WP631 are blockers of Smad signal transduction pathway. They abrogate excessive proliferation, decrease the expression of p21 and plasminogen activator inhibitor-1 following radiation, and reduce TGF-β1 in human lung fibroblasts (93). SM16 (94) and LY2109761 (95) are two small-molecule TGF-β inhibitors which have been confirmed to be valuable in alleviating RILI based on different biological rationales.

Platelet-derived growth factor (PDGF) receptor tyrosine kinase inhibitors (RTKIs) are reportedly beneficial in mitigating RILI. Abdollahi *et al* (96) applied three different PDGF RTKIs (SU9518, SU11657 or imatinib) to irradiated mice during the acute RP phase; markedly reversal of lung fibrosis development was observed based on the clinical, histological, and CT imaging results. In a further study by the same authors, which assessed whether imatinib administration following subsidence of acute inflammation was effective in attenuating lung fibrosis in mice, a positive result was obtained (97). In these two studies, the therapeutic effect of PDGF RTKIs was considered to be associated with the regulation of TGF-β. Furthermore, Thomas *et al* (98) noted that imatinib relieved alveolitis or fibrosis by means of preventing the mast cell influx into the lungs following irradiation in mice.

Other treatment schemes. Yazici *et al* (99) revealed that the use of vitamin D significantly reduced interstitial inflammation and collagen deposition in irradiated rat lungs, and that the corresponding alveolar structure and pneumocytes were protected. MSX-122, a novel inhibitor of C-X-C chemokine receptor type 4, has demonstrated a benefit in suppressing radiation-induced fibrotic processes in mice (100). In addition to these pharmacological therapies, certain other approaches, including physiotherapy, hyperbaric oxygen therapy and impedance-controlled microcurrent therapy may be promising in reducing radiation-related late lung fibrosis (101).

8. Conclusions

RILI is a dynamic process characterized by RP and lung fibrosis. Clinically, dyspnea, non-productive cough and low-grade fever are the most typical symptoms of acute RP, accompanied by a decline in pulmonary function. The exact mechanisms of RILI remain unclear; hyperplasia of normal

pneumocytes, and the overexpression of proinflammatory and profibrogenic cytokines are suspected causes. TGF-β has been widely investigated for its multiple functions in the development of RILI, on the molecular asnd genetic levels, in recent years. CT imaging is a common method in evaluating RILI, while SPECT, MRI and PET are more sensitive means that have been studied recently. Several grading criteria, incorporating clinical manifestations, imaging findings, and proper treatment measures, are employed in estimating the severity of RILI. Aiming at the potential underlying mechanisms, novel approaches for the prevention and treatment of RILI are under research.

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