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Nondosimetric Risk Factors for Radiation-Induced Lung Toxicity

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The decision to administer a radical course of radiotherapy (RT) is largely influenced by the dose-volume metrics of the treatment plan, but what are the patient-related and other factors that may independently increase the risk of radiation lung toxicity? Poor pulmonary function has been regarded as a risk factor and a relative contraindication for patients undergoing radical RT, but recent evidence suggests that patients with poor spirometry results may tolerate conventional or high-dose RT as well as, if not better than, patients with normal function. However, caution may need to be exercised in patients with underlying interstitial pulmonary fibrosis. Furthermore, there is emerging evidence of molecular markers of increased risk of toxicity. This review discusses patient-related risk factors other than dosimetry for radiation lung toxicity.
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Radiotherapy (RT) is a mainstay local treatment for non–small cell lung cancer. Radiation-induced lung toxicity (RILT) is one of the most common dose-limiting toxicities from thoracic irradiation, especially for patients with lung cancer who require a high radiation dose and frequently have reduced lung function caused by tumor or pre-existing lung diseases. RILT includes radiation pneumonitis (RP) and pulmonary fibrosis. RP develops in the first few weeks or months after RT with symptoms of cough, shortness of breath, chest pain, and low-grade fever. It can be reversible, but in severe cases, may be life threatening. Pulmonary fibrosis can develop even years after RT, sometimes as a sequential effect of acute injury, leading to permanent impairment of lung function. RP has been more widely investigated than pulmonary fibrosis because it develops earlier and is thus more conveniently evaluated.

The risk of RILT for each individual patient remains unclear. In general, it is related to clinical patient factors, inherited biological factor, tumor factors, dosimetric parameters, and other interventions. Dosimetric parameters such as mean lung dose (MLD) have been consistently found to be related to RILT and have been well documented.[1,2] Patient-related factors have also been investigated, and identifying those who have an increased risk of RILT to tailor RT would make the treatment safer and more beneficial. In this review, we discuss the most relevant risk factors other than dosimetry for RILT in patients with lung cancer, including patient age, sex, smoking status, pre-existing lung disease, pulmonary function (PF), previous treatment, tumor location, genetic phenotypes, and inflammatory cytokines, to better select patients for RT or prescribe radiation dose based on personalized toxicity estimate.

Age

Older patients are believed to have poorer tolerance to RT and are often given less aggressive treatment. Indeed, some studies[3-7] and a pooled analysis of 13 studies before 2012[8] showed older age significantly increased the risk of RILT, but others did not find an association between age and the risk of RILT.[9-13] A study including 369 patients found that age ($\geq$70 years) was an independent predictor for both grade $\geq$2 (odds ratio [OR] = 1.99) and grade $\geq$3 RP (OR = 8.90).[4] Severe RP (grade $\geq$4) was also more common in elderly patients, occurring in 1% of those <70 years, compared with 6% of elderly patients.[7] Another study found age ($\geq$68 years) increased the risk of grade $\geq$3 RP, and combining age with dosimetric factors and pulmonary fibrosis score improved the predictability of severe RP.[6] However, in a study of 576 patients by Jin et al,[10] there was

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no difference in the incidence of grade ≥ 3 RP between patients ≤ 60 and > 60 years. It was not clear whether there was a difference between patients ≤ 70 and > 70 years. In all, age should be considered a risk factor for RILT, but a clear cut-off value may not exist owing to the heterogeneity among the older patients. A comprehensive evaluation of other risk factors such as comorbidities, performance status, frailty, and PF should be done before making a determination on RT.

Sex

The effect of sex on RILT is not clear. Women often have smaller lung volumes than men do, and they are prone to have autoimmune diseases that may predispose them to a greater risk of lung injury. It has been shown that the absolute lung volume spared from 5 Gy (sV5) was significantly associated with the risk of RILT—the smaller the sV5, the higher the risk of RP.[14] The sV5 would be smaller for women than for men given similar radiation field sizes. However, women also have, on average, smaller tumor volumes.[15] On the contrary, women are often nonsmokers and thus have better lung reserve. A study showed that sex was independently associated with grade ≥ 3 RP, 15% for women and 4% for men.[11] In another study, when using decision trees in the model, sex was selected as an input variable in which women had higher risk of grade ≥ 2 RP.[16] However, in most studies[12-14,17,18] and a meta-analysis,[8] no association of sex with RP risk was seen. Therefore, sex should not be given too much consideration when prescribing RT.

Smoking Status

The association between smoking and RILT is controversial. Smoking has been found to have a protective effect on the risk of RILT in several studies[10,12,19] and in a pooled analysis (OR = 0.65).[8] Ongoing tobacco use,[12] or current smokers,[20] or recent quitters[19] had less risk of RP than others. Jin et al found in 575 patients that smoking status was the only clinical factor that affected the risk of grade ≥ 3 RP independent of dosimetric factors. Patients who had never smoked ("nonsmokers") had the highest incidence RP (37%), whereas patients who reported being smokers at the time of diagnostic workup ("smokers") had the lowest incidence (14%).[10] Indeed, smoking damaged lung, that is, "dead lung" may not be as sensitive to radiation injury as healthy, well-perfused lung, as it is mostly fibrotic or has nonfunctional airspace. Tobacco-induced immunosuppression could be another possible explanation for this effect.[21,22] However, these findings should in no way be taken to encourage smoking among patients, because smoking is a risk factor for poorer survival.[23,24] In fact, smokers often have limited pulmonary reserve and are at a greater risk to develop respiratory failure even after a modest reduction of lung function.

Pre-Existing Lung Disease

There are 2 types of pre-existing lung disease that might influence the risk of RILT: interstitial lung disease (ILD) and chronic obstructive pulmonary disease (COPD), which includes pulmonary emphysema. Clinically, acute exacerbation of pre-existing lung disease following RT can confound the definitive diagnosis of RP.[25]

Patients with pre-existing ILD appear to be more susceptible to acute lung injury after RT, resulting in acute ILD exacerbation. It has been reported that for patients with pre-existing interstitial changes on computed tomography (CT), the incidence of RP ≥ grade 3 was significantly increased to 26% as compared with 3% for those with normal lung.[26] In another study, grades 4-5 RP occurred in 57% of patients with interstitial pneumonitis as compared with 2% of those without.[27] Ueki et al recently reported that pre-existing ILD was a significant risk factor for symptomatic and severe RP in patients with non–small cell lung cancer (NSCLC) treated with stereotactic body RT (SBRT). The incidence of ≥ G2 RP (55.0% vs 13.3%) and ≥ G3 RP (10.0% vs 1.5%) was significantly higher in patients with ILD (+) than without ILD (−).[28] Yamaguchi et al[29] reported that subclinical ILD was not a predictor of grade ≥ 2 RP in patients treated with thoracic SBRT, but the rate of extensive RP beyond the irradiated field was significantly higher in the patients with subclinical ILD. Therefore, caution must be taken when considering RT for patients with ILD, particularly interstitial pneumonitis. Safe dosimetric dose limits of standard practice may not be safe for this population.

There are no consistent results regarding the predictive role of COPD on RILT. Some studies showed that the presence of COPD significantly increased the risk of RILT,[30,31] whereas others did not.[10,14,29,32] In Kimura's study, using CT classification of pulmonary emphysema, the incidence of RP increased significantly as the emphysema grade increased. In patients with emphysema grades 0, 1, 2, and 3 or greater, the incidence of RP was 16.5%, 9.1%, 8.6%, and 54.0%, respectively.[31] Using PF (forced expiratory volume at the first second [FEV1] and forced vital capacity) to grade COPD, Takeda et al found severe COPD did not increase the risk of grade ≥ 2 RP in patients with lung cancer treated with SBRT. Patients with COPD tended to have milder RP than those with normal lungs.[32] At least 2 factors need to be considered for the effect of COPD on a patient's risk for RILT. On one side, emphysematous lung is often filled with trapped air, contains less lung parenchyma to radiation exposure. On the other side, patients with COPD can also have borderline lung function so that they have limited tolerance to any reduction in lung function. In all, contrary to patients with ILD, patients with emphysema might tolerate RT better than what has been traditionally believed. COPD is not a contraindication to definitive RT. The tolerance of patients with COPD may be associated with the functional level of the lung.

Pulmonary Function

Adequate PF is required for cancer treatment such as thoracic surgery to decrease the risk of pulmonary complications, and patients with very poor PF are generally considered unfit for surgery. Traditionally, PF was also used to select patients for RT. PF parameters such as percent predicted value of FEV1, forced vital capacity, and diffusion capacity of lung for carbon monoxide (DLCO) have been used as the primary indicators of

whole lung function. Earlier Radiation Therapy Oncology Group (RTOG) studies limited patients with FEV1 of greater than 0.85, later to 0.75 L for RT protocol participation. However, there is no consistent evidence to support the association between PF parameters and RILT. A few studies reported that impaired baseline PF predicted higher risk of symptomatic RILT, in which lower baseline levels of absolute FEV1,[11,33] or FEV1%,[34] DLCO%,[35] or PaO_2[36] were significantly associated with the risk of RILT. Other studies have not shown significant correlations between PF and RILT.[10,12,37-40] Interestingly, a recent study with 260 patients showed that lower FEV1 may associate with reduced risk of RILT; patients with symptomatic RILT had marginally higher FEV1 than those without (71.7% vs 65.9% of predicted, $P = 0.077$).[18] It is of course possible that the patients included in the studies had already been selected by physicians, and typically those who had very poor PF were not offered definitive RT. The jury is still out whether poor lung function is associated with high or lower risk of RILT.

The physiological changes in PF because of RT for patients with lung cancer are quite complex. Tumor shrinkage after RT could alleviate bronchial obstruction or compression, thus improve lung ventilation. As noted previously, impaired lung may be less susceptible to radiation damage compared with normal lung, which has better cellular oxygenation. An early prospective study showed that patients with better ($> 50\%$) baseline FEV1 tended to lose significant lung function after RT, whereas most of those with poor FEV1 before RT underwent only a mild decrease or even an improvement in PF.[41] A recent study reported more reduction in diffusing capacity than ventilation after RT.[42] DLCO fell in most patients after RT, and pre-RT DLCO $\leq 50\%$ was associated with greater post-RT declines in DLCO, whereas the FEV1 per unit of vital capacity showed an increase and decrease after RT in a similar percentage of patients.

The global lung function is a result of a combination of regional function of different functioning parts of the lung. Based on regional function level, cause of dysfunction, and potentially recoverability, the whole lung can be divided into the following different regions: normal functioning lung, temporarily dysfunctional lung caused by tumor, and unrecoverable nonfunctioning or low-functioning lung caused by pre-existing lung disease. Through regional function mapping by ventilation (V) or perfusion (Q) single-photon emission CT, we can understand more about the radiosensitivity of the different functioning lungs. A study from our group[43] indicated that the normal functioning lung is most susceptible to RT damage, and approximately 20% of patients had worsened function in this region after RT; unrecoverable nonfunctioning or low-functioning lungs only experienced worsened regional function in 3.6% and 9.3% of patients—they cannot be injured more because they are already or nearly "dead"; and 55% of temporarily dysfunctional lung caused by tumor can partially or completely recover to normal function levels. This finding indicated that lung is not a uniform organ, instead it has regional differences in function, and patients with lung cancer experience heterogeneous changes to RT in different functioning regions. Regional function mapping, especially accessing combined regional V/Q function,[44] or optimizing the treatment plan accordingly[45] might be more helpful in guiding RT.

Tumor Factors and Tumor Location

Tumor location may influence the risk of RILT based on the findings in several studies, indicating patients with tumors in the lower lobes had higher risk of RP,[13,46-48] though some inconsistent findings exist.[49] Bradley et al[13] reported a significantly greater risk for patients with tumors located in the inferior part of the lung. A study by Seppenwoolde et al[46] also found that irradiation of caudally located lung tumors resulted in a greater risk of RP than irradiation of tumors located in other parts of the lungs, and the incidence of RP was 11% and 40% for cranial and caudal tumors, respectively. Similarly, another study showed when the lower part of the lung was included in the radiation site, the incidence of pneumonitis was 70% compared with 20% for other lobes.[47] The MLD of the lower portion instead of the upper portion of the lungs was significantly correlated with grade ≥ 3 RP.[50] A pooled meta-analysis confirmed that middle or inferior part of the lung tumors is associated with increased risk of RP compared with upper lung locations.[8] Increased RP risk with lower tumor locations possibly reflects radiosensitivity differences among different lung regions, owing to a greater density of target cells in the lower part of the lung[51] or strong out-of-field effect of irradiation of lower part of the lung.[52] The other explanations may be more physiologically pronounced perfusion and ventilation of the lower part of the lung (better oxygenation) or increased tumor motion during RT causing more normal lung to be irradiated at a low dose. Therefore, caution should be taken when lower part of the lung is included in the RT field.

Tumor Volume and Tumor Stage

Tumor volume and tumor stage themselves may not be important in predicting the risk of RILT. Some studies showed T2 tumors had a higher rate of G2 RP than T1 in patients treated with SBRT (17.9% vs 4.4%, $P = 0.02$),[53] but other studies showed field size (≥ 200 cm^2 vs < 200 cm^2)[47] or tumor volume (cutoff at median) was not associated with $\geq$ G2 RP.[54] There are some data suggesting that stages I-II disease predicted lower risk of RILT than stage III[20] or stages III-IV did[55]; however, most found that tumor stage was not associated with the risk of $\geq$ G2 RP[5,18,33,56,57] or $\geq$ G3 RP.[4,10,11,14,36,58-61] It is understandable that the effect of tumor volume and stage may be confounded by other risk factors and also depends on the lung dosimetry, which is related to an individual's lung volume[54]: larger or more advanced tumors do not necessarily result in poorer lung dosimetry result.

Previous Radiation

For patients who develop recurrent or secondary lung tumors after previous thoracic RT, reirradiation is often the only

treatment option. Under such a circumstance, RT-associated risk of serious RILT should be considered. The literature is limited on this topic. A study showed 1 of 19 patients developed grade 3 RP, and a survival benefit was found for those who had longer intervals between initial RT and reirradiation (>12 months) and good performance status (Eastern Cooperative Oncology Group Performance Status [ECOG PS] scores of 0-2).[62] Other studies showed grades 1-2 RP in 22% of patients and no grade 3 or greater RP in 23 patients[63] or grades 2-3 RP in 19 of 34 of patients.[64] Recently, Liu et al analyzed 72 patients treated with stereotactic ablative radiation therapy (SABR) after previous thoracic RT and found 20.8% of patients developed grade ≥3 RP. ECOG PS scores of 2-3 before SABR, FEV1 ≤ 65% before SABR, V_{20} ≥ 30% of the composite plan, and an initial planning target volume in the bilateral mediastinum were significantly associated with increased risk of RP.[65] Therefore, previous thoracic RT is not a contraindication for RT when recurrent or secondary lung tumors occurred. However, patient selection criteria should be strict, requiring consideration of other risk factors such as PS, pulmonary function, complete lung dosimetry including V_{20} of the composite plan, and initial radiation area for lung safety. For such cases, lung functional mapping using V/Q single-photon emission CT is recommended to avoid further damage of the functioning lung.[44,45]

Previous Chemotherapy

There are conflicting results on the influence of previous chemotherapy on the risk of RILT. For an individual patient with bulky tumor, induction chemotherapy may shrink the tumor, thus decrease the radiation field and the volume of normal lung and the risk of RILT. A dosimetric analysis of 25 patients with NSCLC showed that approximately 30% of patients had at least a 20% reduction in tumor volume after induction chemotherapy, which translated into a small statistically significant reduction (5%) in the predicted risk of RP.[66] However, a retrospective analysis of 223 patients by Wang et al[14] did not show a significant association in the risk of grade ≥3 RP between patients with and without induction chemotherapy. In contrast, in a model using decision tree analysis, another study demonstrate that chemotherapy before RT was a risk factor for grade ≥2 RP.[16] Some patients may also progress during induction chemotherapy. Induction of mitomycin C was found to increase the risk of RP: grade ≥2 RP was 31.2% among patients who received induction mitomycin C and 10.6% among those who did not.[30] In summary, the use of induction chemotherapy should be on an individual basis, and there is no consistent evidence regarding its use and the risk of RILT.

Treatment Factors

The most important treatment factor is radiation lung dosimetry, which is not the focus of this review. In brief, MLD and V_{20} are the most frequently reported and the most reproducible lung dosimetric factors. It is recommended to limit V_{20} to ≤30%-35%, and MLD to ≤20-23 Gy (with conventional fractionation), if one wants to limit the risk of RP to ≤20% in patients with NSCLC treated with definitive RT.[67] One must note that each dosimetric parameter is highly correlated with one another.[37] There is an unanswered question of what is associated with higher risk of RILT: "a little (dose) to a lot (lung)," vs "a lot (dose) to a little (lung)." Tucker et al[68] found that given the same MLD, high doses to small lung volumes ("a lot to a little") were worse than low doses to large volumes ("a little to a lot"). In addition, functional dosimetric parameters may provide better predictive outcome than physical dosimetric factors, which were reported in very limited studies with small size of patients.[33,69,70]

The other important treatment factor is concurrent chemotherapy with RT (CCRT), which is the standard of care in patients with a locally advanced NSCLC or limited-stage small cell lung cancer. CCRT is often considered to be a risk factor for RILT, as it is a more aggressive form of treatment. Indeed, patients treated in early RTOG trials showed CCRT significantly increased grade ≥3 late lung toxicity as compared with sequential chemotherapy and RT (20% vs 10%).[71] Agents associated with known risk to escalate RILT such as bleomycin and gemcitabine are not used in concurrent practice any more. A meta-analysis by Palma et al based on individual patient data suggested that the choice of concurrent chemotherapy regimen played an important role in RP risk, particularly in the elderly. The risk of grade ≥2 RP for patients treated with combination of concomitant carboplatin and paclitaxel with RT was 3.3-fold that of cisplatin and etoposide with RT. Patients >65 years receiving concurrent carboplatin-paclitaxel regimens had the highest risk of RP.[72] In another study with 369 patients analyzed, a higher rate of grade ≥3 RP was also found for concurrent docetaxel-cisplatin schedule (18.4%) than that for concurrent vinorelbine-cisplatin schedule (9.5%).[4] However, a weekly carboplatin-paclitaxel regimen remains in common use in practice and RTOG trials, such as RTOG0617 and RTOG1107. The RP rate was acceptable from preliminary report of RTOG0617. Nevertheless, concurrent taxane chemotherapy regimens may increase the risk of RP and should be chosen carefully, maybe with stricter dose constraints of the lung.

Biological Factors or Genetic Phenotypes

Individual genetic phenotypes determine the intrinsic radiosensitivity of lung to radiation. The pathogenesis of RILT may involve direct radiation cytotoxicity to normal lung tissue, secondary inflammatory changes, and fibrotic remodeling.[73] Thus, genetic variation in key genes in DNA repair, inflammation, and oxidative stress pathways may ameliorate or exacerbate the effects of a given radiation dose to the lungs. In recent years, the candidate gene single nucleotide polymorphism (SNP) approach has been used in several studies to evaluate the intrinsic radiosensitivity of lung to radiation. SNPs in a series of genes associated primarily with radiation-related

processes were genotyped in patients with lung cancer (white or Han Chinese) who developed RILT (Table 1).

There were 2 studies that provided independent replication cohorts for validation. Pang et al[55] showed patients with lung cancer who had the CC genotype heat-shock protein B1 (as opposed to CG or GG) had a higher probability of severe RP after RT in both the training and validation data sets. Pu et al[74] further evaluated the functional correlation of SNPs with radiosensitivity. In his study, 11,930 SNPs from 904 inflammation-related genes were included in the discovery analysis. Of these, 1321 were significantly associated with RP. Overall, 9 SNPs were significantly associated with RP in the validation population. These SNPs were also selected to assess for functional correlation with radiation sensitivity via the lymphoblastoid cell line model system that incorporates baseline host gene expression and cytotoxicity following RT. In total, 45 SNPs in 3 genes (PRKCE, DDX58, and TNFSF7) were found to be significantly associated with radiation response, which are more than 5.8 that would be expected by chance

alone. DDX58 Rs11795343 was consistently significantly associated with increased risk of developing RP.

The risk of RP increased as the number of unfavorable genotypes increased. In a study by Hildebrandt et al,[19] 12 common polymorphisms were found to be significantly associated with the risk of RP. Compared with patients with 0-2 risk genotypes, the risk of RP was 13.3-fold and 69.4-fold for those carrying 3 and 4 or more unfavorable genotypes, respectively. In a study by Yang et al,[75] compared with the absence of unfavorable genotype, the risk of RP increased with presence of P53 72Arg/Arg genotype (hazard ratio [HR] = 2.24) or ataxia telangiectasia mutated (ATM)–111A allele (AA or GA genotype) (HR = 2.36). The presence of both risk genotypes, that is, the P53 72Arg/Arg and the ATM-111AA or GA genotypes, had a significantly greater risk of RP (HR = 6.17).

Incorporation of genetic patient information in the form of SNPs from a relatively small set of genes can markedly improve the ability of the Lyman-Kutcher-Burman MLD model to

Table 1 Studies Evaluating SNPs and Radiation-Induced Lung Toxicity

Study	Patients No.	End Point	Gene Associated With Lung Toxicity	Gene Function
Pu et al[74]	421	≥G2 RP	CDC2 (rs10711) and (rs1871445) DDX58 (rs11795343) and (rs7865082) FGF5 (rs3733336) ETS2 (rs2298560) LIMS1 (rs12469016) GHR (rs4292454) TFEB (rs13202921)	Inflammation
Wen et al[9]	362	≥G3 RP	LIN28B (rs314280) LIN28B (rs314276)	RNA binding protein
Pang et al[55]	271	≥G3 RP	HSPB1 (rs2868371)	Oxidative stress pathways
Xiong et al[59]	362	≥G3 RP	ATM (rs189037) and (rs228590)	DNA repair
Kelsey et al[80]	39	Radiologic change	XRCC1 (rs25487) BRCA1 (rs16942)	DNA repair
Mak et al[56]	136	≥G2(G3) RP	MTHFR (rs1801131)	Oxidative stress pathways
Yin et al[60]	195	≥G3 RP	LIG4 (rs1805388)	DNA repair (NHEJ)
Yin et al[81]	193	≥G3 RP	VEGF (rs2010963) and (rs3025039)	Angiogenesis
Niu et al[58]	46	≥G3 RP	TGFβ1 (rs11466345)	Inflammation
Yin et al[20]	261	≥G2 RP	APEX1 D148E GG XRCC1 Q399R AA	DNA repair (BER)
Yang et al[75]	253	≥G2 RP	P53 Arg72Pro	Cell-cycle regulation, apoptosis, and DNA repair
Hildebrandt et al[19]	173	≥G2 RP	IL1A (rs1800587/rs17561) IL-8 (rs4073) TNF (rs1799724) TNFRSF1B (rs1061622) MIF (rs7555622) IL4 (rs2243250) IL4R (rs2070874) IL13 (rs10800925) IL13 (rs20541) NFKBIA (rs1799983) NOS3 (rs1799983)	Inflammation
Zhang et al[57]	253	≥G2 RP	ATM (rs189037) and (rs373759)	DNA repair
Yuan et al[61]	164	≥G2(G3) RP	TGFβ1 (rs1982073)	Inflammation

Abbreviations: BER, base excision repair; NHEJ, nonhomologous end joining.

predict RP risk. In Tucker's study, with 5 SNPs in the TGFβ, TNFα, VEGF, XRCC1, and APEX1 genes, it was possible to distinguish cohorts with > 50% risk vs < 10% risk of RP when exposed to high MLDs.[76] Vinogradskiy et al[77] found a model-generated personalized lung-dose limit from dosimetric constraints, and SNPs could result in a clinically significant change to the prescription, which would help to determine how much dose can be safely delivered to the tumor and normal tissues on an individual basis.

Future studies using a genome-wide association studies approach with sufficient numbers of patients to investigate SNPs associated with RILT may find more accurate RILT-related genotypes than the target gene approach. However, in addition to genetic makeup, epigenetics and other proteins also play a role in determining the individual risk of RILT. For example, our group identified serum microRNA expression (Bi et al, unpublished data) and plasma levels of proteins[78,79] such as C4b-binding protein α chain, complement C3, and vitronectin as predicting risk factors for RILT using a proteomic approach, and these biomarkers play important roles in the inflammatory response.

Biological Factors or Cytokines

Inflammatory cytokines released by cells trigger inflammation and respond to infections, and their levels have been inconsistently shown to serve as early surrogate markers for RILT.

Blood inflammatory cytokines such as TGF-β1, interleukin 8 (IL-8), and Krebs von den Lungen-6 have been reported to predict RILT in some studies.

Although it is likely that no single molecule or cytokine will provide adequate predictive power in all cases, TGF-β1—a prototype of multifunctional regulators of cell growth and differentiation, a proinflammatory and profibrotic cytokine—has been singled out to play a pivotal role in promoting lung damage via various pathways. TGF-β1, normally present in a latent form, can be activated by ionizing radiation–induced free radicals. Activated TGF-β1 directly stimulates connective tissue formation and decreases collagen degradation and plays an important role in the inhibition of epithelial cell proliferation and the development of tissue fibrosis and radiation-induced inflammation. Increased local TGF-β1 expression is accompanied by an elevated plasma concentration. The predictive value of TGF-β1 for human RILT was first reported by Anscher et al[82] in individuals with advanced breast cancer treated by high-dose chemotherapy and autologous bone marrow transplantation. Further studies including those from our group demonstrated that changes in plasma TGF-β1 levels may identify individuals at high risk for the development of RILT.[83-86] A persistently elevated plasma TGF-β1 above baseline level at the end of RT,[83,87] the ratio of TGF-β1 level over baseline during RT,[88] and a significant elevation of TGF-β1 level at 4 weeks after RT[89] were significantly associated with symptomatic RILT. A return of the plasma TGF-β1 to normal level could identify patients who would not develop RP.[83] An

Table 2 Studies Evaluating the Association of Plasma Cytokines With Radiation-Induced Lung Toxicity

Study	Patients No.	End Point	Cytokines (*P* value)	Sample Handling Process
Stenmark et al[98]	58	≥G2 RP or symptomatic pulmonary fibrosis	IL-8 pre-RT and at weeks 2 and 4 during RT (*P* < 0.01); TGF-β1 ratios at 2 and 4 wk during RT or baseline (*P* = 0.41 and 0.26)	Platelet-poor plasma[*]
Zhao et al[99]	165	≥G2 RILT	TGF-β1 ratio at 4-5 wk during RT or baseline (*P* < 0.001)	Platelet-poor plasma[*]
Kim et al[89]	34	≥G2 RP	Change of TGF-β1 level during RT (*P* = 0.0001)	Platelet-poor plasma[*]
Zhao et al[88]	26	≥G2 RILT	TGF-β1 ratio at 4 wk during RT or baseline (*P* = 0.015)	Platelet-poor plasma[*]
Evans et al[90]	121	≥G1 RP	TGF-β1 ratio at end-RT or baseline (*P* < 0.001)	Platelet-poor plasma[*]
Hart et al[97]	55	SRILT	IL-8 at pre-RT (*P* < 0.005)	Platelet-poor plasma[*]
De Jaeger et al[95]	68	≥G2 RP	TGF-β1 ratio at 4-6 wk during RT or baseline (*P* = 0.01 *inverse relation*)	Plasma[†]
Novakova-Jiresova et al[96]	46	Symptomatic RP	TGF-β1 level (*P* > 0.05)	Plasma[†]
Fu et al[87]	103	Symptomatic RILT	TGF-β1 level at end-RT (*P* = 0.007)	Platelet-poor plasma[*]
Anscher et al[83]	73	Symptomatic RP	TGF-β1 level at end-RT (*P* < 0.05)	Platelet-poor plasma[*]

*These studies used procedures of plasma preparation to minimize the platelet contamination or degradation by using enough gravities, controlling time and temperature of blood setting before centrifuge, and avoiding platelet contamination by using top layer of plasma.

†Plasma samples may have been contaminated by platelets, as they used 1200 or 1000*g*, which was not enough to remove the platelets in plasma supernatant.

earlier study from Fu et al[87] also reported that the combination of end-RT-to-pre-RT TGF-β1 level and lung V_{30} could stratify patients into low-, intermediate-, and high-risk groups, and patients with both high end-RT-to-pre-RT TGF-β1 level and $V_{30} \geq 30\%$ had the highest risk of SRILT at 43%. Furthermore, study from that group using grade ≥ 1 RP as an end point found TGF-β1 was not predictive of RILT except for the group of patients with a high V_{30}. Among patients with lung $V_{30} > 30\%$, those with higher end-RT-to-pre-RT TGF-β1 ratio had a significantly higher incidence of RILT.[90] Others reported that TGF-β1 levels in the bronchial alveolar lavage fluid were also predictive of RILT.[91]

One must note that the role of TGF-β1 on RILT can be confounded by tumors, as circulating TGF-β1 levels may be produced by lung tumors. The dynamics of the plasma TGF-β1 could be a marker of RILT as well as a marker of tumor response to treatment.[92] Elevation of plasma TGF-β1 levels in patients with lung cancer may also contribute to individual inabilities to normally process TGF-β1.[93] These individuals have often lost the mannose 6-phosphate or insulinlike growth factor 2 receptor, a key factor associated with TGF-β1 activation. As TGF-β1 is richly stored with platelets, careful sample handling is important to avoid artificially elevated plasma TGF-β1 level from platelet contamination or degradation.[93,94] Some studies reported that plasma TGF-β1 was not significantly associated with the risk of RILT[95,96]; some of these studies applied sample handling procedures that were not controlled for platelet contamination (Table 2). Nevertheless, a meta-analysis including 7 studies showed end-RT-to-pre-RT TGF-β1 ratio ≥ 1 was a risk factor for RP.[1] Plasma TGF-β1 level, particularly the radiation-induced elevation, would possibly allow for identifying patients at high risk for RILT.

A complex cytokine network is involved in the process of RILT. A comprehensive illustration of cytokine cascade is beyond the scope of this review, but a few studies reporting the potential for combining multiple cytokines in predicting the risk of RILT are noted. Plasma inflammatory cytokine profiling assays were performed in 55 patients analyzing the levels of 17 cytokines before RT, but the study failed to identify a specific signature to predict the risk of RILT, and only lower baseline levels of IL-8 were associated with an increased risk of developing symptomatic RILT.[97] A model combining pretreatment levels of multiple circulating cytokines and MLD may more accurately predict RILT. Our group[98] reported that combining IL-8, TGF-β1, and MLD into a single model yielded an improved predictive ability compared with either variable alone. Combination of cytokines and other parameters could also serve as a prescreening tool for patients before RT. By prescreening patients for serum Krebs von den Lungen-6 and surfactant protein-D as biomarkers and considering ILD on CT scans, appropriate patients were selected for SBRT. As a result, the frequency of grades 4-5 RP in a Japanese study has shown a decrease, from 18.8% before 2005 to 3.5% after 2006.[27] Because these parameters can be obtained during the early course of RT or at baseline, this model has the potential to serve as a predictive tool to prescribe personalized RT.

Summary

Older patients, pre-existing ILD, tumor located in lower lung, concurrent taxane chemotherapy, several SNPs phenotypes, radiation-induced elevation in TGF-β1, and lower levels of IL-8 have been shown to increase the risk of RILT, in addition to the standard parameters of lung dosimetry. However, a consistent predictive model for the risk of RILT is not available. There is potential in investigating the intrinsic sensitivity of individual patients by focusing on genetic and epigenetic characteristics, and combining them with clinical and dosimetric factors in a model, but large numbers of patients and validations are needed.

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