Radiation Oncology

REVIEW

Open Access

Radiation-induced lung injury: from mechanism to prognosis and drug therapy

Sheng Wang[2†], Duo Xu[1†], Lingyan Xiao[1], Bo Liu[1*] and Xianglin Yuan[1*]

Abstract

Radiation induced lung injury, known as the main complication of thoracic radiation, remains to be a major resistance to tumor treatment. Based on the recent studies on radiation-induced lung injury, this review collated the possible mechanisms at the level of target cells and key pathways, corresponding prognostic models including predictors, patient size, number of centers, radiotherapy technology, construction methods and accuracy, and pharmacotherapy including drugs, targets, therapeutic effects, impact on anti-tumor treatment and research types. The research priorities and limitations are summarized to provide a reference for the research and management of radiation-induced lung injury.

Clinical trial number

Not applicable.

Keywords Radiation-induced lung injury, Target cells, Signaling pathways, Predictive models, Pharmacotherapy

Introduction

Currently, thoracic tumors have high morbidity and mortality rates worldwide [1]. Radiotherapy is an important treatment for thoracic tumors, but radiation-induced lung injury (RILI), the most common adverse effect of thoracic radiotherapy, has a prevalence up to 31.4% [2]. RILI, divided into grade 1 to 5 sequentially based on severity, causes cough, shortness of breath, and fever in the short term, and lung fibrosis, weakened pulmonary functions, and death in severe cases in the late stage, which remains a major resistance to tumor treatment [3]. The traditional view is that RILI is caused by direct damage to type II alveolar epithelial cells and capillaries by ionizing radiation [4], but recent studies have shown that RILI is a cascade of oxidative stress damage, target cell injury, and cytokine release [5–7]. RILI manifests as a pathological process of immune response induced by inflammatory mediator in the acute/subacute phase and fibroblast activation and proliferation, extracellular matrix (ECM) deposition and eventual development of pulmonary fibrosis in the chronic phase [8].

Notably, the risk of RILI triggered by combination therapy has further increased with the widespread use of immune checkpoints in clinic. Recent research has revealed functional pathological features of alveolar epithelial cells, myeloid immune cells and fibroblasts in RILI [9]. Therefore, based on the research on RILI

†Sheng Wang and Duo Xu contributed equally to this work.

*Correspondence:
Bo Liu
boliu888@hotmail.com
Xianglin Yuan
yuanxianglin@hust.edu.cn
[1]Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China
[2]Department of Radiation Oncology, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, Nanjing Medical University Affiliated Cancer Hospital, Nanjing, Jiangsu 210000, China

in recent years, this paper elaborated the mechanisms related to the occurrence and development of the disease from the perspectives of key effector cells including alveolar epithelial cells, vascular endothelial cells, myofibroblasts/ fibroblasts, and macrophages. Besides, the roles of crucial pathways including TGF-β classical and non-classical pathways, HMGB1/NF-κB pathway and autophagy-related pathways are also summarized. Furthermore, the research progress related to the prediction and medication treatment of RILI is generalized in this paper, attempting to provide assistance for the prevention, assessment and management of RILI.

Key effector cells in radiation-induced lung injury

Alveolar epithelial cells (AECs)

After exposure to ionizing radiation, alveolar epithelial cells, an important component of the capillary barrier, are damaged by oxidative stress from reactive oxygen species (ROS) initially. Type I AECs lack proliferative capacity and undergo senescence, necrosis, and apoptosis induced by ionizing radiation. Type II AECs can differentiate into type I AECs as their progenitor cells and can function to remove excess alveolar fluid, reduce lung inflammation and intrinsic immune response. After radiation injury, type II AECs become myofibroblasts through epithelial- mesenchymal transition (EMT) driven by TGF-β signal and undergo aberrant proliferation and accumulation, which exacerbates pulmonary fibrosis [10]. In addition, the secretion of pulmonic surface active proteins is reduced due to dysfunction of type II AECs, resulting in increased alveolar tension and decreased structural stability, which can lead to pneumonedema and atelectasis [11]. Meanwhile, damage to alveolar epithelial cells promotes the secretion of pro-inflammatory and pro-fibrotic factors such as IL-13, TGF-β1, and PDGF, which exacerbate radiologic lung injury [12].

Vascular endothelial cells (VECs)

VECs, as an important component of the alveolar gas exchange mechanism and one of the components of the capillary barrier, can be injured by ROS, causing decreased endothelial nitric oxide production owing to impaired nitric oxide synthase activity, leading to endothelium- dependent vasodilatory dysfunction [13]. Meanwhile, VECs, as a continuous layer on the surface of the vascular lumen, lose the barrier function and induce a consequent deterioration in vascular morphology in response to ionizing radiation-induced release of oxygen radicals and proteases, which leads to vascular endothelial swelling, increased vascular permeability, inflammatory infiltration, and tissue edema during the acute phase, while capillary collapse and loss of clone-forming function during the chronic phase [14]. Recent studies have suggested that VECs develop a high degree of heterogeneity after acute lung injury [15]. Single cell sequencing has shown that new subpopulations of endothelial cells with high expression of PD-L1 and TGF-β emerge after radiotherapy may be associated with extracellular matrix deposition and pulmonary fibrosis [16]. These findings suggest that VECs may play different roles in the RILI process due to their heterogeneity and altered functions.

Myofibroblasts and fibroblasts

Myofibroblasts, considered as the principal effector cells for extracellular matrix synthesis, are low in normal lung tissue and can be transformed during the RILI process by three main pathways: fibroblast differentiation, epithelial/endothelial cells undergoing mesenchymal cell transformation, and bone marrow stem cell origin. And fibroblasts, which are the main source of myofibroblasts, play an important role in the promotion of wound healing, the remodeling of the extracellular matrix and the inflammatory immune response [17]. Recent applications of single-cell sequencing have revealed a highly heterogeneous and functionally diverse population of fibroblasts in different tissues and activation states [18]. Fibroblasts can act as inflammatory mediators and sense damage-associated molecular patterns (DAMPs) released during tissue injury and remodeling via toll-like receptors to memorize inflammatory injury, secrete a variety of cytokines and chemokines subsequently, which can rebuild the ECM, recruit immune cells and modulate chronic inflammation [19]. Following ionizing radiation stimulation, quiescent fibroblasts are activated and differentiate into myofibroblasts, and subsequent persistent inflammatory signals together with resident myofibroblasts initiate type II EMT [20]. It causes disruption of epithelial cell connectivity, loss of polarity and acquisition of motility and invasiveness, upregulation of mesenchymal gene expression, increased ECM synthesis and accumulation, and excessive enhancement of tissue repair and wound healing, ultimately resulting in pulmonary fibrosis [21]. Therefore, intervention of the pathways that drive the EMT process and identification of the source cells in the transformation are key to RILI treatment.

Macrophages

Macrophages, as a critical component of the intrinsic immune system of myeloid origin, participate in maintaining homeostasis, modulating inflammation, and repairing injury in lung tissues, and their remarkable plasticity results in exhibition of a high degree of heterogeneity under pathological conditions [22]. Typically, macrophages can be divided into 2 subpopulations broadly, the classically activated macrophages M1 and the alternatively activated macrophages M2. In the acute injury, lung-resident macrophages and monocyte-derived

macrophages can be abnormally activated by ROS, DAMPs, and cytokines including TNF-α and IL-6 [23], to polarize to the M1, which can exert pro-inflammatory and cytotoxic effects, secrete chemokines and inflammatory factors. This effect induces inflammatory storms, which form an inflammatory microenvironment and recruit other immune cells, including neutrophils and monocytes, to infiltrate the lung tissue and cause prolonged inflammation [24]. Meanwhile, the differentiation of AECs can be inhibited by IL1-β secreted by interstitial macrophages, resulting in incomplete repair and impaired regeneration of lung tissue [25].

In the chronic stage, the mitochondrial dysfunction of macrophages is mediated by persistent alveolar injury and incomplete repair [26]. Alveolar macrophages are polarized to M2 in response to IL-4 and IL-13, and M1 is converted to M2 in response to MCP-inducible protein 1 [27], which induces overexpression of fibrosis promoting and wound healing phenotypes to exacerbate pulmonary fibrosis. Additionally, studies have revealed that the interaction between macrophages and other effector cells, such as fibroblasts [28], VECs and type II AECs [29], plays a contributory role in the lung fibrosis, which may provide new targets for RILI therapy.

Key effector cells and relevant mechanisms during RILI occurrence and development are shown in Fig. 1. As the major effector cell population in fibrosis, myofibroblasts and fibroblasts have received much attention and a large number of studies have investigated them as potential targets for the treatment of fibrosis. Research interests include targeting stretch-activated channels, intercellular communication such as gap junction and tight junction, ECM adhesion and integrins, and TGF-β release [30–33]. However, the specificity of radiation-induced lung injury is that the patient may have a co-existing tumor burden. For this kind of patients, targeting the myofibroblasts and fibroblasts, some of which are highly heterogeneous cancer-associated fibroblasts (CAF) [34], is a barrier of the transition from preclinical to clinical trials.

Key signaling pathways in radiation-induced lung injury

TGF-β/Smad signaling pathway

The TGF-β/Smad signaling pathway is a classic cell membrane-nuclear signaling pathway that plays an important role in the pathophysiological processes of multiple organ systems through interactions with various spectrum-defining, signal-driven transcription factors [35]. Under physiological conditions, TGF-β cross-links with a latency-associated peptide (LAP) dimer to form a complex, which is deposited in the ECM [36]. Under pathological conditions, the L-TGF-β complex is cleaved by a variety of serine proteases to release active TGF-β [37], or tension generated by integrin-transduced cell contraction causes unfolding of the LAP structural domains and TGF-β release [38]. During the fibrotic process, TGF-β can be activated by ROS to recognize and bind to TGF-β receptor II on the surface of the cell membrane, which in turn recognizes and phosphorylates TGF-β receptor I. In the cytoplasm, the phosphorylation of Smad2 and Smad3 is mediated through the intermediary of Smad7 protein and forms a complex with Smad4, which is translocated

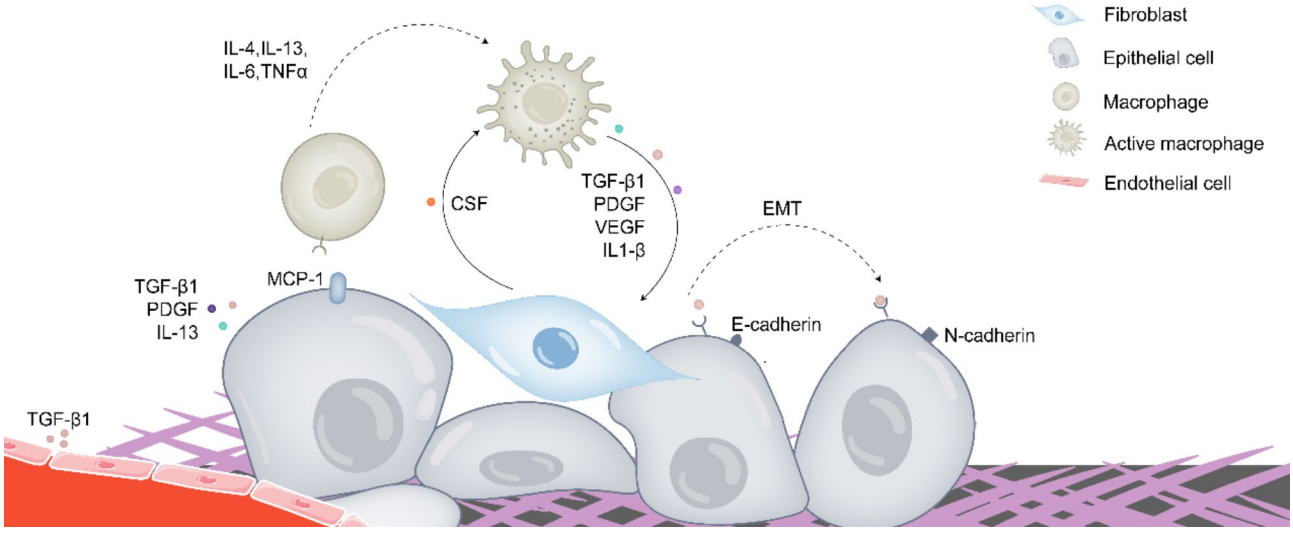

Fig. 1 Key effector cells in radiation-induced lung injury. After radiation injury, alveolar epithelial cells secrete various factors and transform into myofibroblasts through EMT. The barrier function of endothelial cells in blood vessels is impaired after radiation injury, leading to the secretion of cytokines and increased vascular permeability. Macrophages respond to MCP-1 signals secreted by alveolar epithelial cells, which are recruited and activated in the lungs, and interact with fibroblasts to reconstruct ECM. Abbreviations: TGF-β1, transforming growth factor-β1; PDGF, platelet derived growth factor; IL-4, interleukin-4; IL-13, interleukin-13; MCP-1, monocyte chemoattractant protein-1; CSF, colony-stimulating factor; VEGF, vascular endothelial growth factor; IL-1β, interleukin-1β; EMT, epithelial-mesenchymal transition

to the nucleus, regulating the expression of target genes and transcription of pro-fibrotic molecules and activating fibroblasts and myofibroblasts [39, 40]. Interestingly, recent studies have shown that associated noncoding RNAs can promote pathological processes dominated by TGF-β/Smad pathway through enhancement and prolongation of signal activity [41, 42], which may reveal novel therapeutic targets for RILI.

To resist the release of active TGF-β, previous studies have achieved the prevention of lung fibrosis in a mouse model by knockout and inhibition of integrin β3 [43], and it is worth mentioning that the radioligand of αvβ6 could be utilized as a marker in combination with PETCT to detect the early diagnosis of RILI in clinic [44]. Targeting the initiating link of the TGF-β pathway, previous research reveals that connective tissue growth factor (CTGF) antibodies could reverse RILI in mice by inhibiting the fibroblast proliferation and migration [45]. While targeting TGF-β receptor I was reported to be a promising strategy for pulmonary fibrosis [46]. To inhibit the interactions of the Smads family of proteins, Cao et al. used thujaplicin to inhibit Smad3 activity and EMT to treat RILI [47]. In addition, Lan et al. Reported that a bifunctional fusion protein, M7824, of which structure is a PD-L1 antibody coupled to TGF-β receptor II, could achieve anti-tumor effects while attenuating RILI in a mouse model [16]. Considering the mediation of immune evasion by the TGF-β/Smad pathway in the tumor microenvironment (TME) [48], it is significant to combine anti-tumor therapy with mitigation of RILI through inhibition of multifunctional pathways.

TGF-β nonclassical pathway

In addition to interacting with Smad family proteins, TGF-β can activate other signaling molecules in a cell type dependent manner, such as TAK1/MAPK, PI3K/AKT and RHOA/ROCK, which are known as the nonclassical pathways [49]. In previous studies, associations between the non-classical signaling pathways and fibrosis have been revealed. A previous study showed that Schisantherin A could inhibit the activation of TAK1/MAPK pathways mediated by TGF-β1, exerting an antifibrotic effect [50]. Qian et al. found that TGF-β1 activates the PI3K/AKT pathway and downregulates FOXO3a expression, which induces EMT in alveolar epithelial cells [51]. Gallic acid has been reported to reduce α-SMA and F-actin formation by inhibiting the RhoA/ROCK signalling cascade stimulated by TGF-β [52]. Furthermore, ROCK2 has been shown to crosstalk with the classical TGF-β/Smad pathway, and targeting ROCK2 effectively attenuated organ fibrosis [53]. These findings have confirmed the prominent role of TGF-β non-classical pathways in fibrosis, and it is therefore worth exploring their potential as therapeutic targets for chronic RILI.

NF- K B signaling pathway

The NF-κB pathway, as one of the core pathways of the intrinsic immune system, is involved in the regulation of a variety of pathophysiological processes including inflammation, proliferation and apoptosis [54]. Radiation can cause immunogenic cell death (ICD) of tumor cells and release DAMPs such as HMGB1, which can bind to various surface receptors such as TLR2 and TLR4 and activate the NF-κB pathway [55]. Macrophages can also secrete HMGB1 after high-dose irradiation, activating NF-κB pathway after binding to TLR4, in which activated NF-κB enters the nucleus and interacts with DNA to upregulate the expression of pro-inflammatory factors including IL-1β, IL-6 and TNF-α [56].

Currently, targeting the HMGB1/NF-κB pathway has shown promising therapeutic effects in relevant studies. Garcia et al. explored the possibility of using DAMPs and TLR4 as therapeutic targets for RILI respectively [57]. Arora achieved therapeutic efficacy for RILI in animal models with amphotericin analogues by inhibiting the cascade of NF-κB and MAPK pathways [58]. Verma et al. utilized Q-3-R, a NF-κB pathway inhibitor, to attenuate RILI by reducing the expression of the inflammatory factors IL-1β, IL-6, IL-18 and TNF-α in mouse lung tissue [59]. These findings suggested that targeting DAMPs and the NF-κB pathway is important in the treatment of RILI. However, given that DAMPs, as a central aspect of ICD, promote dendritic cell (DC) maturation and cytotoxic T lymphocyte (CTL) infiltration [60], targeting them for RILI must be accompanied by careful consideration of the possible impact on the anti-tumour effects.

Autophagy-related pathways

Autophagy, as a conserved catabolic process which can recycle the excess organelles and proteins through lysosome-mediated degradation, plays a critical role in maintaining cellular homeostasis under a variety of stresses and diseases [61]. In the RILI process, Ionizing radiation induces ROS-dependent and -independent damage to cells, the latter including DNA damage and endoplasmic reticulum stress that can activate autophagy [62]. Mild and moderate oxidative stress-induced autophagy promotes lysosomal degradation of misfolded proteins in fibroblasts and reduces apoptosis in type II alveolar epithelial cells. Severe and prolonged oxidative stress can lead to autophagy disorder induced by endoplasmic reticulum stress and further increase intracellular ROS, lysosomal membrane damage and apoptosis of lung effector cells, promoting chronic inflammation and lung fibrosis [63].

The signaling pathways associated with autophagy, including AKT/mTOR, MAPK/ ERK1/2, HIF1-α/BNIP3 pathways, have been reported to participate in pulmonary diseases such as idiopathic pulmonary fibrosis (IPF)

and cystic pulmonary fibrosis through induction of epithelial cell damage, autophagic flux block and inhibition of collagen degradation [64]. For radiation-induced lung injury, a previous study revealed that leptin inhibits autophagy and promotes EMT in lung epithelial cells through activation of AKT/mTOR and that rapamycin reverses this process [65]. Li et al. attenuated RILI both in vivo and vitro by inhibiting lysosomal degradation of GXP4 induced by chaperone-mediated autophagy [66]. Furthermore, Wen et al. found that single nucleotide polymorphisms (SNPs) in autophagy-related genes are associated with the incidence and grade of RILI and have potential as predictive targets [67]. Although autophagy-related pathways and genes have showed some potential as therapeutic and prognostic targets for RILI, relevant studies are still insufficient, and the mechanism of autophagy involvement in RILI and the possibility of clinical translation need to be further explored.

Key signaling pathways during RILI occurrence and development are summarized in Fig. 2, of which the classical TGF-β signalling pathway has received extensive attention from clinical and preclinical investigators. Given that TGF-β signaling pathway plays a critical role in EMT, ECM deposition and CAF formation, targeting the TGF-β pathway appears to be a highly promising strategy for both RILI and anti-tumor therapy [68]. However, The success of M7824 in preclinical studies but failure in both a phase II clinical trial (NCT02699515) for advanced biliary tract cancer and a phase III trial (NCT03631706) for non-small cell lung cancer (NSCLC) indicates the dilemma of transitioning from animal models to clinical trials. Interestingly, SHR-1701, a bifunctional protein targeting PD-L1 and TGF-β, was reported to exhibit a manageable safety profile and potent antitumor activity in unresectable metastatic colorectal cancer [69], implying a significance difference between human and animal TGF-β signal pathway. Moreover, since TGF-β signal plays an important role from embryonic development to the maintenance of immune homeostasis [70], systemic TGF-β deficiency caused by widespread inhibition may lead to the disturbance of normal physiological processes [71]. Therefore, it may be worthwhile to explore the possibility of targeting the downstream of TGF-β signalling, such as integrins [72] and non-coding effectors [73]. These findings demonstrate that the targeting of TGF-β signaling pathway in the therapy of RILI need to be flexible, specific and accurate.

Prognosis of radiation-induced lung injury

It is important to note that predictive modeling, identifying at-risk populations, and early intervention are important in combating RILI. Previous studies to predict RILI continually focused on dose-volume parameters [74], anti-tumor treatment modalities [75], pulmonary

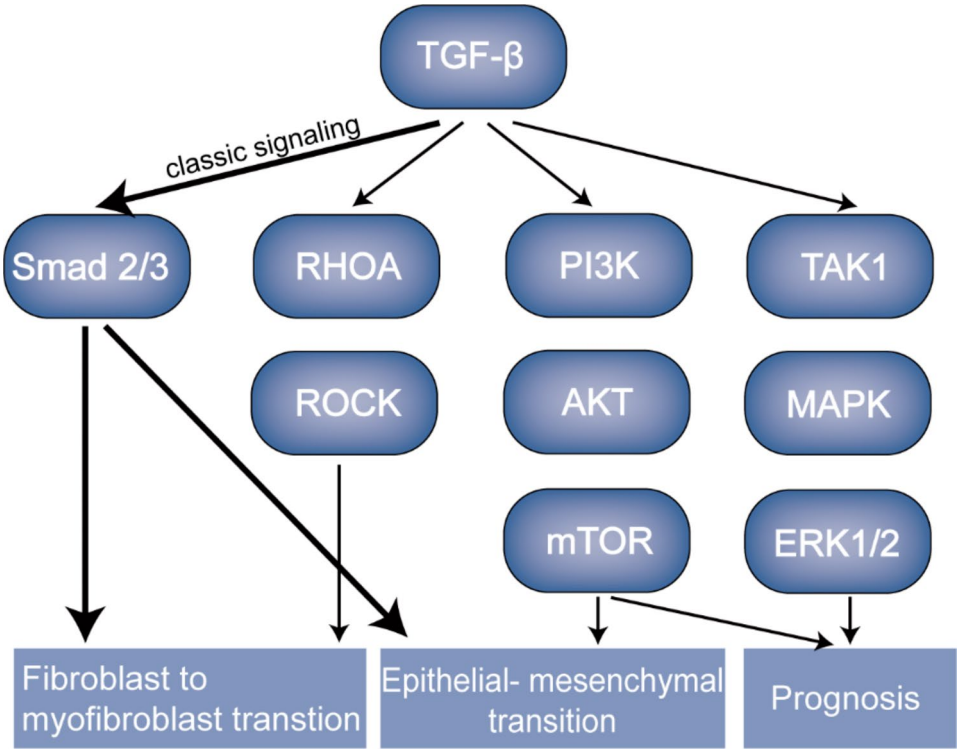

Fig. 2 Key effector cells in radiation-induced lung injury. TGFβ is a key signaling pathway that drives the occurrence of radiation-induced lung injury, divided into classical and non classical pathways

functions [76], comorbid underlying diseases [77] and serum cytokines [78]. Our study found that genetic polymorphisms are also correlated to the development of RILI [79], which may function as predictive targets. As the mechanisms of RILI have been studied in depth, the selection of predictors has become more pluralistic. Furthermore, in order to systematically and individually predict the RILI occurrence of patients, the screening and integration of multifaceted factors as well as the construction and validation of prognostic models are prominent. In this review, we summarized relevant studies on predictive models of RILI in recent years, including predictors, patient size, number of centers, radiotherapy technology, construction methods, RILI grade and area under curve (AUC) of the validation cohort, as shown in Table 1.

With the development of artificial intelligence in recent years, machine learning and deep learning have been increasingly applied to build predictive models, which contributes to model accuracy and offers an attempt to integrate medicine and industry [90]. However, the predictive models are poorly applied in clinical practice currently due to low generalizability, difficulty in objective evaluation of RILI [91] and differences in RT technology and target delineation. Moreover, with the widespread application of immune checkpoint blockade (ICB), the combination of ICB and RT increases pulmonary toxicity (anti-PD-L1 + RT vs. anti-PD-L1, 13.6% vs. 1.9%) [92], which has become a significant resistance to clinical oncology. While predictive models for RILI induced by radioimmunotherapy remain to be developed. Furthermore, most relevant studies have focused on acute RILI, with insufficient attention to the prediction of advanced radiation-induced pulmonary fibrosis in clinic.

Pharmacotherapy for radiation-induced lung injury

With the deep exploration of the mechanisms, various targets have been attempted for early intervention and treatment for RILI. We have summarized the drugs, targets, therapeutic effects, impact on anti-tumor treatment and research types of relevant studies in recent years, as shown in Table 2, which indicated that the research related to RILI medication has progressed considerably. With the development of organ chip technology, RILI models have become various and are not limited to the cellular or animal level. For example, Dasgupta et al. utilized a microfluidic organ-on-a-chip to imitate the human lung more closely and evaluate the effects of lovastatin and prednisolone on acute RILI [102]. Moreover, in addition to the exploration of novel targets, the interest in the multiple effects of targets in different pathophysiological processes is also increasing. For example, Lan et al. reported a novel combination strategy of RT and M7824, a bifunctional fusion protein targeting both

Table 1 Summary of predictive models for RILI

Predictors	Sample size	Center number	Radiotherapy technology	Modeling method	RILI grade	AUC	Reference
IL-8,CCL-2,MLD, hypertension	131	1	3D conformal RT	Generalized linear model	≥ 2	0.863	Yu et al. [78]
Radiomics and dosiomics risk score, ILD, age	314	1	IMRT/VMAT	Nomogram	≥ 2	0.855	Zhang et al. [80]
SII, SGA score, PFS, PTV/LV	416	2	3D conformal RT/ IMRT/ TOMO	Nomogram	≥ 3	0.852	Wang et al. [81]
Total RD, MLD	965	12	PBT	GBM	≥ 2	0.75	Valdes et al. [82]
Dosimetric 3D matrix, clinical 1D matrix	105	1	LinacRT/TOMO	RseNet18 architecture	≥ 2	0.91	Sheng et al. [83]
Age, LV, Hb, dose fraction, V_{10}	186	1	SBRT	Logistic regression model	≥ 2	0.83	Huang et al. [84]
TNM stage, post- RT percentage of CD8 + T cell, V_{15}	121	1	IMRT	Nomogram	≥ 2	0.621	Zhang et al. [85]
CT matrix, RD matrix	314	1	IMRT/VMAT	3D ResNet architecture	≥ 2	0.65 and 0.70	Zhang et al. [86]
V_{35} and V_{40} EQD2	333	1	3D conformal RT/ IMRT/ VMAT	Logistic regression model	≥ 1	0.71	Puttanawarut et al. [74]
Respiratory comorbidity, previous lung radiation, right lung location, MLD, V_{20}	339	2	SBRT	Logistic regression model	≥ 2	0.77	Liu et al. [87]
MLD, ITV, V_{5-40}, dosiomic features	247	3	SBRT	LightGBM	≥ 2	0.846	Adachi et al. [88]
Radiomics and dosiomic features	126	1	IMRT	Ridge regression algorithm	≥ 2	0.88	Li et al. [89]

Abbreviation: CT, computed tomography; EQD2, equivalent dose in the 2 Gy fraction; GBM, gradient boosting machine; Hb, hemoglobin; ILD, interstitial lung disease; IMRT, intensity modulated radiation therapy; ITV, internal target volume; LV, lung volume; MLD, mean lung dose; PBT, proton beam therapy; PFS, pulmonary fibrosis score; PTV, planning target volume; RD, radiation dose; SBRT, stereotactic body radiation therapy; SGA, subjective global assessment; SII, systemic immune-inflammation index; TOMO, helical tomotherapy; VMAT, volumetric modulation arc therapy; Vx, the percentage of total lungs volume receiving x Gy

Table 2 Summary of pharmacotherapy for RILI

Drugs	Targets	Inhibition of pneumonia	Inhibition of fibrosis	Effects on anti-tumor	Research type	References
Pulmozyme	cGAS/ STING/ NLRP3 pathway	Yes	Yes	Undetected	Preclinical study	Zhang et al. [93]
Pirfenidone	M2; TGF-β1/Smad3 pathway	Undetected	Yes	Undetected	Preclinical study	Ying et al. [94]
MSC-EVs	VECs; ATM/P53/P21 pathway	Yes	Yes	Undetected	Preclinical study	Lei et al. [95]
IR-780	Fibroblasts; Macrophages	Yes	Yes	Positive	Preclinical study	Luo et al. [96]
2-ME	HIF-1α; VECs	Undetected	Yes	Positive	Preclinical study	Nam et al. [97]
Glibenclamide	VECs	Yes	Yes	Undetected	Preclinical study	Xia et al. [98]
Glucosamine	AECs	Yes	Yes	Undetected	Preclinical study	Lei et al. [99]
Isoflavone	NF-κB pathway	Yes	Undetected	Undetected	Preclinical study	Fountain et al. [100]
Thyroid hormone	M2; TGF-β1/Smads pathway	Undetected	Yes	Undetected	Preclinical study	Li et al. [101]
Bintrafusp alfa	Fibroblasts; TGF-β1/Smads pathway	Undetected	Yes	Positive	Preclinical study	Lan et al. [16]
Lovastatin	ROS; HMOX1	Yes	Undetected	Undetected	Preclinical study	Dasgupta et al. [102]
Anisodamine	ROS; Nrf2/ARE pathway	Yes	Undetected	Undetected	Preclinical study	Guo et al. [103]
Antioxidant liposome	Macrophages; Neutrophils	Yes	Yes	Undetected	Preclinical study	Zhou et al. [104]
ACT001	NLRP3; ROS	Yes	Yes	Undetected	Preclinical study	Luo et al. [105]

Abbreviation: AECs, alveolar epithelial cells; EVs, extracellular vesicles; HIF, hypoxia inducible factor; HMOX1, heme oxygenase 1; MSC, mesenchymal stem cell; NLRP3, NOD-like receptor thermal protein domain associated protein 3; ROS, reactive oxygen species; TGF-β, transforming growth factor-β

PD-L1 and TGF-β signaling, to attenuate RILI while enhancing anti-tumor effects [16] as the TGF-β signaling plays a critical role in both lung fibrosis and tumor immune evasion [106]. Though M7824 has failed in subsequent clinical trials for oncotherapy [107, 108], the research has provided a new line of research about mitigating RILI while also focusing on various roles of the target in other biological processes.

However, a problem similar to that of predictive models also exists in RILI treatment-related studies, namely poor clinical translation. Most of the relevant studies are preclinical and only a few are ongoing clinical trials (NCT02296281, Pirfenidone vs. Placebo; NCT05637216, Losartan). Furthermore, pharmacotherapy for RILI should be quested on the base that does not interfere with tumor therapy, which are often ignored by relevant studies.

Immune checkpoint inhibitors (ICIs) and RILI

In the era of cancer immunotherapy, the combination of ICIs and radiotherapy has gained attention for the quality of translating focal anti-tumour activity into multisite effects [109]. Correspondingly, there is an elevated risk of pneumonitis, which is not a simple superposition mode of RILI and ICI-related pneumonitis (CIP) according to the previous study [110], sometimes also referred as anti-tumor treatment related pneumonitis.

Overall, the incidence of CIP is roughly from 3 to 6% [111], of which potential mechanism may be increased immune injury mediated by the aggregation of CD4 Th2 cell population [112], the loss of the inhibitory phenotype of Tregs [113], up-regulated circulating cytokines [114] and increased preexisting and emerging autoantibodies [115]. Moreover, the combination of CTLA4 inhibitors significantly increased the risk of pneumonitis compared to Durvalumab monotherapy (6.7% vs. 2.2%) [116], indicating that the mechanisms by which different ICIs cause pneumonia may differ. For the combination of PD-1/PD-L1 and RT, the senescence-like subtypes of fibroblasts, alveolar epithelial cells, B cells, and myeloid immune cells expressing Apolipoprotein E may contribute to RILI [9]. Moreover, PD-1/PD-L1 antibody therapy has shaped the inflammatory microenvironment through lymphocytes, cytokines, and proteins, which makes it favourable for RILI occurrence [117–119]. For the combination of CTLA-4 and RT, the anti-tumour activity has been confirmed in clinical and preclinical studies [120–123]. However, there are still few studies on the mechanism of the effect of the CTLA-4 antibody combined with radiotherapy on RILI, which may be a future research direction.

Furthermore, another unique and rare pattern of RILI, known as radiation recall pneumonitis (RRP), of which specific manifestation is the inflammation located in the previously irradiated fields of patients induced by ICIs [124]. RRP occurrence may be associated with long-term pulmonary mediated by RT, of which alternations include lymphocyte infiltration, CD4/CD8 imbalance and accumulation of cytokines such as IL-4 [125], NF-kB [126] and CXCR4 [127], causing lung tissues easily stimulated by ICIs to initiate inflammation. Additionally, compared to anti-PD-L1, stimulation by PD-1 antibodies tends to

exhibit a higher risk of PPR [128], indicating that there may be differences in the mechanisms by which different ICIs contribute to PPR.

Conclusion

In summary, RILI has a broad research perspective and its management holds important clinical implications. For mechanism exploration, the understanding of target cells may be deeper with the help of technologies such as sequencing and organ chips. For prognosis, the models remain to be developed focusing on different stages and treatment combinations and need to enhance the universality and objectivity for clinical applications. For pharmacotherapy, it is necessary to promote clinical trials to improve the translation of basic research. For the combination with ICIs, it would be interesting to explore the mechanisms underlying the effects of ICIs on RILI stratified by the ICI type, especially for anti CLTA-4 therapy.

Author contributions

S.W. wrote the main manuscript. D.X. and L.Y. prepared Figs. 1 and 2. B.L. and X.L. revised the manuscript. All authors reviewed the manuscript.

Funding

This work was supported by the State Key Program of National Natural Science of China (Grant No. 82130092) for Xianglin Yuan.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 14 November 2024 / Accepted: 28 February 2025
Published online: 13 March 2025

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Yegya-Raman N, Friedes C, Lee SH et al. Pneumonitis rates before and after adoption of immunotherapy consolidation in patients with locally advanced non-small cell lung cancer treated with concurrent chemoradiation. Int J Radiat Oncol Biol Phys. 2023;118(5):1445–54.
3. Hanania AN, Mainwaring W, Ghebre YT, Hanania NA, Ludwig M. Radiation-Induced lung injury: assessment and management. Chest. 2019;156(1):150–62.
4. Coggle JE, Lambert BE, Moores SR. Radiation effects in the lung. Environ Health Perspect. 1986;70:261–91.
5. Yin Z, Yang G, Deng S, Wang Q. Oxidative stress levels and dynamic changes in mitochondrial gene expression in a radiation-induced lung injury model. J Radiat Res. 2019;60(2):204–14.
6. Yang M, Fan Q, Hei TK, et al. Single-Cell transcriptome analysis of radiation pneumonitis mice. Antioxid (Basel). 2022;11(8):1457.
7. Zhang Z, Zhou J, Verma V, et al. Crossed pathways for Radiation-Induced and Immunotherapy-Related lung injury. Front Immunol. 2021;12:774807.
8. Roy S, Salerno KE, Citrin DE. Biology of Radiation-Induced lung injury. Semin Radiat Oncol. 2021;31(2):155–61.
9. Wu F, Zhang Z, Wang M, et al. Cellular atlas of senescent lineages in Radiation- or Immunotherapy-Induced lung injury by Single-Cell RNA-Sequencing analysis. Int J Radiat Oncol Biol Phys. 2023;116(5):1175–89.
10. Ruaro B, Salton F, Braga L, et al. The history and mystery of alveolar epithelial type II cells: focus on their physiologic and pathologic role in lung. Int J Mol Sci. 2021;22(5):2566.
11. Liberti DC, Kremp MM, Liberti WA 3rd, et al. Alveolar epithelial cell fate is maintained in a spatially restricted manner to promote lung regeneration after acute injury. Cell Rep. 2021;35(6):109092.
12. Otoupalova E, Smith S, Cheng G, Thannickal VJ. Oxidative stress in pulmonary fibrosis. Compr Physiol. 2020;10(2):509–47.
13. Cen M, Ouyang W, Zhang W, et al. MitoQ protects against hyperpermeability of endothelium barrier in acute lung injury via a Nrf2-dependent mechanism. Redox Biol. 2021;41:101936.
14. Wijerathne H, Langston JC, Yang Q, et al. Mechanisms of radiation-induced endothelium damage: emerging models and technologies. Radiother Oncol. 2021;158:21–32.
15. Rodor J, Chen SH, Scanlon JP, et al. Single-cell RNA sequencing profiling of mouse endothelial cells in response to pulmonary arterial hypertension. Cardiovasc Res. 2022;118(11):2519–34.
16. Lan Y, Moustafa M, Knoll M, et al. Simultaneous targeting of TGF-β/PD-L1 synergizes with radiotherapy by reprogramming the tumor microenvironment to overcome immune evasion. Cancer Cell. 2021;39(10):1388–e140310.
17. Wei K, Nguyen HN, Brenner MB. Fibroblast pathology in inflammatory diseases. J Clin Invest. 2021;131(20):e149538.
18. Buechler MB, Pradhan RN, Krishnamurty AT, et al. Cross-tissue organization of the fibroblast lineage. Nature. 2021;593(7860):575–9.
19. Davidson S, Coles M, Thomas T, et al. Fibroblasts as immune regulators in infection, inflammation and cancer. Nat Rev Immunol. 2021;21(11):704–17.
20. Marconi GD, Fonticoli L, Rajan TS, et al. Epithelial-Mesenchymal transition (EMT): the Type-2 EMT in wound healing, tissue regeneration and organ fibrosis. Cells. 2021;10(7):1587.
21. Phan THG, Paliogiannis P, Nasrallah GK, et al. Emerging cellular and molecular determinants of idiopathic pulmonary fibrosis. Cell Mol Life Sci. 2021;78(5):2031–57.
22. Locati M, Curtale G, Mantovani A. Diversity, mechanisms, and significance of macrophage plasticity. Annu Rev Pathol. 2020;15:123–47.
23. Lee JW, Chun W, Lee HJ, et al. The role of macrophages in the development of acute and chronic inflammatory lung diseases. Cells. 2021;10(4):897.
24. Li M, Hou Q, Zhong L, Zhao Y, Fu X. Macrophage related chronic inflammation in Non-Healing wounds. Front Immunol. 2021;12:681710.
25. Melms JC, Biermann J, Huang H, et al. A molecular single-cell lung atlas of lethal COVID-19. Nature. 2021;595(7865):114–9.
26. Dong T, Chen X, Xu H, et al. Mitochondrial metabolism mediated macrophage polarization in chronic lung diseases. Pharmacol Ther. 2022;239:108208.
27. Cheng P, Li S, Chen H. Macrophages in lung injury, repair, and fibrosis. Cells. 2021;10(2):436.
28. Meziani L, Mondini M, Petit B, et al. CSF1R Inhibition prevents radiation pulmonary fibrosis by depletion of interstitial macrophages. Eur Respir J. 2018;51(3):1702120.
29. Feng Z, Zhou J, Liu Y, et al. Epithelium- and endothelium-derived exosomes regulate the alveolar macrophages by targeting RGS1 mediated calcium signaling-dependent immune response. Cell Death Differ. 2021;28(7):2238–56.
30. Boyd DF, Allen EK, Randolph AG, et al. Exuberant fibroblast activity compromises lung function via ADAMTS4. Nature. 2020;587(7834):466–71.
31. Jiang D, Christ S, Correa-Gallegos D, et al. Injury triggers fascia fibroblast collective cell migration to drive Scar formation through N-cadherin. Nat Commun. 2020;11(1):5653.
32. Xie X, Wu X, Zhao D, et al. Fluvoxamine alleviates bleomycin-induced lung fibrosis via regulating the cGAS-STING pathway. Pharmacol Res. 2023;187:106577.
33. Ezzo M, Hinz B. Novel approaches to target fibroblast mechanotransduction in fibroproliferative diseases. Pharmacol Ther. 2023;250:108528.
34. Cords L, Engler S, Haberecker M, et al. Cancer-associated fibroblast phenotypes are associated with patient outcome in non-small cell lung cancer. Cancer Cell. 2024;42(3):396–e4125.

35. David CJ, Massagué J. Contextual determinants of TGFβ action in development, immunity and cancer. Nat Rev Mol Cell Biol. 2018;19(7):419–35.
36. Shi M, Zhu J, Wang R, et al. Latent TGF-β structure and activation. Nature. 2011;474(7351):343–9.
37. Travis MA, Sheppard D. TGF-β activation and function in immunity. Annu Rev Immunol. 2014;32:51–82.
38. Liénart S, Merceron R, Vanderaa C, et al. Structural basis of latent TGF-β1 presentation and activation by GARP on human regulatory T cells[J]. Science. 2018;362(6417):952–6.
39. Frangogiannis N. Transforming growth factor-β in tissue fibrosis[J]. J Exp Med. 2020;217(3):e20190103.
40. de Oliveira Camargo R, Abual'anaz B, Rattan SG, Filomeno KL, Dixon IMC. Novel factors that activate and deactivate cardiac fibroblasts: A new perspective for treatment of cardiac fibrosis. Wound Repair Regen. 2021;29(4):667–77.
41. Ghafouri-Fard S, Abak A, Talebi SF, et al. Role of MiRNA and LncRNAs in organ fibrosis and aging. Biomed Pharmacother. 2021;143:112132.
42. Chen HY, Chan SJ, Liu X, et al. Long noncoding RNA Smyca coactivates TGF-β/Smad and Myc pathways to drive tumor progression. J Hematol Oncol. 2022;15(1):85.
43. Mei S, Xu Q, Hu Y, et al. Integrin β3-PKM2 pathway-mediated aerobic Glycolysis contributes to mechanical ventilation-induced pulmonary fibrosis. Theranostics. 2022;12(14):6057–68.
44. Saleem A, Helo Y, Win Z, et al. Integrin Avβ6 positron emission tomography imaging in lung Cancer patients treated with pulmonary radiation therapy. Int J Radiat Oncol Biol Phys. 2020;107(2):370–6.
45. Bickelhaupt S, Erbel C, Timke C, et al. Effects of CTGF Blockade on Attenuation and reversal of Radiation-Induced pulmonary fibrosis. J Natl Cancer Inst. 2017;109(8). https://doi.org/10.1093/jnci/djw339.
46. Xu H, Qu J, Wang J, et al. Discovery of pulmonary fibrosis inhibitor targeting TGF-β RI in Polygonum cuspidatum by high resolution mass spectrometry with in Silico strategy. J Pharm Anal. 2022;12(6):860–8.
47. Cao K, Lei X, Liu H, et al. Polydatin alleviated radiation-induced lung injury through activation of Sirt3 and Inhibition of epithelial-mesenchymal transition. J Cell Mol Med. 2017;21(12):3264–76.
48. Tauriello DVF, Sancho E, Batlle E. Overcoming TGFβ-mediated immune evasion in cancer. Nat Rev Cancer. 2022;22(1):25–44.
49. Batlle E, Massagué J. Transforming growth Factor-β signaling in immunity and Cancer. Immunity. 2019;50(4):924–40.
50. Wang H, Che J, Cui K, et al. Schisantherin A ameliorates liver fibrosis through TGF-β1mediated activation of TAK1/MAPK and NF-κB pathways in vitro and in vivo. Phytomedicine. 2021;88:153609.
51. Qian W, Cai X, Qian Q, Zhang W, Wang D. Astragaloside IV modulates TGF-β1-dependent epithelial-mesenchymal transition in bleomycin-induced pulmonary fibrosis. J Cell Mol Med. 2018;22(9):4354–65.
52. Hsieh SC, Wu CC, Hsu SL, Feng CH, Yen JH. Gallic acid attenuates TGF-β1-stimulated collagen gel contraction via suppression of RhoA/Rho-kinase pathway in hypertrophic Scar fibroblasts. Life Sci. 2016;161:19–26.
53. Liu Q, Li HY, Wang SJ, et al. Belumosudil, ROCK2-specific inhibitor, alleviates cardiac fibrosis by inhibiting cardiac fibroblasts activation. Am J Physiol Heart Circ Physiol. 2022;323(1):H235–47.
54. Mortezaee K, Najafi M, Farhood B, et al. NF-κB targeting for overcoming tumor resistance and normal tissues toxicity. J Cell Physiol. 2019;234(10):17187–204.
55. Wang S, Zhang Y. HMGB1 in inflammation and cancer. J Hematol Oncol. 2020;13(1):116.
56. Mei Z, Tian X, Chen J, et al. α7–nAchR agonist GTS–21 reduces radiation-induced lung injury. Oncol Rep. 2018;40(4):2287–97.
57. Garcia AN, Casanova NG, Valera DG, et al. Involvement of eNAMPT/TLR4 signaling in murine radiation pneumonitis: protection by eNAMPT neutralization. Transl Res. 2022;239:44–57.
58. Arora A, Bhuria V, Singh S, et al. Amifostine analog, DRDE-30, alleviates radiation induced lung damage by attenuating inflammation and fibrosis. Life Sci. 2022;298:120518.
59. Verma S, Dutta A, Dahiya A, Kalra N. Quercetin-3-Rutinoside alleviates radiation-induced lung inflammation and fibrosis via regulation of NF-κB/TGF-β1 signaling. Phytomedicine. 2022;99:154004.
60. Li Z, Lai X, Fu S, et al. Immunogenic cell death activates the tumor immune microenvironment to boost the immunotherapy efficiency. Adv Sci (Weinh). 2022;9(22):e2201734.
61. Levine B, Kroemer G. Biological functions of autophagy genes: A disease perspective. Cell. 2019;176(1–2):11–42.
62. Chaurasia M, Bhatt AN, Das A, Dwarakanath BS, Sharma K. Radiation-induced autophagy: mechanisms and consequences. Free Radic Res. 2016;50(3):273–90.
63. Racanelli AC, Kikkers SA, Choi AMK, Cloonan SM. Autophagy and inflammation in chronic respiratory disease. Autophagy. 2018;14(2):221–32.
64. Lv X, Li K, Hu Z. Autophagy and pulmonary fibrosis. Adv Exp Med Biol. 2020;1207:569–79.
65. Gui X, Chen H, Cai H, Sun L, Gu L. Leptin promotes pulmonary fibrosis development by inhibiting autophagy via PI3K/Akt/mTOR pathway. Biochem Biophys Res Commun. 2018;498(3):660–6.
66. Li L, Wu D, Deng S, et al. NVP-AUY922 alleviates radiation-induced lung injury via Inhibition of autophagy-dependent ferroptosis. Cell Death Discov. 2022;8(1):86.
67. Wen J, Liu H, Wang L, et al. Potentially functional variants of ATG16L2 predict radiation pneumonitis and outcomes in patients with Non-Small cell lung Cancer after definitive radiotherapy. J Thorac Oncol. 2018;13(5):660–75.
68. Peng D, Fu M, Wang M, Wei Y, Wei X. Targeting TGF-β signal transduction for fibrosis and cancer therapy. Mol Cancer. 2022;21(1):104.
69. Qiu MZ, Bai Y, Wang J, et al. Addition of SHR-1701 to first-line capecitabine and oxaliplatin (XELOX) plus bevacizumab for unresectable metastatic colorectal cancer. Signal Transduct Target Ther. 2024;9(1):349.
70. Deng Z, Fan T, Xiao C, et al. TGF-β signaling in health, disease, and therapeutics. Signal Transduct Target Ther. 2024;9(1):61.
71. Kong P, Shinde AV, Su Y, et al. Opposing actions of fibroblast and cardiomyocyte Smad3 signaling in the infarcted myocardium. Circulation. 2018;137(7):707–24.
72. Slack RJ, Macdonald SJF, Roper JA, Jenkins RG, Hatley RJD. Emerging therapeutic opportunities for integrin inhibitors. Nat Rev Drug Discov. 2022;21(1):60–78.
73. Savary G, Dewaeles E, Diazzi S, et al. The long noncoding RNA DNM3OS is a reservoir of fibromirs with major functions in lung fibroblast response to TGF-β and pulmonary fibrosis. Am J Respir Crit Care Med. 2019;200(2):184–98.
74. Puttanawarut C, Sirirutbunkajorn N, Khachonkham S, Pattaranutaporn P, Wongsawat Y. Biological dosiomic features for the prediction of radiation pneumonitis in esophageal cancer patients. Radiat Oncol. 2021;16(1):220.
75. Sheng L, Cui X, Cheng L, Chen Y, Du X. Risk factors of grade ≥ 2 radiation pneumonitis after gemcitabine induction chemotherapy for patients with non-small cell lung cancer. Radiat Oncol. 2019;14(1):229.
76. Zhou Y, Yan T, Zhou X, et al. Acute severe radiation pneumonitis among non-small cell lung cancer (NSCLC) patients with moderate pulmonary dysfunction receiving definitive concurrent chemoradiotherapy: impact of pre-treatment pulmonary function parameters. Strahlenther Onkol. 2020;196(6):505–14.
77. Takeda A, Kunieda E, Ohashi T, et al. Severe COPD is correlated with mild radiation pneumonitis following stereotactic body radiotherapy. Chest. 2012;141(4):858–66.
78. Yu H, Wu H, Wang W, et al. Machine learning to build and validate a model for radiation pneumonitis prediction in patients with Non-Small cell lung Cancer. Clin Cancer Res. 2019;25(14):4343–50.
79. Tang Y, Yang L, Qin W, Yi MX, Liu B, Yuan X. Impact of genetic variant of HIPK2 on the risk of severe radiation pneumonitis in lung cancer patients treated with radiation therapy. Radiat Oncol. 2020;15(1):9.
80. Zhang Z, Wang Z, Yan M, et al. Radiomics and dosiomics signature from whole lung predicts radiation pneumonitis: A model development study with prospective external validation and Decision-curve analysis. Int J Radiat Oncol Biol Phys. 2023;115(3):746–58.
81. Wang L, Liang S, Li C, et al. A novel nomogram and risk classification system predicting radiation pneumonitis in patients with esophageal Cancer receiving radiation therapy. Int J Radiat Oncol Biol Phys. 2019;105(5):1074–85.
82. Valdes G, Scholey J, Nano T et al. Predicting the impact of proton beam therapy technology on pulmonary toxicities for locally advanced lung cancer patients enrolled on the proton collaborative group prospective clinical trial. Int J Radiat Oncol Biol Phys 2023 Nov 22;119(1):S0360-3016(23)08154-3.
83. Sheng L, Zhuang L, Yang J, et al. Radiation pneumonia predictive model for radiotherapy in esophageal carcinoma patients. BMC Cancer. 2023;23(1):988.
84. Huang BT, Lin PX, Wang Y, Luo LM. Developing a prediction model for radiation pneumonitis in lung Cancer patients treated with stereotactic body radiation therapy combined with clinical, dosimetric factors, and laboratory biomarkers. Clin Lung Cancer. 2023;24(8):e323-e331.e2.
85. Zhang XZ, Tao SP, Liang SX, et al. Nomogram based on Circulating lymphocyte subsets for predicting radiation pneumonia in esophageal squamous cell carcinoma. Front Immunol. 2022;13:938795.

86. Zhang Z, Wang Z, Luo T, et al. Computed tomography and radiation dose images-based deep-learning model for predicting radiation pneumonitis in lung cancer patients after radiation therapy. Radiother Oncol. 2023;182:109581.
87. Liu Y, Wang W, Shiue K, et al. Risk factors for symptomatic radiation pneumonitis after stereotactic body radiation therapy (SBRT) in patients with non-small cell lung cancer. Radiother Oncol. 2021;156:231–8.
88. Adachi T, Nakamura M, Shintani T, et al. Multi-institutional dose-segmented dosiomic analysis for predicting radiation pneumonitis after lung stereotactic body radiation therapy. Med Phys. 2021;48(4):1781–91.
89. Li B, Zheng X, Zhang J, et al. Lung subregion partitioning by incremental dose intervals improves Omics-Based prediction for acute radiation pneumonitis in Non-Small-Cell lung Cancer patients. Cancers (Basel). 2022;14(19):4889.
90. Avanzo M, Stancanello J, Pirrone G, Sartor G. Radiomics and deep learning in lung cancer. Strahlenther Onkol. 2020;196(10):879–87.
91. Kuipers ME, van Doorn-Wink KCJ, Hiemstra PS, Slats AM. Predicting radiation-induced lung injury in lung cancer patients - challenges and opportunities: predicting radiation-induced lung injury. Int J Radiat Oncol Biol Phys 2023 Nov 2;118(3):639–49.
92. Anscher MS, Arora S, Weinstock C, et al. Association of radiation therapy with risk of adverse events in patients receiving immunotherapy: A pooled analysis of trials in the US food and drug administration database. JAMA Oncol. 2022;8(2):232–40.
93. Zhang Y, Li Z, Hong W, et al. STING-Dependent sensing of Self-DNA driving pyroptosis contributes to Radiation-Induced lung injury. Int J Radiat Oncol Biol Phys. 2023;117(4):928–41.
94. Ying H, Fang M, Hang QQ, Chen Y, Qian X, Chen M. Pirfenidone modulates macrophage polarization and ameliorates radiation-induced lung fibrosis by inhibiting the TGF-β1/Smad3 pathway. J Cell Mol Med. 2021;25(18):8662–75.
95. Lei X, He N, Zhu L, et al. Mesenchymal stem Cell-Derived extracellular vesicles attenuate Radiation-Induced lung injury via miRNA-214-3p. Antioxid Redox Signal. 2021;35(11):849–62.
96. Luo M, Chen L, Zheng J, et al. Mitigation of radiation-induced pulmonary fibrosis by small-molecule dye IR-780. Free Radic Biol Med. 2021;164:417–28.
97. Nam JK, Kim AR, Choi SH, et al. Pharmacologic Inhibition of HIF-1α attenuates radiation-Induced pulmonary fibrosis in a preclinical image guided radiation therapy. Int J Radiat Oncol Biol Phys. 2021;109(2):553–66.
98. Xia P, Cao K, Hu X, et al. KATP channel blocker Glibenclamide prevents Radiation-Induced lung injury and inhibits Radiation-Induced apoptosis of vascular endothelial cells by increased Ca2 + Influx and subsequent PKC activation. Radiat Res. 2020;193(2):171–85.
99. Lei X, Ma N, Liang Y, et al. Glucosamine protects against radiation-induced lung injury via Inhibition of epithelial-mesenchymal transition. J Cell Mol Med. 2020;24(18):11018–23.
100. Fountain MD, McLellan LA, Smith NL, et al. Isoflavone-mediated radioprotection involves regulation of early endothelial cell death and inflammatory signaling in Radiation-Induced lung injury. Int J Radiat Biol. 2020;96(2):245–56.
101. Li L, Nie X, Yi M, et al. Aerosolized thyroid hormone prevents radiation induced lung fibrosis. Front Oncol. 2020;10:528686.
102. Dasgupta Q, Jiang A, Wen AM, et al. A human lung alveolus-on-a-chip model of acute radiation-induced lung injury. Nat Commun. 2023;14(1):6506.
103. Guo H, Chen J, Yu H, et al. Activation of Nrf2/ARE pathway by anisodamine (654-2) for Inhibition of cellular aging and alleviation of Radiation-Induced lung injury. Int Immunopharmacol. 2023;124(Pt A):110864.
104. Zhou H, Zhang Y, Pei P, Shen W, Yi X, Yang K. Liposome-anchored mesenchymal stem cells for radiation pneumonia/fibrosis treatment. Biomaterials. 2023;300:122202.
105. Luo H, Liu X, Liu H, et al. ACT001 ameliorates ionizing radiation-induced lung injury by inhibiting NLRP3 inflammasome pathway. Biomed Pharmacother. 2023;163:114808.
106. Massagué J, Sheppard D. TGF-β signaling in health and disease. Cell. 2023;186(19):4007–37.
107. Cho BC, Lee JS, Wu YL, et al. Bintrafusp Alfa versus pembrolizumab in patients with Treatment-Naive, programmed Death-Ligand 1-High advanced NSCLC: A randomized, Open-Label, phase 3 trial. J Thorac Oncol. 2023;S1556(23):00738–4.
108. Yoo C, Javle MM, Verdaguer Mata H, et al. Phase 2 trial of bintrafusp Alfa as second-line therapy for patients with locally advanced/metastatic biliary tract cancers. Hepatology. 2023;78(3):758–70.
109. Arina A, Gutiontov SI, Weichselbaum RR. Radiotherapy and immunotherapy for cancer: from systemic to multisite. Clin Cancer Res. 2020;26(12):2777–82.
110. Peiliang Wang MD, Yikun Li MM, Mengyu Zhao MM, Jinming Yu MD, Feifei Teng MD. Distinguishing immune checkpoint inhibitor-related pneumonitis from radiation pneumonitis by CT radiomics features in non-small cell lung cancer. Int Immunopharmacol. 2024;128:111489.
111. Kalisz KR, Ramaiya NH, Laukamp KR, Gupta A. Immune checkpoint inhibitor Therapy-related pneumonitis: patterns and management. Radiographics. 2019;39(7):1923–37.
112. Bukhari S, Henick BS, Winchester RJ, et al. Single-cell RNA sequencing reveals distinct T cell populations in immune-related adverse events of checkpoint inhibitors. Cell Rep Med. 2023;4(1):100868.
113. Suresh K, Naidoo J, Zhong Q, et al. The alveolar immune cell landscape is dysregulated in checkpoint inhibitor pneumonitis. J Clin Invest. 2019;129(10):4305–15.
114. Lim SY, Lee JH, Gide TN, et al. Circulating cytokines predict Immune-Related toxicity in melanoma patients receiving Anti-PD-1-Based immunotherapy. Clin Cancer Res. 2019;25(5):1557–63.
115. Tahir SA, Gao J, Miura Y, et al. Autoimmune antibodies correlate with immune checkpoint therapy-induced toxicities. Proc Natl Acad Sci U S A. 2019;116(44):22246–51.
116. Johnson ML, Cho BC, Luft A, et al. Durvalumab with or without Tremelimumab in combination with chemotherapy as First-Line therapy for metastatic Non-Small-Cell lung cancer: the phase III POSEIDON study. J Clin Oncol. 2023;41(6):1213–27.
117. Rashdan S, Minna JD, Gerber DE. Diagnosis and management of pulmonary toxicity associated with cancer immunotherapy. Lancet Respir Med. 2018;6(6):472–8.
118. Asrir A, Tardiveau C, Coudert J, et al. Tumor-associated high endothelial venules mediate lymphocyte entry into tumors and predict response to PD-1 plus CTLA-4 combination immunotherapy. Cancer Cell. 2022;40(3):318–34.
119. Zhang Q, Tang L, Zhou Y, He W, Li W. Immune checkpoint Inhibitor-Associated pneumonitis in Non-Small cell lung cancer: current Understanding in characteristics, diagnosis, and management. Front Immunol. 2021;12:663986.
120. Formenti SC, Rudqvist NP, Golden E, et al. Radiotherapy induces responses of lung cancer to CTLA-4 Blockade. Nat Med. 2018;24(12):1845–51.
121. Ji D, Song C, Li Y, et al. Combination of radiotherapy and suppression of Tregs enhances abscopal antitumor effect and inhibits metastasis in rectal cancer. J Immunother Cancer. 2020;8(2):e000826.
122. Hartmann L, Osen W, Eichmüller OL, et al. Carbon ion irradiation plus CTLA4 Blockade elicits therapeutic immune responses in a murine tumor model. Cancer Lett. 2022;550:215928.
123. Rudqvist NP, Charpentier M, Lhuillier C, et al. Immunotherapy targeting different immune compartments in combination with radiation therapy induces regression of resistant tumors. Nat Commun. 2023;14(1):5146.
124. Jo NC, Shroff GS, Ahuja J, Agrawal R, Price MC, Wu CC. Radiation recall pneumonitis: imaging appearance and differential considerations. Korean J Radiol. 2024;25(9):843–50.
125. Teng F, Li M, Yu J. Radiation recall pneumonitis induced by PD-1/PD-L1 Blockades: mechanisms and therapeutic implications. BMC Med. 2020;18(1):275.
126. Liu X, Song Y, Hu S, et al. Serum amyloid A contributes to radiation-induced lung injury by activating macrophages through FPR2/Rac1/NF-κB pathway. Int J Biol Sci. 2024;20(12):4941–56.
127. Pei J, Cheng K, Liu T, et al. Early, non-invasive detection of radiation-induced lung injury using PET/CT by targeting CXCR4. Eur J Nucl Med Mol Imaging. 2024;51(4):1109–20.
128. Sprung CN, Forrester HB, Siva S, Martin OA. Immunological markers that predict radiation toxicity. Cancer Lett. 2015;368(2):191–7.

Publisher's note