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Biomarkers Associated with Radiation-Induced Lung Injury in Cancer Patients

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Abstract

Radiotherapy (RT) is a common and effective non-surgical treatment for thoracic solid tumors, and radiation-induced lung injury (RILI) is the most common side effect of radiotherapy. Even if RT is effective in the treatment of cancer patients, severe radiation pneumonitis (RP) or pulmonary fibrosis (PF) can reduce the quality of life of patients and may even lead to serious consequences of death. Therefore, how to overcome the problem of accurate prediction and early diagnosis of RT for pulmonary toxicity is very important. This review summarizes the related factors of RILI and the related biomarkers for early prediction of RILI.

Keywords

Radiation Induced Lung Injury, RILI, Fibrosis, Biomarkers

1. Introduction

Lung cancer is a tumor that occurs in the epithelium or lung cells of the respiratory tract. Lung cancer is basically divided into two main categories based on pathological type, namely small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), of which NSCLC accounts for the majority and is subdivided into squamous, adenocarcinoma and large cell carcinoma types [1]. Because of the differences between different types and stages of lung cancer, the selected therapeutic measures are also different [2]. And RT has a potential role in all stages of lung cancer of different types either in controlling progression or in palliative care [3] [4].

With advances in treatment technology and improvements in radiotherapy,

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the adverse effects of RT have gradually decreased and the therapeutic efficacy has gradually improved, but RILI is inevitable in sensitive normal lung tissue [5] [6]. RILI is divided into two stages: acute radiation pneumonitis (RP) and chronic radiation pulmonary fibrosis (RPF) [7]. While RP occurs early in RT and is potentially curable, PF occurring later is considered irreversibly harmful [8] [9]. Current therapeutic techniques are very limited for the widespread occurrence of RF and there is no clear effective clinical treatment, which would severely affect the survival time and quality of life of patients [10]. Therefore, determining the early occurrence of RILI by biomarkers and treating it aggressively is important for the clinical application of RT.

2. Risk Factors Associated with Radiation-Induced Lung Injury

Due to patient variability, the specific risk of developing RILI after radiotherapy for each patient is not known. The factors associated with the development of RILI can now be broadly classified into patient-related factors (age, gender, smoking; comorbidities, tumor location, etc.) and treatment factors (total radiation dose, dose per fraction, irradiated lung volume; chemotherapy; immunotherapy; targeted therapy, etc.) [11] [12].

2.1. Patient Factors

It is clear that older patients are more likely to develop radiation pneumonia due to reduced pulmonary function (PF) and more comorbidities than younger patients. PF parameters such as percent predicted value of first-second forceful expiratory volume (FEV1%), forceful spirometry (FVC) and pulmonary carbon monoxide dispersion (DLCO) have been used as primary measures of overall lung function. However, there is no consistent evidence to support an association between PF parameters and RILI. Only lower baseline FEV1% [13], DLCO% [14] [15], and PaO_2 [16] are significantly associated with the risk of RILI.

Pre-existing lung disease prior to radiotherapy may also increase the risk of RILI. Studies have shown that patients with pre-existing interstitial lung disease (ILD) appear to be more susceptible to acute lung injury after radiotherapy, leading to an exacerbation of acute ILD [17] [18], which can be quantified by FDG uptake in the lungs. Lung cancer combined with chronic obstructive pulmonary disease (LC-COPD) is a common complication. Recent international expert consensus suggests that LC-COPD should treat both lung cancer and COPD, taking into account their interaction in the treatment and monitoring of adverse reactions [19]. It has long been known that patients with comorbid chronic obstructive pulmonary disease (COPD) also experience higher pulmonary toxicity than patients without comorbidities [20] [21]. Therefore, it is very important to evaluate and monitor the lung function of LC-COPD patients during radiotherapy. Before radiotherapy, pulmonary function and emphysema staging should

be carefully evaluated to identify potential ILD, and the risks and benefits of radiotherapy should be repeatedly weighed. In addition, multi-parameter models for prediction [22] and imaging techniques including perfusion imaging, functional imaging, and 4D-CT [23] can be used to guide radiotherapy field settings and dose limits, which in turn may further reduce radiotherapy-related lung injury.

And surprisingly, a long history of smoking is a high-risk factor for the prevalence and survival of patients with lung cancer [24], but is a protective factor for RILI. A study by Jin *et al.* showed the highest incidence of RP in patients who had never smoked (37%) and the lowest incidence in patients who were reported as smokers at the time of diagnostic condition screening (14%) [25]. However, this result should not be regarded as encouraging patients to smoke. On the contrary, smoking cessation is an effective intervention to prevent tumor progression and improve survival rate [26]. In response to this result, the current possible explanations mainly include the reduction of inflammatory response in smokers [27], the role of glutathione in preventing oxidant-induced lung injury [28] [29], and the impaired DNA damage repair ability of non-smoking patients with lung cancer [30], resulting in increased lung toxicity after radiotherapy.

The effect of gender on RILI is currently unknown, but the current study suggests that women are at a slightly higher risk of developing RILI [31], possibly due to their smaller lung volumes and often combined autoimmune diseases [32] [33] [34]. The possible explanation for the more sensitive female population mentioned by Ronnett *et al.* is that radiation pneumonitis is similar to autoimmune response and has a greater impact on women, so the likelihood of severe RP in women is significantly higher than that in men ($p = 0.01$) [35].

And the current findings indicate that tumor location and tumor size may influence the risk of developing RILT, while tumor type and tumor stage may not be important in predicting the risk of RILT. The results suggest that patients with lower lobe lung cancer have a higher risk of RP [36] and larger tumors are also important adverse risk factors for RILT. And in recent years, studies have suggested the relationship between the risk of RP and the regional dose distribution of lung cancer patients receiving radiotherapy. The results suggest a higher incidence of RP in apical compared to bottom tumors, about 11% and 40%, respectively [37]. Also, some current studies suggest a higher likelihood of severe pneumonia in the left lung compared to the right lung during radiotherapy, which is considered to be related to cardiac exposure during radiotherapy to the left lung, but at present this idea still needs to be supported by more research evidence [38] [39].

2.2. Treatment Factors

Although the risk of developing radiation-induced pulmonary toxicity remains unpredictable, it is clear that the likelihood and severity of adverse pulmonary effects after radiotherapy are closely related to the dosimetric parameters of the

patient's radiotherapy [40] [41]. In patients with non-small cell lung cancer treated with intensity-modulated radiotherapy, an increase in mean lung dose (MLD) leads to an increase in the area of lung fibrosis [42] [43]. Meanwhile, other studies have highlighted that lung volume receiving 20 Gy (V20) and 30 Gy (V30), respectively, is the only significant parameter for predicting RP [44] [45] [46]. And the daily fraction size of radiotherapy is another key parameter in RILI. A fraction > 2.67 Gy increases the risk of RILI compared to a lower daily fraction [47].

Current studies suggest that for early NSCLC, SBRT has been shown to confer survival benefits to patients with severe COPD (GOLD 3 - 4) [48]. For patients with locally advanced NSCLC who are not suitable for surgical treatment or are not suitable for SBRT, conventional radiotherapy is still considered, intensity-modulated conformal radiotherapy plus involved field irradiation is performed on the primary lesion [49], and the radiation dose of the lung is further limited to V20 ≤ 20% and MLD ≤ 12.3 Gy [50]. In addition, more sophisticated radiotherapy techniques such as proton and carbon ion radiotherapy [51] [52] may further reduce pulmonary toxicity and thus help configure the treatment landscape of lung cancer.

Numerous studies have now demonstrated that radiotherapy combined with platinum-containing regimens of chemotherapy increases the incidence of RILI [34] [35] [53], with a significant survival benefit seen with concurrent radiotherapy compared to sequential radiotherapy for patients with locally advanced NSCLC, but at the cost of increased radiotherapy toxicity [54] [55]. The use of radiotherapy combined with targeted therapy or immunotherapy is often considered for patients with advanced NSCLC who are not responding to chemotherapy, and this also increases the incidence of RILI, which is considered to be related to the development of interstitial lung disease following the use of targeted or immunological agents [56] [57] [58]. Therefore, relevant risk factors must be identified before drug treatment, and the potential occurrence of drug-related lung injury must be closely monitored. Any new or worsening respiratory symptoms were closely observed during treatment, and PS scores were dynamically assessed. For patients with confirmed or highly suspected RILI, radiotherapy should be suspended according to the severity of the disease.

3. Biomarkers for Monitoring Radiation-Induced Lung Injury

3.1. Pro- and Anti-Inflammatory Cytokines

Based on the mechanism of radiation lung injury, pro-inflammatory, pro-fibrotic and pro-angiogenic cytokines are considered as potential markers of RILI, among which the three main classes are Tumor Necrosis Factor-α, Interleukins and Transforming Growth Factor-β1 [59] [60] [61].

TNF-α is a pro-inflammatory cytokine produced by macrophages that trigger the production of other pro-inflammatory cytokines, growth factors, and acute

phase proteins. Also, TNF-α is a major trigger of the pro-inflammatory cascade response, promoting fibroblast growth, ECM protein secretion and collagen deposition, and activating other pro-inflammatory cytokines (IL-1, IL-6 and IFN) for cascade responses [62] [63]. The enhanced plasma levels of TNF-α after radiation therapy are now well documented to be associated with early apoptosis and latent lung function impairment [64] [65] [66]. Despite the correlation between TNF-α and PR, however, there is still insufficient evidence as to whether TNF-α can be used as a predictor of RILT.

Interleukins can be synthesized by a variety of cells, including monocytes, alveolar macrophages, type II pneumocytes, fibroblasts and T lymphocytes, which play a crucial role in immune system host defense and tumorigenic processes. At present, interleukin is considered to be a potential marker of human RILI. The initial process after lung injury includes acute inflammatory response, immune cell recruitment, and the diffusion and migration of epithelial cells on the self-secreted temporary matrix. Injuries lead to the release of factors that contribute to the repair mechanism, including IL-1α and IL-6 [67] [68] [69] [70]. Studies have demonstrated the feasibility of applying IL-1α and IL-6 to measure blood samples to predict RP, where both cytokines had better specificity than sensitivity, and IL-6 performed better than IL-1α in predicting RP. In another study with follow-up of 90 patients with non-small cell lung cancer, changes in IL-6 plasma levels after 2 weeks of radiation therapy were associated with the occurrence of RP 6 to 8 weeks after the end of radiation therapy was significantly correlated ($p = 0.025$) [71]. In addition, studies have shown that naringenin improves radiation-induced lung injury by reducing IL-1β levels, thereby further verifying the relationship between the interleukin family and RILI [72].

TGF-β1 is the most critical inflammatory molecule involved in pulmonary fibrosis and exerts its pro-fibrotic effects mainly through binding to transmembrane proteins of serine/threonine kinases and activating several signaling pathways including ERK/GSK3β/Snail, Smad/Snail, and PI3K/AKT/mTOR axis [73] [74]. At the same time, current studies have demonstrated that TGF-β can further activate the ERK signaling pathway to promote EMT in alveolar type II epithelial cells, thereby exacerbating pulmonary fibrosis [75]. Prior to radiotherapy, elevated TGF-β1 levels do not represent an increased risk of RP and subsequent fibrosis in patients; however, persistently high TGF-β1 levels after treatment suggest a much higher likelihood of radiation-induced inflammation [59] [76]. At present, there is no clinical consensus on the treatment based on TGF-β1 level. We believe that this is a problem worthy of further study, but it still needs a lot of work to meet the publicly recognized standards. In view of the inflammatory response in the acute phase of RILI, antioxidant therapy including thiol compounds, antioxidant enzymes and plant antioxidants has been applied clinically.

3.2. Indicators of Pneumocytes Damage

In addition to inflammatory factors, indicators related to cellular damage are al-

so closely associated with the development of RILI, such as soluble intercellular adhesion molecule-1 (sICAM-1), mucin-like glycoprotein antigen KL-6, and pulmonary surface-active protein A (SP-A) & D (SP-D).

A study by Ishii *et al.* showed significantly higher levels of sICAM-1 in patients with RP compared to baseline levels ($p < 0.05$) [75]. Another trial also showed that a significant decrease in sICAM-1 levels was seen after a decrease in the incidence of RILI [77]. This suggests that sICAM-1 may be a useful marker for early detection of radiation pneumonia.

KL-6 antigen, produced by epithelial cells, particularly AEC II, and released from these damaged cells after irradiation, makes KL-6 an indicator of interstitial lung disease and acute lung injury. In patients with NSCLC, serum KL-6 levels have been reported to be almost consistent with the occurrence of grade ≥ 2 RP and to decrease after steroid administration [78]. Serum KL-6 levels were significantly correlated with the severity of pulmonary fibrosis and response to therapy [79] [80] [81].

SP-A and SP-D are primarily associated with the secretion of lung surface-active substances, surfactants that reduce surface tension in the alveoli and promote alveolar expansion, thereby allowing normal gas exchange. Surfactant proteins stimulate macrophages to produce pro-inflammatory cytokines (TGF-β1, interleukins) and ROS. Radiation-induced degradation of type II pneumocytes leads to the release of SP-A and SP-D, which leads to the progression of inflammation. SP-D plays a role in host defense, regulating immune response and lung phospholipid levels [82]. The usefulness of SP-A and SP-D in the early detection of RP was previously demonstrated by Sasaki *et al.* [83]. Also, a series of studies showed that SP-D is a more sensitive marker of pathological changes in the lung than SP-A [84] [85].

3.3. Genetic Characteristics

Even after taking into account dosimetric, therapeutic, clinical and demographic factors, late radiotherapy adverse effects show significant differences in incidence and severity across patients, thus considering individual genetic characteristics significantly associated with the development of RILI [86]. Radiogenomics has two goals: the first is to identify methods to predict the risk of radiation damage in patients after radiotherapy, and the second is to investigate the molecular mechanisms of radiation-induced toxicity in normal tissues. Single nucleotide polymorphisms (SNPs) are a current research hotspot, representing a wealth of sequence combinations and variant types in the human genome, and are a major source of genetic variation between individuals [87] [88]. So far, a series of studies have reported a possible correlation between SNPs and radiosensitivity of clinically normal tissues in patients. This usually includes genes encoding DNA repair genes and stress response-related genes [89]. Some of the current RP-related SNPs are summarized in **Table 1** below.

Table 1. SNPs in genes associated with RP.

SNPs	Function	Conclusions	Reference
TOPBP1 rs1051772	DNA repair	Decreased risk of RP in NSCLC patients	[90]
ATM rs1801516, ATM rs189037, ATM rs228590	DNA repair	Decreased risk of grade ≥ 3 RP in LC patients	[91] [92]
NEIL1 rs4462560, NEIL1 rs7402844	DNA repair	rs4462560 decreased risk of grade ≥ 2 RP in LC patients, rs7402844 increased risk of grade ≥ 2 RP in LC patients	[93]
LIG4 rs1805388	DNA repair	Increased risk of grade ≥ 3 RP in LC patients	[94]
HIPK2 rs2030712	Apoptosis, proliferation, DNA repair, Inflammation	Increased risk of grade ≥ 2 RP in LC patients	[95]
TGFbeta1 rs1982073	Inflammation	Decreased risk of RP in NSCLC patients	[96]
IL4 rs2243250	Inflammation	Increased risk of grade ≥ 3 RP in LC patients	[97]
ITGB6 rs4665162	Inflammation	Increased risk of grade ≥ 2 RP in LC patients	[98]
BMP2 rs235768 BMP2 rs1980499	Inflammation	Increased risk of grade ≥ 2 RP in LC patients	[99]
ATG16L2 rs10898880	Autophagy	Increased risk of RP in NSCLC patients	[100]
PAI-1 rs7242	Plasmin system inhibition	Increased risk of grade ≥ 3 RP in LC patients	[101]

3.4. MicroRNAs

MicroRNAs (miRNAs) are single-stranded, highly conserved small noncoding RNAs involved in the regulation of gene expression, transcription, translation, and epigenetic modifications. The role of miRNAs in radiosensitivity and radiotoxicity in patients' response to radiotherapy has been reported [102] [103]. Han *et al.* showed that exosomal microRNA-26b-5p enhances radiosensitivity of lung adenocarcinoma cells and may be a potential marker of radiotherapy sensitivity in lung adenocarcinoma [104]. In recent years, it has also been reported that MiR-18-5p and miR-219a-5p enhance the radiosensitivity of NSCLC cells by regulating HIF-1α and CD164, respectively [105]. miR-101 acts as a radiosensitizer and its overexpression enhances radiosensitivity by decreasing the levels of DNA-PKcs and ATM [106].

MiRNAs influence the response to ionizing radiation by participating in regulatory mechanisms of the DNA damage response at different levels and through three different processes: signaling pathways, checkpoints in the cell cycle and specific repair processes that restore single- or double-strand breaks (SSB, DSB) [107]. It was shown that in the acute phase after radiotherapy, miR-21 inhibits PD-CD4 expression and activates the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR signaling pathway.MiR-21 overexpression blocks the pro-inflammatory pathway of macrophages and reduces the incidence and severity of RILI in patients [108] [109]. Similarly, miR-140 is a key protective molecule against RILF by blocking TGF-β1 signaling and inhibiting myofibroblast differentiation and inflammation [110]. A study by Yin *et al.* suggested that low expression of let-7 leading to

overexpression of its target gene LIN28 could regulate the proliferative capacity of NSCLC cells, leading to a let-7/LIN28 dual negative feedback loop disruption, thereby promoting resistance to RT or cisplatin treatment [111].

Because of its stability in tissues and body fluids and its easy and rapid detection of expression, microRNA can be considered as an ideal marker to explore its value for monitoring RILI and thus provide practical guidance for clinical treatment.

4. Conclusion and Perspectives

Acute inflammation of the lungs or pulmonary fibrosis is unavoidable side effects after chest radiotherapy, and pulmonary fibrosis is considered an irreversible pathological process that can lead to dyspnea, impaired lung function or respiratory failure, thereby increasing the financial burden on patients and affecting their long-term quality of survival. Therefore, the use of various markers to monitor RT can significantly benefit patients in terms of better prevention and control of complications. Although some of the molecular mechanisms, risk factors and associated markers associated with RILI have been explored in this paper, there are still no ideal and reliable indicators or risk models to predict the risk of developing pulmonary toxicity in current clinical practice. It is promising that more and more prospective or retrospective studies are being conducted to clarify the mechanisms of RILI and that a comprehensive predictive model incorporating individualized genetic susceptibility, clinical background parameters and biological variants will emerge.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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