REVIEW ARTICLE

Radiation-induced lung injury — what do we know in the era of modern radiotherapy?

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ABSTRACT

Radiation-induced lung injury (RILI) that is usually divided into an early radiation-induced pneumonitis (RIP) and late chronic radiation-induced lung fibrosis (RILF) remains a clinically significant toxicity in radiation oncology. Thus, a thorough understanding of underlying molecular mechanisms and risk factors is crucial. This review, focused on patients treated with modern radiotherapy (RT) techniques, describes the different clinical presentations of RIP, with most typical imaging findings and usefulness of pulmonary function tests and laboratory assessment in differential diagnosis. The most critical patient- and treatment-related predictors are summarized and discussed — age and sex, comorbidities, tumour characteristics, concomitant treatment, and RT-plan parameters. The conventional grading scales and contemporary approach to quantitative assessment (radiomics, CT density changes) is described as well as treatment methods.

Key words: radiation-induced lung injury; lung toxicity; radiation pneumonitis; lung cancer radiotherapy; CT-density changes; lung fibrosis

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Introduction

Radiation-induced lung injury (RILI) was already described in the early 1900s, alongside an X-ray radiation discovery [1]. Until now, it remains a clinically significant toxicity in radiation oncology, mainly in lung cancer patients, irrespective of how sophisticated delivery technique is used. Thus, a thorough understanding of underlying mechanisms, risk and predictive factors is crucial. This review summarizes the current state of the art in this field.

Clinical presentation of RILI

RILI is a common term for lung damage caused by ionizing radiation. The early inflammatory response of lung tissue is known as radiation-induced pneumonitis (RIP), in contrast to the term "pneumonia", usually referring to the condition caused by an infectious agent [2]. RIP usually occurs within the first three months after treatment (1–6 months), hence, can be classified as subacute toxicity related to the infiltration of immune effector cells like neutrocytes, monocytes, macro-

phages, and release of proinflammatory cytokines and chemokines. In contrast, radiation-induced lung fibrosis (RILF) is a late, chronic complication that can lead to dyspnoea and decreased respiratory function.

Presentation of RIP can vary from subclinical radiographic findings to a life-threatening disease requiring hospitalization. The most common symptoms are general fatigue, dry, non-productive cough (rarely with hemoptysis), dyspnea (mild to severe), fever — usually moderate, sometimes pleural pain. If the damaged volume of the lung is advanced enough, RIP might lead to respiratory failure. Extensive RILF can present as progressive dyspnea, developing pulmonary hypertension and *cor pulmonale*, including a possible fatal scenario.

As the symptoms are often non-typical, to diagnose RILI, physicians should first confirm a time relation to prior radiation therapy and then eliminate other possible causes, like acute infection, cancer progression, cardiac or pulmonary diseases worsening, pulmonary embolism and systemic agent-induced pneumonitis [3]. A careful clinical examination with electrocardiography and echocardiography should be performed, and a chest CT-scan assessed for typical image findings (described below). Laboratory tests are also indicated; however, it must be considered that they can be hampered by the fact that C-reactive protein (CRP) and white blood count (WBC) levels usually do not differ significantly from bacterial infection. It is helpful to determine serum procalcitonin (PCT) levels because they remain lower than those for bacterial pneumonia [4]. In clinical trials, some new markers, like Serum Krebs von den Lungen-6 (KL-6) produced by type 2 pneumocytes or serum surfactant protein-D (SP-D), are used because they correlate with symptomatic RIP [5].

FDG-PET-CT also has a limited value for diagnosis of acute RIP, as a diffuse increased FDG uptake can last up to a few months after thoracic radiotherapy regardless of the reason for inflammation. Thus, it is not recommended that this examination is performed within the first six months after RT (Fig. 1). Nevertheless, it is possible to detect FDG-avid tumour recurrence among late fibrotic lesions, especially when RILF reaches its plateau after 12 months [6]. Eventually, an im-

age-guided biopsy might be the only way to confirm a final diagnosis.

Epidemiology

Because of a different clinical-radiological RIP presentation and difficulty of precise diagnosis in many cases, a broad range of incidence rates is found in the literature and vary from 5% to 58% for lung cancer patients [9]. However, it is noticeable that with the improvement of radiation delivery techniques, the incidence of RIP is decreasing. For any symptomatic pneumonitis G2+ (grade 2 or higher), it is reported 30-35% for static 3D radiotherapy and 24–34%, 9.4%, < 5% for intensity-modulated RT (IMRT)/volumetric — arc techniques (VMAT), stereotactic body RT (SBRT) and proton therapy, respectively [10, 11]. Modern radiotherapy methods significantly decrease particularly the highest grades of toxicity. In the present trial with stage III NSCLC patients qualified sequentially to durvalumab consolidation, the incidence of G3+ pneumonitis was 7% (34% for G2+). Similarly, Hu et al. [13] reported G3+ RIP in 1% of patients and Shintani et al. [14] 5% (35% for G2+). Although proton therapy seems promising in reducing RIP, a direct comparison with modern photon techniques is needed [11].

Late RILF is less frequently reported, and for IMRT is around 30% (G1) and single cases of G3+ [13]. It is worth underlining that many papers indicate a "year of patient enrolment" (or similar) as an independent risk factor of lung toxicity, which proves the importance of treating centre experience and learning curve when implementing any new method in medicine [11, 15].

Molecular mechanisms of RILI

Radiation-induced lung injury relates to alveolar epithelium and endothelium damage with a blood-air barrier dysfunction. Radiation promotes extensive inflammatory response with cytokine release and consolidation, leading to chronic RILI.

Post-radiotherapy lung toxicity can be divided into consecutive phases [9, 16]:

The early phase starts within days after RT. It consists of acute inflammatory response with oedema, capillary vessels congestion and alveolar pneumocytes injury leading to apoptosis. Infiltration of in-
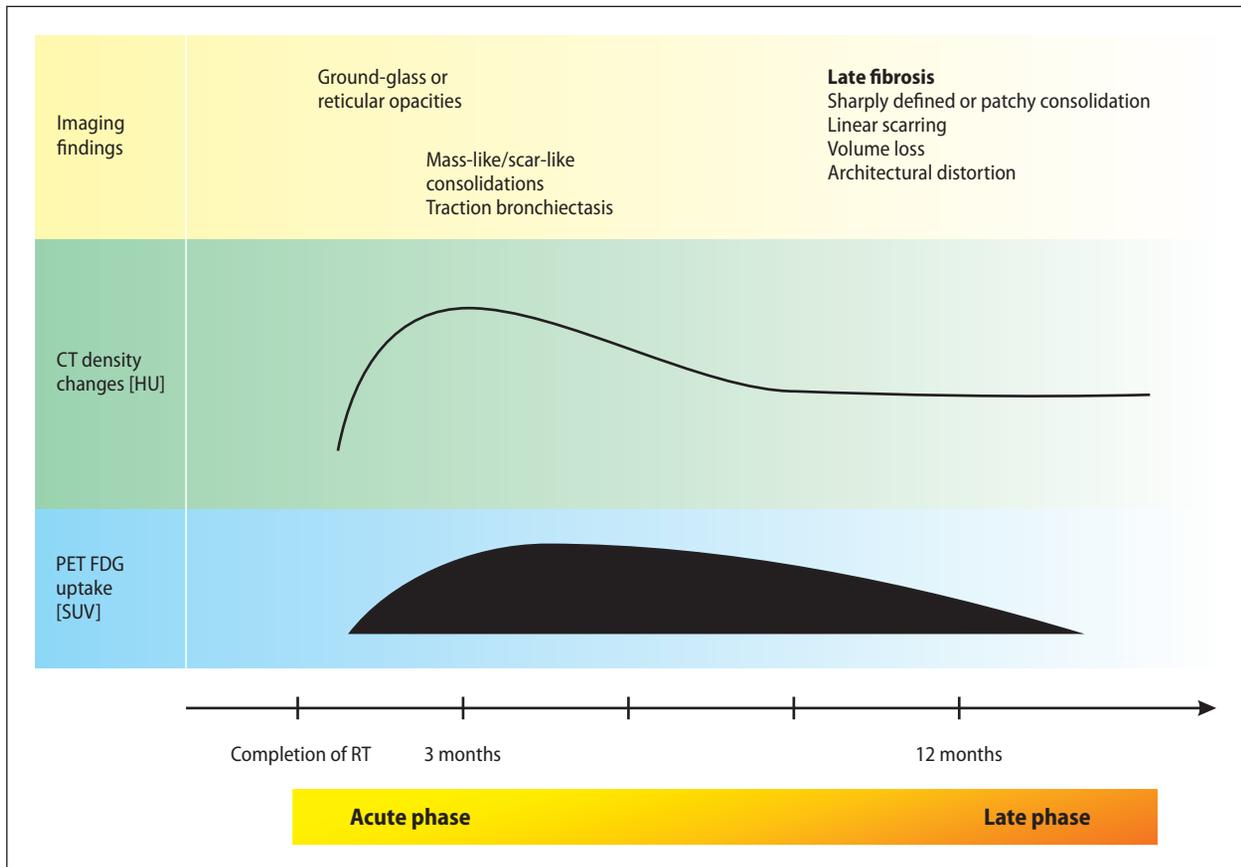
Figure 1. Imaging findings after thoracic radiotherapy (RT); CT — computed tomography; HU — Houndsfield units; PET — positron emission tomography; FDG — fluorodeoxyglucose; SUV — standardized uptake value. Elaborated on the basis of [6–8]

flammatory cells can be observed, and first cytokines are released: tumour necrosis factor alpha (TNF-α), inteleukins (ILs): IL-1 and IL-6, high-molecular-weight mucin-like antigen KL6, platelet-derived growth factor beta (PDGF-β) and basic fibroblast growth factor (bFGF). About six weeks post-RT, decreased lung perfusion leads to hypoxia and transforming growth factor beta (TGF-β) expression.

The next phase was called latent because any changes can be seen clinically, radiologically or in light microscopy. Proliferations of goblet cells and ciliary cell dysfunction propagates tenacious hypersecretion; degenerative changes in the alveoli progresses.

The exudative phase corresponds with clinical RIP and can be observed about 2–3 months after RT. It is characterized by endothelial and epithelial detachment with surfactant loss leading to alveolar collapse and minor vessels dysfunction. Alveolar hypersecretions of a fibrin-rich exudate promote the formation of hyaline membranes. It is

also a period of first repair and re-epithelialization by type II pneumocytes.

During the intermediate phase, tissue integrity is restored by the migration of fibroblasts and its conversion to myofibroblasts, increasing collagen synthesis. Hyaline membranes are dissolute.

Intensifying hypoxia promotes further profibrogenic and proangiogenic stimulation that leads to the fibrotic phase (6–9 months after RT); hyperplastic pneumocytes and myofibroblasts, collagen deposits in the lung interstitium can be observed; collapsed alveolar spaces reduce pulmonary volume. Thus, some patients can present dyspnea and right heart dysfunction several months after RT without earlier RIP symptoms.

However, there are still some open questions regarding the RILI course, which are not explained by these processes. Symptomatic acute pneumonitis occurs only in some patients, often inadequate to irradiated volume and sometimes resolves without progression to fibrosis. Some authors suggest

an occurrence of "sporadic RIP", which mimics hypersensitivity pneumonitis and can affect up to 10% of patients [17].

Senescence is a permanent growth arrest that can occur in a normal lifecycle or as a response to stress, mainly oxidative. The senescence of type II pneumocytes (AECs) seems to play a crucial role in the radiation-induced injury. These cells can interact with entire lung tissue by elaborating the senescence-associated secretory phenotype (SASP) — the set of immunomodulatory, proinflammatory, angiogenic and mitogenic molecules. SASP associated factors can secondarily promote senescence within uninvolved cells.

Image findings

There is a whole spectrum of post-RT image changes. During the early phase, even 3–4 weeks after the radiation therapy, CT findings are mainly ground-glass and reticular opacities progressing to airspace mass-like and scar-like consolidation and traction bronchiectasis. The ipsilateral pleural effusion is also possible [8]. All of these changes can resolve entirely within weeks.

It was common to describe post-radiotherapy image abnormalities as limited to RT fields, regardless of anatomic boundaries, with sporadic findings outside the beam path, which could help distinguish other pathologies. However, this assumption is valid for photon static delivery techniques or old passive-scattering proton beam methods. In the era of intensity-modulated ultra-conformal radiotherapy with more diffuse low- and medium-dose distribution, lung damage is much more tumour-shaped and corresponds with isodose lines [6].

Image patterns of radiation pneumonitis can also be classified using ATS/ERS universal classification of interstitial pneumonias and related conditions. They include:
- acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) pattern;
- cryptogenic organizing pneumonia (COP) pattern;
- non-specific interstitial pneumonia (NSIP) pattern;
- hypersensitivity pneumonitis (HP) pattern;
- indistinguishable from post-radiation change [19]. The most common radiographic pattern of RIP is COP, followed by AIP/ARDS, which is

associated with high-grade pneumonitis and related death [8].

During subsequent months (6–9 after RT) in some patients, noticeable areas of fibrosis can be seen along beam paths or isodose lines. Late fibrosis radiologically manifests as sharply defined consolidation or linear scarring with volume loss and architectural distortion [20]. Septal wall thickening over the opacities may also cause a "crazy paving" pattern [21]. In some cases, pleural thickening or mediastinum shift can be seen [20].

Similar changes occur after the SBRT therapy. Early phase findings — diffuse consolidation, diffuse ground-glass opacities, patchy consolidations and opacities — are usually not visible until three months post-treatment. Mostly, they resolve without radiologic sequelae. Nevertheless, this injury can progress to late changes — mass-like fibrosis and scar-like patterns (linear band of fibrosis). SBRT-induced areas of consolidation can evolve within the first year, and after a gradual decrease in size, a transient increase can be sometimes observed, which can be misleading and mimic a tumour recurrence. Finally, though, after 12 months, the image usually remains stable [22].

To avoid missing a recurrence, high-risk radiologic features (HRFs) after SBRT has been described in the literature: enlarging opacity (EO), sequential enlarging opacity (sEO), enlarging opacity after 12 months (EO12), bulging margin, loss of linear margins, craniocaudal growth, and loss of air bronchogram [23]. However, the authors of research describing post-stereotactic RT image changes in a 2-year follow-up [24] showed that 50% of patients without a local recurrence develop HRFs. What is more, 25% of them presented more than 3 HRFs. Dominant patterns in non-recurrent patients are EO (65%), sEO (50%) and EO12 (14%). On the other hand, loss of linear margins and craniocaudal growth is very infrequent (2%), so they seem to be a very high-risk feature and indicate the true relapse.

As mentioned earlier, FDG-PET can be helpful for the identification of tumour recurrence, especially within the fibrotic scar. We need to be conscious that metabolic hyperactivity can exist for years after SBRT [25, 26]. There are also first attempts to use different imaging modalities, like 3T MRI with DWI and DCE [27].

Table 1. Clinical scales for radiation-induced lung toxicity assessment

Criteria	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE v5.0	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
LENT-SOMA	Asymptomatic or mild symptoms; slight imaging changes	Moderate symptoms; patchy imaging changes	Severe symptoms; increased density imaging changes	Severe symptoms requiring continuous O2 or assisted ventilation	Death
RTOG	Mild symptoms or asymptomatic	Persistent symptoms requiring symptomatic treatment (severe cough)	Severe symptoms, possibly requiring intermittent O2 or steroids	Severe symptoms requiring continuous O2 or assisted ventilation	–
SWOG	Imaging changes; mild symptoms without steroids	Symptoms requiring steroids or tap for effusion	Symptoms requiring oxygen	Symptoms requiring assisted ventilation	Death

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self-care ADL refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden. CTCAE — common terminology criteria for adverse events, version 5.0; LENT-SOMA — Late Effects in Normal Tissue — Subjective Objective Management Analysis; RTOG — Radiation Therapy Oncology Group; SWOG — Southwest Oncology Group; ADL — activities of daily living

Grading scales

There are different clinical scales to assess radiation-induced lung toxicity. The commonly used are the CTCAE v5.0, LENT-SOMA, RTOG, SWOG (Tab. 1).

Differences in scales and unclear definitions often influence the research results, e.g., when looking for predictive factors of developing RILD [28]. There are, therefore, different attempts to develop more helpful criteria. Kouloulias et al. [29] suggested a new grading scale for RIP based on CT imaging (Tab. 2). They found the grades correlated highly with forced expiratory volume in one second (FEV1) and V20, which gives a satisfactory clinical validity.

During COVID-19 pandemic, it is crucial to differentiate coronaviral lung changes from radiation-induced ones, especially since many image findings can be shared. There are first artificial intelligence (AI)-based algorithms used in this appli-

cation, having decent sensitivity (76%) and specificity (63%) [30].

Pulmonary function tests in RILI assessment

Pulmonary function tests (PFTs), like spirometry and diffusing capacity of the lung for carbon monoxide (DLCO), are usually used when assessing post-RT lung toxicity. A measurable decrease in FEV1 can suggest obturation related to lung tissue oedema, while forced vital capacity (FVC)/total lung capacity (TLC) decrease indicates a lung stiffening. However, gradual worsening of spirometry values can be observed in most patients after thoracic RT, regardless of the incidence of RIP [15]. Clinically dominant radiation injury in the lungs presents as damage of the alveolar barrier that compromises the gas transfer through the alveolocapillary membrane. Hence, most of the trials indicate DLCO as the proper test for a post-radiation lung

Table 2. Radiological grading scale of radiation induced pneumonitis (RP) [29]

Grade	CT Findings	Time of manifestation
0	No findings	ACUTE
1	Ground glass opacities without fuzziness of the subjacent pulmonary vessels	
2	The findings may vary from ground glass opacities, extending beyond the radiation field, to consolidations	
3	Clear focal consolidation ± elements of fibrosis	
4	Dense consolidation, cicatrisation atelectasis, aerobronchogram and bronchial extension (traction bronchiectasis), significant pulmonary volume loss, and pleural thickening	LATE

dysfunction assessment [31], e.g., Guerra et al. [32] showed a direct correlation between subjective clinical scoring of RIP and DLCO results.

Quantitative assessment of lung density changes after radiotherapy

Because pneumonitis symptoms are assessed using nonquantitative, subjective scales, its implementation to dose-response modelling is difficult. Thus, there are attempts to use image-based objective features to provide a more precise, quantitative assessment of pulmonary damage. The lung tissue density change expressed in Hounsfield Units (HU) derived from CT scans can be a numeric surrogate as it seems to fit the most commonly implemented NTCP models of lung response to radiation [33]. There are also some examples of dedicated software for big-data analysis of DICOM lung images [34].

Bernchou et al. [7] comprehensively described lung CT HU changes in NSCLC patients treated with conventionally fractionated IMRT. This trial measured density differences between initial and post-treatment follow-up CT scans.

After the first three months post-RT, a significant increase in HU value was observed in proportion to the dose delivered, reaching its plateau around 45 Gy. For a 3–9 months follow-up period in a 5–45 Gy dose range, a moderate density decrease was noticed, while a continuous growth occurred in higher doses. Finally, after 12 months, density changes stabilized. To explain the course of obtained image changes, the authors proposed a two-component mathematical model reflecting two overlapping processes — early and late toxicity. It was also shown that early changes were more clearly pronounced compared to the late phase.

Similarly, Defraene et al. [35] have compared initial and 3-month follow-up CT scans of lung cancer patients after a PET-boost trial, where the doses were escalated above 66 Gy, up to a limit of organs at risk constraints. They have noticed a HU increase in voxels of all doses-bins up to 60 Gy, where it reached its plateau. Similar sigmoid-like shaped curves of density change in function of radiation dose were described by Shroder et al. [36].

These IMRT studies reveal that the image changes are visible even in low-dose regions, and the threshold dose level of lung damage — if it exists — must be around or below 5 Gy. The range of 0–5 Gy has not been precisely studied and, in most cases, it was used as an offset for baseline differences between CT scanners. In previous trials from a 3D-era, such intensive changes were not observed, suggesting an impact of low-dose bath and dose distribution on other organs at risk in modern delivery techniques [37].

In SBRT treatment, increased CT density correlates with a higher dose, PTV size, and grows in time. Changes can be observed even within volumes receiving doses as low as 6 Gy and are most pronounced above 20 Gy to reach a plateau around 40 Gy. For patients with PTV size > 100 cm^3 a noticeable increase of HU values was seen at lower doses [38]. What is more, there is also a clinical relation with image changes on post-SBRT CT scans. Al Feghali et al. observed a strong positive correlation between RIP and delta HU in a region covered by 20 Gy isodose [39].

Assessing the ΔHU — dose relation can also help differentiate the post-radiation injury from a recurrence [40]. There is also a suggestion that the baseline CT-number can be predictive for a future lung injury, and primarily high-density regions (mainly in the lower lobes) can produce a response in more extensive damage [41] which is consistent with a higher risk of severe RIP mentioned in previous chapters.

Another approach to providing a better understanding of post-radiation toxicity is to use radiomics techniques that extract multiple quantitative features from image data. Moran et al. [42] used CT-based radiomics to assess post-SBRT changes and showed that especially gray level co-occurrence matrix (GLCM) features performed well in distinguishing lung injury severity levels, being concordant with radiation oncologist scores. There was also a significant dose-response relationship.

Predictors of RILI

COPD/ILD

The risk factors of developing RIP can be related to patient's characteristics and disease or treatment administered. Initial diagnosis of any lung disorder — like chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD) seems to be particularly significant.

COPD is a common problem in lung cancer patients diagnosed in 40–70% [9], although decreasing lung parameters can be linked with tumour progression and impede proper differentiation. The role of COPD as a prognostic factor of developing RIP remains unclear, and the literature data is confusing — some suggest an influence of worse initial FEV1 values on RIP prediction [28, 43], whereas others prove that COPD does not impact a post-radiation injury or even can be somehow protective [44].

In contrast, the baseline history of ILD is the best described risk factor of severe RIP, both in conventionally fractionated RT [45, 46], and SBRT [47–49]. It is also linked with a risk of in-hospital death in patients with lung cancer admitted for acute pneumonitis [50]. Some studies reported grade 5 RIP in ILD patients even when meeting restrictive constraints of dose distribution, e.g. V20 < 10% (V20 — the volume of lung receiving at least 20 Gy) or MLD < 10 Gy (MLD — mean lung dose) [51]. Thus, radiation oncologists must be alert for any signs and symptoms of ILD when qualifying patients for thoracic radiotherapy, even in palliative intent [52]. In addition to a standard examination, CT scans should be carefully inspected for subtle ground-glass abnormalities known as interstitial lung abnormalities (ILAs) or peripheral reticulation and fibrosis because fibrotic ILD seems the most associated with radiation-induced toxicity [10]. The explanation could be that idiopathic pulmonary fibrosis, which is the largest subtype of ILD, has several pathologies common with RILI, e.g. alveolar endothelium cells (AECs) damage and senescence leading to TGF-β increase and fibroblast activation.

Apart from increased toxicity, a history of ILD is correlated with worse overall survival rates (OS), whereas decreased initial FEV1 values do not affect treatment results.

However, both severe ILD and COPD can lead to respiratory insufficiency and a need for oxygen therapy [43, 53, 54].

Age and sex

Some authors point out an older age (65+) as a risk factor of RIP [28, 55, 56]. This relation can result from numerous comorbidities, which are independent risk factors.

When analysing the biggest trials — probably with the most precise selection of patients — this assumption, however, is not that clear [12]. The influence of sex is also doubtful. In most cases, it was not shown [57].

Smoking

The most critical risk factor for developing lung cancer is tobacco smoking, and the data supporting this correlation are compelling [58]. At the same time, smoking stimulates other comorbidities that significantly impact overall survival. However, its role in the development of RILI is unclear. There are even suggestions for it to be somehow protective [15, 56, 59]. It could be explained by the decreased sensitivity to radiation injury of non-functional lung volumes previously damaged by smoking.

Tumor location and size

Disease-related risk factors are mainly primary tumour location and size. Many trials indicate that GTVs in the middle or lower lung segments are correlated with RIP incidence [55, 56, 60]. It is explained by a more significant tumour motion and, as a result, larger volume to be irradiated or spatial functional heterogeneity across the lung volume that can be assessed using 4D CT ventilation maps [61]. These image-derived ventilation metrics have been already validated with clinical data [62] and led to clinical trials on functional avoidance of radiotherapy [63–65]. As the irradiated volume has a significant influence on toxicity, the PTV size is often used as a predictive factor, e.g. PTV > 350 cm^3 [28] or even > 100 cm^3 [38].

Fractionation

The fraction dose used in radiotherapy must also be considered in the context of possible RILI. There is a different profile of developing lung damage after conventional fractionation than after mild- or ultrahypofractionation. Even fraction doses above 2.5 Gy can increase post-radiation injury in conventional, large-volume targets [28, 55, 66, 67]; therefore, qualification to SBRT treatment presumes a limitation in tumour size and use of highly conformal, precise delivery technique. Another issue is a delivery scheme in SBRT — Verma et al. [68] showed that receipt of daily radiation therapy (as opposed to every other day regimen) was associated with a higher toxicity rate. However, it must

be noticed that this trial concerned relatively large tumours (> 5 cm), which is often an exclusion criterion from 1–5 fraction SBRT.

Dosimetric factors

Among all treatment-related risk factors, information written in dose-volume histograms (DVH), like a mean lung dose (MLD) and a volume receiving at least × Gy dose (Vx), remains a basic predictor in radiation oncology. The present recommendation for conventional radiotherapy is to keep V20 < 30–35% (7% risk of RILI) and MLD < 20 Gy (20% risk) [69, 70]. Nevertheless, Saito et al. [12] identified V20 < 25% and MLD < 10 Gy as a predictive factor for G2+ pneumonitis. Additionally, in the literature, we can find some more parameters related to lung injury — V5 (V5 < 65%), V10 or V13 [71, 72].

When considering ultrahypofractionated regimens, authors present different conclusions, e.g. V20 < 10% and V10 < 6.14% (as RIP G2+ predictor) or MLD < 6–7.84 Gy (RIP G3+ risk) [73, 74].

In many trials, especially concerning SBRT, a critical volume constraint is applied when irradiating parallel tissues like lungs. It is described as a maximum volume of tissue that should receive a dose equal to or less than a given threshold value to keep the basic lung function. For example, the constraint limits at least 1500 cm³ of the lungs in males and 950 cm³ in females, to receive less than 7.2 Gy in 1 fraction regime, up to 14.4 Gy for 8 fractions [75, 76]. Contemporary SBRT lung dose constraints are summarized in Table 3.

It is worth underlining that some suggest a dose-volume relationship in the heart to be even more critical than in the lungs. Although a simple explanation is missing, we can suspect that radiation-induced right-heart dysfunction can promote pulmonary hypertension, oedema, and transudate. Suggested parameters with the strongest correlation with G2+ pneumonitis are the mean heart dose (MHD), V65 and V43 (V43 > 16%) [66, 77, 78].

Multimodality treatment

Comprehensive thoracic cancer treatment needs a multidisciplinary approach and the use of different modalities. Each of them can be an independent risk factor of developing RILI.

Surgery, the first-line treatment for many lung cancer patients, is generally reported to be unrelated to RIP [56]. However, some authors point to a possible correlation with radiation-induced toxicity [66] that can be observed despite low V20, MLD and MHD values in postoperative radiotherapy.

In the case of chemotherapy, there is an agreement that some cytotoxic drugs can promote lung injury. Well-known agents increasing the risk of RIP are taxanes, doxorubicin, bleomycin, cyclophosphamide, vincristine, mitomycin, gemcitabine, recombinant interferon alfa and bevacizumab [70]. Because of the synergistic effect with radiotherapy, they possibly act like radiosensitizers [9]. Exceptionally high risk is reported for paclitaxel-based chemotherapy, mainly used in patients ineligible for platinum-based chemotherapy [55].

Most researchers, including Auperin et al. [79] have not found any differences in pulmonary toxicity between concurrent and sequential radio-chemotherapy. Few papers suggest a sequential treatment [56] or induction chemo (e.g. gemcitabine) to be more RIP-related [71].

Nowadays, it is crucial to recognize the influence of immunotherapy. Immune checkpoint inhibitors (ICI) can develop pneumonitis itself — ICI-associated pneumonitis is a well-known complication, occurring in up to 19% of NSCLC patients [80]. Still, there is a relation between immunotherapy and radiotherapy.

Previous thoracic radiotherapy was a risk factor of pulmonary toxicity in patients treated with pembrolizumab, which we know from the Keynote-001 study [81]. Nevertheless, Jabbour et al. suggested that combined treatment with PD-1 inhibitors and chemoradiotherapy for stage III NSCLC is tolerable [82]. Likewise, in the PACIFIC trial,

Table 3. Stereotactic body radiation therapy (SBRT) lung dose constraints "Timmerman tables" [76]

1 fraction	2 fractions	3 fractions	4 fractions	5 fractions	8 fractions
D_{CVmax} = 7.2 Gy	D_{CVmax} = 9.4 Gy	D_{CVmax} = 10.8 Gy	D_{CVmax} = 12 Gy	D_{CVmax} = 12.5 Gy	D_{CVmax} = 14.4 Gy
V8 < 37%	V10 < 37%	V11.4 < 37%	V12.8 < 37%	V13.5 < 37%	V15.2 < 37%

D_{CVmax} — critical volume max dose; critical volume — 1500 cm³ for males and 950 cm3 for females

where all the patients had undergone a concurrent chemoradiation, similar G3+ pulmonary toxicity (defined as pneumonitis/radiation pneumonitis) was noted — 3.4%/2.6% for durvalumab and placebo group, respectively [83]. However, it must be underlined that this analysis did not take a type of chemo regimen (taxanes or induction gemcitabine) into account.

Finally, the lack of apparent differences in clinically significant lung toxicity between sequential and concurrent thoracic radiotherapy and immunotherapy (e.g. CTLA-4 and/or PD-1 inhibitors) proves that it may be a safe option, especially in palliative intent [84, 85].

Radiation recall pneumonitis

Radiation recall pneumonitis (RRP) is a poorly understood, unpredictable, acute inflammatory phenomenon developed in the irradiated field long after the RT completion, triggered by an anti-cancer drug [86]. It can occur within hours to years after the exposur to the drug, and its severity does not correlate with a time interval from RT [87]. RRP is usually described to be linked with the use of conventional chemotherapy like taxanes or anthracyclines. However, many studies on nivolumab and durvalumab report an increased incidence of severe pneumonitis in the previously irradiated lung. It is estimated that RRP can be observed in up to 18% of cases when ICIs are used [88, 89].

Prevention and treatment of RILI

Dose distribution parameters remain one of the most important risk factors of developing RILI. Hence, the use of modern radiation delivery techniques, like IMRT, ARC or particle therapy, is crucial to meet restrictive dose constraints preventing lung toxicity. One of the latest directions is FLASH radiotherapy is ultra-high dose rate irradiation (> 40 Gy/s) delivered in short pulses that have been described as selective to kill tumour cells, minimalizing healthy tissue injury [90].

There are many protectors, modifiers and mitigators of lung injury in clinical trials.

Unfortunately, no pharmacological therapy has been proved to be doubtless effective so far. Amifostine is a well-known agent reducing side effects in radiotherapy, especially in head and neck cancer.

It was also described to decrease TGF-B1 levels, and clinical symptoms of RILI in a rat model [91] and possibly reduce severe pneumonitis in humans according to metanalyses [92]. However, because of the critical methodological limitations of all existing studies, its actual role is unclear and clinical use is limited. It is only generally accepted that amifostine does not impact tumour response to treatment [93].

Angiotensin-converting enzyme (ACE) inhibitors and pentoxifylline seem to be protective by targeting pro-fibrogenic and pro-inflammatory pathways in preclinical models. Nevertheless, further randomized trials are needed. The strategy of TGF-β inhibitions appears attractive as well. Thus, different agents, like pirfenidone, imatinib or nintedanib, are being investigated [10].

Treatment of RIP is usually limited to symptomatic cases and is based on steroids which decrease alveolitis with interstitial oedema; however, not it necessarily prevents further progression of the injury leading to fibrosis [94].

Observation is recommended in subclinical or mildly symptomatic patients, but some G2 patients can benefit from inhaled corticosteroids (e.g. short-course of budesonide) [95]. High-grade pneumonitis requires intravenous steroid treatment — equivalents of 2–4 mg/kg/day of methylprednisolone, carried out over at least several weeks and tapered over six weeks. Rapid discontinuation can lead to early relapse of RIP (rebound phenomenon). Prophylactic antibiotics (especially pneumocystis prevention) and antifungal treatment should also be considered [96]. Some data support the use of oral steroids instead (prednisone 0.5–2 mg/kg/day) [61]. Some patients, however, are resistant to steroids exhibiting elevated KL-6 protein levels. Such patients can benefit from azathioprine or cyclosporine A.

Nevertheless, it must be underlined that we do not have convincing evidence from randomized controlled trials on the long-term benefits of steroid treatment [9]. There is also no confirmation for steroids to be helpful in executed fibrosis [97].

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