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

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 neutrophils, 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 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-
Inflammatory cells can be observed, and first cytokines are released: tumour necrosis factor alpha (TNF-α), interleukins (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

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**Table 1. Imaging findings after thoracic radiotherapy (RT); CT — computed tomography; HU — Hounsfield units; PET — positron emission tomography; FDG — fluorodeoxyglucose; SUV — standardized uptake value. Elaborated on the basis of [6–8]**

| Imaging findings | Ground-glass or reticular opacities | Late fibrosis |
|------------------|-----------------------------------|--------------|
| CT density changes [HU] | Mass-like/scar-like consolidations Traction bronchiectasis | Sharply defined or patchy consolidation Linear scarring Volume loss Architectural distortion |
| PET FDG uptake [SUV] | | |

**Figure 1.** Imaging findings after thoracic radiotherapy (RT); CT — computed tomography; HU — Hounsfield units; PET — positron emission tomography; FDG — fluorodeoxyglucose; SUV — standardized uptake value. Elaborated on the basis of [6–8]
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].
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).

| 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 assisted 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.

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

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, cicatrization atelectasis, aerobronchogram and bronchial extension (traction bronchiectasis), significant pulmonary volume loss, and pleural thickening | LATE                  |
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 old 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 cm³ 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 cm³ [28] or even > 100 cm³ [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_{crmax} = 7.2 Gy | D_{crmax} = 9.4 Gy | D_{crmax} = 10.8 Gy | D_{crmax} = 12 Gy | D_{crmax} = 12.5 Gy | D_{crmax} = 14.4 Gy |
| V8 < 37% | V10 < 37% | V11.4 < 37% | V12.8 < 37% | V13.5 < 37% | V15.2 < 37% |

D_{crmax} — 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 exposure 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, minimizing 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 metaanalyses [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 inhibitors 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 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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References

1. Libshitz H, Southard M. Complications of radiation therapy: The thorax. Semin Roentgenol. 1974; 9(1): 41–49, doi: 10.1016/0037-198x(74)90008-x, indexed in Pubmed: 4813630.

2. Kollekas L, Costabel U, Tzouvelekis A, et al. Idiopathic interstitial pneumonia or idiopathic interstitial pneumonitis: what’s in a name? Eur Respir J. 2019; 53(2), doi: 10.1183/13993003.00994-2018, indexed in Pubmed: 30765482.

3. Hanania AN, Mainwaring W, Ghebre YT, et al. Radiation-Induced Lung Injury: Assessment and Management. Chest. 2019; 156(1): 150–162, doi: 10.1016/j.chest.2019.03.033, indexed in Pubmed: 30998908.

4. Wang Z, Huo B, Wu Q, et al. The role of procalcitonin in differential diagnosis between acute radiation pneumonitis and bacterial pneumonia in lung cancer patients receiving thoracic radiotherapy. Sci Rep. 2020; 10(1): 2941, doi: 10.1038/s41598-020-60063-w, indexed in Pubmed: 32076108.

5. Zhong D, Wu C, Bai J, et al. Comparative diagnostic efficacy of serum Krebs von den Lungen-6 and surfactant D for connective tissue disease-associated interstitial lung diseases: A meta-analysis. Medicine (Baltimore). 2020; 99(16): e19695, doi: 10.1097/MD.0000000000019695, indexed in Pubmed: 32311947.

6. Benveniste MF, Gomez D, Carter BW, et al. Recognizing Radiation Therapy-related Complications in the Chest. Radiographics. 2019; 39(2): 344–366, doi: 10.1148/rg.2019180061, indexed in Pubmed: 30844346.

7. Bernchou U, Schytte T, Bertelsen A, et al. Time evolution of regional CT density changes in normal lung after IMRT for NSCLC. Radiother Oncol. 2013; 109(1): 89–94, doi: 10.1016/j.radonc.2013.08.041, indexed in Pubmed: 24060177.

8. Thomas R, Chen YH, Hatabu H, et al. Radiographic patterns of symptomatic radiation pneumonitis in lung cancer patients: Imaging predictors for clinical severity and outcome. Lung Cancer. 2020; 145: 132–139, doi: 10.1016/j. lungcan.2020.03.023, indexed in Pubmed: 32447116.

9. Arroyo-Hernández M, Maldonado F, Lozano-Ruíz F, et al. Radiation-induced lung injury: current evidence. BMC Pulm Med. 2021; 21(1): 9, doi: 10.1186/s12890-020-01376-4, indexed in Pubmed: 33407290.

10. Käsmann L, Dietrich A, Staab-Weinritz CA, et al. Radiation-induced lung toxicity - cellular and molecular mechanisms of pathogenesis, management, and literature review. Radiat Oncol. 2020; 15(1): 214, doi: 10.1186/s13014-020-01654-9, indexed in Pubmed: 32912295.

11. Liao Z, Lee JJ, Komaki R, et al. Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2018; 36(18): 1813–1822, doi: 10.1200/JCO.2017.74.0720, indexed in Pubmed: 29293386.

12. Saito Go, Oya Y, Taniguchi Y, et al. Real-world survey of pneumonitis and its impact on durvalumab consolidation therapy in patients with non-small cell lung cancer who received chemoradiotherapy after durvalumab approval (HOPE-005/CRIMSON). Lung Cancer. 2021; 161: 86–93, doi: 10.1016/j.lungcan.2021.08.019, indexed in Pubmed: 34543942.

13. Hu X, Bao Y, Xu YJ, et al. Final report of a prospective randomized study on thoracic radiotherapy target volume for limited-stage small cell lung cancer with radiation dosimetric analyses. Cancer. 2020; 126(4): 840–849, doi: 10.1002/cncr.32586, indexed in Pubmed: 31714592.

14. Shintani T, Kishi N, Matsuoy, et al. Incidence and Risk Factors of Symptomatic Radiation Pneumonitis in Non-Small-Cell Lung Cancer Patients Treated with Concurrent Chemoradiotherapy and Consolidation Durvalumab. Clin Lung Cancer. 2021; 22(5): 401–410, doi: 10.1016/j. clinc.2021.01.017, indexed in Pubmed: 33678582.

15. Schytte T, Bentzen SM, Brink C, et al. Changes in pulmonary function after definitive radiotherapy for NSCLC. Radiother Oncol. 2015; 117(1): 23–28, doi: 10.1016/j.radonc.2015.09.029, indexed in Pubmed: 26455451.

16. Rahi MS, Parekh J, Pednekar P, et al. Radiation-Induced Lung Injury: Current Perspectives and Management. Clin Pract. 2021; 11(3): 410–429, doi: 10.3390/clinpract.11030056, indexed in Pubmed: 34287252.

17. Morgan G, Pharm B, Brits S. Radiation and the Lung: A reevaluation of the mechanisms mediating pulmonary injury. Int J Radiat Oncol Biol Phys. 1995; 31(2): 361–369, doi: 10.1016/0360-3016(94)00477-3, indexed in Pubmed: 7836090.

18. He Y, Thummuri D, Zheng G, et al. Cellular senescence and radiation-induced pulmonary fibrosis. Transl Res. 2019; 209: 14–21, doi: 10.1016/j.trsl.2019.03.006, indexed in Pubmed: 30981698.

19. Travis WD, Costabel U, Hansell DM, et al. ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013; 188(6): 733–748, doi: 10.1164/rccm.201308-1483ST, indexed in Pubmed: 24032382.

20. Choi YW, Munden RF, Erasmus JJ, et al. Effects of radiation therapy on the lung: radiologic appearances and differential diagnosis. Radiographics. 2004; 24(4): 985–97; discussion 998, doi: 10.1148/rad.244035160, indexed in Pubmed: 15256622.

21. De Wever W, Meerschaert J, Coolen J, et al. The crazy-paving pattern: a radiological-pathological correlation. Insights Imaging. 2011; 2(2): 117–132, doi: 10.1007/s13244-010-0060-5, indexed in Pubmed: 22347941.

22. Linda A, Trovo M, Bradley JD. Radiation injury of the lung after stereotactic body radiation therapy (SBRT) for lung cancer: a timeline and pattern of CT changes. Eur J Radiol. 2011; 79(1): 147–154, doi: 10.1016/j.ejrad.2009.10.029, indexed in Pubmed: 19954913.

23. Huang K, Senthi S, Palma Da, et al. High-risk CT features for detection of local recurrence after stereotactic ablative radiotherapy for lung cancer. Radiother Oncol. 2013; 109(1): 51–57, doi: 10.1016/j.radonc.2013.06.047, indexed in Pubmed: 23953413.

24. Ronden M, van Sörnsen de Koste JR, Johnson C, et al. Incidence of High-Risk Radiologic Features in Patients Without Local Recurrence After Stereotactic Ablative Radiation Therapy for Early-Stage Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2018; 100(1):
115–121, doi: 10.1016/j.jrjing.2017.09.035, indexed in Pubmed: 29102278.
25. Hoopes DJ, Tann M, Fletcher JW, et al. FDG-PET and stereotactic body radiotherapy (SBRT) for stage I non-small-cell lung cancer. Lung Cancer. 2007; 56(2): 229–234, doi: 10.1016/j.lungcan.2006.12.009, indexed in Pubmed: 17353064.
26. Ronden MI, Palma D, Slotman BJ, et al. Advanced Radiation Technology Committee of the International Association for the Study of Lung Cancer. Brief Report on Radiological Changes following Stereotactic Ablative Radiotherapy (SABR) for Early-Stage Lung Tumors: A Pictorial Essay. J Thorac Oncol. 2018; 13(6): 855–862, doi: 10.1016/j.jtho.2018.02.023, indexed in Pubmed: 29518554.
27. Munoz-Schuffenegger P, Kandel S, Alibhai Z, et al. A Prospective Study of Magnetic Resonance Imaging Assessment of Post-radiation Changes Following Stereotactic Body Radiation Therapy for Non-small Cell Lung Cancer. Clin Oncol (R Coll Radiol). 2019; 31(10): 720–727, doi: 10.1016/j.clon.2019.05.014, indexed in Pubmed: 31176537.
28. Torre-Bouscoulet L, Muñoz-Montaño WR, Martinez-Briseno D, et al. Abnormal pulmonary function tests predict the development of radiation-induced pneumonitis in advanced non-small-cell lung cancer. Respir Res. 2018; 19(1): 72, doi: 10.1186/s12931-018-0775-2, indexed in Pubmed: 29690880.
29. Kouloulias V, Zygojiani A, Efstathopoulos E, et al. Suggestion for a new grading scale for radiation induced pneumonitis based on radiological findings of computerized tomography: correlation with clinical and radiotherapeutic parameters in lung cancer patients. Asian Pac J Cancer Prev. 2021; 23(10): 711–717, doi: 10.14336/apjc.2021.10.010, indexed in Pubmed: 33921652.
30. Giordano FM, Ippolito E, Quattrocchi CC, et al. Radiation-Induced Pneumonitis in the Era of the COVID-19 Pandemic: Artificial Intelligence for Differential Diagnosis. Cancers (Basel). 2021; 13(8), doi: 10.3390/cancers13081960, indexed in Pubmed: 33921652.
31. Gopal R, Starkschall G, Tucker S, et al. Effects of radiotherapy and chemotherapy on lung function in patients with non–small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2003; 56(1): 114–120, doi: 10.1016/s0360-3016(03)00774-4, indexed in Pubmed: 12694829.
32. Lopez Guerra JL, Gomez D, Zhuang Y, et al. Change in diffusing capacity after radiation as an objective measure for grading radiation pneumonitis in patients treated for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2012; 83(5): 1573–1579, doi: 10.1016/j.jrobp.2011.10.005, indexed in Pubmed: 22768989.
33. Begosh-Mayne D, Kumar SS, Toffel S, et al. The dose-response characteristics of four NTCP models: using a novel CT-based radiomic method to quantify radiation-induced lung density changes. Sci Rep. 2020; 10(1): 10559, doi: 10.1038/s41598-020-67499-0, indexed in Pubmed: 32600297.
34. Konkol M, Sniatka K, Sniatka P, et al. Computer Tools to Analyze Lung CT Changes after Radiotherapy. Applied Sci. 2021; 11(4): 1582, doi: 10.3390/app11041582.
35. Defraene G, La Fontaine M, van Kransen S, et al. Radiation-Induced Lung Density Changes on CT Scan for NSCLC: No Impact of Dose-Escalation Level or Volume. Int J Radiat Oncol Biol Phys. 2018; 102(3): 642–650, doi: 10.1016/j.jrobp.2018.06.038, indexed in Pubmed: 30244882.
36. Schröder C, Engenhart-Cabillic R, Kirschner S, et al. Changes of lung parenchyma density following high dose radiation therapy for thoracic carcinomas - an automated analysis of follow up CT scans. Radiat Oncol. 2019; 14(1): 72, doi: 10.1186/s13041-019-1276-2, indexed in Pubmed: 31036015.
37. Lee S, Stroian G, Kopek N, et al. Analytical modelling of regional radiotherapy dose response of lung. Phys Med Biol. 2012; 57(11): 3309–3321, doi: 10.1088/0031-9155/57/11/3309, indexed in Pubmed: 22572393.
38. Palma DA, von Sörnsen de Koste J, Verbakel WF, et al. Lung density changes after stereotactic radiotherapy: a quantitative analysis in 50 patients. Int J Radiat Oncol Biol Phys. 2011; 81(4): 974–978, doi: 10.1016/j.jrobp.2010.07.025, indexed in Pubmed: 20932655.
39. Al Feghali KA, Wu QC, Devpura S, et al. Correlation of normal lung density changes with dose after stereotactic body radiotherapy (SBRT) for early stage lung cancer. Clin Transl Radiat Oncol. 2020; 22: 1–8, doi: 10.1016/j.ctoro.2020.02.004, indexed in Pubmed: 32140574.
40. Avanzo M, Barbiero S, Trovo M, et al. Voxel-by-voxel correlation between radiologically radiation induced lung injury and dose after image-guided, intensity modulated radiotherapy for lung tumors. Phys Med. 2017; 42: 150–156, doi: 10.1016/j.ejmp.2017.09.127, indexed in Pubmed: 29179099.
41. Defraene G, van Elmpet W, Crijns W, et al. Regional variability in radiation-induced lung damage can be predicted by baseline CT numbers. Radiother Oncol. 2017; 122(2): 300–306, doi: 10.1016/j.radonc.2016.11.021, indexed in Pubmed: 27979369.
42. Moran A, Daly ME, Yip SSF, et al. Radiomics-based Assessment of Radiation-induced Lung Injury After Stereotactic Body Radiotherapy. Clin Lung Cancer. 2017; 18(6): e425–e431, doi: 10.1016/j.clcancer.2017.05.014, indexed in Pubmed: 28623121.
43. Inoue T, Shiomi H, Oh RJ. Stereotactic body radiotherapy for Stage I lung cancer with chronic obstructive pulmonary disease: special reference to survival and radiation-induced pneumonitis. J Radiat Res. 2015; 56(4): 727–734, doi: 10.1093/jrr/jrv019, indexed in Pubmed: 25887042.
44. Takeda A, Kunieda E, Ohashi T, et al. Severe COPD is correlated with mild radiation pneumonitis following stereotactic body radiotherapy. Chest. 2012; 141(4): 858–866, doi: 10.1378/chest.11-1193, indexed in Pubmed: 21885726.
45. Goodman CD, Nijman SFM, Senan S, et al. International Association for the Study of Lung Cancer Advanced Radiation Technology Committee. A Primer on Intermittent Lung Disease and Thoracic Radiation. J Thorac Oncol. 2020; 15(6): 902–913, doi: 10.1016/j.jto.2020.02.005, indexed in Pubmed: 32105810.
46. Ozawa Y, Abe T, Omae M, et al. Impact of Preexisting Disease and Thoracic Radiation. J Thorac Oncol. 2018; 13(6): 852–860, doi: 10.1016/j.jto.2018.06.038, indexed in Pubmed: 32105810.
47. Ueki N, Matsuo Y, Tagoshi Y, et al. Impact of pretreatment intermittent lung disease on radiation pneumonitis and survival after stereotactic body radiation therapy for lung
cancer. J Thorac Oncol. 2015; 10(1): 116–125, doi: 10.1097/JTO.0000000000000359, indexed in Pubmed: 25376512.

48. Finazzi T, Ronden-Kianoush M, Spoelstra FOB, et al. Stereotactic ablative radiotherapy in patients with early-stage non-small cell lung cancer and co-existing interstitial lung disease. Acta Oncol. 2020; 59(5): 569–573, doi: 10.1080/0284186X.2020.1730002, indexed in Pubmed: 32079446.

49. Glick D, Lyns S, Kandel S, et al. Impact of Pretreatment Interstitial Lung Disease on Radiation Pneumonitis and Survival in Patients Treated With Lung Stereotactic Body Radiation Therapy (SBRT). Clin Lung Cancer. 2018; 19(2): e219–e226, doi: 10.1016/j.clcc.2017.06.021, indexed in Pubmed: 29066051.

50. Kirkland RS, Kole AJ, Batra H, et al. Predictors of In-Hospital Death in Patients with Lung Cancer Admitted for Acute Radiation Pneumonitis: A Healthcare Cost and Utilization Project (HCUP) Analysis. Clin Lung Cancer. 2021; 22(5): e716–e722, doi: 10.1016/j.clcc.2021.01.016, indexed in Pubmed: 33558160.

51. Lee YH, Kim YS, Lee SN, et al. Interstitial Lung Change in Pre-Radiation Therapy Computed Tomography Is a Risk Factor for Severe Radiation Pneumonitis. Cancer Res Treat. 2015; 47(4): 676–686, doi: 10.4143/crt.2014.180, indexed in Pubmed: 25687856.

52. Okumura M, Hojo H, Nakamura M, et al. Radiation pneumonitis after palliative radiotherapy in cancer patients with interstitial lung disease. Radiother Oncol. 2021; 161: 47–54, doi: 10.1016/j.radonc.2021.05.026, indexed in Pubmed: 34089755.

53. Tang C, Mistry H, Bayman N, et al. Outcomes of curative-intent radiotherapy in non-small cell lung cancer (NSCLC) patients with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD). Radiother Oncol. 2021; 160: 78–81, doi: 10.1016/j.radonc.2021.04.014, indexed in Pubmed: 33901563.

54. Kim H, Yoo H, Pyo H, et al. Impact Of Underlying Pulmonary Diseases On Treatment Outcomes In Early-Stage Non-Small Cell Lung Cancer Treated With Definitive Radiotherapy. Int J Chron Obstruct Pulmon Dis. 2019; 14: 2273–2281, doi: 10.2147/cOPD.S210759, indexed in Pubmed: 31631997.

55. Palma DA, Senan S, Tsujino K, et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. Int J Radiat Oncol Biol Phys. 2013; 85(2): 444–450, doi: 10.1016/j.ijrobp.2012.04.043, indexed in Pubmed: 22682812.

56. Vogelius IR, Bentzen SM. A literature-based meta-analysis of clinical risk factors for development of radiation induced pneumonitis. Acta Oncol. 2012; 51(8): 975–983, doi: 10.3109/0284186X.2012.718093, indexed in Pubmed: 22950387.

57. Kong FMS, Wang S. Nondosimetric risk factors for radiation-induced lung toxicity. Semin Radiat Oncol. 2015; 25(2): 100–109, doi: 10.1016/j.semradonc.2014.12.003, indexed in Pubmed: 25771414.

58. Youlden DR, Crumb SM, Baade PD. The International Epidemiology of Lung Cancer: geographical distribution and secular trends. J Thorac Oncol. 2008; 3(8): 819–831, doi: 10.1097/JTO.0b013e31818020eb, indexed in Pubmed: 18670299.

59. Jin H, Tucker SL, Liu HH, et al. Dose-volume thresholds and smoking status for the risk of treatment-related pneumonitis in inoperable non-small cell lung cancer treated with definitive radiotherapy. Radiother Oncol. 2009; 91(3): 427–432, doi: 10.1016/j.radonc.2008.09.009, indexed in Pubmed: 18937989.

60. Bradley JD, Hope A, El Naqa I, et al. RTG-1. A nomogram to predict radiation pneumonitis, derived from a combined analysis of RTOG 9311 and institutional data. Int J Radiat Oncol Biol Phys. 2007; 69(4): 985–992, doi: 10.1016/j.ijrobp.2007.04.077, indexed in Pubmed: 17689035.

61. Jain V, Berman AT. Radiation Pneumonitis: Old Problem, New Tricks. Cancers (Basel). 2018; 10(7), doi: 10.3390/cancers10070222, indexed in Pubmed: 29970850.

62. Brennan D, Schubert L, Diot Q, et al. Clinical validation of 4-dimensional computed tomography ventilation with pulmonary function test data. Int J Radiat Oncol Biol Phys. 2015; 92(2): 423–429, doi: 10.1016/j.ijrobp.2015.01.019, indexed in Pubmed: 25817531.

63. Waxweiler T, Schubert L, Diot Q, et al. A complete 4DCT-ventilation functional avoidance virtual trial: Developing strategies for prospective clinical trials. J Appl Clin Med Phys. 2017; 18(3): 144–152, doi: 10.1002/acm2.12086, indexed in Pubmed: 28436107.

64. Yamamoto T, Kabus S, Bal M, et al. The first patient treatment of computed tomography ventilation functional image-guided radiotherapy for lung cancer. Radiother Oncol. 2016; 118(2): 227–231, doi: 10.1016/j.radonc.2015.11.006, indexed in Pubmed: 26687903.

65. Faught AM, Miyasaka Y, Kadoya N, et al. Evaluating the Toxicity Reduction With Computed Tomographic Ventilation Functional Avoidance Radiation Therapy. Int J Radiat Oncol Biol Phys. 2017; 99(2): 325–333, doi: 10.1016/j.ijrobp.2017.04.024, indexed in Pubmed: 28871982.

66. Dang J, Li G, Zang S, et al. Comparison of risk and predictors for early radiation pneumonitis in patients with locally advanced non-small cell lung cancer treated with radiotherapy with or without surgery. Lung Cancer. 2014; 86(3): 329–333, doi: 10.1016/j.lungcan.2014.10.005, indexed in Pubmed: 25454199.

67. Thor M, Deasy Jo, Iyer A, et al. Toward personalized dose-prescription in locally advanced non-small cell lung cancer: Validation of published normal tissue complication probability models. Radiother Oncol. 2019; 138: 45–51, doi: 10.1016/j.radonc.2019.05.011, indexed in Pubmed: 31146070.

68. Verma V, Shostrom VK, Zhen W, et al. Influence of Fractionation Scheme and Tumor Location on Toxicities After Stereotactic Body Radiation Therapy for Large (≤5 cm) Non-Small Cell Lung Cancer: A Multi-institutional Analysis. Int J Radiat Oncol Biol Phys. 2017; 97(4): 778–785, doi: 10.1016/j.ijrobp.2016.11.049, indexed in Pubmed: 28244441.

69. McFarlane MR, Hochstedler KA, Laucis AM, et al. Michigan Radiation Oncology Quality Consortium as part of the Blue Cross Blue Shield of Michigan and Blue Care Network Michigan Value Partnerships Program. Predictors of Pneumonitis After Conventionally Fractionated Radiotherapy for Locally Advanced Lung Cancer. Int J Radiat Oncol Biol Phys. 2021; 111(5): 1176–1185, doi: 10.1016/j.ijrobp.2021.07.1691, indexed in Pubmed: 34314815.
70. Bledsoe TJ, Nath SK, Decker RH. Radiation Pneumonitis. Clin Chest Med. 2017; 38(2): 201–208, doi: 10.1016/j.ccm.2016.12.004, indexed in Pubmed: 28477633.

71. Leprieur EG, Fernandez D, Chatellier G, et al. Acute radiation pneumonitis after conformational radiotherapy for non-small cell lung cancer: clinical, dosimetric, and associated-treatment risk factors. J Cancer Res Ther. 2013; 9(3): 447–451, doi: 10.4103/0973-1482.119339, indexed in Pubmed: 24125981.

72. Yorke ED, Jackson A, Rosenzweig KE, et al. Correlation of dosimetric factors and radiation pneumonitis for non-small-cell lung cancer patients in a recently completed dose escalation study. Int J Radiat Oncol Biol Phys. 2016; 94(4): 886–895, doi: 10.1016/j.ijrobp.2015.08.025, indexed in Pubmed: 26375713.

73. Harder EM, Park HS, Chen ZJ, et al. Pulmonary dose-volume predictors of radiation pneumonitis following stereotactic body radiation therapy. Pract Radiat Oncol. 2016; 6(6): e353–e359, doi: 10.1016/j.prro.2016.01.015, indexed in Pubmed: 27156424.

74. Jo IY, Kay CS, Kim JY, et al. Significance of low-dose radiation dose distribution in development of radiation pneumonitis after helical-tomotherapy-based hypofractionated radiotherapy for pulmonary metastases. J Radiat Res. 2014; 55(1): 105–112, doi: 10.1093/jrr/rmt080, indexed in Pubmed: 23757513.

75. Ritter TA, Matuszak M, Chetty IJ, et al. Application of Critical Volume-Dose Constraints for Stereotactic Body Radiation Therapy in NRG Radiation Therapy Trials. Int J Radiat Oncol Biol Phys. 2017; 98(1): 34–36, doi: 10.1016/j.ijrobp.2017.01.024, indexed in Pubmed: 28587050.

76. Timmerman R. A Story of Hypofractionation and the Table on the Wall. Int J Radiat Oncol Biol Phys. 2022; 112(1): 4–21, doi: 10.1016/j.ijrobp.2021.09.027, indexed in Pubmed: 34919882.

77. Huang EX, Hope AJ, Lindsay PE, et al. Heart irradiation as a risk factor for radiation pneumonitis. Acta Oncol. 2011; 50(1): 51–60, doi: 10.3109/0284186X.2010.521192, indexed in Pubmed: 20874426.

78. Yorke ED, Jackson A, Kuo LiC, et al. Heart Dosimetry is Correlated With Risk of Radiation Pneumonitis After Lung-Sparing Hemithoracic Pleural Intensity Modulated Radiation Therapy for Malignant Pleural Mesothelioma. Int J Radiat Oncol Biol Phys. 2017; 99(1): 61–69, doi: 10.1016/j.ijrobp.2017.04.025, indexed in Pubmed: 28816162.

79. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010; 28(13): 2181–2190, doi: 10.1200/JCO.2009.26.2543, indexed in Pubmed: 20351327.

80. Suresh K, Voong KR, Shanka B, et al. Pneumonitis in Non-Small Cell Lung Cancer Patients Receiving Immune Checkpoint Immunotherapy: Incidence and Risk Factors. J Thorac Oncol. 2018; 13(12): 1930–1939, doi: 10.1016/j.jtho.2018.08.035, indexed in Pubmed: 30267842.

81. Shaverdian N, Lisberg A, Bornzayan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol. 2017; 18(7): 895–903, doi: 10.1016/s1470-2045(17)30380-7, indexed in Pubmed: 28551359.

82. Jabbour SK, Berman AT, Decker RH, et al. Phase 1 Trial of Pembrolizumab Administered Concurrently With Chemoradiotherapy for Locally Advanced Non-Small Cell Lung Cancer: A Nonrandomized Controlled Trial. JAMA Oncol. 2020; 6(6): 848–855, doi: 10.1001/jamaoncol.2019.6731, indexed in Pubmed: 32077891.

83. Antonia SJ, Villegas A, Daniel D, et al. PACIFIC Investigators. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017; 377(20): 1919–1929, doi: 10.1056/NEJMoa1709937, indexed in Pubmed: 28885881.

84. von Reibnitz D, Chaft JE, Wu AJ, et al. Safety of combining thoracic radiation therapy with concurrent versus sequential immune checkpoint inhibition. Adv Radiat Oncol. 2018; 3(3): 391–398, doi: 10.1016/j.adro.2018.05.001, indexed in Pubmed: 30202807.

85. Bang A, Willhite TJ, Pike LRG, et al. Multicenter Evaluation of the Tolerability of Combined Treatment With PD-1 and CTLA-4 Immune Checkpoint Inhibitors and Palliative Radiation Therapy. Int J Radiat Oncol Biol Phys. 2017; 98(2): 344–351, doi: 10.1016/j.ijrobp.2017.02.003, indexed in Pubmed: 28463153.

86. Levy A, Hollebecque A, Bourgier C, et al. Targeted therapy-induced radiation recall. Eur J Cancer. 2013; 49(7): 1662–1668, doi: 10.1016/j.ejca.2012.12.009, indexed in Pubmed: 23312391.

87. Ding X, Ji W, Li J, et al. Radiation recall pneumonitis induced by chemotherapy after thoracic radiotherapy for lung cancer. Radiat Oncol. 2011; 6: 24, doi: 10.1186/1748-717X-6-24, indexed in Pubmed: 21375774.

88. Cousin F, Desir C, Ben Mustapha S, et al. Incidence, risk factors, and CT characteristics of radiation recall pneumonitis induced by immune checkpoint inhibitor in lung cancer. Radiother Oncol. 2021; 157: 47–55, doi: 10.1016/j.radonc.2021.01.001, indexed in Pubmed: 33453313.

89. Antonia SJ, Villegas A, Daniel D, et al. PACIFIC Investigators. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017; 377(20): 1919–1929, doi: 10.1056/NEJMoa1709937, indexed in Pubmed: 28885881.

90. Roy S, Salerno KE, Citrin DE. Biology of Radiation-Induced Lung Injury. Semin Radiat Oncol. 2021; 31(2): 155–161, doi: 10.1016/j.semradonc.2020.11.006, indexed in Pubmed: 33610273.

91. Vujakovic Z, Feng Q Fu, Rabbani ZN, et al. Assessment of the protective effect of amifostine on radiation-induced pulmonary toxicity. Exp Lung Res. 2002; 28(7): 577–590, doi: 10.1080/0190214029006791, indexed in Pubmed: 12396250.

92. Sasse AD, Clark LG, Sasse EC, et al. Amifostine reduces side effects and improves complete response rate during radiotherapy: results of a meta-analysis. Int J Radiat Oncol Biol Phys. 2006; 64(3): 784–791, doi: 10.1016/j.ijrobp.2005.06.023, indexed in Pubmed: 16198504.

93. Mell LK, Malik R, Komaki R, et al. Effect of amifostine on response rates in locally advanced non-small-cell lung cancer patients treated on randomized controlled trials: a meta-analysis. Int J Radiat Oncol Biol Phys. 2007; 68(1): 111–118, doi: 10.1016/j.ijrobp.2006.11.043, indexed in Pubmed: 17289291.
94. Ward HE, Kemsley L, Davies L, et al. The effect of steroids on radiation-induced lung disease in the rat. Radiat Res. 1993; 136(1): 22–28, indexed in Pubmed: 8210334.
95. Henkenberens C, Janssen S, Lavae-Mokhtari M, et al. Inhalative steroids as an individual treatment in symptomatic lung cancer patients with radiation pneumonitis grade II after radiotherapy - a single-centre experience. Radiat Oncol. 2016; 11: 12, doi: 10.1186/s13014-016-0580-3, indexed in Pubmed: 26830686.
96. Fu Z, Yang Xu, Bi N, et al. Radiation pneumonitis complicated by Pneumocystis carinii in patients with thoracic neoplasia: a clinical analysis of 7 cases. Cancer Commun (Lond). 2019; 39(1): 47, doi: 10.1186/s40880-019-0392-6, indexed in Pubmed: 31443740.
97. Abratt R, Morgan G, Silvestri G, et al. Pulmonary complications of radiation therapy. Clin Chest Med. 2004; 25(1): 167–177, doi: 10.1016/s0272-5231(03)00126-6, indexed in Pubmed: 15062608.