Radiation-induced lung toxicity – cellular and molecular mechanisms of pathogenesis, management, and literature review

Lukas Käsmann1,2,3*, Alexander Dietrich4, Claudia A. Staab-Weijnitz2,5, Farkhad Manapov1,2,3, Jürgen Behr2,6, Andreas Rimner7, Branislav Jeremic8, Suresh Senan9, Dirk De Ruyscher10, Kirsten Lauber1,3† and Claus Belka1,2,3†

Abstract

Lung, breast, and esophageal cancer represent three common malignancies with high incidence and mortality worldwide. The management of these tumors critically relies on radiotherapy as a major part of multi-modality care, and treatment-related toxicities, such as radiation-induced pneumonitis and/or lung fibrosis, are important dose limiting factors with direct impact on patient outcomes and quality of life. In this review, we summarize the current understanding of radiation-induced pneumonitis and pulmonary fibrosis, present predictive factors as well as recent diagnostic and therapeutic advances. Novel candidates for molecularly targeted approaches to prevent and/or treat radiation-induced pneumonitis and pulmonary fibrosis are discussed.

Introduction

Lung, breast, and esophageal cancer are common thoracic malignancies with high cancer-associated mortality [1]. In the majority of cases thoracic radiotherapy represents a central part of multi-modal treatment concepts [2]. Several diagnostic and therapeutic advances, such as PET-imaging [3, 4], improved radiation delivery techniques [5–9], implementation of immunotherapy [10–16], and molecularly targeted therapy [17–19], have led to improved outcome in terms of overall survival, local and distant control as well as quality of life. However, between 10 and 30% of all patients with lung or breast cancer receiving thoracic radiotherapy develop radiation-induced pneumonitis (RIP) as a subacute treatment-associated toxicity, and they are at high risk of developing radiation-induced lung fibrosis (RILF) as late toxicity, although treatment-related death is uncommon [5, 20–24]. Accordingly, lung toxicity remains a crucial dose limiting factor, and dose escalation trials with conventionally fractionated radiotherapy have been limited by severe lung toxicity [25–27]. Due to the development of novel radiotherapy techniques, including intensity modulated radiotherapy (IMRT) [5, 6] and volumetric modulated arc therapy (VMAT) [20], and radiation qualities, such as and proton therapy [28], radiation exposure of normal lung tissue can be significantly reduced. Consequently, the occurrence of RIP grade ≥2 in the treatment of lung cancer has gradually decreased from 30 to 47% using 2D-radiotherapy [29], to 30–35% with 3D-radiotherapy [30, 31], 29–32% with IMRT [31, 32], 24–29% with VMAT [32, 33], and <5% with proton therapy [28, 34]. The radiation delivery technique is also of importance for the development of RIP and RILF. Different fractionation regimens, such as classically fractionated radiotherapy with 2 Gy per fraction for the...
treatment of rather large tumor volumes, and high precision radiation delivery techniques for the treatment of smaller volumes, such as stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR), are associated with different risk profiles of RIP/RILF arising from differences in the delivered doses and target volumes. In addition, single- versus multi-fraction course SBRT/ SABR regimens and the localization of the tumor (central versus peripheral) impact radiation-induced lung toxicity [35–37]. Central tumors treated with SBRT often receive more conservative dose fractionation regimens (e.g. SBRT with 3–8 fractions) compared to peripheral tumors resulting in less treatment-related toxicity but comparable outcome [37–39]. High dose single-fraction lung SBRT (e.g. ≥ 30 Gy) may be associated with increased toxicity [40, 41]. However, several studies reported low rates of ≥ grade III side effects in selected patient cohorts [35, 42].

This review summarizes the current understanding of the cellular and molecular mechanisms underlying the pathogenesis of RIP and RILF. We present predictive factors and the current standards of diagnostic and therapeutic management. Finally, we discuss novel candidates for molecularly targeted approaches to prevent and/or treat RIP and RILF.

**Diagnosis of RIP and RILF**

The diagnosis of RIP and RILF is based on clinical presentation and may be supported by associated imaging findings. Various grading scales are used (see Tables 1 and 2). In clinical practice, Radiation Therapy Oncology Group (RTOG) criteria and the Common Terminology Criteria for Adverse Events (CTCAE) are the ones most widely used [43, 44]. However, the majority of all patients will not show any clinical symptoms. Upon conventional thoracic radiotherapy, RIP occurs 1 and 6 months after treatment, typically within 3 months following completion of irradiation. Clinical symptoms include persistent, dry and non-productive coughing, dyspnea (on physical exertion or at rest), low-grade fever, pleuritic pain, and chest discomfort [45]. To date, no standard laboratory test can unequivocally identify RIP. Most patients exhibit normal levels of C-reactive protein (CRP) and diagnostic differentiation from bacterial pneumonia remains challenging [46]. Nevertheless the performance of bronchial lavage sampling with subsequent cytology and immunomonitoring analyses for differential diagnosis of RIP from infectious lung disease is currently under investigation [47].

The benefit of lung function tests for determining the grade of RIP, such as spirometry with lung diffusion capacity test, remains unclear. Several studies investigated changes in lung function after thoracic radiotherapy, and the extent of change in diffusing capacity of lung for carbon monoxide (DLCO) upon radiotherapy of non-small cell lung cancer (NSCLC) patients was reported to be associated with the RIP grade [48, 49]. However, no national or international consensus has yet been established.

Imaging of RIP upon conventional radiotherapy may present with non-specific chest X-ray changes which typically are confined to the irradiated field, with airspace opacities being most common [50]. Pleural effusions or atelectasis may be associated as well. The preferred imaging modality to detect RIP is chest computed tomography (CT), preferably high-resolution computed tomography (HRCT). Chest CTs provide more detailed information about parenchymal changes and often reveal alterations that are localized to the irradiated field, rendering the diagnosis of RIP for clinicians rather obvious [51].

The radiological characteristics of RIP change over time. In the initial phase they include ground-glass opacities and/or airspace consolidation [52]. In some cases, a small ipsilateral pleural effusion may occur in the first 6 months after thoracic irradiation and may persist for several months. In the later phase of RIP after conventional radiotherapy, septal wall thickening may occur with the alveolar opacities producing a “crazy paving” pattern [53]. Upon SABR, radiographic changes will occur in most of the patients within 6 months and can be described as diffuse consolidation (> 20%), patchy consolidation (> 20%), and

### Table 1: Overview about grading scales for radiation-induced pneumonitis

| Grading scale | 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 |
| **RTOG** | Asymptomatic or mild symptoms (dry cough); slight radiographic appearances | Moderate symptomatic pneumonitis (severe cough); low grade fever; patchy radiographic appearances | Severe symptomatic pneumonitis; dense radiographic changes | Severe respiratory insufficiency/ Continuous O2/ Assisted ventilation | Death |
| **LENT-SOMA (EORTC)** | Asymptomatic or mild symptoms; slight imaging changes | Moderate symptoms; moderate imaging changes | Severe symptoms; increased density imaging changes | Severe symptoms requiring continuous O2 or assisted ventilation | Death |

*CTCAE v5.0 Common terminology criteria for adverse events, version 5.0, RTOG Radiation Therapy Oncology Group, EORTC European Organization for Research and Treatment of Cancer, LENT-SOMA Late effects in normal tissue-subjective objective management analysis*
Table 3 Overview of radiographic changes after completion of conventionally fractionated radiotherapy compared to stereotactic ablative radiotherapy (SABR) of the thorax

| Radiographic changes within 6 months after completion of radiotherapy | Conventionally fractionated radiotherapy | Stereotactic ablative radiotherapy (SABR) |
|---|---|---|
| Consolidation conform to irradiation field | | • diffuse and/or patchy consolidation |
| Diffuse ground glass opacities and/or airspace consolidation | • nodular pattern | • diffuse and/or patchy ground glass opacities |
| Atelectasis | • ipsilateral pleural effusion | |
| Radiographio changes after 6 months following completion of radiotherapy | • scar-like fibrosis > conventional pattern > mass-like fibrosis | • modified conventional pattern > scar-like fibrosis > mass-like fibrosis |
| Volume loss | • linear scarring/restriction to radiation fields | • chronic consolidation > air-bronchograms |
| Chronic consolidation ± air-bronchograms | • bronchiectasis | • bronchiectasis |
| Pleural thickening | • hilar vascular displacement | • volume loss |
| Mediastinal shift | • ipsilateral pleural effusion | • bronchiectasis |

CTCAE v5.0 Common terminology criteria for adverse events, version 5.0, RTOG Radiation Therapy Oncology Group, EORTC European Organization for Research and Treatment of Cancer, LENT-SOMA Late effects in normal tissue-subjective objective management analysis

diffuse or patchy ground glass opacities (> 5%) (see Table 3) [54, 55]. In contrast to conventional radiotherapy, these changes do usually not occur before 2–3 months after completion of treatment – presumably due to the relevantly shorter treatment course. [18F]fluoro-2-deoxy-2-D-glucose positron emission tomography combined with computed tomography (18F-FDG PET/CT) does not contribute to confirming a RIP diagnosis [56]. Inflammatory processes usually demonstrate an increased metabolic activity and are common after thoracic radiotherapy, causing significant confusion when PET/CT is used in the first 6 months after irradiation. However, only the minority of these patients develop clinical RIP. RILF is typically observed between 6 and 12 months after thoracic radiotherapy and can continuously progress for several years. Several grading scales have been established to categorize RILF (see Table 2). Nearly all patients show (radiographic) signs of RILF following thoracic irradiation [50]. However, the majority of patients with RILF remain asymptomatic, and clinical manifestations are mostly linked to established comorbidities, such as pre-existing lung or heart disorders. Symptoms include dyspnea (upon physical exertion or at rest), persistent and dry coughing, fatigue, and weight loss [45]. Radiographic pulmonary changes are usually observed in the irradiated field but can occur in the rest of the lung as well [57]. Chest X-ray imaging can show volume loss and architectural distortion [56]. In some cases, a mediastinal shift and traction bronchiectasis can be found. Compared to previous chest X-ray scans, progression from RIP increasingly becoming more reticular or linear is typical for RILF. Again, HRCT imaging can better delineate...
parenchymal changes as compared to chest X-ray imaging, including volume loss, linear scarring, and traction bronchiectasis [58]. Chronic consolidation is often found together with air-bronchograms usually exhibiting a non-anatomical distribution. Upon SABR the most frequent late radiographic changes are characterized by consolidation, volume loss, and bronchiectasis in a so-called “modified conventional pattern”. Previously, straight lines or edges were typically reported as pulmonary changes following conventional 2D- or 3D-radiotherapy. Yet, with current delivery techniques, such as IMRT, VMAT, or SABR, these changes have become rather uncommon, and/or may be more difficult to appreciate without information on the beam configurations used.

A special and very rare form of lung toxicity upon RT for breast cancer is radiation-induced bronchiolitis obliterans organizing pneumonia (BOOP, <2% of cases) which may develop several months after RT, commonly with longer latency time compared to RIP [59]. Clinical presentation and radiographic changes are similar to RIP. In contrast to RIP which largely remains limited to the non-irradiated fields, BOOP is frequently found also in the non-irradiated lung with diffuse patterns and may show patchy alveolar infiltrations ± air bronchograms and consolidations [60].

The severity of RILF can be radiologically measured with the help of semi-quantitative grading (1–5 points) using radiographic features (see Table 3). “Scar-like” patterns as characterized by streaky opacities in the tumor region are usually associated with less severe RILF due to the mild loss of volume [56]. Conversely, “mass-like” patterns as depicted by focal consolidation and/or ground glass opacification in the tumor region typically with air bronchograms and/or traction bronchiectasis represent rather severe forms of RILF [56]. Upon SABR, “mass-like” fibrosis has been observed more frequently (in up to 14% of cases) and challenges the diagnosis of local recurrence [54]. In contrast to the equivocal value of 18F-FDG-PET/CT for RIP diagnosis, it can be helpful in differentiating pulmonary fibrosis of radiation-induced origin from recurrent malignancy [56].

**Cellular and molecular mechanisms and pathogenesis of RIP and RILF**

The alveolar tissue of the lung is relatively sensitive to ionizing radiation [61, 62]. Therefore, RIP and RILF are major dose limiting adverse effects interfering with the radiotherapeutic success in the treatment course of thoracic malignancies [63–66]. The pathogenesis of RIP and RILF is a complex multi-step process involving several resident cells of the lung as well as recruited immune cells and is initiated and perpetuated via pleiotropic inter- and intracellular communication and signaling events [67–69]. According to the current understanding, an overwhelming cascade of damage-associated molecular patterns (DAMPs), pro-inflammatory cytokines, and chemokines released by dying and/or senescent epithelial cells, endothelial cells, and activated immune cells essentially contribute to the development of RIP and RILF (see Figs. 1 and 2) [66, 70].

Radiation-induced lung toxicity can be divided into three phases: Acute, subacute, and late radiation toxicity. In the acute phase, occurring minutes to days after irradiation, repair of radiation-induced DNA damage takes place in the lung tissue. This includes base modifications, single and double strand breaks of varying complexity, DNA crosslinks, and bulky lesions which arise from direct ionization events or are indirectly mediated by free reactive oxygen species (ROS), respectively [71]. Acute radiation-induced toxicity appears to primarily involve alveolar type I (AT I) and II (AT II) epithelial cells, and endothelial cells [62]. Whereas most tumor cells preferentially undergo necrotic forms of cell death upon radiation at clinically relevant doses, normal tissue epithelial cells and endothelial cells predominantly show phenotypes of cellular senescence [66, 72]. Intriguingly, radiation-induced senescence is accompanied by an altered gene expression profile and the release of several pro-inflammatory cytokines and chemokines, constituting the senescence-associated secretory phenotype (SASP) [73]. Major representatives of SASP cytokines include transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), interleukins (IL) -1, -6, and – 8 as well as ligands of the CXCR1/2 and CCR2/5 chemokine receptors. These mediators enforce cellular senescence in parenchymal cells, stimulate endothelial cell activation, and contribute to the recruitment and activation of immune cells [68]. Moreover, DNA damage-induced senescence and death of AT I and AT II cells result in a loss of barrier function and reduced surfactant production, decreased surface tension, and possible atelectasis due to the lack of surfactant eventually leading to interstitial edema, exudation of proteins into the alveolar space, and further reduction of the alveolar septa [74–77]. The microvascular system of the lung tissue and particularly endothelial cells are also affected by radiotherapy, both directly via DNA damage-induced senescence and indirectly via released DAMPs and SASP cytokines giving rise to increased vascular permeability and decreased vascular integrity further amplifying the damage of AT I and AT II cells (see Fig. 1) [76]. Ultimately, the affected lung tissue will develop sterile alveolitis with further infiltration of immune cells.

The subacute phase, which can last for several months, is defined by the recruitment of several effector cells of the innate and adaptive immune system (neutrophils, monocytes, macrophages, and lymphocytes) and the concomitant release of pro-inflammatory cytokines which
trigger extensive tissue remodeling of the lung. Immune cell infiltration into the injured lung is facilitated by increased vascular permeability, augmented expression of adhesion molecules (e.g., intercellular adhesion molecule 1 (ICAM-1) and platelet endothelial cell adhesion molecule 1 (PECAM-1) on activated endothelial cells, and release and deposition of chemokines [78]. The initial recruitment of neutrophils is followed by monocytes, macrophages, and lymphocytes (see Fig. 1) [79, 80], and immune-cell derived cytokines, including tumor necrosis factor (TNF), TGF-β, IL-2, IL-3, IL-4, IL-6, IL-7, and IL-8, enforce the activation and proliferation of fibroblasts [81–84]. For a more detailed assessment of the contribution of distinct immune cell subsets, the interested reader is referred to Wirsdörfer et al. [85], Kainthola et al. [86] and McKelvey et al. [87].

Apart from the described immune-mediated tissue remodeling events, hypoxia has been reported to contribute to the onset and the perpetuation of RIP and RILF [76]. Radiation-induced hypoxia occurs several days after thoracic radiotherapy and has been reported to increase over time in different animal models [76, 88]. Importantly, hypoxia-induced downstream signaling leads to upregulation of TGF-β, enhanced collagen synthesis, and changes in the lung architecture (see Fig. 2). In summary, all these events contribute to the development and establishment of RIP which represents the acute, but reversible scenario of radiation-induced lung toxicity. Of note, elevated serum levels of TGF-β are associated with increased risk of RIP [89].

The late phase of radiation-induced lung injury can be defined by the irreversible rearrangement of lung architecture which occurs several months following thoracic radiotherapy [58]. Again, TGF-β produced by activated immune cells as well as by AT I/II cells and fibroblasts, appears to be a key player due to its profibrotic functions (see Fig. 2) [89, 90]. TGF-β acts by binding to two serine/threonine kinase receptors, namely TGF-β type I and type II receptors, resulting in the activation of multiple signaling cascades, including the small mother against decapentaplegic (SMAD) 2/3, mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) signaling pathways [77, 91–93]. Activated Smad2/3 forms complexes with Smad4, subsequently translocating to the nucleus and regulating the expression of genes associated with fibroblast proliferation, migration, and collagen synthesis in the lung tissue [77, 91]. TGF-β stimulates the expression of fibrillar collagens (type I, III and type V) and fibronectin by fibroblasts in the interstitial space resulting in stiffening of the alveolar area and reduction of gas exchange [94–96]. Additionally, overexpression of TGF-β in
experimental models of fibrosis was observed to be accom-
panied by upregulation of protease inhibitors, such as tissue
inhibitor of metalloproteinases (TIMP) and plasminogen
activator inhibitor-1 (PAI-1), along with an excessive accu-
mulation of matrix proteins and collagens [97, 98]. TGF-
β stimulates the differentiation of fibroblasts into myofibro-
blasts which comes along with induction of α-smooth
muscle actin (α-SMA) and increased contractility [99].
Thus, lung architecture remodeling culminates in increas-
ing stiffness and thickening of the lung parenchyma due to
the overproduction of extracellular matrix proteins, and the
alveolar space is severely reduced [100]. These architectural
changes in the lung and the expansion of irreversibly fi-
brotic regions during the late phase after thoracic radio-
therapy are apparent in chest CTs as pulmonary fibrosis.

Predictors of RIP
RIP occurs in the subacute phase after radiotherapy and is
mainly characterized by increased infiltration of immune
effector cells, such as neutrophils, monocytes, and macro-
phages, and the release of pro-inflammatory cytokines and
chemokines. In order to prevent the development of RIP
and RILF in the radiotherapeutic routine, several risk fac-
tors have been identified. The predictors of RIP can be pa-
tient-, disease-, and/or treatment-related.

Patient-related risk factors of RIP
Several patient-related characteristics, such as age, sex,
performance status, smoking status, and comorbidities,
have been suggested as risk factors for RIP. In a meta-
analysis of 31 independent studies with patients of differ-
ent thoracic malignancies (lung, breast, and esophageal
cancer), older age (odds ratio (OR) = 1.7, \( p < 0.0001 \)) and
pre-existing comorbidities (OR = 2.3, \( p = 0.007 \)) were iden-
tified as potential risk factors for the development of RIP
[101]. In contrast, a subsequent study with 576 patients
identified no significant differences in the incidence of
grade ≥ 3 RIP between patients ≤60 and > 60 years (\( p =
0.943 \)) [102], and other studies also failed to find signifi-
cant associations between increasing age and the occur-
rence of RIP [102–104]. In summary, age should be con-
sidered as a relevant risk factor for RIP, but lung co-
morbidities and radiotherapy features may be more im-
portant risk factors compared to chronological age alone.
The role of the patients’ sex remains controversial. In average, women appear to have smaller tumor volumes and have more often a non-smoking history compared to men [105]. Therefore, their pre-radiotherapy lung capacity (FEV1, DLCO) is usually better than the one of male patients.

Pre-existing lung disease, such as chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD), can confound the diagnosis of RIP and occurs quite frequently in lung cancer patients. The predictive role of COPD appears controversial. While patients with extensive emphysema experience RIP in more than 50%, and several studies suggest an increased risk of RIP in patients with underlying COPD [106, 107], other reports do not confirm these observations [102, 108]. Patients with pre-existing ILD seem to be more susceptible to RIP and are at markedly increased risk of radiation-induced toxicity [109, 110]. A retrospective analysis of 504 patients undergoing thoracic SABR reported grade ≥ 3 RIP in 32% and grade 5 pneumonitis in 21% of all ILD patients compared to a general risk of less than 10% of grade ≥ III RIP after SBRT [111–113]. Further studies observed an SABR-related mortality rate of 16%, and it was recommended to reduce the radiation dose for patients with pre-existing ILD in order to prevent radiation-induced lung toxicity [114]. Accordingly, stricter than normal dose constraints may need to be applied in these cases [110, 115], and careful weighing of the risks and benefits for each individual patient is critical in this population at high risk for severe toxicity. Informed consent should include a clear description of the risks. Alternative treatment options, including close observation, should be explored and considered [109]. Interstitial lung abnormalities (ILAs) are defined as precursor stages of idiopathic pulmonary fibrosis and show similar, but less severe radiological changes compared to ILD [116]. Although ILAs mostly remain asymptomatic or subclinical, they are frequently observed in lung cancer screening trials and need particular attention [117]. The ILA classifying radiographic changes include non-fibrotic (ground glass opacification, areas of consolidation, mosaic attenuation) as well as fibrotic features (ground glass opacification with reticulation, honeycombing). Importantly, patients with ILAs show lower exercise tolerance, a restrictive pattern in lung function tests, higher risk of developing clinically significant ILD, and an increased overall mortality [118].

Along these lines, patients with pre-existing ILAs also seem to be more susceptible to radiation-induced toxicity [109, 110]. Therefore, physicians should perform a comprehensive risk assessment, including clinical (prior symptoms, diagnosis, lung function with DLCO) and image-based evaluation, and the radiotherapeutic treatment of patients with ILA should be carefully discussed – preferentially in a process of shared decision-making. Ongoing trials, such as ASPIRE-ILD phase II study (NCT03485378), are currently prospectively investigating the safety and efficacy of SBRT in patients with inoperable early stage NSCLC with pre-existing ILD and ILA [119].

**Disease-related risk factors of RIP**

Disease-related factors of RIP include the tumor location and the tumor volume. The location of the tumor was reported to be associated with the risk of RIP in several studies and meta-analyses identifying patients with tumors in the middle or lower lobes to be at higher risk [101, 103, 120]. A significantly elevated risk of RIP was described for patients with tumors in the inferior part of the lung [103]. The increased risk of RIP may reflect differences in radiosensitivity between different regions of the lung. The caudal part of the lung contains more lung volume and shows stronger movements compared to the cranial part – especially in patients with emphysema.

In addition, increasing tumor volumes seem to be associated with higher probabilities to develop RIP [121–124]. Accordingly, treatment volume planning, motion management, and delivery verification strategies are critical. Nevertheless, there is currently no consensus in the literature on the reporting of cut-offs as well as on the used radiation delivery techniques. Moreover, tumor volumes can be described by different measures which are inconsistently used, including gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV) ± involved lymph node volume, and lung volume minus GTV, CTV, or PTV, respectively. Interestingly, the irradiated lung volume was not significantly associated with radiation-induced BOOP after radiotherapy for breast cancer [60].

Apart from the tumor volume and its location, its proximity to the heart and – in consequence – the radiation dose delivered to the heart impacts the risk of RIP and RILF [125–127]. Importantly, the dosimetric values of the heart are not simply surrogate markers for dosimetric lung parameters [127]. The underlying mechanisms have not been understood yet, but dose constraints to the heart need to be critically considered to prevent RIP and RILF.

In contrast, the tumor stage has not been confirmed as a risk factor for RIP [46, 102, 128]. Hence, tumor volume rather than tumor stage should be considered as a relevant risk factor for RIP, but clear cut-off values remain to be defined for both conventional and SABR populations.

**Treatment-related risk factors of RIP**

Treatment of thoracic malignancies involves radiotherapy, surgery, and various systemic therapies. As a result, different treatment modalities are accompanied by different risks for the development of RIP. Several studies reported that previous surgery leads to a higher risk of
RIP [126, 129]. However, in a meta-analysis including 6 studies with 800 patients, surgery was not confirmed as a risk factor for RIP [101]. The extent of resection and differences in postoperative treatments may represent confounding factors and thus should be analyzed in greater detail.

Systemic treatment options include several different agents, combinations, and that affect radiation-induced lung toxicity [130]. Compared to other anticancer drugs, paclitaxel-based chemotherapy has been described to be associated with higher risks of RIP [124, 131–133]. Additionally, a meta-analysis found that sequential rather than concurrent chemotherapy (OR = 1.6, \( p = 0.01 \)) seems to increase the RIP risk. Yet, treatment intensity and patient selection may confound these findings and thus need to be considered [101]. Conflicting results were reported in a different meta-analysis including 1205 patients from seven randomized clinical trials which showed no significant differences between concomitant and sequential chemotherapy for grade ≥ 3 acute pulmonary toxicity (relative risk (RR): 0.69; 95% CI: 0.42 to 1.12; \( p = 0.13 \)) [134].

Parameters extracted from dose-volume histograms may offer the most resilient predictors of radiation-induced toxicity. In the literature, the mean lung dose (MLD) and the lung volume receiving 20 Gy (V20) are the most frequently and robustly reported risk factors [124, 135]. It is recommended to limit V20 to ≤ 30–35%, and MLD to ≤ 20–23 Gy in normofractionated radiotherapy to limit the risk of RIP to ≤ 20% in patients with NSCLC [124]. Hypofractionated radiotherapy with single doses of ≥ 2.5 Gy is associated with higher rates of RIP [124, 136]. For SBRT, V20 > 10% and MLD > 6 Gy were associated with higher risk of grade 2–4 RIP [137–139]. Apart from these established dose constraints, the concept of the “critical volume” has been increasingly used [140]. According to this concept, a minimum of approximately one-third of the total native lung volume (with connection to the body via a functional hilum) needs to be spared from the threshold dose in order to maintain the basic organ function. Several protocols defining the critical lung volume have been published, ranging from 1000 to 1500 cm³ [140–142]. Future studies are needed to provide additional guidance for physicians and to assess the performance of the critical volume concept with regards to preventing radiation-induced toxicity.

With the clinical implementation of immunotherapeutic protocols, the impact of immune checkpoint inhibition (ICI) on the development of RIP needs to be examined and is currently under investigation [143, 144]. Programmed cell death 1 (PD-1)/ Programmed cell death 1 ligand 1 (PD-L1) inhibition alone can cause immune-mediated pneumonitis in less than 5% [145]. Furthermore, radiation recalls several months after thoracic radiotherapy while ICI is still being administered have been described in some cases [144, 146]. The first systematic retro- and prospective studies have shown acceptable toxicity of sequential and concurrent radio-immunotherapy [147–150]. However, the risk of RIP and immune-mediated pneumonitis may still be underestimated [144, 151]. Unfortunately, predictive biomarkers and/or patient- or disease-related characteristics that can identify patients with elevated risk of RIP with ICI treatment are currently not available [152], but several ongoing studies are investigating these multi-modal treatment approaches and aim at establishing such biomarkers (NCT03519971 (PACIFIC-2), NCT04245514 (SAKK 16/18), NCT03801902 (NRG-LU004), NCT03217071). For the time being, careful monitoring of radiation and/or immune-mediated pneumonitis and appropriate treatment management strategies with the aim of reducing risk and/or enabling early symptom detection are needed [153].

**Prevention of radiation-induced lung injury**

Although distinct improvements in radiation treatment planning and delivery techniques (IMRT, VMAT) allow sparing the healthy tissue while escalating the dose administered to the tumor, RIP and RILF remain dose limiting factors of thoracic radiotherapy which strongly affect the therapeutic outcome and quality of life. In order to improve outcome in patients with locally advanced stages of thoracic cancer, multi-modal treatments combining radio-, chemo- and/or immunotherapy are increasingly being employed and often represent the standard of care [13, 14, 154]. Besides technical advances to reduce radiation-induced toxicity, such as the implementation of IMRT and VMAT, no evidence-based pharmacological intervention has been found so far. Several agents are currently under investigation to prevent and/or treat RIP and RILF, namely protectors, modifiers, and mitigators of radiation-induced lung toxicity. Diverse mechanisms of action have been suggested. As such, radiation protectors would be given before radiotherapy, mitigators would be administered during or immediately after irradiation but before the occurrence of radiation-induced toxicity, and modifiers of radiation-induced lung toxicity would be employed after the appearance of RIP or RILF in order to attenuate progression or to reverse the damage. However, the best strategy seems to be investigating novel radiation delivery techniques (image-guided radiotherapy (IGRT), magnetic resonance (MR)-guided radiotherapy) and radiation qualities (proton, particle therapy) combined with promising pharmacological intervention in order to obtain optimal results.

ACE (angiotensin-converting enzyme) inhibitors and angiotensin-II receptor subtype 1 (AT-1) antagonists have been shown to be helpful in mitigating radiation-induced damage by targeting inflammatory and fibrogenic pathways in preclinical model systems [90, 155, 156]. Angiotensin-II
stimates TGF-β expression via upregulation of toll-like receptor 4 (TLR4) [157] and α-SMA via mechanisms involving serum response factor (SRF) [158]. Accordingly, AT-1 receptor antagonists may counteract these effects. The ACE inhibitor enalaprilat as the active metabolite of enalapril has been reported to attenuate levels of TGF-β, vascular remodeling, and subsequent lung fibrosis [156]. Similarly, the application of captopril was associated with a reduction in pulmonary complication-associated mortality after total body irradiation in a randomized controlled trial [159]. Despite of the strong preclinical evidence, ACE inhibitors and AT-1 receptor antagonists need to be investigated further in prospective trials.

Amifostine is traditionally used to attenuate accumulating renal toxicity and/or xerostomia during anti-cancer chemo (radio)therapy. Several clinical trials incorporating amifostine reported a particularly low rate of clinically apparent pneumonitis upon thoracic chemoradiotherapy for lung cancer patients [160–165]. However, major methodological limitations, including lacking predefinition of time, type of evaluation, lacking inclusion of established risk factors (radiotherapy doses and volumes), and missing control groups limit the informative value of these studies. In the so far largest clinical trial on amifostine only “late lung toxicity” was evaluated [166], and none of the mentioned studies found a reduced rate of clinically and/or radiologically detectable subacute or late lung toxicity upon administration of amifostine [167]. In contrast to radioprotective effects on normal tissues, tumor-protective effects of amifostine can be largely ruled out [167, 168]. However, amifostine can cause adverse effects ranging from nausea and hypotension to myocardial infarction and a poor tolerability (especially when administered intravenously), thus limiting its clinical use.

Prophylactic use of inhalative corticosteroids has been suggested to prevent radiation-induced lung toxicity. However, despite encouraging preclinical results, clinical trials failed to show efficacy of inhalative corticosteroids in the prevention of RIP and RILF [169, 170]. Symptomatic RIP grade 2 patients were successfully treated with inhaled steroids, such as beclomethasone [170]. Nevertheless, not all patients may respond to inhaled treatment, and treatment intensification could be necessary with close clinical observation. In contrast to the oral application with a high first pass effect, inhaled application of corticosteroids is accompanied by lower risks of systemic side effects, such as weight gain, hyperglycemia, and sleep disturbances, and thus should be investigated in larger trials.

Pentoxifylline is a phosphodiesterase inhibitor which downregulates the production of pro-inflammatory cytokines, particularly TNF. In preclinical studies, administration of pentoxifylline prior to whole thorax irradiation has been reported to reduce TNF mRNA and protein levels [171]. Furthermore, pentoxifylline-mediated phosphodiesterase inhibition results in reduced leukocyte adherence to endothelial cells, less platelet aggregation, and dilatation of capillaries. In a small placebo-controlled phase II study, pentoxifylline reduced the occurrence of high grade pneumonitis and decreased lung function loss after 3 and 6 months [172] confirming earlier results [173, 174]. However, the small number of included patients, heterogeneous treatment and follow-up monitoring as well as the different primary endpoints of the studies need to be considered, and further randomized controlled trials are warranted.

Mechanistically, TGF-β is a central player in the development of both RIP and RILF. Thus, inhibition of TGF-β and/or its downstream signaling cascades represents an attractive strategy to prevent radiation-induced lung toxicity. Several in vivo studies described reduced inflammation and lung fibrosis upon TGF-β receptor inhibition with LY2109761, a TGF-β receptor I/II kinase inhibitor which interferes with SMAD1/2 phosphorylation, attenuates TGF-β signaling, and suppresses production of the pro-inflammatory cytokines IL-6, IL-7R, and IL-8 [175, 176]. LY2157299 (galunisertib) more specifically inhibits TGF-β receptor 1 and has already convinced in phase II clinical trials for idiopathic pulmonary fibrosis (IPF) with manageable toxicity [177]. Its relevance for the prevention of RILF remains to be evaluated. Pirfenidone is an anti-fibrotic agent with approval for the treatment of idiopathic pulmonary fibrosis (IPF) that also counteracts TGF-β signaling by downregulating pro-fibrotic cytokines, attenuating lung fibroblast proliferation, and decreasing extracellular matrix deposition [178–181]. Several ongoing or unpublished trials currently investigate pirfenidone for its prophylactic performance in radiation-induced lung toxicity (NCT02296281, NCT00020631).

Platelet-derived growth factor (PDGF) is another cytokine involved in the development of RILF via its engagement in downstream signaling of fibrotic cytokines, such as TGF-β, IL-1, and TNF [176]. Along these lines, the preventive potential of several PDGF receptor inhibitors has been investigated in the context of radiation-induced lung toxicity in vitro and in vivo [182, 183]. Collectively, the findings suggest that the development of lung fibrosis can be inhibited by perturbing fibrotic signaling events and that this strategy is more promising than interfering with inflammation [183]. However, in clinical trials for idiopathic pulmonary fibrosis (IPF), PDGF inhibitors, such as imatinib, failed to prolong survival and/or improve lung function [184] – in contrast to nintedanib which appears safe and slowed down IPF progression considerably [185, 186]. Clinical performance of PDGF inhibitors for the prevention of radiation-induced lung toxicity is currently being trialed (NCT02496585, NCT02452463).

Connective tissue growth factor (CTGF) is a further potential target for the prevention of RILF that was adopted from trials on IPF. It is a matricellular protein
involved in tissue remodeling, myofibroblast differentiation, adhesion, and angiogenesis. In vivo experiments demonstrated that CTGF inhibition can attenuate the development of radiation-induced lung fibrosis and even to revert the fibrotic processes in a therapeutic setting \[187\]. Moreover, FG-3019 (pamrevlumab), a neutralizing antibody designed against CTGF, appears to be more potent than pirfenidone or nintedanib (PDGFR/VEGFR/FGFR inhibitor) in a mouse model of radiation-induced lung fibrosis \[188\]. Nevertheless, despite successfully completed phase II clinical trials of pamrevlumab in IPF \[189\], its potential to prevent radiation-induced lung toxicity needs further evaluation.

Apart from cytokines, extracellular adenosine contributes to the development of RILF. It is released by irradiated cells or generated from extracellular adenine nucleotides by the interplay of the ectoenzymes ectoapyrase (CD39) and 5’ectonucleotidase (CD73), respectively \[190\]. Targeting the CD39/CD73/adenosine axis via administration of PEGylated adenosine deaminase or CD73 antibodies resulted in significantly attenuated RILF in preclinical settings \[191\] and thus represents a promising pharmacological strategy for future clinical trials.

Several transient receptor potential cation channels (TRPs) are expressed in the lung and have been found to mediate inflammatory and fibrotic processes, such as interstitial edema and lung fibrosis. TRPM2 is involved in acute and late radiation-induced toxicity, and its PARP1-dependent activation upon exposure to ionizing irradiation has been described to contribute to the development of xerostomia in a mouse model \[192\]. Furthermore, TRPM2-deficient mice exhibit less inflammation and dermatofibrosis in response to radiotherapy as compared to wild type mice \[193\]. Thus, the role of TRP channels as potential therapeutic target in the prevention of RIP and RILF needs further investigation \[194\].

Finally, mesenchymal stem cells (MSCs) have been shown to exhibit strong regenerative capacity for several forms of tissue damage \[195\]. MSCs can successfully migrate towards the injured site in the lung upon irradiation and differentiate into distinct lung cell types, including AT I/II cells and endothelial cells. Preclinical studies reported that lung fibrosis can be modulated by administration of MSCs \[195, 196\]. In these settings, adoptive transfer of MSCs did limit radiation-induced endothelial cell loss in the early phase after irradiation and promoted tissue repair through the secretion of superoxide dismutase 1 (SOD1) \[197\] and the anti-fibrotic factors hepatocyte growth factor (HGF) and prostaglandin E2 (PGE2) \[198\].

### Treatment of RIP and RILF
National and international guidelines recommend treating RIP only if symptomatic with corticosteroids according to clinical severity based on consensus guidelines due to limited clinical data. The treatment should be carried out over at least several weeks and subsequently should be slowly tapered (see Table 4) \[201\]. Abrupt discontinuation should be avoided in order to prevent early relapse of RIP (rebound phenomenon) with increased severity and higher risk of RILF development. For asymptomatic or subclinical patients, clinical observation without further treatment is recommended. Patients with radiation-induced BOOP usually show fast and effective responses to steroid treatment \[202\]. Prophylactic administration of antibiotics in RIP can be considered for patients at high risk of bacterial infection, for instance with cancer-associated bronchial stenosis, or for immunocompromised patients. If symptoms persist under treatment with steroids and/or antibiotics, antifungal treatment may be subscribed. Steroid doses can be reduced in combination with azathioprine or cyclosporine A. For individual cases, these agents can be used if corticosteroid treatment fails. Respiratory gymnastics and inhalation of β-sympathomimetics have been reported to be supportive. In severe cases of RIP (CTCAE ≥III), administering oxygen, assisted ventilation and prophylaxis of right heart failure are needed. A successful treatment option for RILF has yet not been established.

### Conclusions
RIP and RILF remain dose limiting forms of radiation-induced lung toxicity with relevant impact on the success of thoracic radiotherapy. Several patient-, disease- and treatment-related factors, namely age, pre-existing lung disease, tumor location, radiation dose, and irradiated volume, need to be considered when trying to predict their risk of occurrence. This is of particular importance in complex settings of multi-modal radiochemo-immunotherapy with or without prior surgery. Refined radiation delivery techniques, including motion management and treatment verification strategies, can reduce the irradiated lung volume and should be considered for patients with high risk of RIP. The current repertoire of preventive and/or therapeutic intervention by administration of radiation protectors, modifiers, and/or mitigators remains rather limited. But with growing knowledge of the underlying cellular and molecular mechanisms of radiation-induced lung toxicity, promising targets and pathways have been and will be identified.

### Table 4 Treatment with corticosteroids in responsive patients with moderate RIP (CTCAE I-II)

| Treatment period (days) | Prednisolone dose (mg/day) |
|------------------------|---------------------------|
| 1–4                    | 60                        |
| 5–8                    | 30                        |
| 9–14                   | 12                        |
| > 15 (ca. 6 weeks)     | 6                         |
to serve as future therapeutic options – preferentially in combination with novel radiation delivery techniques.

Abbreviations
2D: 2-dimensional; 3D: 3-dimensional; 18F-FDG PET/CT: [18F]fluoro-2-deoxy-2-glucose positron emission tomography combined with computed tomography; ACE: Angiotensin-converting enzyme; AT I: Alveolar type I; AT II: Alveolar type II; BOOP: Bronchiolitis obliterans organizing pneumonia; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; CT: Computed tomography; CTCAE: Common terminology criteria for adverse events; CTGF: Connective tissue growth factor; CTV: Clinical target volume; DAMP: Damage-associated molecular pattern; DLCO: Diffusing capacity of lung for carbon monoxide; DNA: Deoxyribonucleic acid; ERK: Extracellular signal-regulated kinase; FEV1: Forced expiratory volume in one second; GTV: Gross tumor volume; HGF: Hepatocyte growth factor; HRTC: High-resolution computed tomography; ICAM-1: Intercellular adhesion molecule 1; IC: Immune checkpoint inhibition; IGRT: Image-guided radiotherapy; IL: Interleukin; ILA: Interstitial lung abnormality; ILD: Interstitial lung disease; IMRT: Intensity modulated radiotherapy; MAPK: Mitogen-activated protein kinase; MDL: Mean lung dose; MRI: Magnetic resonance imaging; MSC: Mesenchymal stem cell; NSCLC: Non-small cell lung cancer; OR: Odds ratio; PAI-1: Plasminogen activator inhibitor-1; PARP-1: Poly [ADP-ribose] polymerase 1; PD-1: Programmed cell death 1; PDFG: Platelet-derived growth factor; PD-L1: Programmed cell death 1 ligand 1; PECA-1: Platelet endothelial cell adhesion molecule 1; PGE2: Prostaglandin E2; PTV: Planning target volume; RLF: Radiation-induced lung fibrosis; RIF: Radiation-induced pneumonitis; ROS: Reactive oxygen species; RTG: Radiation Therapy Oncology Group; SABR: Stereotactic ablative radiotherapy; SASP: Senescence-associated secretory phenotype; SBRT: Stereotactic body radiotherapy; SMAD: Small mother against decapentaplegic; SOD1: Superoxide dismutase 1; SRF: Serum response factor; TGF-β: Transforming growth factor-β; TIMP: Tissue inhibitor of metalloproteinases; TLR4: Toll-like receptor 4; TNF: Tumor necrosis factor; TRP: Transient receptor potential cation channel; TRPM2: Transient receptor potential cation channel member 2; V20: Lung volume receiving 20 Gy; VMAT: Volumetric modulated arc therapy; α-SMA: α-smooth muscle actin

Acknowledgements
This manuscript has not been previously published and is not under consideration elsewhere. The persons listed as authors have given their approval for the submission.

Authors’ contributions
LK, AD, KL and CB wrote the manuscript. All authors read and commented on the manuscript and approved submission of the final version.

Funding
This study was supported by the Munich Excellence Training Initiative for Physicians Scientists (Metaphys, to LK), the CPC-M translational funds (German Center for Lung Research (DZL) to AD, CASW, and CB), and the German Cancer Consortium (DKTK to CB). Research in the authors’ laboratories is supported by the DFG (GRK 2338 “Targets in Toxicology” to AD and CASW) and the BMBF (“Z2S3RAS” 02NUK047C to KL). This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA08748.

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that competing interests do not exist.

Author details
1Department of Radiation Oncology, University Hospital, LMU Munich, Marchioninistrasse 15, 81377 Munich, Germany. 2German Center for Lung Research (DZL), partner site Munich, Munich, Germany. 3German Cancer Consortium (DKTK), partner site Munich, Munich, Germany. 4Walther Straub Institute of Pharmacology and Toxicology, Member of the German Center for Lung Research (DZL), Medical Faculty, LMU-Munich, Munich, Germany. 5Institute of Lung Biology and Disease, Helmholtz Zentrum München, Munich, Germany. 6Department of Internal Medicine V, LMU Munich, Munich, Germany. 7Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, USA. 8Research Institute of Clinical Medicine, Tbilisi, Georgia. 9Department of Radiation Oncology, Amsterdam University Medical Centers, Amsterdam, Netherlands. 10Department of Radiation Oncology (MAASTRO), GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, the Netherlands.

Received: 1 July 2020 Accepted: 20 August 2020

Published online: 10 September 2020

References
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7–34.
2. Delaney G, Barton M, Jacob S, Jalaludin B. A model for decision making for the use of radiotherapy in lung cancer. Lancet Oncol. 2003;4:210–8.
3. Nestle U, Schimke-Jasch T, Kemp S, Scharer-Schuler A, Mix M, Küsters A, Tosch M, Hehr T, Eschmann SM, Bulte YP, Hass P. Imaging-based target volume reduction in chemoradiotherapy for locally advanced non-small-cell lung cancer (PET-Plan): a multicentre, open-label, randomised, controlled trial. The Lancet Oncol. 2020;21(4):581–92.
4. Unterrainer M, Eze C, Ihan H, Marschner S, Roengvoraphoj O, Schmidt-Hegemann N, Walter F, Kunz W, AF Rosenshöld PM, Jere J. Recent advances of PET imaging in clinical radiation oncology. Radiat Oncol. 2020;15:1–15.
5. Chun S, Hu C, Choy H, Komari R, Timmerman R, Schild S, Bogart J, Drobela W, Bosch W, Galvin J. Comparison of 3-D conformal and intensity modulated radiation therapy outcomes for locally advanced non-small cell lung cancer in NRG oncology/RTSG 0617. Int J Radiat Oncol Biol Phys. 2015;93:51–2.
6. Ling DC, Hess CB, Chen AM, Daly ME. Comparison of toxicity between intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy for locally advanced non–small-cell lung cancer. Clin Lung Cancer. 2016;17:18–23.
7. Finazzi T, Haasbeek CJ, Spoelstra FO, Palacios MA, Admiraal MA, Brunzeel AM, Slotman BJ, Lagerwaard FJ, Senan S. Clinical outcomes of stereotactic MR-guided adaptive radiotherapy for high-risk lung tumors. Int J Radiat Oncol Biol Phys. 2020;107(2):270–78.
8. De Ruyscher D, Niedermann G, Burnet NG, Siva S, Lee AW, Hegi-Johanson F. Radiotherapy toxicity. Nat Rev Dis Primers. 2019;5:1–20.
9. Kurz C, Buizza G, Landry G, Kamp F, Faber M, Paganielli C, Baroni G, Reiner M, Keil PJ, van den Berg CA. Medical physics challenges in clinical MR-guided adaptive radiotherapy. Radiat Oncol. 2020;15:1–16.
10. Borghesi H, Langer CJ, Gadgell S, Papadimitrakopoulou VA, Patnaik A, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Jalal SI. 24-month overall survival from KEYNOTE-021 cohort G: Pemetrexed and carboplatin with or without Pembrolizumab as first-line therapy for advanced nonsquamous non–small-cell lung cancer. J Thorac Oncol. 2019;14:124–9.
11. Reck M, Rodríguez-Abreu D, Robinson AG, et al. LBA8-PR – KEYNOTE-024: Pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) as first-line therapy for advanced NSCLC with a PD-L1 tumor proportion score (TPS) ≥50%. Abstract presented at ESMO 2016 Congress, October 7 - 11, 2016, Copenhagen, Denmark. Available online: https://cslide.ctimeetingtech.com/library/esmo/browse/itinerary/32956/2016-10-09#2d91e75v. Accessed 27 Aug 2020.
12. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gürmüz M, Mazieres J, Hermes B, Çay Ş, Çenler F, Cósoţ T, Fülöp A, Pembrolizumab plus chemotherapy for squamous non–small-cell lung cancer. N Engl J Med. 2018;379:2040–51.
13. Gandhi L, Rodríguez-Abreu D, Gadgell S, Esteban E, Felip E, De Angelis F, Domine M, Clínic P, Hochmair MJ, Powell SF. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med. 2018;379:2078–92.
14. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Kurata T, Chiapponi A, Lee KH, de Wit M. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med. 2018;379:2342–50.
26. Cannon DM, Mehta MP, Adkison JB, Khuntia D, Traynor AM, Tomé WA, Sejpal S, Komaki R, Tsao A, Chang JY, Liao Z, Wei X, Allen PK, Lu C, Gillin M, Wurstbauer K, Zehentmayr F, Deutschmann H, Dagn K, Exeli A-K, Kopp P, Rehman S, Speirs C, Molotievschi A, Mullen D, Fergus S, DeWees T, Velez M, Keffer S, Guy CL, Weiss E. Fatal radiation pneumonitis: literature review and but no good survival due to radiation pneumonitis. Lung Cancer Amst Neth. 2015;115:367–78.

21. Chao P-J, Lee H-F, Lan J-H, Guo S-S, Ting H-M, Huang Y-J, Chen H-C, Lee T-F. Propensity-score-matched evaluation of the incidence of radiation pneumonitis and secondary cancer risk for breast cancer patients treated with IMRT/VMAT. Sci Rep. 2017;7:1–9.

20. Wijsman R, Dankers F, Troost EG, Hoffmann AL, van der Heijden EH, de Geus-Oei L-F, Buskens J. Comparison of toxicity and outcome in advanced stage non-small cell lung cancer patients treated with intensity-modulated (chemo-) radiotherapy using IMRT or VMAT. Radiat Oncol. 2017;12:295–9.

19. Shaw AT, Kim D-W, Nakagawa K, Seto T, Grin J, Miles T, Besse B, Solomon BJ, Blackhall F. Crotidotin versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013;369:2385–94.

18. Rosell R, Baier K, Polat B, Richter A, Krieger T, Wilbert J, Muller G, Fiertje M. Dose-response relationship for radiation-induced pneumonitis after pulmonary stereotactic body radiotherapy. Radiother Oncol. 2010;97:65–70.

17. Mok TS, Wu Y-L, Thongprasert S, Yang C-H, Chu D-T, Saijo N, Nakanishi K, Okumura K, Ise K, Shi W, Sunpaweravong P, Han B, Margono B, Ichinose Y. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361:947–57.

16. Wannenmacher M, Serbescu A, Alexe M, Cervis L, Ionita D, Bogdan MA. The state of clinical research of radiotherapy/chemoradiotherapy and its impact in inoperable non-small cell lung cancer: which metastatic site should be irradiated to induce immunogenic cell death?. Int J Radiat Oncol Biol Phys. 2020;108(1):225–32.

15. Käsmann L, Eze C, Dantes M, Roengvirojaphoj O, Niyaz M, Belka C, Manapov F. State of clinical research of radiotherapy/chemo- and immune checkpoint inhibitor therapy combinations in solid tumours—a German radiation oncology survey. Eur J Cancer. 2019;108:530–4.

14. Käsmann L, Eze C, Manapov F. Stereotactic body radiotherapy (SBRT) combined with immune check-point inhibition (ICI) in advanced lung cancer: which metastatic site should be irradiated to induce immunogenic cell death?. Int J Radiat Oncol Biol Phys. 2020;108(1):225–6.

13. Mok TS, Wu Y-L, Thongprasert S, Yang C-H, Chu D-T, Saigo N, Sunpaweravong P, Han B, Margono B, Ichinose Y. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361:947–57.

12. Rosell R, Carcereny E, Gazzeri R, Vergnenegre A, Massuti B, Felip E, Palmero S, Garcia-Gomez R, Pallares C, Sanchez JM. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13:239–46.

11. Shaw AT, Kim D-W, Nakagawa K, Seto T, Grin J, Miles T, Besse B, Solomon BJ, Blackhall F. Crotidotin versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013;369:2385–94.

10. Wijman R, Dankers F, Troost EG, Hoffmann AL, van der Heijden EH, de Geus-Oei L-F, Buskens J. Comparison of toxicity and outcome in advanced stage non-small cell lung cancer patients treated with intensity-modulated (chemo-) radiotherapy using IMRT or VMAT. Radiat Oncol. 2017;12:295–9.

9. Chao P-J, Lee H-F, Lan J-H, Guo S-S, Ting H-M, Huang Y-J, Chen H-C, Lee T-F. Propensity-score-matched evaluation of the incidence of radiation pneumonitis and secondary cancer risk for breast cancer patients treated with IMRT/VMAT. Sci Rep. 2017;7:1–9.

8. Wennberg B, Gagliardi G, Sundborn L, Svane G, Lind P. Early response of lung in breast cancer irradiation: radiologic density changes measured by CT and symptomatic radiation pneumonitis. Int J Radiat Oncol Biol Phys. 2002;52:1196–206.

7. Nishikawa A, Ogawa Y, Hamada N, Terashima M, Inomata T, Yoshida S. Analysis of radiation pneumonitis and radiation-induced lung fibrosis in breast cancer patients after breast conservation treatment. Oncol Rep. 1999;6:513–20.

6. Keffe S, Guy CL, Weiss E. Fatal radiation pneumonitis: literature review and case series. Adv Radiat Oncol. 2020 Mar. 5(2):238–49.

5. Sun L-M, Leung SW, Wang C-J, Chen H-C, Fang F-M, Huang E-Y, Hsu H-C, Yeh C-J, Hsiung C-Y, Huang DT. Concomitant boost radiation therapy for inoperable non-small-cell lung cancer: preliminary report of a prospective randomized study. Int J Radiat Oncol Biol Phys. 2000;47:413–8.

4. Cannon DM, Mehta MP, Adkison JB, Khuntia D, Traynor AM, Tomé WA, Chappell RJ, Tolakanahalli R, Mohindra P, Bentzen SM. Dose-limiting toxicity of proton beam therapy with concurrent chemotherapy for nonsmall cell lung cancer. Cancer. 2011;117:3004–10.

3. Kalnussakate GC, Tinhoff F, Kuffeld MM, Kluge AA, Grün AA, Budach W, Senger CC, Stromberg CC. Radiosurgery and fractionated stereotactic body radiotherapy for patients with lung oligometastases. BMC Cancer. 2020;20:1–10.

2. Cox JD, Stetz J, Pazak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31:1341–6.
toxicity after stereotactic body radiation therapy of the thorax: a pooled analysis of 88 studies. Int J Radiat Oncol Biol Phys. 2016;95:1357–66.

140. Ritter TA, Matuszak M, Chetty U, Mayo CS, Wu J, Iyengar P, Weldon M, Robinson C, Xiao Y, Timmerman RD. Application of critical volume-dose constraints for stereotactic body radiation therapy in NRG radiation therapy trials. Int J Radiat Oncol Biol Phys. 2017;98:334–46.

141. Videtic G, Singh A, Chang J, Le Q, Parker W, Olivier K. A randomized phase II study of stereotactic body radiotherapy (SBRT) schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer. Radiation therapy oncology group 0915. Philadelphia: Radiat Ther Oncol Group; 2014.

142. Bezjak A, Bradley J, Gaspar L, Robert D, Papiez L, Gore E. Seamless phase II/III study of stereotactic lung radiotherapy (SBRT) for early stage, centrally located, non-small cell lung cancer (NSCLC) in medically inoperable patients. RTOG. 2012;8:131–75.

143. Winsdörfer F, De Leve S, Jendrossek V. Combining radiotherapy and immunotherapy in lung cancer: can we expect limitations due to altered normal tissue toxicity? Int J Mol Sci. 2019;20,224.

144. Manapov F, Roengvoraphoj O, Dantes M, Marschner S, Li M, Eze C. Pneumonitis in irradiated lungs after nivolumab: a brief communication and review of the literature. J Immunother. 2018;41:96–9.

145. Tian S, Switchenko JM, Buchwald ZS, Patel PR, Shelton JW, Kahn SE, Pillai RN, Steuer CE, Owonikoko TK, Behera M, Curan WJ. Lung Stereotactic Body Radiation Therapy and Concurrent Immunotherapy: A Multicenter Safety and Toxicity Analysis. Int J Radiat Oncol Biol Phys. 2020;2019(1):309–13.

146. McGovern K, Ghaly M, Espósito M, Bamaby K, Seetharamu N. Radiation recall pneumonitis in the setting of immunotherapy and radiation: a focused review. Future Sci OA. 2019;5:FOS378.

147. von Reibnitz D, Chaft JE, Wu AJ, Samstein R, Hellmann MD, Plodkowski AJ, Robinson C, Xiao Y, Timmerman RD, Steuer CE, Owonikoko TK, Behera M, Curran WJ. Lung Stereotactic Body Radiotherapy: A Single-Centre Experience. Radiat Oncol. 2016;11:12.

148. Jabbour SK, Berman AT, Decker RH, Lin Y, Feigenberg SJ, Gettingen SN, Aggarwai C, Langer CJ, Simone CB, Bradley JD, Aisner J. Phase III trial of radiation treatment±amifostine in patients with locally advanced non–small-cell lung cancer: A Randomized Controlled Trial. JAMA oncology. 2020;6(6):848–53. https://doi.org/10.1001/jamaoncology.2019.6781.

149. Shaverdian N, Thor M, Shepherd AF, Olfen MD, Jackson A, Wu AJ, Gelbman DY, Yorde KE, Simone CB, Chaft JE, Hellmann MD. Radiation pneumonitis in lung cancer patients treated with chemoradiation plus durvalumab. Cancer Med. 2020;9(3):4622–31.

150. Naidoo J, Page D, Liu B, Connell L, Schindler K, Lacouture M, Postow M, Wolchok J. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol. 2015;26:2375–91.

151. Käsmann L, Eze C, Taugner J. Roengvoraphoj O, Belka C, Manapov F. Implementation of durvalumab maintenance treatment after concurrent chemoradiotherapy in inoperable stage III non-small cell lung cancer (NSCLC)—a German radiation oncology survey. Transl Lung Cancer Res. 2020;9:288.

152. Theelen WSM, Peelen HMU, Lalezzari F, van der Noort V, de Vries JF, JGJV A, Käsmann L, Eze C, Taugner J, Roengvoraphoj O, Belka C, Manapov F. Angiotensin II facilitates fibrogenic effect of TGF-β1 through enhancing the down-regulation of BAMBI caused by LPS: a new pro-fibrotic mechanism of angiotensin II. PLoS One. 2013;8(10):e76289.

153. Hautmann MB, Thompson MM, Swartz EA, Olson EN, Owens GK. Angiotensin II–induced stimulation of smooth muscle α-actin expression by serum response factor and the homeodomain transcription factor Mrf4. Circ Res. 1997;81:100–10.

154. Cohen EP, Bedi M, Irving AA, Jacobs E, Tomic R, Klein J, Lawton CA, Moulder JE. Mitigation of late renal and pulmonary injury after hematopoietic stem cell transplantation. Int J Radiat Oncol Biol Phys. 2012;83:292–6.

155. Antonadou D, Petridis A, Synodinou M, Throuvalas N, Bolanos N, Veslemes M, Sariotis A. Amifostine reduces radiochemotherapy-induced toxicities in patients with locally advanced non–small cell lung cancer. Seminars in oncology. 2003;18(2–9. https://doi.org/10.1053/j.semioncol.2003.11.008.

156. Li YS, Ni SY, Meng Y, Shi XL, Zhao XW, Luo HH, Li X. Angiotensin II facilitates radiation-induced stimulation of smooth muscle α-actin expression by serum response factor and the homeodomain transcription factor Mrf4. Circ Res. 1997;81:100–10.

157. Hautmann MB, Thompson MM, Swartz EA, Olson EN, Owens GK. Angiotensin II–induced stimulation of smooth muscle α-actin expression by serum response factor and the homeodomain transcription factor Mrf4. Circ Res. 1997;81:100–10.

158. Hautmann MB, Thompson MM, Swartz EA, Olson EN, Owens GK. Angiotensin II–induced stimulation of smooth muscle α-actin expression by serum response factor and the homeodomain transcription factor Mrf4. Circ Res. 1997;81:100–10.
pulmonary murine fibrosis via reversal of TGF-β and BMP-associated proinflammatory and proangiogenic signals. Clin Cancer Res. 2012;18:3616–27.

176. Dadrich M, Nicolay NH, Flechsig P, Bickelhaupt S, Hoeltgen L, Roeder F, Hauser K, Tietz A, Jenne J, Lopez R. Combined inhibition of TGFβ and PDGF signaling attenuates radiation-induced pulmonary fibrosis. Oncoimmunology. 2016;5:e1123366.

177. Kelley RK, Gane E, Assenat E, Siebler J, Galle PR, Merle P, Hournand IO, Cleverly A, Zhao Y, Guerguieva I, Lahn A. M phase 2 study of galunisertib (TGF-β type 1 inhibitor) and sorafenib in patients with advanced hepatocellular carcinoma. Clinical and translational gastroenterology. 2019; 10(7):e00056.

178. Knüppel L, Kawa Y, Aichler M, Heizelmann K, Hatz R, Behr J, Wolch A, Bächinger HP, Eickenberg O, Staab-Weijntz CA. A novel antifibrotic mechanism of nintedanib and pirfenidone. Inhibition of collagen fibril assembly. Am J Respir Cell Mol Biol. 2017;57:77–90.

179. Kwapiszewska G, Gungl A, Wilhelm J, March LM, Puthenparampil HT, Sinn K, Didasova M, Kiepetko W, Kosmacek EA, Dagunts A, Borschke W, Hausen N, Knüppel L, Ishikawa Y, Aichler M, Heinzelmann K, Hatz R, Behr J, Walch A, Dadrich M, Nicolay NH, Flechsig P, Bickelhaupt S, Hoeltgen L, Roeder F, Pföhler J, Gross W, Peschke P. Effects of CTGF blockade on attenuation and reversal of radiation-induced pulmonary fibrosis. JNCI J Natl Cancer Inst. 2018;110(10):e00056. https://doi.org/10.1158/1097-4247.JNCI-18-026.

180. Lin J, Togo S, Kadoya K, Tufalu M, Namiba Y, Iwai M, Watanabe N, Nagahama K, Okabe T, Hidaya M. Pirfenidone attenuates lung fibrotic fibroblast responses to transforming growth factor-β1. Respir Res. 2019;20:119.

181. King TE Jr, Bradford WJ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg K, Kwapiszewska G, Gungl A, Wilhelm J, Marsh LM, Puthenparampil HT, Sinn K, Danilevskaya O, Nikitin A, Sotnikova A, Kotova S. First-in-human high-cumulative-dose stem cell therapy in idiopathic pulmonary fibrosis with rapid lung function decline. Stem Cells Transl Med. 2020;9:6–16.

182. Chambers DC, Enever D, Ilcz J, Sparks L, Whitelaw K, Ayres J, Yerkovich ST, Khall D, Atkinson KM, Hopkins PM. A phase 1b study of placenta-derived mesenchymal stromal cells in patients with idiopathic pulmonary fibrosis. Respiratory. 2014;19:1013–8.

183. Hanania NA, Mainwaring W, Chehre YT, Hanania NA, Ludwig M. Radiation-induced lung injury: assessment and management. Chest. 2019;156(1):150–62.

184. Sara A-G, Hamdan A-I, Hanaa B, Nawaz KA. Broncholitis obliterans organizing pneumonia: pathogenesis, clinical features, imaging and therapy review. Ann Thorac Med. 2008;3:67.