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Original Article

Diagnosis and treatment of radiation induced pneumonitis in patients with lung cancer: An ESTRO clinical practice guideline

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ABSTRACT

The incidence of radiation pneumonitis (RP) has decreased significantly compared to historical series, mainly due to improved radiotherapy techniques and patient selection. Nevertheless, some patients still develop RP. This guideline provides user-friendly flowcharts to address common clinical practice questions regarding RP.

We summarize the current state of the art regarding the mechanisms, risk factors, diagnosis and treatment of RP. Dosimetric constraints to minimize the incidence of RP, as well as risk factors for developing RP, such as idiopathic pulmonary fibrosis (IPF) were identified. The combination of radiotherapy and medication as a risk factor for the development of RP was reviewed. RP remains a diagnosis of exclusion, but an algorithm for reaching the diagnosis has been proposed. Finally, practical approaches to the treatment of RP are outlined.

Introduction

Radiation pneumonitis (RP) was first described as a side effect of thoracic radiotherapy (RT) as early as 1896 [1]. RP proved to be a dose-limiting and potentially fatal complication, which lead to the 1922 recommendation to treat breast cancer using tangential fields.

Subsequently, radiation-induced lung fibrosis was described in 1934. Based on animal and clinical studies conducted in the 1930s and 1940s, it was concluded that RP was often indistinguishable from lung cancer growth or infection on a chest X-ray [1]. In the early days of RT, most patients were treated with parallel opposed or tangential fields. RP was defined by the presence of cough, dyspnoea and infiltrates within the

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radiation field, in the absence of other causes for these symptoms [1,2].

As early as in 1954, it was recommended to avoid treating "large volumes", such as more than one-third of the lung, with doses exceeding 2000 roentgens, recognizing the importance of both dose and volume in the occurrence of RP. The use of corticosteroids to treat RP was introduced in 1953 [3]. Since that time, RP has been recognized as a dose-limiting factor in lung cancer, often preventing the delivery of curative-intent doses and leading to poor treatment outcomes. The high incidence of RP and radiation-induced lung fibrosis observed in patients with Hodgkin lymphoma treated with ~~large~~ mantle fields, coupled with the realization that prednisone could not prevent these complications, further fuelled research efforts to identify risk factors, gain deeper biological insights into the development of RP and improve treatment strategies [4].

Thanks to numerous advancements, most lung cancer patients can now receive high, radical doses of radiotherapy, with or without systemic treatments, without experiencing excessive pulmonary toxicity [5].

Although RP remains an significant clinical issue, in recent studies, the incidence is low compared to historical series [6]. In a recent randomized phase II study investigating the role of adjuvant immunotherapy after stereotactic ablative radiotherapy (SABR), in the control arm, only 1 out of 75 patients experienced pneumonitis grade 2 and none grade 3 or higher [7]. In the multi-centric RTOG 0617 randomized trial, which allowed both 3D-CRT and IMRT, 4 % of patients experienced grade 2 pneumonitis and 4 % grade 3 in the 60 Gy control arm [8], with more favourable outcomes observed in IMRT-treated patients [9].

Due to the lack of evidence-based multidisciplinary guidelines and existing knowledge gaps, the European Society for Radiotherapy and Oncology (ESTRO) initiated the development of the current clinical practice guideline. Formulated by a multidisciplinary expert group, this guideline addresses various aspects such as molecular mechanisms, diagnosis, risk factors, recall pneumonitis and treatment of RP, based on a comprehensive and systematic review of the literature.

Systematic review

Search strategies (see supplementary file)

In February 2024, a comprehensive literature search was performed across the databases Medline (Ovid), Embase (Ovid), Cochrane Library, and Web of Science. The search focused on the concepts of "radiation pneumonitis" and "lung cancer". For Medline, Embase, and Web of Science, additional search terms were used to target specific aspects such as "diagnosis", "risk factors", "radiation recall pneumonitis", and "treatment". Results from the Cochrane Library search results were manually sorted into these categories. Detailed search strategies for each concept, including the number of results retrieved, are provided in the Appendix.

Study selection

Studies were included if they met the following inclusion criteria:

- Population: adult patients with RP following radiotherapy for lung cancer;
- Type of article: peer-reviewed journal articles reporting original research;
- Radiation therapy techniques: studies must include information on techniques used

For the "risk factors" topic, only retrospective studies involving at least 100 patients were eligible for inclusion.

Articles reporting solely on animal studies or published prior to 2010 were excluded.

For the diagnosis chapter, the initial search yielded 709 results. After removing duplicates papers, 204 articles were screened. Among these, 43 articles were deemed relevant, and they were sent to the authors of this guideline.

For the treatment chapter, the search yielded 928 results (529 results after de-duplication). Ultimately, only 4 papers met the screening criteria and were considered as relevant. For the radiation recall pneumonitis chapter, 108 total articles were identified during the search and 64 articles after de-duplication were screened. Among those, 19 articles were deemed relevant and were sent to the authors. For this chapter, given the limited information available on such a complex and varied clinical scenario, we decided to include 2 case series. These case series were sent to the authors, alongside the other relevant papers retrieved.

Despite efforts to reduce the number of retrieved articles by filtering out irrelevant or redundant information, the search for the risk factors chapter yielded a substantial number of articles. Initially, the search returned 1802 results, which were narrowed down to 923 articles after the de-duplication. Flowing screening, 343 articles were identified as relevant. Due to the volume of redundant information, we summarize the main findings of risk factors chapter here. Despite the large number of articles, no new information emerged on risk factors for RP. Most of the information was redundant and presented across multiple articles. However, our search included all the relevant findings available in literature to date, demonstrating both the quality of our search and the limited evidence in this field. The relevant papers primarily focused on patients' clinical risk factors (e.g. baseline performance status, age at diagnosis, smoking status) and dosimetric criteria associated with the development of RP. The study populations were highly heterogenous, differing not only in clinical characteristics but also in treatment schedules. Although we aimed to include only studies relating to intensity-modulated radiotherapy (IMRT) and Volumetric-Modulated Arc Therapy (VMAT) for photon therapy or proton therapy (both passive scattered or intensity modulated), the final search also included studies involving patients treated with three-dimensional conformal radiotherapy techniques.

A wide range of radiation dose was administered, including both patients treated with stereotactic radiotherapy and those receiving with conventional fractionation. This variability likely stems from the inclusion of patients with different TNM stages of lung cancer in our search. The treatment schedules also varied widely, encompassing different combinations of chemoradiation, immunotherapy, targeted therapies and surgery, depending on the clinical scenarios. This diversity makes it challenging to compare results across studies.

Many papers focused on organs at risk (OAR) constraints that might predict of RP. These studies typically evaluated dosimetric criteria retrospectively extracted from Dose Volume Histograms, primarily analysing the dose received by the ipsilateral and contralateral lung. Various dosimetric values were considered, often specific to treatment protocols, including V5, V5 (i.e. the percentage of normal lung receiving at least 5 Gy), V10, V15, V20, V30 for both the ipsilateral lung, and the contralateral lung, as well as the mean lung dose (MLD), with different values cut-off values used across studies, which is partly explained by the varying definition of the Vx or MLD, for instance subtracting the gross tumour volume (GTV) or the planning target volume (PTV) from the lungs for calculations.

Mechanisms

Most of our understanding of the mechanisms of RP comes from preclinical studies conducted in mice. More human studies are needed to elucidate which of these mechanisms are also relevant in patients, as this knowledge will be crucial for improving diagnosis and treatment strategies. A schematic overview of the mechanisms of RP and RPF is depicted in Figs. 1A and 1b.

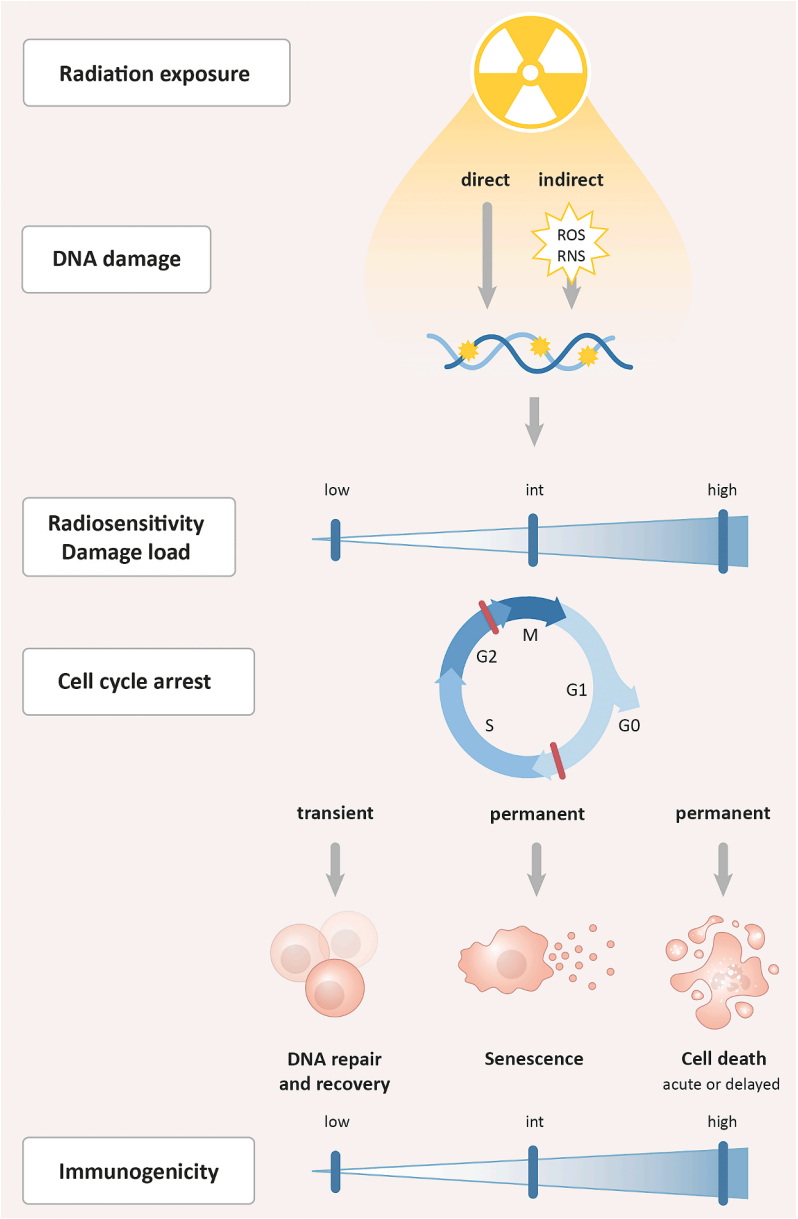

Fig. 1A. Acute cellular responses to ionizing radiation. Exposure to ionizing radiation induces damage to cellular macromolecules (proteins, lipids, organelles, nuclear and mitochondrial DNA) either directly or indirectly by the generation of free radicals, like reactive oxygen (ROS) and nitrogen (NOS) species. Depending on the cells intrinsic radiosensitivity and repair capacity, exposure to ionizing radiation results in a cell type-specific damage load and response. Cells with low damage load primarily enter transient cell cycle arrest that allows for DNA repair and recovery. Cells with unrepairable damage load might enter permanent cell cycle arrest and a senescent state or acute or delayed forms of cell death. Cellular responses to higher degrees of damage load are generally associated with a higher immunogenicity.

Molecular mechanisms

Radiation-induced lung disease (RILD) is a complex, multifactorial process initiated by direct damage and destruction of normal lung tissue cells and immune cells caused by radiotherapy. This damage disrupts proper tissue function and activates cellular signalling cascades triggered by cell damage and death. These cascades lead to both local and systemic effects, including dynamic innate and adaptive immune responses that amplify inflammatory tissue damage. This amplification contributes to the development of subacute RP) and can potentially lead to chronic radiation-induced pulmonary fibrosis (RPF).

Acute phase

At the molecular level, ionizing radiation causes immediate oxidative damage to cellular macromolecules, particularly mitochondrial and nuclear DNA, as well as alterations in redox-sensitive molecular switches [10–12]. Within hours, radiation damage activates a multifaceted DNA-damage response, leading primarily to a transient cell cycle arrest. The outcome of this response—whether cells resume proliferation, undergo permanent cell cycle arrest (senescence), or experience acute or delayed cell death—depends on several factors. These include the physical aspects of the radiation (such as dose, fractionation, and type of irradiation), the extent and quality of the DNA damage, and cellular parameters like turnover kinetics, the capacity to repair sublethal damage, and intrinsic radiosensitivity [13–17].

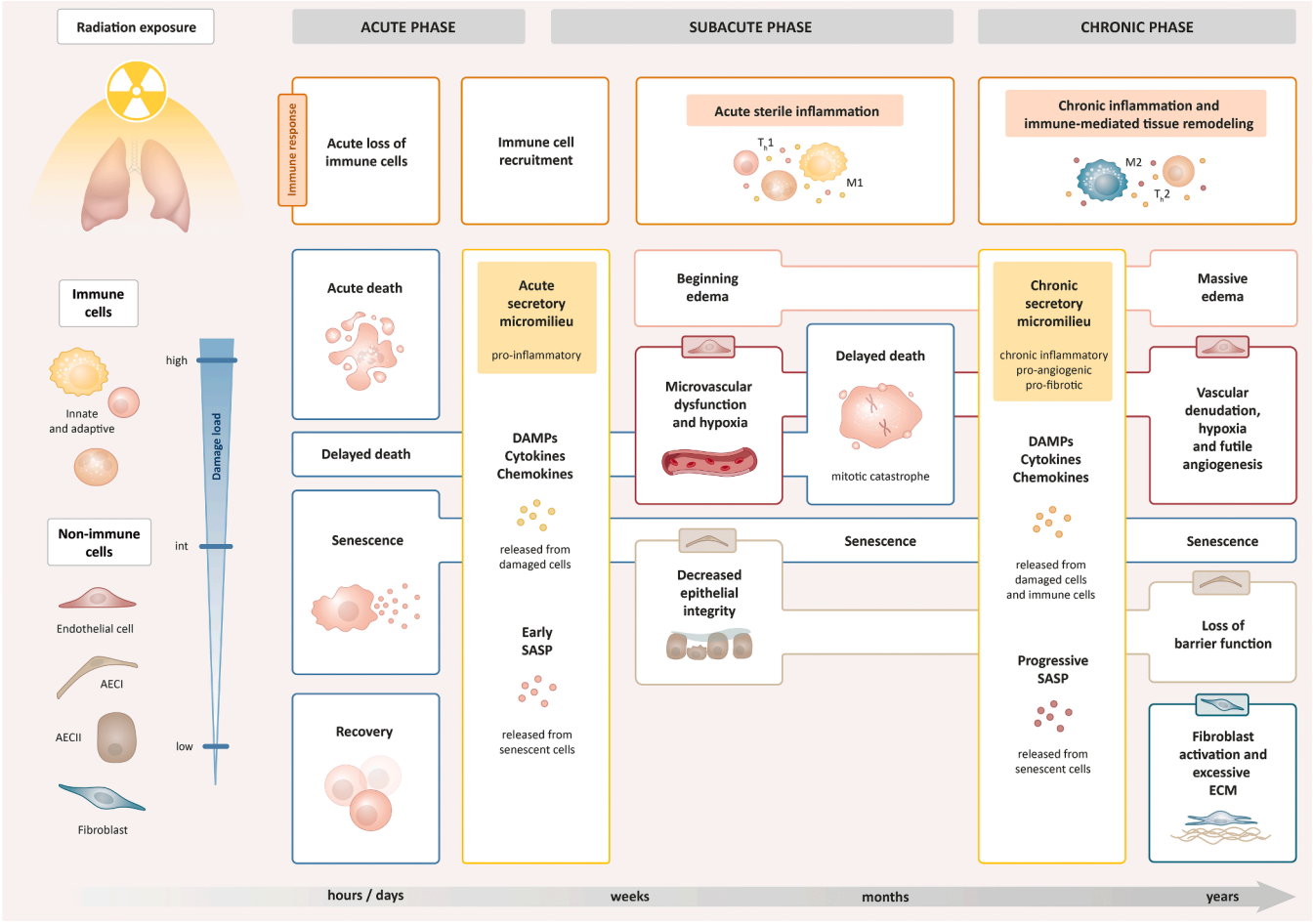

Fig. 1B. Radiation response of the lung over time. Exposure to ionizing radiation initiates a multifaceted response of the normal lung tissue that can be divided into an acute phase (hours to days after irradiation), a sub-acute phase (days to weeks after irradiation) and a chronic phase (months to years after irradiation). Each phase is marked by intensive cellular interactions between non-immune cells, like endothelial, alveolar epithelial type I (AECI) and II (AECII) cells and fibroblasts, as well as cells from the innate and adaptive immune system. Depending on their intrinsic radiosensitivity, lung tissue cells acquire differential degrees of damage load and respond with acute or delayed cell death, senescence, or achieve recovery. In the early phase of the radiation response, an acute loss of highly radiosensitive immune cells from peripheral blood and lung tissue is observed. The entirety of DAMPs, cytokines and chemokines released from stressed, damaged or dying cells, as well as signaling molecules of the senescence-associated secretory phenotype (SASP) constitutes the acute secretory micromilieu, which is mainly pro-inflammatory and fosters a time-dependent recruitment and activation of a variety of immune cells. The levels and temporal patterns of cytokine/chemokine responses in mice are dose, volume, and strain-dependent and include, for example, C–C motif chemokine ligand 2 (CCL2), interleukin (IL)-1a and IL-1b, IL-6, IL-17, tumor necrosis factor a (TNF-a), and transforming growth factor β (TGF-β). Accumulating lymphocytes and other leukocytes, as well as senescent cells provide a secondary wave of cytokines/chemokines. If not resolved, these inflammatory responses lead within weeks to a pronounced sterile lung inflammation (subacute RP). The progression to the sub-acute phase is further marked by microvascular dysfunction, beginning hypoxia and edema, as well as decreased epithelial integrity. At later stages, DAMPs, cytokines, chemokines, growth factors and proteases released from cells undergoing delayed cell death as they attempt to enter mitosis (mitotic catastrophe) and persistent senescent cells further shape the chronic secretory micromilieu, which has pro-angiogenic and pro-fibrotic effects and promotes chronic inflammation of the lung, a shift towards M2-like macrophages and T_h2-polarized $CD4^+$ T cell phenotypes, and immune-mediated tissue remodeling. Ultimately, the chronic inflammatory micromilieu fosters the accumulation and activation of fibroblast that produce excessive amounts of extracellular matrix (ECM) molecules, resulting in lung fibrosis.

Many immune cells, particularly B-lymphocytes, natural killer (NK) cells and red blood cell precursors, are highly radiosensitive and can undergo acute apoptosis, even at low doses of irradiation. T cells, on the other hand, exhibit a range of radiosensitivity depending on their specific subset.

Myeloid cells and dendritic cells (DCs) are more radioresistant than lymphoid cells, while myeloid progenitor cells are more sensitive to radiation than macrophages and DCs [18]. This differential sensitivity results in an early, transient drop in blood lymphocyte cell counts and resident alveolar macrophages is observed in animal models and patients [19,20]. Acute toxicity from thoracic irradiation also leads to an early reduction in proliferation, senescence, or death of endothelial cells, as well as a loss of alveolar epithelial type I cells (AEC I), which cover about 90 % of the healthy alveolar surface. In contrast, alveolar epithelial type II cells (AEC II) undergo dose-dependent acute changes, and subsequently hyperproliferate to compensate for the loss of AEC I cells [21,22].

Signalling cascades in damaged and dying cells trigger the release of damage-associated molecular patterns (DAMPs) and pro-inflammatory cytokines/chemokines, which recruit effector cells from the innate and adaptive immune system. The first wave of infiltrating immune cells is observed within hours to days post-irradiation and includes neutrophils, followed by eosinophils, basophils, inflammatory monocytes, and lymphocytes – all of which are crucial for promotion of tissue protection and repair [20,23–26] (Figs. 1b). In parallel, radiation exposure induces inhibitory signals, such as programmed cell death 1 (PD-1) and programmed cell death 1 ligand 1 (PD-L1) immune checkpoint proteins [27], and inhibitory cell types such as regulatory T cells (T_{regs}) [19] to

avoid excessive inflammation.

Subacute and chronic phase

The extent, dynamics and mode (immunogenic or silent) of radiation-induced cell inactivation strongly impact the pathogenesis of RILD [28]. Functional changes induced by the senescence or death of AEC I and microvascular endothelial cells disrupt the epithelial barrier, leading to increased vascular permeability and the development of alveolar and interstitial oedema, typically within the first weeks after thoracic irradiation. The upregulation of adhesion molecules, such as intercellular adhesion molecule I (ICAM-I), on activated endothelial cells [23,29,30], and a dynamic secondary wave of secreted factors released by recruited leukocytes and senescent cells (e.g., pro-inflammatory TNF-alpha [31,32], growth factors and proteases) intensify the inflammatory response and drive degenerative changes in the alveolar epithelia and endothelium. If unresolved, these overwhelming inflammatory responses can lead to pronounced sterile lung inflammation (subacute RP) within 4–12 weeks [33] in sensitive individuals.

This environment promotes futile angiogenesis, chronic inflammation, excessive deposition of extracellular matrix molecules, and ultimately leads to RP [28,34–36]. The pro-fibrotic phase starts only months after irradiation and is marked by local activation of microvascular endothelial cells and pathologic myofibroblasts, deregulation of stem cells, and a phenotypic switch of recruited inflammatory monocytes and T cells towards immunoregulatory cell phenotypes [30,37–44] (Figs. 2). This shift in immune cell phenotypes plays a crucial role in the development and persistence of radiation-induced pulmonary fibrosis.

Biomarkers and targets derived from preclinical studies

(Epi)genetic factors that influence the induction, sensing, signalling and repair [45–47], as well as individual variations in immunological responses, contribute to the heterogeneity in the risk of developing RILD [12,23,28,48].

Currently, the ability to predict an individual's risk of developing RILD is limited and is primarily feasible in rare cases involving patients who suffer from one of the few genetic syndromes associated with DNA repair disorders and radiation hypersensitivity caused by mutations in DNA repair genes, e.g., ataxia telangiectasia mutated (*ATM*), ligase 4 (*LIG4*), Artemis (*DCLRE1C*), Meiotic recombination 11 (*Mre11*), Nijmegen breakage syndrome (*Nbs1*), Bloom syndrome (*BLM*), and potentially Rothmund-Thomson syndrome (*RECQ4*), or certain genes associated with Fanconi anaemia, dyskeratosis congenita or Xeroderma pigmentosum [46].

Suggested immune biomarkers for RILD include altered basal or radiation-induced levels of purinergic signalling (e.g., ATP) [49], surfactant proteins [47,50], soluble ICAM [51] or baseline and radiation-induced variations in cytokines/chemokine levels [26,52,53] or specific immune cell types (lymphocytes, myeloid cells) in serum, bronchoalveolar lavage or lung tissue.

For example, elevated serum levels of TNF-alpha or (activated) TGF-beta1, or increased tissue levels of TGF-beta mRNA are associated with an increased risk of RP [32,54–56]. Increased levels of TGF-beta also correlate with the initiation of RPF [21,31,57]. Furthermore, an acute decrease in lymphocyte counts and neutrophilia in peripheral blood has been observed before the onset of RP [20] and has been found to correlate with RP severity [58].

Emerging biomarkers from studies comparing mice with distinct sensitivity to RP and RPF have been identified but translation to humans is lacking [20,38,41,59–62]. At present, none of these suggested predictive markers are used in clinical practice.

Mechanism-based principles for radioprotective treatments include mitigation of radiation-induced oxidative stress by free radical scavengers (amifostine, manganese superoxide dismutase), or inhibition of pathologic signalling through the renin-angiotensin system (angiotensin converting enzyme inhibitors) [63], fibrosis-promoting TGF-beta [56,64], platelet-derived growth factor (PDGF) [65] or connective tissue growth factor (CTGF) [35]. Accumulating knowledge about pathology-promoting immune changes provides novel targets for the attenuation of RILD. These include the IL-1beta/C–C motif chemokine ligand 2 (CCL2)/C–C motif chemokine receptor 2 (CCR2) axis [42,66], colony stimulating factor-1 receptor (CSF-1R) [67], the 5ectonucleotidase (CD73)/adenosine immune checkpoint [68], and senescence [17,69,70]. These factors are thought to impact the recruitment and pathologic differentiation and expansion of pathology-promoting myofibroblasts, M2-like macrophage-subpopulations and T_{regs}.

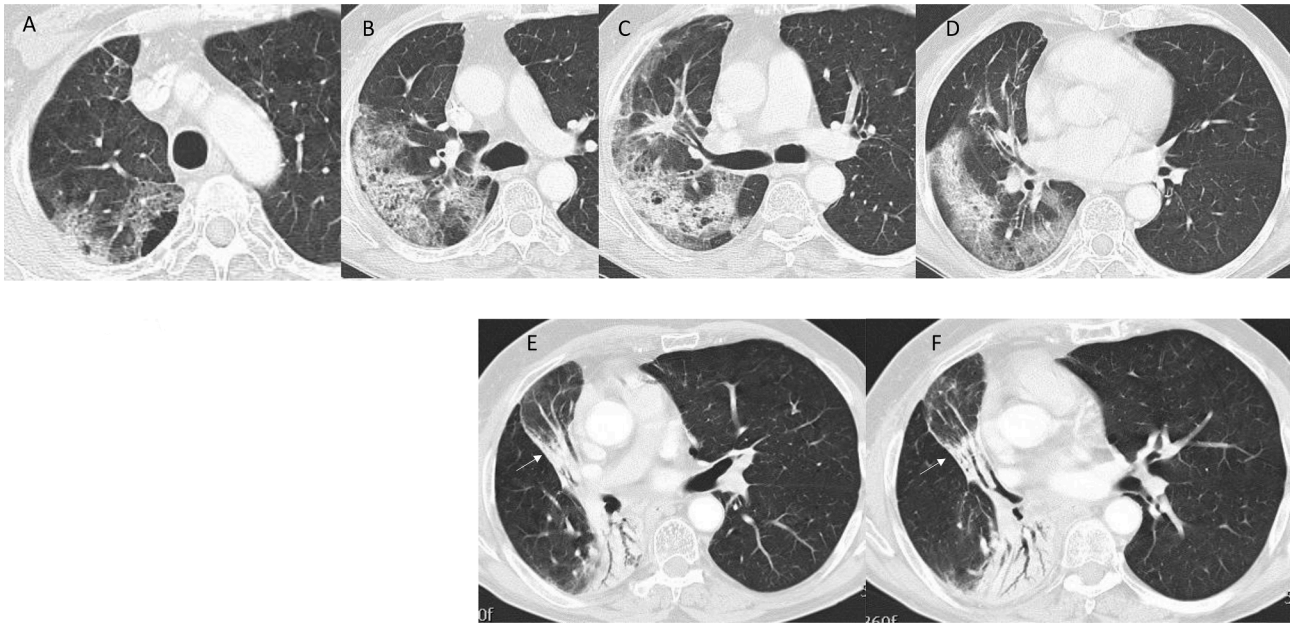

Fig. 2A. Acute and late phase of radiation pneumonitis. A 68-year-old man was treated by a combination of chemo and radiotherapy (65 Gy) for a squamous cell carcinoma of the right upper lobe. (A-D) Acute radiation pneumonitis with cough and fever occurred at 2 months following radiotherapy and was characterized by extensive ground glass opacity. The patient received steroid therapy (EF) Six months later, characteristics indicative of radiation fibrosis emerge, including consolidation, traction bronchiectasis and volume loss. Note the sagittal displacement of the minor fissure (white arrows).

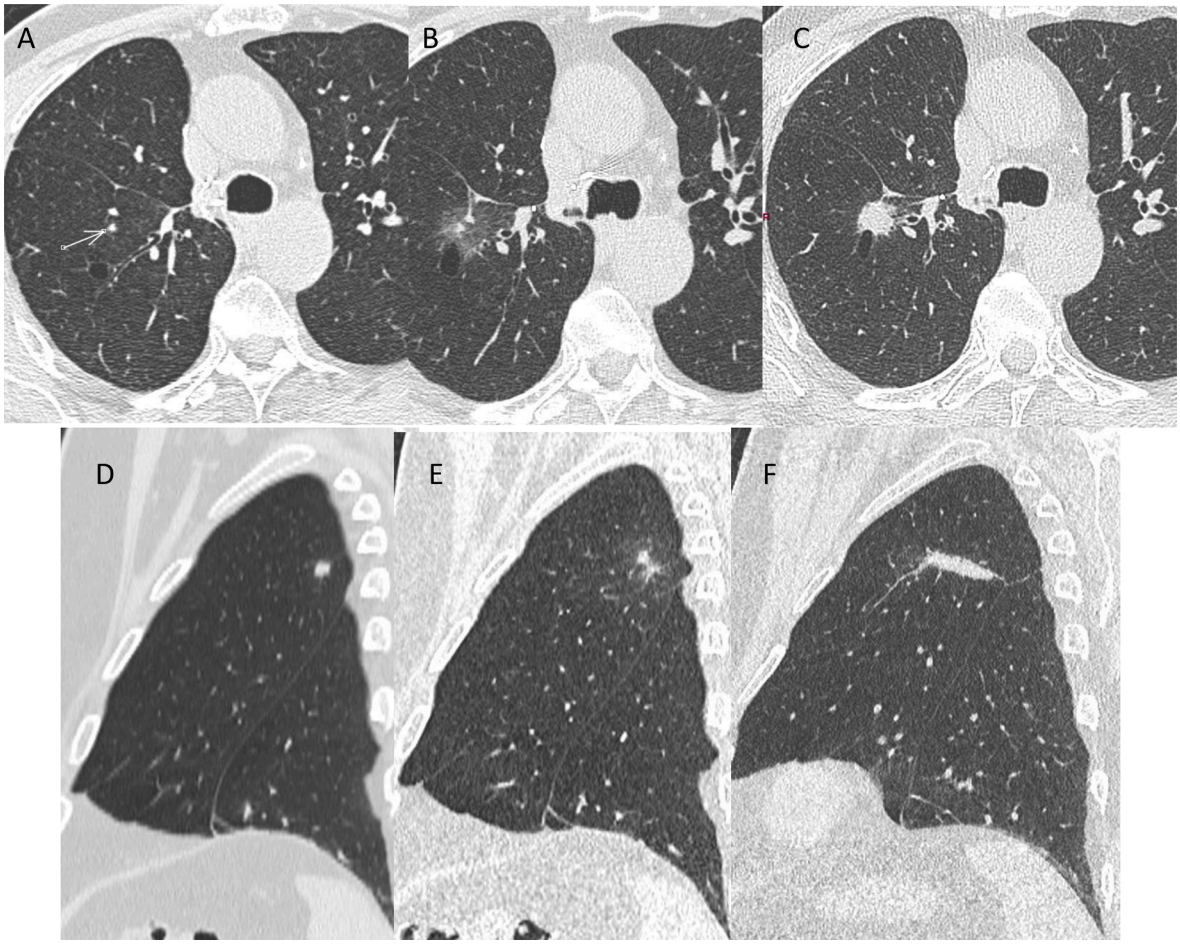

Fig. 2B. Imaging changes after SBRT. (A) A 5 mm growing nodule (white arrow) was detected in a 64 year-old patient with previous right upper lobectomy (B) At 9-month following SBRT, the nodule was surrounded by ground glass opacity (C) A mass-type fibrosis was observed at 2 years' follow-up and remained unchanged 9 years after SBRT. (D) Growing nodule of the left upper lobe in a 86-year old man. (E) 2 months after SBRT, the nodule has an irregular shape and is surrounded by ground glass. (F) A scar-like fibrosis is observed at 9 months after SBRT.

Heterogeneity in the individual risk for adverse pulmonary effects

Only a fraction of patients develops severe RP or RPF. Therefore, it is crucial to define biomarkers that can identify patients at increased risk for higher grade toxicity. The individual tolerance of a patient will depend on factors such as genetic susceptibility, the physiological state of the tissue, and the immune status of the patient at the time of irradiation. Factors with impact health status and immune status, including repertoire such as lifestyle choices (such as including smoking), comorbidities, sex, MHC/HLA status, and the microbiome, have emerged as potential influences on the risk for immune-mediated RP and RPF. The role of these factors needs to be further investigated in future studies [71,72].

Pulmonary toxicity when combining radiotherapy with systemic treatments

The preclinical evaluation of potentially increased pulmonary toxicity associated with combination treatments and of its implications for patient outcome, remains a largely neglected area of radiobiology. A single preclinical study reported that combining thoracic irradiation (19 Gy) with acute treatment using an anti-VEGF antibody resulted in more severe RPF in healthy mice [73].

Radiotherapy and ICI therapy may evoke immune-related, potentially overlapping adverse effects to the lung [74,75] and potentially to the heart. Despite their distinct initiation events, both radiation-induced oxidative tissue damage and anti-PD-1/PD-L1-induced reactivation of cytotoxic T cells lead to dynamic and partially overlapping alterations in the cytokine and immune cell repertoire [38,46,48,76].

Furthermore, significant decreases in absolute lymphocyte counts and increases in neutrophil to lymphocyte ratio (NLR) have been associated with ICI-pneumonitis and RP [58,77,78]. (Re-)activation of autoreactive T cells by anti-PD-1/PD-L1 therapy may cause recall-phenomena in previously irradiated lungs [79], suggesting an autoimmune component of radiation-induced adverse effects.

Other preclinical studies have highlighted increased cardiac toxicity when combining radiotherapy and anti PD-1 treatment, attributing this to increased toxicity of $CD8^+$ T cells towards cardiomyocytes [80,81].

Risk factors

Drawing practical conclusions from the available literature on risk factors of RP remains challenging. The wide range of potentially relevant factors, combined with the limited detail in many studies, complicates the cross-comparison of findings. Many articles reported clinical risk factors such as baseline performance status, age at diagnosis, smoking status, pulmonary function tests and dosimetric parameters as risk factors for the development of RP. However, these studies often differ significantly in terms of population and treatment regimens, leading to considerable variability in the findings.

Interestingly, smoking status, tumour location, pulmonary function tests, concurrent medications such as chemotherapy, immune therapy and targeted agents and dosimetric parameters as risk factors for the

development of RP. However, these studies often differ significantly in terms of population and treatment regimens, leading to considerable variability in the findings.

Interestingly, smoking during radiotherapy has consistently been associated with a lower risk of RP, both in the absence of adjuvant immunotherapy and with immunotherapy, as demonstrated in the PACIFIC trial [82]. The mechanisms underlying this observation are unclear, and the causality between smoking habits and RP risk remain uncertain. Despite these findings, smoking cessation is recommended due to its widely recognized and numerous health benefits [83].

Radiotherapy technique

As radiotherapy techniques have advanced from 3D to more sophisticated methods such as intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and proton therapy, the ability to meet typical target constraints, such as V_{20} and MLD, has significantly improved. However, some of these techniques are associated with higher volumes of pulmonary tissue receiving lower doses. Despite evidence showing that the low-dose irradiation parameters (e.g. high V_5 values) of the lungs can increase risk of RP, optimizing for this particular constraint is currently not the primary goal during radiotherapy planning in lung cancer. A secondary analysis of the RTOG 0617 trial demonstrated that the lung V_5 was not associated with grade 3 toxicity, whereas lung V_{20} was associated with increased grade 3 pneumonitis risk in multivariable analysis. In addition, the rates of severe pneumonitis were lower with IMRT compared to 3D RT, indirectly confirming the limited impact of the exposure of normal lung tissue to lower doses [84].

For early stage peripheral lung cancer patients not suitable for surgery, stereotactic body radiotherapy (SBRT) is the standard of care and is associated with low rates of toxicity. Despite of fragility of this patient population, symptomatic pneumonitis rates with SBRT are below 5 % [85].

Interstitial lung disease / IPF

Interstitial lung disease (ILD) is a broad term that covers a variety of conditions affecting the lung tissue. Patients with ILD have a higher likelihood of developing lung cancer and a poorer prognosis compared to lung cancer without having ILD [86]. This field, previously characterized by low-level evidence, has recently experienced significant improvements, particularly in early-stage disease, largely due to the contribution from the prospective ASPIRE-ILD [87] phase 2 non-randomized study. The study evaluated the use of stereotactic ablative radiotherapy (SABR) in patients with early-stage NSCLC (T1-2 N0) and moderate ILD. It should be noted that 70 % of patients reported dyspnoea at baseline. The median overall survival was 25 months. Thirty-one percent of patients experienced grade 1–2 events, 10 % grade 3, and 7.7 % grade 5 (all due to respiratory deterioration).

Impact of concurrent systemic anti-cancer treatment

Treatment approaches in the literature vary widely according to the different clinical scenarios, including chemo-radiotherapy and immunotherapy, and targeted therapies in case of driver mutations, making it challenging to draw meaningful comparisons between studies with regards to safety and efficacy.

Immunotherapy consolidation following chemo-radiotherapy may increase the incidence of RP, especially among patients with pre-existing interstitial lung disease [88]. Additionally, immunotherapy on its own is associated with an increased risk of pneumonitis, independently from radiotherapy [86]. Data and understanding of the complex interactions between radiotherapy, systemic therapy, pre-existing lung conditions and dosimetric parameters are very limited.

Dosimetric constraints

Many reports suggest OAR constraints predictive of RP. These studies evaluated dosimetric criteria retrospectively, extracted from dose volume histograms (DVH), mainly analysing the dose to the total lungs (ipsilateral and contralateral lung). Various dosimetric values were reported, such as V_5, V_{10}, V_{15}, V_{20}, V_{30} and mean lung dose (MLD), with different cut-off values. In clinical practice, largely guided by the QUANTEC analyses and EORTC recommendations [5,89], it is generally considered reasonable to aim for a V_{20} below 35 % and a MLD of less than 23 Gy. For hypofractionated and stereotactic radiotherapy, many clinicians refer to the Timmerman tables [90] or the UK consensus guidelines [91] which provide useful dose constraints for various fractionations schemes (ranging from a single to 30 fractions).

Clinical consequences of ambiguous definitions

It is important to acknowledge certain flaws in the existing literature that complicate the integration of findings on risk factors for RP into daily clinical practice. Patient-related risk factors have been mostly investigated retrospectively and in heterogeneous populations, with a potential selection bias. In addition, treatment-related risk factors are mostly reported in a descriptive manner with barely any underlying predictive models. The full dose–effect relationship is often inadequately detailed; for example, the average lung dose and pneumonitis risk typically remain stable at lower doses, while increasing significantly at higher doses. Most recommendations set a threshold for the MLD, based on a dose point associated with increased risk, resulting in weak correlations between dose and the incidence of pneumonitis. The most significant issue, however, is the inconsistent definition of RP across different studies.

For instance, in a recently published interventional trial the primary endpoint was freedom from pulmonary exacerbations at 1 year, defined as follows: "*Acute pulmonary exacerbations were defined as unexplained worsening or development of new cough, dyspnoea, hypoxia, or pneumonia lasting more than 4 days with new or worse diffuse pulmonary infiltrates on CT chest without significant pneumothorax or pleural effusion, and exclusion of alternative causes such as pneumonia, congestive heart failure, pulmonary emboli, or cancer progression*" [92]. In this context, the maximum dyspnoea score following radiotherapy was used as an indicator of pneumonitis. However, the baseline dyspnoea score is often assumed to be grade 0, despite the fact that, in clinical practice, many patients already have symptomatic underlying lung disease before the initiation of radiotherapy [93,94].

In summary, identifying risk factors to prevent the appearance of RP is a first step to prevent radiotherapy-related lung damage. Lung cancer treatment strategies are continuously changing with the introduction of new systemic treatments; the literature reviewing RP risk factors is inadequate and a comparison between different studies is challenging. Table 1 shows a list of risk factors and a weighing of their importance based on expert consensus.

Diagnosis of RP

RILD is a common occurrence in patients undergoing external radiation therapy (RT), manifesting with varying clinical presentations and degrees of severity across individuals [95]. The clinical diagnosis of RP, the acute manifestation of RILD, relies on a comprehensive assessment of symptoms, timing to RT, pertinent medical history, and corroborative imaging findings. In addition, the diagnosis of RP hinges on the meticulous exclusion of alternative aetiologies, including – but not limited to- lung infection, exacerbation of heart failure or chronic obstructive pulmonary disease, pulmonary embolism, drug-induced pneumonitis, and progression of malignant disease such as lymphangitis carcinomatosis. However, ruling out alternative diagnoses can be challenging. In a prospective study involving 318 patients undergoing thoracic

Table 1
Selected risk factors in curative-intent conventionally fractionated radiotherapy for lung cancer and a weighing of their importance based on expert consensus.

Significance for decision-making	Examples	Expert advice
High	ILD V20 > 45 % MLD > 30 Gy	These cases require a very individualized approach including potential compromises in dose-coverage or sequencing of treatment. Recommendations for radiotherapy need to be critically discussed with the patient.
Medium	V20 > 35 % MLD > 23 Gy Concurrent treatment with Carboplatin / Paclitaxel or Immune Checkpoint Inhibitors	These situations are associated with a higher risk for pneumonitis. If possible these situations are to be avoided, but can be considered routine after critical assessment.
Typical	Established standard concurrent systemic treatments. V20 < 35 % MLD < 23 Gy	Even when special risk factors are present, radiation pneumonitis is possible. While the risk is kept as low as possible, it typically cannot be avoided completely. This risk is routinely accepted.

MLD: Mean Lung Dose; V20: The percentage of normal lung receiving at least 20 Gy. We recommend to use the volume of both lungs subtracted by the gross tumour volume (GTV) to define the MLD or the V20.

radiotherapy for lung cancer, challenges in diagnosing RILD were observed in 28 % of cases, primarily attributed to the presence of confounding medical conditions [96].

The findings of RP include an array of symptoms typically emerging within 1–6 months following the completion of radiotherapy. Symptoms are not specific and may consist of low-grade fever, shortness of breath, non-productive cough, pleuritic chest pain, and a progressive decline in exercise capacity as RP evolves [97].

Physical examination may reveal crepitations on lung auscultation, and laboratory findings may indicate acute inflammation (such as raised inflammatory markers).

Pulmonary Function Tests (PFTs) assess the severity of respiratory impairment and typically show a reduction in lung volumes and diffusing capacity of the lungs for carbon monoxide, the latter being more sensitive. However, changes in PFTs are not always correlated with clinical and radiological findings. In addition, such changes may persist despite therapeutic interventions [98]. Conversely, in some cases, PFTs may improve after RT completion due to tumour response. Consequently, relying solely on PFT parameters to diagnose RP is not advisable [99]. Instead, a comprehensive evaluation should ensure an accurate diagnosis, including clinical symptoms and radiological findings, evaluation of the temporal relationship with radiotherapy, and exclusion of alternative diagnoses. Bronchial endoscopy may be performed to rule out other possible causes, such as infection or disease progression [98]. A bronchoalveolar lavage (BAL) and microbiological analysis of BAL fluid are sometimes advised. However, this may not always be feasible from a practical or clinical point of view (such as in a clinically unstable patient). In a retrospective study of 118 patients, procalcitonin (PCT) levels in the blood enabled to differentiate between acute RP and bacterial pneumonia in lung cancer patients receiving thoracic radiotherapy [100]. These findings need to be confirmed in prospective studies.

Currently, the CTCAE (Common Terminology Criteria for Adverse Events) version 5 is widely used to score pneumonitis. Pneumonitis grade 1 is asymptomatic with clinical or diagnostic observations only and no intervention is needed. Grade 2 is symptomatic and medical intervention is needed because the pneumonitis is limiting instrumental ADL (activities of daily living). Grade 3 is causing symptoms, limiting self-care ADL or oxygen is needed and grade 4 is life-threatening respiratory compromise.

It should be noted that pneumonitis grading within CTCAEv5 is different from the grading for dyspnoea (supplementary file). Grade 1 dyspnoea is shortness of breath with moderate exertion, thus symptomatic. A patient presenting with grade 1 dyspnoea cannot be classified as either asymptomatic grade 1 pneumonitis or grade 2 pneumonitis without additional information, such as radiological evidence indicative of pneumonitis.

Radiological changes

All patients undergoing radiotherapy directed at the lungs are expected to develop some radiographic changes over time. If asymptomatic, these patients would be categorized as having grade 1 pneumonitis [97] (Figs. 1A and 1B). These radiological changes may not necessarily correlate with clinical symptoms [101].

Radiological changes may occur in asymptomatic patients and sometimes correlate with decreased FEV1, particularly in patients with COPD, who are at greater risk [102].

Computed tomography (CT) is the primary imaging technique for diagnosis of RP, with contrast administration. Multidetector CT technology enables high-resolution imaging, essential for accurately detecting interstitial lung injury in routine assessment. Low dose protocol can be applied when modern image reconstruction algorithms, such as iterative or deep learning reconstruction is used. The imaging appearance of irradiated tissues varies according to the time elapsed since the completion of therapy. During the acute phase (1–6 months), ground-glass opacities (GGO) and consolidation are the main radiological features. In the late phase (6–12 months), characteristics indicative of radiation fibrosis emerge, such as volume loss, consolidation, and traction bronchiectasis [103].

Typical features after fractionated (chemo)-radiotherapy

There are several classification systems based on CT findings, and the results vary according to the time elapsed since the RT was completed. Jenkins and Welsh assessed CT changes at 3 months in 146 patients who had received RT for non-small cell lung cancer [104]. New CT abnormalities such as GGO and patchy diffuse consolidation were observed in 63 % of patients, but only 17 % developed symptoms. A marked variability in the severity of radiologic toxicity was reported. The minimum isodose encompassing the volume of radiologic abnormality was generally $\geq$ 27 Gy.

A classification system for quantifying common radiologic findings observed 12 months after lung cancer RT has been published [105]. This classification system includes parenchymal changes (GGO, consolidation, traction bronchiectasis, and reticulation), volume reduction (such as fissural distortion, elevation or tenting of the hemidiaphragm), and pleural changes (such as effusion, thickening, or both).

A PET-based diagnosis of RP features includes a relative intensity of ^{18}FDG-uptake in the non-tumoral lung parenchyma compared to background, mediastinum, and liver. It has been reported to occur in 71 % of patients after radical RT for lung cancer [106]. ^{18}F-FDG PET/CT is not routinely used to detect RP but can be used to distinguish between RP and tumour progression. A recurrence is to be suspected when an increase in metabolic activity or a lack of a trend toward normalization of ^{18}FDG uptake is observed during follow-up [107].

In patients who have undergone chemo-radiotherapy and present with symptoms such as fever, cough, and breathlessness, the two primary differential diagnoses are lower respiratory tract infection and RP [108]. For those undergoing consolidation immunotherapy following CRT, immune-related pneumonitis should also be considered in the diagnostic evaluation [109]. Differentiating between RP and ICI-related pneumonitis is critical due to their differing treatment implications and potential impacts on patient outcomes. ICI-related pneumonitis is one of the most severe and life-threatening adverse events associated with

immunotherapy. Its diagnosis is further complicated in patients undergoing consolidation immunotherapy after concurrent chemoradiation therapy (CRT), as both RP and immune-related pneumonitis must be considered during the clinical assessment. Misdiagnosing ICI-pneumonitis as RP—or vice versa—can significantly influence treatment decisions. Overdiagnosing ICI-pneumonitis may unnecessarily interrupt or discontinue beneficial immunotherapy. This underscores the need for a multidisciplinary approach involving radiologists, radiation oncologists, medical oncologists, and pulmonologists to achieve an accurate diagnosis and guide appropriate management.

When radiological changes are strictly confined to the irradiated zone, distinctly separate from unaffected areas, this strongly supports the diagnosis of RP. However, this criterion is not always conclusive, as radiological changes can occasionally extend beyond the irradiated area or involve the contralateral lung. The interpretation of radiological changes is particularly complex when systemic therapy is delivered in addition to radiotherapy [103].

Radiomics holds promise in differentiating between ICI-related and RT-induced pneumonitis. However, the performance of these radiomic models remains constrained and often lacks external validation, a limitation seen across many publications in the field [110,111].

As previously mentioned, multi-parameter models are emerging for differential diagnosis. For instance, a model integrating serum biomarkers (such as procalcitonin and white blood cell count) with dosimetric parameters (such as mean lung dose and the volume receiving 20 Gy or more (V_{20Gy}), and the spatial relationship between lesions and radiation dose distribution has shown promising results, achieving a sensitivity and specificity of 82 % [112]. However, it is worth noting that some models may not integrate imaging features, which could potentially enhance diagnostic accuracy. Therefore, ongoing research efforts focus on developing comprehensive and validated models incorporating multiple clinical features, circulating biomarkers, and imaging parameters to improve diagnostic accuracy.

Typical features after stereotactic body radiation therapy (SBRT)

Clinically significant RP is less frequent (4 %) following SBRT, in which a smaller volume of lung tissue is exposed to a high dose of radiation [103].

Late radiographic changes after lung SBRT have been evaluated in 77 patients [113] and categorized into four groups: a) modified conventional pattern (GGO and consolidation less extensive than after conventional RT), b) mass-like fibrosis, c) scar-like fibrosis and d) no evidence of increased density. The modified conventional pattern of late fibrosis was the most prevalent category (45 %), followed by no evidence of increased density and mass-like fibrosis. Another series reported mass-like and conventional patterns as the most frequent [114], and it has been described that the fibrotic remodelling process may be ongoing for years after treatment [115].

The mass-like pattern observed in imaging studies challenges distinguishing between tumour progression and RP, as both demonstrate high FDG-uptake on PET-CT [116]. In such a situation, a multidisciplinary approach involving radiation oncologists, radiologists, and nuclear medicine specialists is essential for accurate interpretation and diagnosis. Close attention to clinical history, temporal relationship to treatment, and correlation with other imaging modalities can assist in making an accurate diagnosis. Additionally, serial imaging studies may provide insights into the evolution of these findings, helping to differentiate between benign radiation-related changes, tumour progression, and infection [117,118].

The diagnostic flow chart is shown in Figs. 2 (See Fig. 3.).

Recall pneumonitis

The delayed onset of radiation-induced lung damage within the previously treated radiation field is a clinical condition known as called “radiation recall pneumonitis” (RRP). This was first reported in the 1960 s and 1970 s and is usually induced by post-radiation treatment

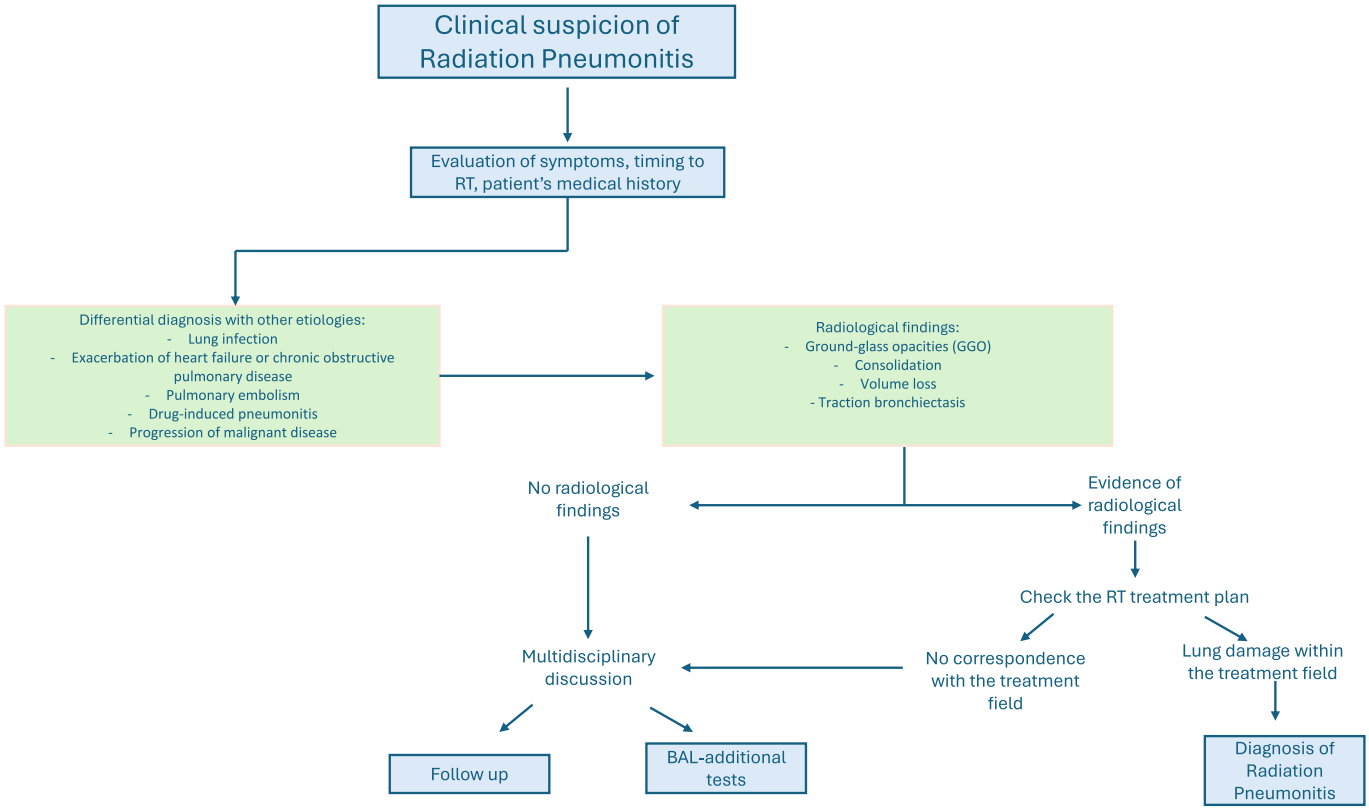

Fig. 3. Diagnostic workflow.

with systemic drugs [119].

As possible mechanisms of RRP, different hypotheses were proposed, such as an abnormal release of reactive oxygen species, anomalies of tissue vasculature, a non-immune fixed drug reaction-like condition or an impaired DNA repair [102–105].

There is significant variation in the time period between the end of radiation therapy and the onset of the recall reaction [120]. This broad range highlights both the heterogeneity of the underlying pathophysiology and the inconsistency in defining radiation recall pneumonitis.

Recall pneumonitis is often more severe than acute pneumonitis and the severity can be particularly pronounced when the interval between radiation-therapy and subsequent systemic treatment is short [121]. When significant and late effect radiation-induced toxicity emerges, radiation recall pneumonitis should be considered, especially if new acute toxicity symptoms appear within the previously treated area.

No absolute radiation dose threshold or specific dosimetric factors have been established for RRP, and no patient- or disease-associated risk factors have been clearly identified. RRP has been observed following the administration of chemotherapy [122,123], immunotherapy [124] or vaccination [125,126] after radiotherapy. The most typical histopathological feature of RRP is a mixed, non-specific inflammatory infiltrate. [119].

Chemotherapy-induced RRP

RRP is associated with different chemotherapeutic agents, such as taxanes [127], anthracyclines [128,129] and gemcitabine [130]. About 20 % of RRP are caused by taxanes and 30 % by anthracyclines, the other by a variety of drugs [119]. The median intervals observed were 95 days between radiation therapy and RRP and 47 days between the start of chemotherapy, and RRP. Notably, some findings suggest that patients with a history of RRP might be safely rechallenged with certain medications provided they receive concurrent steroid treatment [131].

Immunotherapy induced RRP

Interstitial lung disease is a known side effect of ICIs, making it challenging to distinguish between drug-induced pneumonitis and RRP. A high association between ICI-related lung damage and RRP has been reported [111,112].

Targeted therapy-induced RRP

RRP can also be related to the administration of targeted therapy. Chiang et al found that among 160 patients who received EGFR-TKI, 12.2 % of patients developed acute interstitial pneumonitis and RRP was observed in 4.4 % of patients [132]. The main feature that differentiates RRP from conventional EGFR-TKI-induced interstitial lung disease is that it is restricted to the previous radiation field with no bilateral or random distribution. A shorter interval between the administration of TKIs and radiation therapy was significantly associated with higher rate of RRP. Specifically, 21 % of patients who received targeted therapy within 90 days after radiation therapy developed RRP, compared to only 2.1 % in those who received targeted therapy after 90 days) [132].

Finally, the administration of vascular Endothelial Growth Factor (VEGF) Receptors, Mammalian Target of Rapamycin (mTOR) Inhibitors, Human Epithelial Growth Factor-2 (HER-2) Inhibitors and BRAF Inhibitors have also been shown to be associated with a potential increase risk of RRP [133].

Treatment

Asymptomatic patients should not be treated solely on the basis of CT changes and a watchful waiting approach with regular follow-up, e.g. every 3–6 months, is justified in this scenario.

In general, treatment is recommended for symptomatic patients (dyspnoea grade ≥ 1) in the subacute inflammatory phase. Glucocorticoids are the current mainstay of treatment. Given the limited number of published prospective series and the absence of prospective studies aimed at comparing glucocorticoids with a non-steroid regimen for symptomatic pneumonitis, clinical practice has been guided by expert opinion and the observed prompt response of most patients with RP to glucocorticoids. As a result, glucocorticoids are typically used as the first-choice treatment for symptomatic RP [134]. However, the optimal dose and duration of glucocorticoids has yet to be determined.

The preventive administration of oral glucocorticoids prior to onset of RP has not been shown to lead to a lower risk of developing RP [135]. Patients with Hodgkin's disease treated with preventive corticosteroids prior to RT can experience a temporary flare phenomenon of RP at the time of glucocorticoid therapy tapering after RT completion [135]. In addition, glucocorticoids are unlikely to be beneficial in the fibrotic phase and should be avoided in this setting to prevent unnecessary side effects.

The treatment approach of RP may vary based on the specific clinical scenario, particularly whether the patient is receiving immunotherapy. In all cases, it is crucial to investigate other causes of dyspnoea, such as infections, cardiac disorders and pulmonary embolism. Specific diagnostic procedures are outlined in Table 3.

1. After radiotherapy without immunotherapy (Table 3).

In a small single-centre retrospective study, 24 patients (ECOG performance status ≤ 1) with grade 2 RP were treated with high-dose inhaled glucocorticoids (budesonide 800 mg twice a day) for 14 days [136]. Eighteen patients (75 %) responded to this treatment with a significant reduction of symptoms, while six did not improve clinically within two weeks. The use of inhaled glucocorticoids requires close observation of the patient every 2–3 days, and non-responders need to be timely switched to oral glucocorticoids. All non-responders were subsequentially started on at least 50 mg of oral prednisolone, to which all of them responded [136].

Although using high-dose inhaled glucocorticosteroids is attractive, these findings need to be confirmed. Nevertheless, in patients with dyspnoea grade 1, inhalation medication may be used with careful monitoring every 2–3 days. In case of deterioration to grade 2, oral glucocorticosteroids should be initiated.

In case of grade 2 RP, Expert opinion suggests starting prednisone at a dose of 0.5 mg/kg/day ideal body weight (approximately 40 mg/day) for two weeks, followed by a gradual tapering with a total treatment duration of 4 to 6 weeks. Treatment is in general started orally, however in more severe cases intravenous (IV) treatment with higher doses is warranted. During tapering, close symptom monitoring is warranted to ensure symptoms do not re-emerge. In case of symptoms relapse, the advice is to return to full dose of prednisone for 2 weeks followed by a slower taper attempt, particularly when the dose is 20 mg a day and less.

A small phase 2 randomized trial suggested a positive effect of nintedanib on reducing the risk of recurrence of RP [92]. Patients who were randomized to receive either nintedanib combined with a standard 8-week prednisone taper or placebo/prednisone showed a numerically lower rate of pulmonary exacerbations at 1 year. Nintedanib, a multikinase inhibitor used in the treatment of fibrosing interstitial lung disease, may indeed impact molecular pathways that are involved in RP. However, confirmation of the results from this small trial is needed before considering any changes to the current standard of care, which remains prednisone monotherapy.

Prophylaxis for Pneumocystis jiroveci pneumonia (PJP) +/- antiviral prophylaxis according to institutional guidelines is commonly recommended when the prednisone dose exceeds 20 mg a day for more than a month [137]. Adverse events of longer-term systemic glucocorticoids (hyperglycemia, weight gain, edema, bone health) should be prevented, and patients should be monitored accordingly.

In cases of no/insufficient response to glucocorticoids, the use of other immunosuppressive agents such as azathioprine and cyclosporine

has been reported in small case reports, but experience is limited [97].

Supportive care is of value for all patients and may include antibiotics, antitussive therapy, supplemental oxygen, pulmonary rehabilitation and treatment of comorbid cardiopulmonary diseases that may contribute to symptoms.

2. After sequential or concurrent chemo-RT with immunotherapy (Table 3).

For the treatment of pneumonitis occurring during immune checkpoint inhibition in patients previously treated with thoracic radiotherapy, we recommend following the latest ESMO guidelines on the management of immune-related toxicities [138]. Patients with newly developed grade 1 pneumonitis should undergo appropriate diagnostic evaluation, followed by close monitoring every 2–3 days. If symptoms worsen, management should proceed as outlined for grade 2 pneumonitis. For grade $\geq$ 2 pneumonitis, the advice is to hold immune checkpoint inhibition (ICI). After exclusion of other diagnoses (including infection), the start of 1 mg/kg/day of oral prednisolone (or equivalent) is recommended for grade 2 pneumonitis [138] for 24–72 h until clinical improvement is seen, followed by a 4–6 week taper. For higher grade $\geq$ 3 events, it is recommended to start with 1–2 mg/kg/day (methyl) prednisolone IV for 24–72 h. Steroid tapering can be considered after improvement to grade $\leq$ 1, over 4–6 weeks for grade 2 and at least 6–8 weeks for grade 3 events. If there is no improvement within 72 h of corticosteroid use, a second immunosuppressive agent could be added. Options include tocilizumab, infliximab, IVIG or mycophenolate mofetil, depending on local availability. The data in support of these options is limited, and based on expert consensus and limited small series [139–141]. Upon recovery to grade $\leq$ 1 pneumonitis, ICI rechallenge can be considered after grade 2 events. For grade $\geq$ 3 events, the recommendation is to permanently stop ICI.

3. Recall pneumonitis.

The current standard approach is comparable to the previous clinical scenarios, including the interruption of ongoing systemic treatments and start of corticosteroids according to the grade of severity of the pneumonitis event.

Discussion

In this practice guideline, we summarize the current state of the art regarding the mechanisms, diagnosis and treatment of RP. Drawing from a systematic review of the literature and expert opinion, we provide practical recommendations for the diagnosis and treatment of RP. We have also summarized dosimetric constraints aimed at minimizing the incidence of RP, as well as identified risk factors for developing RP, such as idiopathic pulmonary fibrosis (IPF). The risk factors and statements are summarized in Tables 1 and 2.

We emphasize the limitations of the available studies, which yield varying results in different and heterogenous groups of patients. Many factors are correlated, and most studies fail to account for this complexity. Most of the research is descriptive, with only a few studies providing information on predictive models, such as the area under the receiver operating characteristic curve (AUC), sensitivity and

Table 2
Statements.

	Statements	Evidence Quality	Strength of recommendation:
Risk Factors	The V20 or the mean lung dose (MLD) should minimized as reasonably possible, taking into account the need for adequate tumor coverage and the sparing of other critical organs. A reasonable target would be to keep the V20 below 35 % and the MLD under 23 Gy. To achieve these goals, modern radiotherapy techniques should be employed, including such as 4D-CT and motion management, VMAT and IGRT, which allow for smaller margins between the clinical target volume (CTV) and the planning target volume (PTV).	Expert opinion	Strong
	Patients with suspected interstitial lung disease (ILD) should be evaluated by a specialized respiratory physician. Patients with ILD and lung cancer treated with radiotherapy are at significantly higher risk of severe side effects, including treatment-related death. However, if dosimetric parameters consistent with the ASPIRE-ILD trial can be achieved, treatment with stereotactic body radiotherapy (SBRT) should not be withheld, provided it is supported by multidisciplinary evaluation and undertaken within the context of shared decision-making. For patients with locally advanced disease, a thorough and individualized assessment is essential to determine the most appropriate course of action.	Expert opinion	Strong
	Several systemic therapies increase the risk of pneumonitis / radiation pneumonitis. The overall risk should be carefully evaluated when selecting drugs and determining their timing in relation to radiotherapy.	Expert opinion	Strong
Recall pneumonitis	Patients treated with thoracic radiotherapy should be considered as a population at risk for late-onset radiation recall pneumonitis, especially if systemic cytotoxic, targeted or immune anti-cancer therapy was administered at any point following thoracic radiotherapy. This approach ensures that both potential causes are appropriately considered in patient care.	Expert opinion	Conditional
	Diagnosis and treatment of radiation recall pneumonitis should follow established guidelines for radiation pneumonitis. If systemic anti-cancer therapy was administered shortly before the onset of pneumonitis symptoms, management should align with guidelines for pneumonitis induced by systemic therapies.	Expert opinion	Conditional
Diagnosis	The diagnosis of RP requires careful differentiation from other conditions, such as drug-induced pneumonitis, pulmonary embolism, lung infection. Combining radiological, clinical and laboratory findings can aid in the diagnostic process and, in specific cases, broncho-alveolar lavage may be considered as an additional investigation.	Expert opinion	Strong
Treatment	– Glucocorticoids is the first choice for patients with newly diagnosed grade 2 or higher pneumonitis. For patients with grade 2 pneumonitis who have not received immunotherapy, the recommended prednisone dosage is 0.5 mg/kg/day based on ideal body weight (approximately 40 mg/day) for two weeks, followed by a gradual taper over a total treatment duration of 4–6 weeks. Treatment is generally started orally, but in more severe cases, intravenous treatment with higher doses is warranted. – For patients developing radiation pneumonitis during immunotherapy, the ESMO guidelines for the management of immune-related toxicities should be followed. Differentiating RP from immune-related pneumonitis at the onset of symptomatic pneumonitis can be challenging and requires a multidisciplinary assessment.	Expert opinion	Strong

Table 3
Treatment.

Any worsening **of dyspnoea (CTCAE 5.0 grade) and no immune therapy**		
	Management	**Evaluation**
Any dyspnoea worsening	Always do a general evaluation to diagnose the cause(s) of dyspnoea, e.g. infection, cardiac disorders (arrythmia, heart failure), pulmonary embolism, …	Always consider supportive care such as anti-tussive, oxygen, rehabilitation …
Grade 1 (dyspnoea at moderate exertion)	General evaluation, chest CT with IV contrast, PFT including TLCO	Consider to start with high-dose inhaled corticosteroids*, if obstructive PFT combine with beta-2 agonist. If no improvement: treat according to grade 2.
Grade 2 (dyspnoea with minimal exertion, limiting instrumental ADL)	General evaluation, chest CT with IV contrast, PFT including TLCO, consider BAL, repeat chest X-ray	**No fast symptom deterioration and ECOG PS 0–1:** treat with oral prednisone 0.5 mg/ day/ ideal body weight (at least 40 mg/day) for 2 weeks, and if resolution to grade 0–1, followed by gradual tapering over the next 4–6 weeks**. Add Pneumocystis jiroveci pneumonia (PJP) prophylaxis*** **Fast symptom deterioration or ECOG PS ≥ 2:** hospitalization and start treat with prednisone 1–2 mg/kg/day IV until resolution, then taper**. Add Pneumocystis jiroveci pneumonia (PJP) prophylaxis***.
Grade 3 (dyspnoea at rest, limiting self-care ADL)	General evaluation, high-resolution chest CT with contrast, PFT including TLCO, consider BAL, repeat chest X-ray	Hospitalization and start treat with prednisone 1–2 mg/kg/day IV until resolution, then taper**. Add Pneumocystis jiroveci pneumonia (PJP) prophylaxis***.

*High-dose inhaled glucocorticoids: e.g. budesonide 800 mg twice a day for 14 days. Then taper according to symptoms.
**Gradual tapering of the oral prednisone dose with a total treatment duration of 4–6 weeks. Close symptom monitoring. In case of symptom relapse, return to full dose of prednisone of two weeks, followed by slower tapering, particularly when the daily prednisone dose is 20 mg or less.
***Pneumocystis jiroveci pneumonia (PJP) prophylaxis: 800 mg of sulfamethoxazole and 160 mg of trimethoprim once a day, 7 days/week.
PFT: pulmonary function tests, TLCO: diffusion capacity of the lungs for carbon monoxide, BAL: broncho-alveolar lavage.
Any worsening **of dyspnoea (CTCAE 5.0 grade)** ***and*** **immune therapy**.
Diagnose and treat according to the ESMO clinical practice guidelines on immune-related pneumonitis.

specificity. Additionally, the full dose–effect relation is often overlooked. For example, the correlation between mean lung dose and pneumonitis risk is generally flat at lower doses but increases significantly at higher dose levels [142]. Most guidelines set a mean lung dose threshold that reflects this inflection point, resulting in only weak correlations between mean lung dose and pneumonitis incidence. Furthermore, there is rarely a consistent, a priori definition of RP used across studies. Some studies assess dyspnoea, while others focus on pneumonitis, and the scoring systems used vary significantly between studies. This lack of standardization complicates the interpretation and comparison of results across different studies.

Although we believe that this work will aid clinicians in their daily practice, we also identified several knowledge gaps. Notably, most of the current understanding of the biological mechanisms underlying the development of RP comes from preclinical experiments. Given the significant differences between the immune and inflammatory system of humans and rodents [143,144], more insight could be gained by incorporating appropriate translational endpoints in clinical trials. These could include serum biomarkers and imaging techniques. Additionally, deep learning based systems may provide valuable insight in distinguishing between different etiologies of pneumonitis, such as differentiating diagnosis between RP and auto-immune pneumonitis in patients receiving immunotherapy [145].

Other avenue for generating more data on the mechanisms of RP include the use of ex-vivo human systems [146] and the development of more appropriate mouse models [147].

Dosimetric factors commonly used as constraints in clinical practice lack high predictive power and are primarily based on retrospective studies, many predating the era of IMRT and VMAT. Most recently published articles confirm the correlation between known DVH parameters and the occurrence of RP, but they have not introduced new and better models. Comprehensive models that include not only DVH parameters but also patient and biological parameters are scarce and often date back to a time when different radiotherapy techniques/ technologies and combinations with anti-cancer drugs were used [142].

To address these limitations, prospective registries, along with the incorporation of ex-vivo models and artificial intelligence (AI) tools could provide more reliable and precise answers [145,148].

Finally, RP remains at present a diagnosis of exclusion, as there are no features that are specific to RP. Therefore, additional diagnostic procedures, such as broncho-alveolar lavage may be required for some patients. Identifying more specific markers for RP continues to be a priority.

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CRediT authorship contribution statement

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.110837.

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