Radiation pneumonitis: occurrence, prediction, prevention and treatment

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Radiation pneumonitis is the most important dose-limiting toxicity in the treatment of thoracic malignancies amendable for high-dose radiotherapy such as lung or oesophageal cancer. Several patient-specific factors (e.g. age, smoking history, pre-existing inflammatory lung disease, tumour location and performance score) as well as treatment-related factors (e.g. radiation dose and volume, chemotherapy, hormonal therapy) have been studied as potential predictors of the risk of radiation pneumonitis. The most robust parameters that correlate with radiation pneumonitis are Dose Volume Histogram-related, such as the mean lung dose, the percentage of a volume receiving a certain dose such as the V20 and more complex models. All of these show a low overall accuracy with an area under the receiver-operator curve of about 0.65, although they might be still clinically useful by virtue of their high negative predictive value.

Besides research in the underlying genetics of radiation pneumonitis, the interaction between radiotherapy and most targeted agents has not been elucidated.

At present, validated Dose Volume Histogram parameters can be used in clinical practice. Drugs administered concurrently with irradiation of the lungs should only be carried out in combinations with proven safety in prospective trials.

Introduction
Radiation pneumonitis (RP) is a well-documented side-effect of lung irradiation. It is usually mild and transient but can, if seldom, result in oxygen dependence or death. Most data on RP are from lung cancer irradiation. However, lung tissue is irradiated in several other neoplastic diseases of the chest and upper abdomen. Symptomatic RP does not occur often but this might be due to the fact that radiation oncologists limit the administered dose. Lowering the dose might, for some of the patients, hamper tumour control.

In the past, a lot of effort has been made to study patient-specific as well as dosimetric factors that might predict RP. New irradiation techniques provide increasing accuracy and flexibility, but often larger areas of the lung receive low doses. Former dose/volume/outcome data of conformal radiotherapy might not be sufficient to predict RP when using these new techniques.

Occurrence
RP typically occurs one to five months after radiotherapy. The clinical syndrome of RP consists of dyspnoea, non-productive cough, pleuritic chest pain and fever. Radiological manifestations are usually limited to the irradiated field (ground-glass opacity or consolidation), with a geometric outline on chest radiograph and CT scan, corresponding to the shape and size of the treatment portals (Figure 1).

However, RP is still a diagnosis of exclusion. Exacerbation of Chronic Obstructive Pulmonary Disease (COPD), tumour growth, opportunistic infections or cardiac disease need to be ruled out.11,13 Even if chest X-rays show abnormalities caused by radiotherapy, it is not certain that dyspnoea is due to radiation damage. In addition, prevention of RP with agents having a possible radioprotective effect have been studied.

Keywords: radiotherapy, radiation pneumonitis, radiation toxicity.
In the clinical course of radiation-induced pulmonary damage, different phases are described. The first phase takes place before the onset of symptoms and has been studied in animal models. The experiments have shown that damage to the pneumocytes, the endothelial cells and the interstitial space already occurs on the first days after radiation. This so-called latent phase is followed by an intermediate or acute pneumonitis phase, with increased inflammatory response, characterised by obstruction of capillaries and increasing collagen and increasing number of leukocytes, plasma cells and fibroblasts. This phase is usually called RP. The alveolar septa thicken and the alveolar space reduces. In the late phase, from six months onwards after radiotherapy, pulmonary fibrosis can develop, which is characterised by loss of capillaries, further thickening of the alveolar septa and obliteration of the alveolar space. The mechanism behind this cascade of different phases is not yet fully understood, but it is clear that Transforming Growth Factor-β1 (TGFβ1), Tumour Necrosis Factor-α, and interleukin-1 and -6 play a role. Experimental models show that intercellular adhesion molecule 1 or CD95/CD95-ligand deficient mice develop virtually no RP and, to a lesser extent, also show less pulmonary fibrosis.9,13 The disparity between clinical symptoms and radiographic findings is well illustrated: five times as many changes in imaging modalities are described compared to the number of patients with clinically evident symptoms.1 Clinical symptoms, if present, can occur with or without changes in pulmonary function tests.

In a recent study with extended follow-up in breast cancer patients, pulmonary function tests showed a reduction in diffusion capacity of carbon monoxide, and total lung capacity of around 10%, eight to ten years after breast cancer irradiation. In this study, the use of tamoxifen had a significant impact on the observed pulmonary function decline.12 Definition and grading of RP differs depending on the scoring system used e.g. grade 2 can be dyspnoea, not interfering with ADL in one and initiation or increase in corticosteroids in another scoring system (Table 1). An attempt has been made to quantify CT scan-based lung densities and to investigate their association with symptomatic RP. Structural changes in the central part of the lung appeared to be more important in the development of RP than changes in the apex.7,8 Concurrent administration of gemcitabine, at 200 mg/m²/w enhances lung toxicity.11 However, for commonly used drugs, a large meta-analysis showed no increase in RP when used concomitantly versus sequentially. Products and doses used concomitantly with standard fractionation were carboplatinum 100 mg weekly, cisplatin 100 mg/m²/days 1,29, cisplatin 20 mg/m² days 1-5, 29-33 or cisplatin 6 mg/m² daily, vindesine 3 mg/m² days 1,8,29,36, mitomycin 8 mg/m² days 1,29, vinblastine 5 mg/m² weekly, etoposide 50 mg/m² days 1-5, 29-33.24 On the other hand some targeted agents, EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib may on their own cause interstitial lung disease, which may be fatal.
Prediction and prevention

It has been suggested that besides treatment-related factors (radiation dose-volume parameters, treatment techniques, concurrent medication) patient-related factors (e.g. tumour location, smoking, pulmonary function, cytokines, coexisting lung disease) may also influence the risk of developing RP.

Treatment-related factors

Several studies examined the influence of radiation dose-volume parameters on the development of RP. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) recommends for lung cancer irradiation, using conventional fractionation, to limit the V20 (volume of the lungs minus the gross tumour volume irradiated to a dose of 20 Gy) to 30-35 % and to limit the mean lung dose (MLD) (to both lungs minus the gross tumour volume) to 20-23 Gy. The study included 382 breast cancer, malignant lymphoma and inoperable non-small cell lung cancer patients. The study included 382 breast cancer, malignant lymphoma and inoperable non-small cell lung cancer patients. The MLD was the most accurate predictor for the incidence of RP. Furthermore, in their study, V13 was more predictive for RP than V20 or V30. RP is uncommon after breast cancer irradiation, because of the usually lower V20 and MLD. When the regional lymph nodes are included in the radiation fields, the risk on RP increases from 0.9% to 4.1%.

New treatment techniques, such as stereotactic body radiotherapy (SBRT), intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and helical tomotherapy (HT), can reduce the exposure of normal lung tissue to high dose radiation allowing very tight margins and extreme hypofractionation. However, as a trade-off, the dose is spread leading to larger low-dose regions, often also to the contralateral lung. The exact meaning of these large low dose volumes is not completely clear, but a recent study showed that arc therapy does not affect the rates of >grade 2 RP. Several studies demonstrated that breathing adaptation techniques can be used to reduce the irradiated lung volumes, primarily by decreasing the amount of lung in the radiation volumes.

Patient-related factors

A single centre study, including 438 Non-Small Cell Lung Cancer (NSCLC) patients treated with curative intent, showed that V20 and MLD were less important than patient characteristics in the prediction of lung toxicity in the first six months after radiotherapy. The radiation dose to normal lung tissue in their patient cohort was rather low (MLD 13.5 Gy, V20 21%). In this patient group, with MLD <20, performance state, age, low Forced Expiratory Volume (FEV) were positively related to radiation induced lung injury. With MLD below 20 Gy, in this study no dose-effect relation was found. Tumour location is an important factor. One group combined data from the RTOG 9311 with their own

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Table 1. Toxicity criteria for pneumonitis

<table>
<thead>
<tr>
<th>Criteria</th>
<th>1</th>
<th>2</th>
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<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td>CTCAE</td>
<td>asymptomatic; radiographic findings only</td>
<td>symptomatic; not interfering with ADL</td>
<td>symptomatic; interfering with ADL; O₂ indicated</td>
<td>life-threatening; ventilatory support indicated</td>
<td>death</td>
</tr>
<tr>
<td>RTOG/EORTC (LENT-SOMA)</td>
<td>asymptomatic or mild symptoms (dry cough), with radiographic findings</td>
<td>moderately symptomatic (severe cough, fever)</td>
<td>severely symptomatic</td>
<td>severe respiratory insufficiency; continuous oxygen/assisted ventilation</td>
<td>death</td>
</tr>
<tr>
<td>SWOG (33)</td>
<td>asymptomatic or symptoms not requiring steroids, with radiographic findings</td>
<td>initiation of or increase in steroids required</td>
<td>O₂ required</td>
<td>assisted ventilation necessary</td>
<td>death</td>
</tr>
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Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ADL = Activities of daily living; O₂ = oxygen; RTOG = Radiation Therapy Oncology Group; EORTC = European Organization for the Research and Treatment of Cancer; LENT-SOMA = Late Effects on Normal Tissues-Subjective, Objective, Management and Analytic Scales; SWOG = Southwest Oncology Group.

Note: Data from Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS, December 12, 2003; Radiation Therapy Oncology Group, Acute Radiation Morbidity Scoring Criteria.
data and created a nomogram to predict RP. With a dataset of 324 patients receiving definitive conformal radiotherapy for NSCLC, they could incorporate two effects in their final model: MLD but also localisation of the tumour in the inferior part of the lung.6

A recent prospective trial showed a large difference in the exhaled nitric oxide (NO) at the end of the radiation course which was significantly higher in patients developing RP. The elevation of exhaled NO preceded peak symptoms by 33 days.16

Pre-treatment inflammation in the lung seems to make pulmonary tissue more susceptible to radiation damage. This has recently been demonstrated. Areas within the lung (excluding tumour) that show an avid uptake of 18F-deoxyglucose (FDG) before radiotherapy (RT) are more susceptible to radiation damage. Therefore, the risk of radiation-induced lung toxicity may be decreased by applying sophisticated RT techniques to avoid areas in the lung with high FDG uptake.25

Early lung damage in patients who later develop RP can be demonstrated by an increase of FDG Positron Emission Tomography (PET) scan of the lung during the first two weeks of irradiation.26

A history of smoking increases the risk of RP as a result of pre-existing lung damage, but active smoking seems to protect the lung from radiotherapy-induced damage.3

The association between single nucleotide polymorphisms in \(TGF\beta1\) gene and risk on RP was studied in patients with NSCLC. In multivariate analysis CT/CC genotypes of \(TGF\beta1\) at rs1982073:T869C were found to be associated with a lower risk of RP grades \(\geq 2\) (P = .013) and grades \(\geq 3\) (P = 0.007) respectively, compared to the TT genotype, after adjustment for Karnofsky performance status, smoking status, pulmonary function, and dosimetrical parameters.17

Radioprotective agents
The effect of giving a radioprotective agent concomitantly with radiation to prevent normal lung tissue, without protecting the effect of radiation on the tumour is the object of research in several studies. Amifostine, an aminothiol with broad-spectrum cytoprotection, did not reduce the incidence of RP in a large randomised Phase III RTOG study. Neither was there evidence of a tumour-protecting effect.18 Pentoxifilline taken during radiation therapy significantly decreased pulmonary toxicity in a small study.19 Incidental ACE inhibitor use decreased the risk of RP in lung cancer patients receiving thoracic irradiation in a retrospective study and in animal models.20

Treatment
There are no controlled, randomised trials on the treatment of RP. Patients with grade I are mostly asymptomatic with only radiographic findings and eventually a dry cough. No treatment is given. For grade II, if patients have more severe complaints, traditionally, corticosteroids are given. However, mild forms of grade II can be treated with inhalation corticosteroids and bronchodilators. More severe forms and grade III are treated with Prednisolone 30–40 mg daily for two weeks followed by a slow reduction for six to twelve weeks.10 A relapse may occur after discontinuation of corticosteroids. A substantial reduction in symptoms is normally seen, as well as an improvement of the radiological abnormalities. For patients with grade 4 RP, with severe respiratory insufficiency, continuous oxygen or even assisted ventilation is required. Some patients with RP are resistant to corticosteroids. This is associated with more than 1.5-times increase of the lung epithelium-specific protein Krebs von den Lungen-6 (KL-6), which is made by and secreted by type II pneumocytes.

It is suggested that these patients can be treated with azathioprine or cyclosporine A.14 There is no proven effective treatment for radiation-induced lung fibrosis. It occurs months to years later, in response to the initial tissue injury, and leads to permanent impairment of oxygen transfer.13 Thus, as much prevention as possible is required.

Conclusion
There are still unanswered questions about the occurrence, prediction and prevention of RP. Patient-related factors seem to play a role and while most cannot be changed, e.g. the location of the tumour, others, e.g. avoiding certain sections of the lung with higher pre-treatment inflammation, are currently being studied. However, the major risk factor is still the radiation dose administered to normal lung tissue. Most studies on different techniques reported correlation between radiation dosimetric parameters and RP. V20 and MLD are most commonly used in clinical practice and guidelines. Other variables, V5, V13, V30 have been shown to be predictive but the relative merit
of decreasing one parameter at the expense of another is not clear.\textsuperscript{29}

At the moment no cytoprotective medication is available with clear effects in reducing the chance of radiation pneumonitis.

Patients with radiation pneumonitis are treated, according to severity of symptoms with corticosteroids (inhaled or oral), oxygen (temporarily or continuous), assisted ventilation. Resistant patients can be treated with azathioprine or cyclosporine A.

The incorporation of patient-related factors needs further research in order to be able to identify the highest risk patients, requiring cautious treatment planning and early detection and treatment of radiation pneumonitis.

References