

# Risk Factors for Radiation Pneumonitis and a Prognostic Instrument for Very Elderly Patients With Lung Cancer

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## Abstract

**Background/Aim:** Elderly and very elderly patients with lung cancer have a comparably high risk of radiation pneumonitis (RP). Risk scores may help to identify these patients. We have developed a risk score for very elderly patients.

**Patients and Methods:** Nine characteristics were retrospectively investigated in 21 patients aged  $\geq 80$  years for associations with symptomatic RP. Characteristics achieving significance or showing a trend were incorporated in the score, which was compared to a previous tool without age limit.

**Results:** The incidence of RP was 33.3% and significantly associated with mean lung dose (MLD)  $> 20$  Gy. Trends were found for MLD  $> 13$  Gy and cardiovascular disease. Based on these characteristics, three risk groups were formed (2-5, 7-9, and 12 points). RP rates were 0.0%, 44.4%, and 100.0%. Positive (PPV) and negative (NPV) predictive values were both 100.0%. When using the previous score, PPV and NPV were 71.4% and 100%.

**Conclusion:** Given the limitations of this study, the newly developed age-specific risk score appears to be a valuable tool for identifying very elderly lung cancer patients at high or low risk of radiation pneumonitis, and may offer improved predictive performance over previously established models.

**Keywords:** Lung cancer, very elderly patients, radiation pneumonitis, risk factors, risk score.

## Introduction

Lung cancer is very common malignancy responsible for many cancer-related deaths and, therefore, considered a serious public health concern (1). Patients with non-metastatic small cell lung cancer (SCLC) are often treated with loco-regional irradiation and systemic therapies (2).

A considerable number of patients with non-small cell lung cancer (NSCLC) undergo thoracic surgery with or without systemic therapies (2). If surgery cannot be performed due to a more advanced tumor stage, the patients may receive definitive radiotherapy plus/minus chemo- and/or immunotherapy. A patient's poor general condition, a poor pulmonary function, or a high co-



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morbidity index may also impede surgical resection. This will likely hold true particularly for very elderly patients considering the generally higher degree of co-morbidity and reduced organ functions (3, 4). Loco-regional radiotherapy of NSCLC and SCLC can be complicated by radiation pneumonitis (RP), a subacute consequence of this treatment modality that can occur up to 24 weeks after completion of radiotherapy (5-8). Symptomatic RP can significantly impair the patient's quality of life and may even lead to death in about 2% of patients with RP (9). Thus, RP needs to be diagnosed and treated as soon as possible. Risk factors and risk scores may contribute to the identification of patients who are more likely than others to experience RP and would benefit from a closer monitoring during and after their radiation treatment. Previously, we presented a risk score that was created in patients without age limit (6). However, elderly and very elderly patients irradiated for lung cancer have a higher risk of RP in comparison to patients younger than 65 years (10-15). Since elderly and very elderly patients are increasingly regarded as separate groups, they may benefit from age-specific risk scores. In this study, we aimed to develop a specific risk score for very elderly patients aged  $\geq 80$  years. To examine whether this age group does really benefit from an age-specific score, the new tool was compared to a previous risk score developed in patients irradiated for lung cancer without age limit (6).

## Patients and Methods

Twenty-one patients with lung cancer aged  $\geq 80$  years and treated with volumetric modulated arc therapy between 2016 and 2024 were included in this retrospective study and investigated with respect to risk factors for symptomatic RP. The study was approved by the ethics committee at the University of Lübeck, Germany (file 2024-147\_1).

Patients were followed until RP or for a minimum of 20 weeks after radiotherapy. Median follow up in patients without RP was 33 weeks (range=20-125 weeks). Thirteen patients treated between 2016 and 2019 were included in our previous study (6). No patient received

upfront surgery for lung cancer, and no patient had a history of autoimmune disease.

Nine characteristics (Table I) were evaluated for associations with symptomatic RP. These characteristics included age, sex (female vs. male), tumor stage according to the American Joint Committee on Cancer [AJCC stage 2 vs. 3, (16)], histology (NSCLC vs. SCLC), systemic therapy before or during radiotherapy (no vs. yes), total radiation dose ( $\leq 56.0$  vs.  $>56.0$  Gy), mean dose to the ipsilateral lung (MLD  $\leq 13.0$  vs. 13.1-20.0 vs.  $>20.0$  Gy), history of other malignancy (no vs. yes), history of significant cardiovascular disease (no vs. yes), and number of pack years before radiotherapy ( $<40$  vs.  $\geq 40$ ).

Statistical analyses were performed with the Fisher's exact test. Factors found to be significantly associated with the development of symptomatic RP ( $p < 0.05$ ) or showing a certain trend ( $p < 0.20$ ) were included in the risk score. For the subgroups of each investigated characteristic, the corresponding RP rates in % were divided by 10. The resulting scoring points (factor scores) were summed up for each individual patient (patient scores). Three risk groups were created depending on the RP rates of the patient scores. In addition, the positive predictive value (PPV) for correct identification of patients with RP (least favorable risk group) and the negative predictive value (NPV) for correct identification of patients without RP (most favorable risk group) were determined using the following two formulas:

$$PPV = \frac{\text{patients with RP}}{\text{patients with RP} + \text{patients without RP}} \times 100 \quad (1)$$

$$NPV = \frac{\text{patients without RP}}{\text{patients without RP} + \text{patients with RP}} \times 100 \quad (2)$$

Subsequently, the PPV and the NPV of the new risk score were compared to the corresponding predictive values when applying a risk score previously developed in patients of any age (6). The previous risk score considers two characteristics. These are the MLD (1 point for  $\leq 13.0$  Gy, 2 points for 13.1-20.0 Gy, and 3 points for  $>20.0$  Gy) and a history of autoimmune disease (1 point for no

Table I. Distribution of patient characteristics.

Characteristic	Subgroup	Frequency, n (%)
Sex	Female	7 (33.3)
	Male	14 (66.7)
AJCC-stage	2	4 (19.0)
	3	15 (71.4)
	Unknown	2 (9.5)
Histology	NSCLC	18 (85.7)
	SCLC	2 (9.5)
	Unknown	1 (4.8)
Upfront surgery	No	21 (100.0)
Systemic treatment	Yes	0 (0.0)
	No	13 (61.9)
Total radiation dose	Yes	8 (38.1)
	No	0 (0.0)
Mean dose to ipsilateral lung	≤56.0 Gy	8 (38.1)
	>56.0 Gy	13 (61.9)
	≤13.0 Gy	5 (23.8)
History of other malignancy	13.1-20.0 Gy	9 (42.9)
	>20.0 Gy	7 (33.3)
	No	14 (66.7)
History of autoimmune disease	Yes	7 (33.3)
	No	21 (100.0)
History of significant CVD	Yes	0 (0.0)
	No	11 (52.4)
Number of pack years	Yes	10 (47.6)
	<40	12 (57.1)
	≥40	6 (28.6)
	Unknown	3 (14.3)

AJCC: American Joint Committee on Cancer; NSCLC: non-small cell lung cancer; SCLC: small-cell lung cancer; CVD: cardiovascular disease.

autoimmune disease and 2 points for autoimmune disease). Thus, the patient scores of the previous risk score were 2, 3, 4, or 5 points. Each patient score represents a risk group (higher score=greater risk of RP).

## Results

Seven patients (33.3%) experienced symptomatic RP after a median of nine weeks (range=2.5-27 weeks) after completion of their course of radiotherapy. The incidence of RP was significantly associated with a MLD >20.0 Gy (vs. ≤20.0 Gy,  $p=0.017$ ) (Table II). A trend for an association with symptomatic RP was observed for a MLD >13.0 Gy (vs. ≤13.0 Gy,  $p=0.124$ ) and a history of significant cardiovascular disease ( $p=0.183$ ). The incidence of symptomatic RP was 0.0% (zero of five patients) after a

Table II. Associations between investigated potential risk factors and occurrence of radiation pneumonitis.

Potential risk factor	Pneumonitis, n (%)			p-value
	Yes	No		
Sex	Female	2 (28.6)	5 (35.7)	>0.999
	Male	5 (71.4)	9 (64.3)	
AJCC-stage	2	0 (0.0)	4 (100.0)	0.245
	3	7 (46.7)	8 (53.3)	
Histology	NSCLC	6 (33.3)	12 (66.7)	>0.999
	SCLC	1 (50.0)	1 (50.0)	
Systemic treatment	No	5 (38.5)	8 (61.5)	0.656
	Yes	2 (25.0)	6 (75.0)	
Total radiation dose	≤56.0 Gy	3 (37.5)	5 (62.5)	>0.999
	>56.0 Gy	4 (30.8)	9 (69.2)	
Mean lung dose (13 Gy)	≤13.0 Gy	0 (0.0)	5 (100.0)	0.124
	>13.0 Gy	7 (43.8)	9 (56.3)	
Mean lung dose (20 Gy)	≤20.0 Gy	2 (14.3)	12 (85.7)	0.017
	>20.0 Gy	5 (71.4)	2 (28.6)	
History of other malignancy	No	4 (28.6)	10 (71.4)	0.638
	Yes	3 (42.9)	4 (57.1)	
History of significant CVD	No	2 (18.2)	9 (81.8)	0.183
	Yes	5 (50.0)	5 (50.0)	
Number of pack years	<40	3 (25.0)	9 (75.0)	>0.999
	≥40	2 (33.3)	4 (66.7)	

AJCC: American Joint Committee on Cancer; NSCLC: non-small cell lung cancer; SCLC: small-cell lung cancer; CVD: cardiovascular disease. The p-values were calculated with the Fisher's exact test.

Table III. Incidence of radiation pneumonitis by risk factor subgroups and corresponding scoring points.

Risk factor	Subgroup	RP rate (%)	Scoring points
Mean lung dose	≤13.0 Gy	0.0	0
	13.1-20.0 Gy	22.2	2
	>20.0 Gy	71.4	7
History of significant CVD	No	18.2	2
	Yes	50.0	5

CVD: Cardiovascular disease.

MLD ≤13.0 Gy, 22.2% (two of nine patients) after 13.1-20.0 Gy, and 71.4% (five of seven patients) after >20.0 Gy, respectively.

For creation of the risk score, MLD and history of significant cardiovascular disease were used. The scoring points assigned to the corresponding subgroups (factor scores) are given in Table III. The addition of the factor scores led to patient scores of 2 (three patients), 4 (four

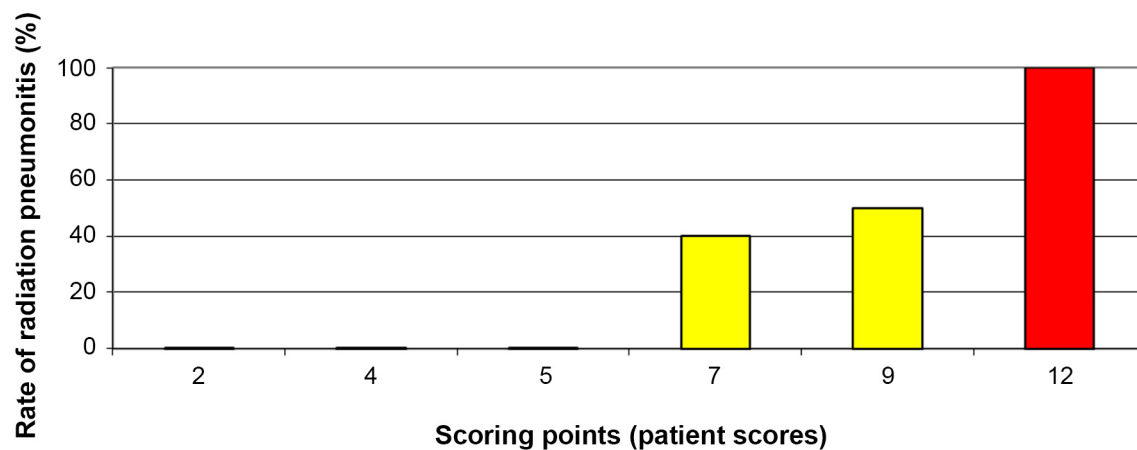


Figure 1. Scoring points (patient scores) and related rates of symptomatic radiation pneumonitis.

patients), 5 (two patients), 7 (five patients), 9 (four patients), or 12 (three patients) points. The RP rates related to these patient scores were 0.0%, 0.0%, 0.0%, 40.0%, 50.0%, and 100.0%, respectively (Figure 1). No patient had 3, 6, 8, 10 or 11 points.

Based on the incidence of RP related to the patient scores, three risk groups were formed, i.e., 2-5 points (nine patients), 7-9 points (nine patients), and 12 points (three patients). The RP rates of these groups were 0.0%, 44.4%, and 100.0%, respectively. Thus, the PPV and the NPV were both 100.0%. When applying the previous risk score created in patients without age limit and originally consisting of four risk groups, only three risk groups were identified for the present cohort, since no patient achieved 5 points due to the fact that no patient had a history of autoimmune disease. The RP rates of the three risk groups (2, 3, or 4 points) were 0.0% (zero of five patients), 22.2% (two of nine patients), and 71.4% (five of seven patients), respectively. PPV and NPV were 71.4% (4 points, least favorable group) and 100.0% (2 points, most favorable group), respectively (6).

## Discussion

Symptomatic RP is a serious situation in patients irradiated for lung cancer and requires immediate

treatment with corticosteroids (7, 17). This radiation-induced complication affects to a greater extent elderly and very elderly patients (10-15). To avoid progression of RP that may even lead to death, it is very important to diagnose RP as soon as possible and to identify patients with a comparably high risk of developing RP (5). Identification of patients at risk may be facilitated by the knowledge of corresponding risk factors and by application of risk scores. A score to estimate the risk of symptomatic RP was created in a cohort of 169 patients receiving loco-regional irradiation for lung cancer without age limit (6). In this previous study, RP was significantly associated with total radiation doses >56 Gy, MLD >20 Gy, MLD >13 Gy, and history of autoimmune disease (6). For building the risk score, MLD and history of autoimmune disease were considered.

However, the elderly and very elderly cancer patients have been increasingly regarded as separate groups. These age groups may require specific treatment protocols, monitoring, and management of treatment-related side effects due to decreased organ function, metabolic disturbance, and a higher co-morbidity index (3, 4, 18). This applies particularly to very elderly patients aged  $\geq 80$  years. Therefore, age-specific prognostic tools were designed for this group, e.g., for patients with bone or brain metastases (3, 4). Thus, it appears reasonable to

create a specific risk score for identification of RP for the group of very elderly patients.

In the present study, we have developed such an age-specific risk score, which is based on MLD and history of significant cardiovascular disease. Cardiovascular disease was not included in the previous score without age limit (6). It has to be noted that 25.4% of the patients in the previous study had a history of significant cardiovascular disease compared to 47.6% in our present study. This difference further supports the idea that very elderly patients with cancer should be considered a specific group.

The new age-specific risk score developed in the present study provided a very high accuracy with respect to the identification of patients developing symptomatic RP (PPV=100.0%) and patients not developing RP (NPV=100.0%). When compared to the previous risk score created in a cohort of lung cancer patients of any age (6), the PPV to identify patients who will experience symptomatic RP was higher (100.0% vs. 71.4%). Since it is more important to identify patients who likely will develop RP than patients who will likely not develop RP, the new age-specific risk score appears preferable. However, when following this recommendation, the limitations of the present study need to be considered. These include mainly the retrospective design (risk of hidden selection biases and missing of RP in some patients) and the small number of patients included, particularly in the 12 points group. Therefore, this risk score needs to be validated in a larger cohort of patients, preferably in a prospective trial.

In summary, given the limitations of the present study, the new age-specific risk score provides high accuracy with respect to the identification of patients who experience symptomatic RP and patients who will not experience RP. The PPV of the new score to predict the occurrence of symptomatic RP was higher than the PPV of the previous tool created in patients of any age. Thus, the age-specific risk score appears preferable for very elderly patients aged  $\geq 80$  years. Validation of the score in a larger patient cohort is required, ideally in a prospective trial.

## Conflicts of Interest

The Authors state no conflicts of interest in relation to this study.

## Authors' Contributions

D.R., C.D., L.D., S.J., S.B., and E.M.G. participated in the study design and the interpretation of the data that were obtained from an existing database or collected by D.R. The article, which was drafted by D.R., was reviewed and approved by all Authors.

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## Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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