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Does the presence of emphysema increase the risk of radiation pneumonitis in lung cancer patients?

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ABSTRACT

Introduction Radiotherapy (RT) plays an important role in the treatment of lung cancer. One of the most common comorbidities in patients with lung cancer is pulmonary emphysema. The literature offers conflicting data about whether emphysema increases the occurrence and severity of radiation pneumonitis (RP). As a result, whether high doses of RT (with curative intent) should be avoided in patients with emphysema is still unclear.

Objective We measured the documented incidence of RP in patients with and without emphysema who received curative radiation treatment.

Methods This retrospective cohort study considered patients in the lung cancer clinical database of the Peter Brojde Lung Cancer Centre. Data from the database has been used previously for research studies, including a recent publication about emphysema grading, based on the percentage of lung occupied by emphysema on computed tomography (CT) imaging.

Results Using previously published methods, chest CT imaging for 498 patients with lung cancer was scored for the presence of emphysema. The analysis considered 114 patients who received at least 30 Gy radiation. Of those 114 patients, 64 (56%) had emphysema, with approximately 23% having severe or very severe disease. The incidence of RP was 34.4% in patients with emphysema ($n = 22$) and 32.0% in patients with no emphysema ($n = 16$, $p = 0.48$). No difference in the incidence of RP was evident between patients with various grades of emphysema ($p = 0.96$). Similarly, no difference in the incidence of RP was evident between the two treatment protocols—that is, definitive RT 17 (37%) and combined chemotherapy–RT 21 (31%, $p = 0.5$).

Conclusions In our cohort, the presence of emphysema on chest CT imaging was not associated with an increased risk of RP. That finding suggests that patients with lung cancer and emphysema should be offered RT when clinically indicated. However, further prospective studies will be needed for confirmation.

Key Words Lung cancer, emphysema, radiation pneumonitis

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INTRODUCTION

Radiotherapy (RT) plays an important role in the treatment of lung cancer[1–5], but its benefits must be balanced against the risk of lung injury. Radiation pneumonitis (RP) often develops insidiously and becomes clinically evident 2–3 months after completion of RT. The diagnosis of acute RP can be challenging[6]; it requires exclusion of allergic, infective, and chemical causes of pneumonitis. In the longer term, RT side effects typically present as well-defined areas of pulmonary fibrosis confined to the field of radiation.

There is consensus that poor pulmonary function is a risk factor and a relative contraindication in patients undergoing radical RT[7,8]. A recent survey about recommendations by radiation oncologists for the treatment of hypothetical patients with stage IIIB non-small-cell lung

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cancer and comorbid pulmonary illness demonstrated that most radiation oncologists would not recommend any radiation therapy in patients with severe pulmonary comorbidities[9]. Furthermore, guidelines from the American College of Chest Physicians state that a patient with a forced expiratory volume in 1 s (FEV1) less than 1 L, is unlikely to be able to tolerate RT therapy of 60 Gy or more[1,5]. In reality, one of the most common lung pathologies in patients with lung cancer is pulmonary emphysema. The few available published data are conflicting about whether emphysema increases the occurrence and severity of RP. As a result, it is still unclear whether the use of higher doses of RT (with curative intent) should be avoided in patients with emphysema[7,10].

The purpose of the present study was to measure the documented incidence of RP in patients with and without emphysema who received curative radiation treatment.

METHODS

Study Design

Data were extracted from the Peter Brojde Lung Cancer Centre's clinical database, which contains prospectively collected data for all patients diagnosed and treated for lung cancer. Patient information is obtained by specialized oncology data managers from clinical charts, weekly tumour board meetings, and patient interviews. Data from the database have previously been used for research studies, including a recent publication on emphysema[11].

Study Subjects and Methods

In a previous study[11], chest CT imaging for 498 patients with lung cancer was scored for the presence of emphysema using previously published methods[12,13]. Emphysema was assigned as present or absent, and if present, was graded based on the percentage of lung occupied by emphysema on CT: none (0%), mild (1%–10%), moderate (11%–25%), severe (26%–50%), or very severe (>50%). Data concerning RT treatment, including dose, site of radiation, and complications, were also collected. According to institutional standards of treatment, the dose of radiation was based on a V_{20} calculation, which is the percentage of the lung volume (with subtraction of the volume involved by the lung cancer) treated with a radiation dose of 20 Gy or more. For the purposes of the present analysis, a patient was deemed to have experienced RP if high-dose steroid treatment (prednisone 40 mg daily minimum) was started to address symptoms in a patient who received at least 30 Gy radiation to the lung. Treatment for RP had to be initiated within 6 months of RT start after all infectious, cardiac, and allergic causes for symptoms were excluded. In the identified cohort, 114 patients had received at least 30 Gy radiation and were included in the analysis (Figure 1). The study was approved by the institutional ethics review board.

Analysis

Means and medians are used to summarize patient characteristics. Data were analyzed using the IBM SPSS Statistics software application (version 20: IBM, Armonk, NY, U.S.A.) for Windows (Microsoft Corporation, Redmond, WA, U.S.A.). Simple descriptive statistics (means with standard deviation, or proportions) are used to summarize the demographic, clinical, and tumour characteristics of the cohort. Comparisons between patients with emphysema and those without emphysema used the chi-square test. To assess characteristics that predict the occurrence of RP, 4 variables (emphysema presence, sex, smoking, lung cancer type) were assessed using logistic regression modelling. A 2-sided p value of 0.05 was considered statistically significant. Because of missing data, pulmonary function (FEV1%) was not included in the analysis.

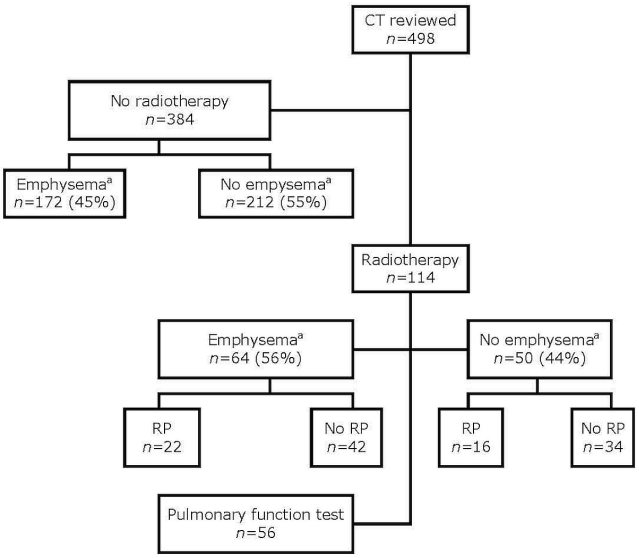

FIGURE 1 Lung cancer patients enrolled in the analysis. [a]Emphysema on computed tomography imaging (CT). RP = radiation pneumonitis.

RESULTS

Of the 114 patients who received RT with curative intent between 2001 and 2015, 68 (60%) received definitive RT, and 46 (40%) received combined chemotherapy–RT. Table I presents the characteristics of the study patients. In this cohort, 56% (n = 64) had emphysema, with 23% having severe or very severe disease.

The median total RT dose delivered was 50.2 Gy (range: 30–66 Gy). Radiation was delivered in fractionated doses of 2 Gy daily for intensity-modulated RT and 10–15 Gy for stereotactic RT. The 38 symptomatic patients with presumed RP (33.3%) were treated with high-dose steroids. Only 6 of those patients required oxygen. The RP was defined as grade 2 in 84% of the symptomatic group and grade 3 in 16%. The rates of any-grade emphysema in patients treated with RT were no different than the rates in patients excluded from the study (Figures 1 and 2). The RP incidence was 34.4% in patients with CT imaging–documented emphysema (n = 22) and 32.0% in patients with no emphysema (n = 16, p = 0.48). No statistical difference in the incidence of RP was evident between patients with the various grades of emphysema (p = 0.96, Figure 3). Similarly, the incidence of RP was not different for the two treatment protocols—that is, definitive RT 17 (37%) and combined chemotherapy–RT 21 (31%, p = 0.5).

TABLE I Clinical characteristics of 114 lung cancer patients who received curative-dose radiotherapy

Characteristic	Value
Age (years)	
Median	69
IQR	60–76
Sex [*n* (%) women]	50 (44)
Histology [*n* (%)]	
Small-cell carcinoma	12 (10)
Adenocarcinoma	64 (56)
Squamous carcinoma	18 (16)
Large-cell and neuroendocrine tumour	8 (7)
Pleomorphic or sarcomatoid carcinoma	1 (1)
Undifferentiated carcinoma	11 (10)
Emphysema [*n* (%)]	
Absent	50 (44)
Present	64 (56)
Grade (*n*=64)	
Mild	29 (45.3)
Moderate	20 (31.3)
Severe	9 (14.1)
Very severe	6 (9.4)
Smoking [*n* (%)]	
Never-smoker	11 (10)
Ever-smoker	103 (90)
Pack–year history	
<30 Pack–years	35 (31)
30–44 Pack–years	27 (23)
45–59 Pack–years	28 (25)
60–74 Pack–years	15 (13)
≥75 Pack–years	9 (8)
Type of radiation therapy	
Definitive radiation alone	68 (60)
Combined chemoradiation	46 (40)

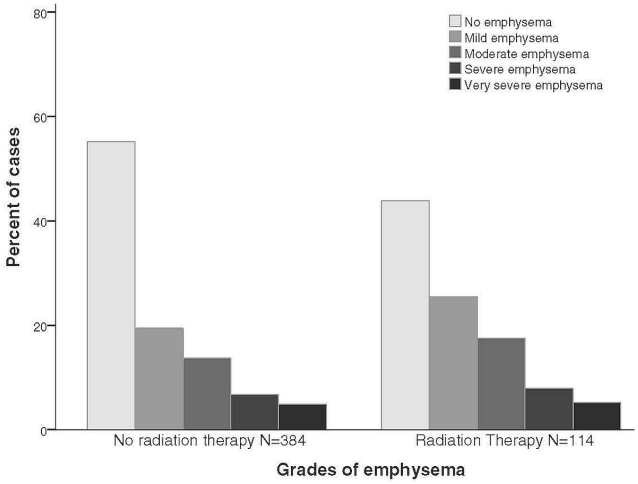

FIGURE 2 Rate of emphysema in patients with lung cancer who did or did not receive radiotherapy.

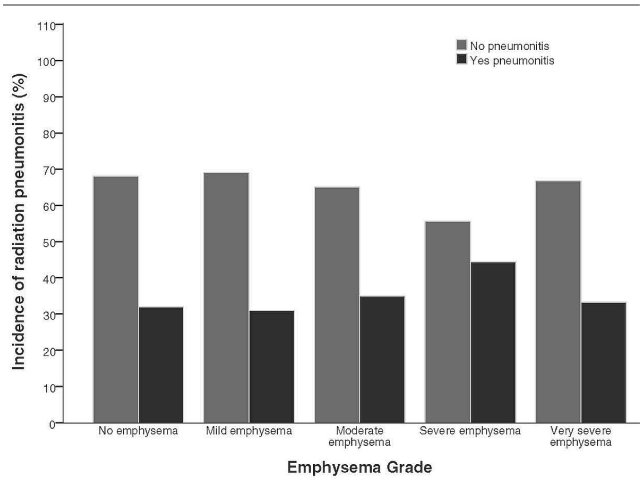

FIGURE 3 Rate of radiation pneumonitis in patients with lung cancer by grade of emphysema.

Most of the primary tumours (76%, $n = 87$) were located in the upper lobes. A slightly higher, but statistically non-significant incidence of RP was observed for patients with a tumour in the lower lobes (37% vs. 32%)

Because of a transition to electronic from paper records in 2007 and the unavailability of paper records on-site, dose–volumetric parameters (V_{20}) were available for only 46 of the 114 patients. The mean V_{20} for that subset was 15.7% (range: 1.4%–40.9%). The V_{20} was no different in the 17 patients who developed RP than in the 29 who did not develop RP: 16.3% ± 10.4% and 15.4% ± 10.5 respectively. However, the V_{20} was slightly higher (18.9%) in patients with RP and emphysema ($n = 10$) than in patients ($n = 6$) with RP and no emphysema (12.0%, $p > 0.05$).

Unfortunately, FEV1 data were available for only 56 patients (49%): 23 with no emphysema (41%) and 33 with mild or moderate grades of emphysema (57%) on CT imaging. Although CT imaging showed lower pulmonary function in patients with emphysema than in other patients (mean FEV1% predicted: 68.5% vs. 78.9%), the difference was not statistically significant ($p = 0.15$). In addition, no statistically significant difference in FEV1 was observed between 18 patients with RP (mean FEV1: 69.8%) and 38 patients without RP (mean FEV1: 75.2%; $p = 0.47$).

Although precise details about the risk factors for developing RP are unclear, it is thought that patient factors (age, smoking), type of cancer (small-cell vs. non-small-cell lung cancer), pre-existing lung disease, and radiation dose are all potentially important. We assessed whether those factors (excluding radiation dose) were related to the occurrence of RP. Univariate analyses for sex, smoking status, emphysema, and type of lung cancer were not predictive for RP. Furthermore, none of those factors were predictive for RP in multivariate analysis (Table II)

TABLE II Multivariate analysis of factors potentially predictive of radiation pneumonitis in lung cancer patients

Variable	Comparison	Exp(B)	95% CI for Exp(B)		*p* Value
			Lower	Upper	
Emphysema	Absent vs. present	1.141	0.482	2.700	0.764
Sex	Women vs. men	1.275	0.566	2.872	0.557
Smoking	Never vs. ever	1.507	0.355	6.396	0.578
Histology	SCLC vs. NSCLC	0.495	0.142	1.726	0.270
RT variant	RT alone vs. chemoRT	1.194	0.520	2.742	0.675

CI = confidence interval; SCLC = small-cell lung cancer; NSCLC = non-small-cell lung cancer; RT = radiotherapy; chemoRT = chemoradiation.

DISCUSSION

Our study describes the relationship between the incidence of RP and emphysema in a cohort of patients with radiologically confirmed emphysema graded by severity. Existing recommendations have suggested that pulmonary emphysema is a risk factor for RP and that RT treatment should be restricted or avoided in patients with emphysema[8–10]. Our results demonstrate an overall incidence of RP of 33%, with rates of RP being similar in patients with and without emphysema. Furthermore, we observed no difference in the RP rate for patients receiving RT alone and those receiving combined chemotherapy–RT. The location of the primary tumour also had no effect on the incidence of RP.

The incidence of symptomatic RP in the present study was similar to the 15%–40% reported in a Radiation Therapy Oncology Group randomized controlled trial of concurrent chemoradiotherapy[14,15] and congruent with the 29.8% rate reported in a meta-analysis by Palma *et al.*[16]. The higher incidence of pneumonitis in an unselected group was demonstrated in small cohort studies by Kimura *et al.*[7] and Ishijima *et al.*[10].

As mentioned earlier, poor lung function or other lung pathology has been suggested to increase the risk of RP. Kimura *et al.*[7] suggested that patients with reduced lung function had greater propensity to develop RP. They reported an overall 88% incidence of grades 1 and 2 RP, with significant correlation between the rate of RP and emphysema grade. In contrast, Ishjima *et al.*[10] reported the incidence of RP to be 43% in patients with early lung cancer undergoing stereotactic RT. Those authors found that the risk of RP was lower in patients with severe emphysema than in patients with no underlying lung disease. The authors reasoned that the emphysematous tissue around the tumour decreased the risk of RP developing despite high local doses of radiation. The results of our study stand somewhere between those two extremes: that is, we observed no significant difference in the rate of RP between patients with and without emphysema, and we observed no correlation between the incidence of RP and the severity of emphysema.

In addition, some authors have reported that chemotherapy increases the risk of RP, especially when used concurrently[17,18]. Those reports contrast with our study results, in which about 40% of patients received radiation in combination with chemotherapy and showed no evidence of an increased risk of RP compared with their counterparts who received comparable doses of RT alone.

We recognize a number of deficiencies in our study. First, the RP was established retrospectively as a diagnosis of exclusion, based on the use of steroids in the absence of other causes within 6 months of treatment completion. Although we believe that the most severe cases of RP (grades 2 and 3) would have been captured in our study cohort, it is possible that, as a result of the foregoing criteria, a somewhat higher proportion of the more mild cases of RP might have been excluded from the analysis because of differences in clinician documentation of such events and because of our definition of RP. Also, high proportions of the cohort lacked data for pulmonary function tests and V_{20}, which could potentially have been used for risk-stratification.

As in any retrospective cohort study, eliminating the possibility of selection bias is hard. However, it appears that the presence of emphysema did not play a decisive role in selection of patients for RT, because the rate of emphysema was no different for patients treated with RT than for patients who were not so treated (Figure 1). We also had no data about other potential confounding factors such as circulating pro-inflammatory cytokines in the study patients.

It is plausible that the malignancy-related systemic inflammatory response might exacerbate the local damaging effects of radiation-induced cytokine release that is thought to have a major role in development of lung toxicity[19,20]. Like other authors, we have not attempted to grade the extent of lung involvement with RP or to include data about the outcome of RP in our cohort. It is still possible that, although the incidence of RP might not be affected by the presence of emphysema, emphysema might have a role in determining the patient's response—for example, resolution without symptoms compared with progressive respiratory failure. Thus, to paint a more nuanced picture of the effect of RP in various patients with lung cancer, future studies should perhaps, in addition to simple incidence rates, include data about the extent of lung involvement and the severity and effect of any symptoms.

CONCLUSIONS

In our study, the presence of emphysema on chest CT imaging was not associated with an increased risk of RP. Those findings suggest that patients with lung cancer and emphysema should be offered RT when clinically indicated. However, further prospective studies will be needed for confirmation and should include data about other clinically

relevant outcomes such as effect on respiratory function and delays in subsequent anticancer treatment.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none. We have full control of all primary data and agree to allow review of our data if requested.

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