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Challenges scoring radiation pneumonitis in patients irradiated for lung cancer

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ABSTRACT

Background and purpose: To quantify uncertainties in scoring radiation pneumonitis.
Materials and methods: Records of 434 patients irradiated for lung cancer from 2000 to 2010 were retrospectively reviewed; IRB-approved study. From these, 121 received ≥60 Gy for non-small cell lung cancer (NSCLC) with ≥6 months follow-up. Patients where the physicians were uncertain of the diagnosis due to confounding factors were deemed "hard to score". Subgroups were defined based on lung dosimetric parameters, and frequencies in different subgroups were compared via Fisher's exact test.
Results: 21/121 of patients were considered to have pneumonitis; median follow 17 months. Of these, 10/21 were "hard to score"; reasons including acute COPD exacerbation, infection, and tumor progression. "Hard to score" pneumonitis was slightly more common in patients with a COPD history (15%) vs. without COPD (4%) ($p = 0.05$); and with a pre-RT FEV1 < 1.7 L (16%) vs. ≥1.7 L (4%) ($p = 0.09$). Rates of "unambiguous" pneumonitis trended to be non-significantly slightly higher in patients higher mean lung doses, V5, and V30.
Conclusion: Radiation pneumonitis occurred in 17% of patients undergoing RT for NSCLC; with diagnostic uncertainty in 48% of these. Poor pre-RT pulmonary function increases the rate of "hard to score" pneumonitis. Dosimetric parameters are slightly better related to "unambiguous" than "hard to score" pneumonitis, as expected.

1. Introduction

Radiotherapy (RT) plays an important role in the treatment of lung cancer' primarily as definitive therapy with or without chemotherapy in patients with unresectable tumors. RT-induced lung injury is a major dose limiting toxicity. Radiation pneumonitis (RP), manifest primarily as shortness of breath, occurs in approximately 15–40% of patients within about 1–6 months post-RT [1,2].

Most studies reporting the rates of pneumonitis do not explicitly acknowledge the uncertainties in identifying and scoring pneumonitis. Kocak et al. [3] noted that the diagnosis of radiation pneumonitis was challenging in 28% of patients suspected of having radiation pneumonitis after RT for lung cancer, with uncertainties related to concurrent medical conditions (e.g. infection, cardiac disease, emphysema).

In order to reassess this issue, we herein perform an analysis of patients receiving thoracic RT for lung cancer to assess the incidence of radiation pneumonitis, and the frequency and causes of ambiguities in scoring radiation pneumonitis. Further, the impact of such ambiguous cases on the apparent relationship between dosimetric parameters and the incidence of radiation pneumonitis is assessed.

2. Methods and materials

2.1. Patient population

As part of an Institutional Review Board-approved study, the records of 434 patients irradiated between 2000 and 2010 for lung cancer were reviewed. Patients were included in the analysis if they received thoracic RT for non-small cell lung cancer (NSCLC) (with or without chemotherapy) with curative intent, and had a minimum received total dose ≥60 Gy. The majority of patients had squamous cell carcinoma (42%), NSCLC not otherwise specified (26%), and adenocarcinoma (21%). Patients who had surgery before and/or after RT were excluded. From the records reviewed, 155 patients

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were identified for inclusion in this analysis. The balance of cases was treated with palliative intent for local/distant disease, received <60 Gy, had small cell histology, or also had surgery. Only patients who had ≥6-months follow-up (121 patients) were considered in the current analysis.

The medical records were reviewed to assess for the development of pulmonary symptoms (typically shortness of breath) consistent with radiation pneumonitis. Typically the diagnosis of radiation pneumonitis was noted in the medical record as a possible or likely cause of the patient's symptoms.

The following grading system for pneumonitis, based on the modified National Cancer Institute Common Toxicity Criteria (CTC) was used: Grade 0, no increase in pulmonary symptoms due to RT; Grade 1, increase in pulmonary symptoms not requiring initiation or increase in steroids and/or oxygen; Grade 2, RT-induced pulmonary symptoms requiring initiation or increase in steroids; Grade 3, RT-induced pulmonary symptoms requiring oxygen; and Grade 4, RT-induced pulmonary symptoms requiring intubation or causing death. Patients with radiologic changes reported as "RP" but without symptoms were *not* considered to have toxicity. The records of all patients with ≥grade 2 of pneumonitis were analyzed further.

2.2. Evaluation of symptomatic radiation pneumonitis

Each case was scored as either "unambiguous" or "hard to score" pneumonitis. A patient with "unambiguous" pneumonitis was one who presented with shortness of breath, with or without cough that responded to steroids and did not have any confounding clinical factors that might be the cause of their dyspnea (e.g. tumor progression, acute exacerbation of chronic obstructive pulmonary disease – COPD, infection and cardiac disease). The records from patients suspected of having radiation pneumonitis were reviewed by at least two physicians who reached a consensus opinion. Cases for which the physicians were uncertain of the diagnosis were deemed "hard to score" pneumonitis. These patients typically had clearly recognized one or more clinical factors that confounded the diagnosis of radiation pneumonitis, the uncertainty was stated in the medical records and the therapeutic approach often addressed multiple etiologies of dyspnea (e.g. antibiotics given concurrently with steroids). Thus, patients in whom there were *potential* confounding factors (as would be the case with many of the patients, with, for example a prior history of COPD), but where the clinical record did *not* reflect any uncertainly, were not considered "hard to score".

2.3. Treatment techniques

All patients were treated at University of North Carolina with 6 MV and/or 15 MV photon beams. Patients were generally treated with opposed anterior–posterior fields to 40–48 Gy, followed by off-cord fields to 60–90 Gy at 1.8–2.0 Gy per daily fraction. Four patients were treated using a hyperfractionated concurrent boost technique (1.25 Gy twice daily to the clinical target volume and 1.6 Gy twice daily to the gross disease to a total dose 60–86.4 Gy) and six patients were treated with split course technique (2.0–3.0 Gy per daily fraction with a break in the middle of treatment to a total dose 60–62.5 Gy).

2.4. Treatment planning and DVH parameters

The archived three dimensional (3D) records between 2002 and 2010 were assessable in the 97 patients. All these patients underwent computed tomography (CT) simulation and dose calculation using PlanUNC (PLUNC, University of North Carolina at Chapel Hill). The contours of the lung were reviewed and were adjusted to be relatively uniform among the patients. Both lungs were regarded as a single organ. Care was taken to exclude the gross tumor volume (GTV), trachea and bronchi from the anatomic lung used to compute the lung DVH used for the analyses. From the lung DVH, the following dosimetric variables were extracted: Mean lung dose (MLD) and the lung volume receiving ≥ a defined dose (Vdose); V5, V30. All doses were calculated to reflect tissue heterogeneity using a finite-size pencil beam algorithm with a Monte–Carlo simulation result based 2-source model and a modified Batho inhomogeneity correction. Patients were sorted into subgroups based on lung dosimetric parameters.

Table 1
Treatment.

	All patients ($n=121$)	RP patients ($n=21$)	
		"Unambiguous" ($n=11$)	"Hard to score" ($n=10$)
Radiotherapy, dose/fraction (total dose)			
1.8–2.0 (60–90 Gy)	111	10	9
1.25–1.6 (60–86.4 Gy)	4	–	1
2.0–3.0 (60–62.5 Gy)	6	1	–
Chemotherapy[a]			
Pre-RT	5	1	–
Concurrent	10	–	2
Combined	85	8	4
No chemotherapy	20	2	4

RP, radiation pneumonitis.
[a] One patient (without RP) was treated with post-RT chemotherapy.

2.5. Statistical analysis

The patient and treatment characteristics, the rates of radiation pneumonitis ("unambiguous" vs. "hard to score" pneumonitis) were described by using simple descriptive statistics. The relation between possible confounding factors such as preexisting COPD history, low pre-RT PFTs and rates of "hard to score" pneumonitis were analyzed with a 2×2 contingency table. Patients were divided into four quartiles based on quantitative data from dosimetric parameters (e.g. MLD, V5, and V30). The rates of radiation pneumonitis (overall, "hard to score" and "unambiguous" pneumonitis) in patient subgroups were compared using Fisher's exact test. All statistical tests were two-tailed and $p \leq 0.05$ was somewhat arbitrarily defined as statistically significant.

3. Results

Of the 121 patients, 21 patients (17%) were considered to possibly have Grade ≥2 radiation pneumonitis and were treated with steroids. The patient and treatment characteristics are shown in Tables 1 and 2.

Of these 21 patients, 11 patients had "unambiguous" pneumonitis, and 10 patients (48%) were deemed "hard to score"; reasons including acute exacerbation of COPD, infection and tumor progression, in 8, 5, and 3 patients, respectively (these numbers sum > 10 as some patients had multiple confounding factors). The patients with a possible acute COPD exacerbation usually had a prior exacerbation of COPD and the clinical notes clearly stated the uncertainty in diagnosis of pneumonitis. Six patients were treated with antibiotics concurrently with steroids.

The median follow up was 17 months (range 6–108). Median time between completion of RT and onset of symptoms was 3 months for all pneumonitis, 4 months for "hard to score" pneumonitis, and 2 months for "unambiguous" pneumonitis.

Forty-eight patients had a pre-RT diagnosis of COPD; 10/48 (21%) were considered to have radiation pneumonitis; 7 "hard to