Published in final edited form as:
Lung Cancer. 2012 June ; 76(3): 350–353. doi:10.1016/j.lungcan.2011.11.025.

Challenges Scoring Radiation Pneumonitis in Patients Irradiated For Lung Cancer

Eda Yirmibesoglu, MD[1,*], **Daniel S. Higginson, MD**[1], **Merdan Fayda, MD**[1,¶], **M. Patricia Rivera, MD**[2], **Jan Halle, MD**[1], **Julian Rosenman, MD, PhD**[1], **Liyi Xie, MD**[1], and **Lawrence B. Marks, MD**[1]

[1]Department of Radiation Oncology, University of North Carolina, Chapel Hill, NC

[2]Department of Pulmonary Medicine, University of North Carolina, Chapel Hill, NC

[*]Department of Radiation Oncology, Kocaeli University Faculty of Medicine, Kocaeli, Turkey

[¶]Department of Radiation Oncology, Istanbul University Institute of Oncology, Istanbul, Turkey

Abstract

Background and Purpose—To quantify uncertainties in scoring radiation pneumonitis.

Materials and Methods—Records of 434 patients irradiated for lung cancer from 2000–2010 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 < 1.7L (16%) vs. ≥ 1.7L (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.

Corresponding Author: Lawrence B. Marks, M.D. Department of Radiation Oncology, Box7512, University of North Carolina, Chapel Hill, NC 27514-7512, Phone: (919) 668-5640, Fax: (919) 684-3953, marks@med.unc.edu.

Conflict of interest statement: None declared.

Keywords

Lung cancer; Non-small cell carcinoma; Radiation therapy; Pneumonitis; Toxicity scoring; Dosimetric parameters

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, 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.

Methods and Materials

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 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.

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".

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).

Treatment planning and DVH parameters

The archived three dimension (3D) records between 2002 and 2010 were assessable in the 97 patients. All these patients underwent computed tomography (CT) simulation and dose calculation using PLUNC (Plan 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.

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.

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 score" and 3 "unambiguous". In the 73 patients without COPD; 11/73 (15%) were considered to have RP; 3 "hard to score" and 8 "unambiguous". Of the 118 patients who had PFTs available, 50 patients had a pre-RT FEV1 < 1.7L (cut-point chosen as it was the population median value). In the 50 patients with a pre-RT FEV1 < 1.7L; 13/50 (26%) were considered to have radiation pneumonitis; 5 "unambiguous" and 8 "hard to score". "Hard to score" pneumonitis was more common in patients with a history of COPD (15%) vs. without COPD (4%), $p = 0.05$; and in those with a pre-RT FEV1 < 1.7L (16%) vs. ≥ 1.7L (4%), $p = 0.09$.

In the 97 patients for whom the archived 3D records were assessable, the MLD ranged from 8.8 to 35.3 Gy (mean 21.2 Gy), V5 ranged from 6.2 to 70.4% (mean 38.3%) and V30 ranged from 3.7 to 46.4% (mean 22.7%).

The frequency of “unambiguous” and “hard to score” pneumonitis among patient quartile subgroups, based on MLD, V5 and V30, is shown in Table 3. The rates of “unambiguous” pneumonitis (but not to “hard to score” pneumonitis) trended to be non-significantly slightly higher in patients higher (vs. lower) MLD, V5 and V30 ($p>0.05$).

Discussion

There are no well established methods to qualitatively or quantitatively describe the certainty of a toxicity score. To our knowledge, the certainty with which radiation pneumonitis can be scored has not been formally evaluated. Kocak et al. noted that 28% of their patients with suspected radiation pneumonitis had confounding medical conditions (infection, cardiac disease, and emphysema), making the clinical diagnosis uncertain (3).

In the present study, approximately 48% of radiation pneumonitis cases were scored as “hard to score” due to confounding factors (e.g. tumor progression, acute exacerbation of COPD, and infection). “Hard to score” pneumonitis was more common in patients with pre-existing lung disease; as assessed by a documented history of COPD or relatively low pre-RT PFTs. The clinical presentation of radiation pneumonitis may mimic that of an exacerbation of preexisting lung disease (e.g. “COPD flare”) which may often be associated with infection (4).

Many individual studies, as well as the recent QUANTEC review, note that the risk of symptomatic radiation pneumonitis generally increases with increasing dose/volume parameters, such as MLD, V20 and V30 (5, 6, 7). However, these predictions are not ideal; there are no apparent “thresholds” for risk, and there are marked inter-study variations in the absolute rates of radiation pneumonitis. This might result from the use of a variety of scoring systems- some that rely solely on symptomatic endpoints (8) while others also include radiographic endpoints. Further, vague terms such as “mild, moderate, and severe” are sometimes used in the scoring system. As noted in the present study, attribution bias (ascribing the patient’s symptoms to the RT vs. other causes) can have a marked impact on the observed rate of radiation pneumonitis (by a factor of two in our analysis as half of the patients with radiation pneumonitis were ambiguous). Further, this ambiguity appears to impact on the ability to relate symptoms to dosimetric parameters. The rate of unambiguous radiation pneumonitis was better related to radiation dosimetric parameters than were the ambiguous cases. Prior analyses similarly noted that predictive models based on dosimetric parameters are better correlated with outcomes when patients with the poorest pre-RT pulmonary function tests are excluded (9, 10). Presently, the uncertainty in scoring radiation pneumonitis is not considered in most reports, and the existing scoring systems do not explicitly acknowledge the potential for such uncertainties. Additional confounding effects result from things such as dose calculation uncertainties particularly at the lung-soft tissue interfaces, day-to-day set up variations, and intra- and inter-fraction motion of thoracic structures. Given the many uncertainties in the precise cause of post-RT symptoms, it might also be reasonable to consider scoring “all-cause post-RT dyspnea”, accepting that an increased incidence of COPD exacerbations, or chest infections or episodes of cardiac failure may also be a radiation-associated.

The current analysis has several limitations. First, the method used to identify patients who are “hard to score” is not perfect. Nevertheless, we included only cases where the clinical records clearly noted some diagnostic uncertainty, and this seems reasonable. This study was entirely retrospective. Methods for documentation and details of medications recommended for patients were inconsistent. Thus, the absolute rate of pneumonitis may have been understated if the application of steroids for dyspnea was not clearly documented. Similarly, the assignment of symptomatic patients in to the “unambiguous” vs. “hard to score” pneumonitis subgroups may have been inexact.

Second, the patients reported in the current study were treated over a long time interval (10 years), during which there were different care providers involved. Nevertheless, the majority of the patients were treated by a stable group of multi-disciplinary clinicians.

Third, grading symptoms based on the use of medications (e.g., steroid use) introduces a potential bias as physicians who are more likely to prescribe steroids may note a higher rate of radiation pneumonitis. This however is a generic concern of all studies that use the commonly-applied grading systems.

Fourth, the confounding impact of chemotherapy on the risk of radiation pneumonitis was not systematically addressed. Clinical data from the RTOG suggests that the chemotherapy may enhance the risk of radiation-associated pulmonary injury, (11), but the data on this are conflicting (7). In the current study, the chemotherapy regimens (agents and doses) were not detailed, and thus its impact was not practical to consider.

Fifth, the small sample size and the retrospective nature of the review, limits the power of the statistical analysis. For example, since the follow-up regiment was inconsistent, and pneumonitis was not assessed for in a uniform manner, some pneumonitis events may not have been apparent from the medical records. Therefore, the reported incidence might understate the true incidence. This is a common problem with retrospective clinical studies. Prospective series including large number of patients with the diagnosis of radiation pneumonitis are challenging since the incidence of pneumonitis is not that high. A more systematic multi-institutional/cooperative group-based study may help to further clarify this issue.

Conclusion

Radiation pneumonitis occurred in 17% of our patients undergoing RT (+/− chemotherapy) for NSCLC. Of these, the diagnosis of radiation pneumonitis is somewhat uncertain in 48%. Recognition of these uncertainties is needed when reporting rates of radiation pneumonitis and when comparing data from multiple institutions. The presence of poor pre-treatment pulmonary functional status (e.g. COPD and low PFTs) may increase the expected fraction of patients who will have “hard to score” pneumonitis. Therefore, differences in the pre-RT pulmonary functional status may account for some of the inter-institutional differences in the reported rates of radiation pneumonitis. Lung dosimetric parameters are slightly better related to “unambiguous” pneumonitis than “hard to score” pneumonitis, as expected. Given

the retrospective nature of this review, and the many uncertainties, the results should be considered as hypothesis generating, and requires further clarification and study.

Acknowledgments

Supported in part by NIH grant CA 69579 (L.B.M.) and Turkish Society of Radiation Oncology (E.Y.; M.F.)

References

1. Mehta V. Radiation pneumonitis and pulmonary fibrosis in non-small-cell lung cancer: pulmonary function, prediction, and prevention. Int J Radiat Oncol Biol Phys. 2005; 63:5–24. Review. [PubMed: 15963660]
2. Marks LB, Yu X, Vujaskovic Z, Small W Jr, Folz R, Anscher MS. Radiation-induced lung injury. Semin Radiat Oncol. 2003; 13:333–45. Review. [PubMed: 12903021]
3. Kocak Z, Evans ES, Zhou SM, et al. Challenges in defining radiation pneumonitis in patients with lung cancer. Int J Radiat Oncol Biol Phys. 2005; 62:635–8. [PubMed: 15936538]
4. Barnes PJ. Chronic obstructive pulmonary disease. N Engl J Med. 2000; 343:269–80. Review. [PubMed: 10911010]
5. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys. 1999; 45:323–9. [PubMed: 10487552]
6. Hernando ML, Marks LB, Bentel GC, et al. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys. 2001; 51:650–9. [PubMed: 11597805]
7. Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys. 2010; 76:70–6. Review.
8. Radiation Therapy Oncology Group. [Accessed March 16, 2011] (RTOG) acute morbidity scoring criteria web site. Available at: http://www.rtog.org/ResearchAssociates/AdverseEventReporting/AcuteRadiationMorbidityScoringCriteria.aspx
9. Lind PA, Marks LB, Hollis D, et al. Receiver operating characteristic curves to assess predictors of radiation-induced symptomatic lung injury. Int J Radiat Oncol Biol Phys. 2002; 54:340–7. [PubMed: 12243806]
10. Marks LB, Munley MT, Bentel GC, et al. Physical and biological predictors of changes in whole-lung function following thoracic irradiation. Int J Radiat Oncol Biol Phys. 1997; 39:563–70. [PubMed: 9336133]
11. Byhardt RW, Scott C, Sause WT, et al. Response, toxicity, failure patterns, and survival in five Radiation Therapy Oncology Group (RTOG) trials of sequential and/or concurrent chemotherapy and radiotherapy for locally advanced non-small-cell carcinoma of the lung. Int J Radiat Oncol Biol Phys. 1998; 42:469–78. [PubMed: 9806503]

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 (60–90Gy)	111	10	9
1.25–1.6 (60–86.4Gy)	4	-	1
2.0–3.0 (60–62.5Gy)	6	1	-
Chemotherapy[*]			
Pre-RT	5	1	-
Concurrent	10	-	2
Combined	85	8	4
No chemotherapy	20	2	4

Abbreviations: RP= radiation pneumonitis

[*] One patient (without RP) was treated with post-RT chemotherapy.

Table 2

Patient characteristics

	All patients (n=121)	RP patients (n=21)	
		"unambiguous" (n=11)	"hard to score" (n= 10)
Mean age (range, years)	60 (39–86)	65 (42–85)	64 (47–85)
Gender (male)	76 (63%)	7 (33%)	6 (29%)
Stage			
I	8 (7%)	-	3 (14%)
II	8 (7%)	1 (5%)	3 (14%)
III	105 (86%)	10 (48%)	4 (19%)
Smoking history*	109 (92%)	10 (48%)	9 (43%)
Ongoing smoking*	56 (47%)	2 (10%)	7 (33%)
Primary tumor location			
Upper lobe	91 (75%)	7 (33%)	8 (38%)
Middle and/or lower lobe	30 (25%)	4 (19%)	2 (95%)
COPD history	48 (40%)	3 (14%)	7 (33%)
Pre-FEV1 <1.7 L **	50 (42%)	5 (24%)	8 (38%)

Abbreviations: RP= radiation pneumonitis

* Available in the 119 patients.

** Using 1.7 L as a cut-point (the median value in our patients). Available in the 118 patients

Table 3

Observed incidence of radiation pneumonitis in quartiles of patients defined based on dosimetric parameters

	MLD			V5			V30		
Quartile	**Mean Gy (range)**	**“unambiguous”**	**“hard to score”**	**Mean % (range)**	**“unambiguous”**	**“hard to score”**	**Mean % (range)**	**“unambiguous”**	**“hard to score”**
1st	16.6 (8.8–18.8)	2/24	6/24	23.9 (6.2–31.9)	1/24	4/24	14.2 (3.7–18.7)	1/24	5/24
2nd	20 (18.9–21.2)	0/24	1/24	35.5 (31.9–38.1)	1/24	3/24	21 (18.9–23.4)	2/24	2/24
3rd	22.3 (21.6–22.3)	3/24	1/24	41.2 (38.3–45)	4/24	1/24	24.8 (23.5–26.9)	1/24	1/24
4th	25.6 (23.2–35.3)	3/25	0/25	51.9 (45.9–70.4)	2/25	0/25	30.4 (27–46.4)	4/25	0/25

Abbreviations: MLD= mean lung dose; V5 and V30= % lung volume receiving ≥5 and 30Gy, respectively.