Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 3, pp. 635–638, 2005

0360-3016/05/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2004.12.023

CLINICAL INVESTIGATION **Lung**

CHALLENGES IN DEFINING RADIATION PNEUMONITIS IN PATIENTS WITH LUNG CANCER

Zafer Kocak, M.D.,*‡ Elizabeth S. Evans, B.S.,* Su-Min Zhou, Ph.D.,* Keith L. Miller, M.D.,* Rodney J. Folz, M.D.,† Timothy D. Shafman, M.D.,* and Lawrence B. Marks, M.D.*

Departments of *Radiation Oncology, Duke University Medical Center, Durham, NC; †Pulmonary Medicine, Duke University Medical Center, Durham, NC; and ‡Department of Radiation Oncology, Trakya University Hospital, Edirne, Turkey

Purpose: To assess the difficulty of assigning a definitive clinical diagnosis of radiation (RT)-induced lung injury in patients irradiated for lung cancer.

Methods: Between 1991 and 2003, 318 patients were enrolled in a prospective study to evaluate RT-induced lung injury. Only patients with lung cancer who had a longer than 6-month follow-up (251 patients) were considered in the current analysis. Of these, 47 of 251 patients had Grade ≥2 (treated with steroids) increasing shortness of breath after RT, thought possibly consistent with pneumonitis/fibrosis. The treating physician, and one to three additional reviewing physicians, evaluated the patients or their medical records, or both. The presence or absence of confounding clinical factors that made the diagnosis of RT-induced uncertain lung injury were recorded.

Results: Thirty-one of 47 patients (66%) with shortness of breath had "classic" pneumonitis, i.e., they responded to steroids and had a definitive diagnosis of pneumonitis. In 13 of 47 patients (28%), the diagnosis of RT-induced toxicity was confounded by possible infection; exacerbation of preexisting lung disease (chronic obstructive pulmonary disease); tumor regrowth/progression; and cardiac disease in 6, 8, 5, and 1 patients, respectively (some of the patients had multiple confounding factors and were counted more than once). An additional 3 patients (6%) had progressive shortness of breath and an overall clinical course more consistent with fibrosis. All 3 had evidence of bronchial stenosis by bronchoscopy.

Conclusions: Scoring of radiation pneumonitis was challenging in 28% of patients treated for lung cancer owing to confounding medical conditions. Recognition of this uncertainty is needed and may limit our ability to understand RT-induced lung injury. **© 2005 Elsevier Inc.**

Confounding factors, Lung cancer, Radiation pneumonitis.

INTRODUCTION

Lung injury induced by radiation (RT) is a major dose-limiting toxicity for patients receiving radiation to the thorax. Acute symptomatic injury to the lung occurs in approximately 5–30% of patients and typically presents 1–6 months after radiation therapy. Characteristic symptoms of radiation pneumonitis include shortness of breath, cough, and occasionally mild fever (1–5). In many irradiated patients, especially those with lung cancer, these symptoms are nonspecific and may present a diagnostic challenge. Other clinical conditions may masquerade as radiation pneumonitis. The certainty with which pneumonitis can be scored has not been formally evaluated. It is important for investigators to recognize the precision of these endpoints, as they will fundamentally limit the ability of models intended to predict the likelihood of radiation pneumonitis.

We herein quantitatively assess the difficulty of assigning a definitive clinical diagnosis of RT-induced lung injury in patients irradiated for lung cancer.

METHODS AND MATERIALS

Patient population

Between 1991 and 2003, 318 patients were enrolled on an Institutional Review Board–approved prospective study to evaluate RT-induced lung injury. Informed consent was obtained from all patients. Only patients with lung cancer who had a longer than

Reprint requests to: Lawrence B. Marks, M.D., Department of Radiation Oncology, Box 3085, Duke University Medical Center, Durham, NC 27710. Tel: (919) 668-5640; Fax: (919) 684-3953; E-mail: marks@radonc.duke.edu

Presented at the 2004 Meeting of the Radiation Research Society, April 24–27, 2004, St. Louis, MO.

Supported in part by National Institutes of Health R01 Grant CA69579.

Acknowledgments—We thank the University of North Carolina for the PLUNC planning software, and Andrea Tisch, Robert Clough, and Phil Antoine for data management.

Received Aug 5, 2004, and in revised form Oct 22, 2004. Accepted for publication Dec 1, 2004.

6-month follow-up (251 patients) were considered in the current analysis. Patients who had post-RT surgery were excluded.

After RT, clinical evaluation to assess for RT-induced pulmonary symptoms was generally performed 1.5, 3, 6, 9, and 12 months post-RT and then at 6-month intervals thereafter. The treating physician, and any other physicians involved in the protocol, prospectively scored the patients for the presence or absence of RT-induced pulmonary 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 irradiation; 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. The records of all patients with any grade of pneumonitis were analyzed further.

Assessing certainty of diagnosis of pneumonitis

One to three additional physicians (Z.K., K.M., and T.S. or L.M.; all four are radiation oncologists, one is also a pulmonologist), depending on the complexity of the situation, reviewed the medical records of all patients who were thought to have Grade ≥2 pneumonitis. Based on this review, each case was scored as either "classic" or "hard to score" radiation pneumonitis. A patient with "classic" radiation pneumonitis was one who presented with shortness of breath that responded to steroids and did not have other confounding clinical factors (tumor regrowth, exacerbation of chronic obstructive pulmonary disease-COPD, infection, and active cardiac disease). Further, the reviewing physicians unanimously agreed with the clinical diagnosis. A "hard to score" patient may or may not have responded to steroids, and also presented with one or more confounding clinical factors. The clinic notes in these patients usually described the uncertainty of the diagnoses.

Treatment techniques

All patients received three-dimensionally planned external beam RT at Duke University Medical Center. The radiation techniques have been described previously (6). In brief, RT was delivered with 6 MV or 15 MV photon beams by linear accelerators. Patients were generally treated with opposed anterior-posterior fields to 40–45 Gy, followed by off-cord oblique fields to approximately 60–66 Gy at 1.8–2.0 Gy per daily fraction. Seventeen 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 (minimum 6-h interfraction interval) to a total of 56–86 Gy (7).

RESULTS

Forty-seven of 251 patients (19%) with lung cancer developed increasing shortness of breath consistent with radiation pneumonitis/fibrosis (Grade ≥2) and were treated with steroids.

Thirty-one of these 47 patients (66%) with shortness of breath had "classic" pneumonitis. In 13 of 47 (28%), the diagnosis of RT-induced toxicity was confounded by possible infection, exacerbation of preexisting chronic obstructive pulmonary disease (COPD), tumor regrowth/progression, and congestive heart failure in 6, 8, 5, and 1 patients, respectively (these numbers sum to more than 13 as some of the patients had multiple confounding factors and were counted more than once). The patients with a possible exacerbation of COPD each had a prior history of COPD, usually with prior exacerbations. These patients were thus termed "hard to score." An additional 3 patients had progressive shortness of breath and an overall clinical course more consistent with fibrosis. All 3 of these had evidence of bronchial stenosis by bronchoscopy.

The patients' treatment and clinical characteristics are shown in Tables 1 and 2. These characteristics are largely similar in the two patient groups. The rate of COPD was higher in the "hard to score" patients than in the "classic" patients ($p = 0.01$). This is expected, because preexisting COPD is one of the clinical factors that confound the diagnosis of pneumonitis. The details of the 13 "hard to score" patients, and interval between radiotherapy and symptoms in all 47 patients, are shown in Fig. 1 and Table 3, respectively.

DISCUSSION

Many investigators are trying to develop methods to relate dosimetric and clinical parameters to the risk of RT-induced lung injury (1–5). These studies generally demonstrate that the risk of radiation pneumonitis increases with increasing dose/volume parameters, such as mean lung dose (MLD) (2, 4, 5), V20 (or V30) (4, 5), and normal tissue complication probability (NTCP) (1, 3). However, the ability to accurately relate dosimetric and clinical parameters to the risk of radiation pneumonitis has been suboptimal. For example, in the data from Graham *et al.*, patients with a V20

Table 1. Treatment variables ($n = 47$)

Treatment type	Classic RP patients	Hard to score patients*	All patients
Radiotherapy, dose/fraction (total dose)			
1.6 (56–86 Gy)†	9 (29%)	8 (50%)	17 (36%)
1.8–2.0 (40–70 Gy)	22 (71%)	8 (50%)	30 (64%)
Chemotherapy			
Pre-RT	17 (55%)	7 (44%)	24 (51%)
Concurrent	2 (6%)	—	2 (4%)
Pre-RT + concurrent	5 (16%)	1 (6%)	6 (13%)
No chemotherapy	7 (23%)	8 (50%)	15 (32%)
Pre-RT surgical procedure			
Thoracotomy, no resection	2 (6%)	1 (6%)	3 (6%)
Wedge resection	1 (3%)	—	1 (2%)
Lobectomy	6 (19%)	3 (19%)	9 (19%)
No surgery	22 (72%)	12 (75%)	34 (73%)

Abbreviations: RP = radiation pneumonitis; RT = radiation therapy.

* Including 3 patients with fibrosis/stenosis.

† hyperfractionated treatment (twice daily).