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Do Angiotensin-Converting Enzyme Inhibitors Reduce the Risk of Symptomatic Radiation Pneumonitis in Patients with Non-small Cell Lung Cancer after Definitive Radiotherapy? Analysis of a Single-Institution Database

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Abstract

Purpose—Preclinical studies have suggested that angiotensin-converting enzyme inhibitors (ACEIs) can mitigate radiation-induced lung injury. We sought here to investigate possible associations between ACEI use and the risk of symptomatic radiation pneumonitis (RP) among patients undergoing radiation therapy (RT) for non–small-cell lung cancer (NSCLC).

Patients and Methods—We retrospectively identified patients who received definitive radiotherapy for stage I–III NSCLC in 2004–2010 at a single tertiary cancer center. Patients must have received a radiation dose of at least 60 Gy for a single primary lung tumor and have had imaging and dosimetric data available for analysis. RP was quantified according to the Common Terminology Criteria for Adverse Events v3.0. A Cox proportional hazard model was used to assess potential associations between ACEI use and risk of symptomatic RP.

Results—Of the 413 patients analyzed, 65 were using ACEIs during RT. In univariate analysis, the rate of grade ≥ 2 RP seemed lower in ACEI users than in nonusers (34% vs 46%), but this apparent difference was not statistically significant ($P=0.06$). In multivariate analysis of all patients, ACEI use was not associated with the risk of symptomatic RP (hazard ratio [HR]=0.66, $P=0.07$) after adjustment for sex, smoking status, mean lung dose (MLD), and concurrent carboplatin and paclitaxel chemotherapy. Subgroup analysis showed that ACEI use did have a protective effect from grade ≥ 2 RP among patients who received a low (≤ 20 Gy) MLD ($P<0.01$) or were male ($P=0.04$).

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The authors declare no conflicts of interest.

Conclusion—A trend towards reduction in symptomatic RP among patients taking ACEIs during RT for NSCLC was not statistically significant on univariate or multivariate analyses, though certain subgroups may benefit from use (i.e., male patients and those with low MLD). The evidence at this point is insufficient to establish whether the use of ACEIs does or does not reduce the risk of RP.

Keywords

ACEI; non-small cell lung cancer; radiation pneumonitis; radiotherapy; lung toxicity

INTRODUCTION

Radiation pneumonitis (RP) is one of the main dose-limiting toxicities associated with radiation therapy (RT) for the definitive treatment of non-small-cell lung cancer (NSCLC) (1–3). Angiotensin-converting enzyme inhibitors (ACEIs) have been shown experimentally to prevent the development of radiation-induced lung injury in preclinical models (4, 5). In clinical retrospective studies, one indicated no benefit from ACEIs among NSCLC patients (6) but two others noted lower rates of symptomatic (grade 2 radiation pneumonitis [RP]) (7, 8). However, each of these clinical studies involved small numbers of patients, which limited the investigators' ability to control for confounding variables and may have affected the conclusions. The purpose of the current study was to evaluate whether the use of ACEIs in a larger population during definitive RT for NSCLC, with or without chemotherapy, was associated with reduced rates of symptomatic RP. Our hypothesis was that the use of these agents would correlate with reduced toxicity and thus that further prospective investigation would be warranted.

PATIENTS AND METHODS

Patients in this retrospective review were selected from a large clinical database of patients who underwent definitive RT for NSCLC from 2004 through 2010 at a single tertiary cancer care center. This database contained detailed information on patient demographics, tumor, RT, chemotherapy, outcomes, normal tissue radiation complications, and mortality. This study was approved by the appropriate institutional review board and was conducted in compliance with the Health Insurance Portability and Accountability Act.

Inclusion criteria were as follows: (1) having newly diagnosed and pathologically confirmed NSCLC; (2) having received definitive RT, with or without concurrent chemotherapy; (3) having received at least 60 Gy (or, for proton therapy, a dose of equivalent relative biological effectiveness); and (4) having information available on the use of ACEIs before and during the entire course of RT. Disease in all cases was staged according to the 2002 (6th) edition of the American Joint Committee on Cancer staging system. Exclusion criteria were (1) being registered in an institutional protocol in which data reporting on RP was prohibited; (2) having more than one primary lung tumor; (3) being treated with stereotactic body RT; (4) having missing data on mean lung dose (MLD) or volume of lung receiving at least 20 Gy (V_{20}); and (5) not having had lung computed tomography (CT) or positron

emission tomography (PET) reevaluation within 1 year after the radiation was completed (Fig. 1).

Follow-up visits included an interval history and physical examination. Other imaging studies such as CT or PET/CT were obtained at the discretion of the treating physician. Patients were evaluated at 1–3 months till 18 months after RT completed.

Study endpoint and covariates

Information on use of ACEI and other medications was retrieved from review of medical and pharmacy records. Patients were included in the ACEI group if they used the medication throughout the duration of the RT. Information was also tabulated on the use of other agents that could potentially affect the development of RP, such as angiotensin receptor blockers (ARBs), inhaled steroids, statins, and nonsteroidal anti-inflammatory drugs (5, 9, 10). The study endpoint (appearance of grade 2 RP) was assessed and scored according to the Common Terminology Criteria for Adverse Events version 3.0. RP had been diagnosed according to clinical symptoms and any of the following radiographic abnormalities: ground-glass opacity, attenuation, or consolidation changes within the radiation field. The times to endpoint development were calculated from the start of RT; patients who had not experienced the endpoint were censored at 18 months after the start of RT.

Potential clinical confounding factors included patient and tumor characteristics, radiation dosimetric variables (8, 11, 12), and aspects of pulmonary function (13). Pulmonary function tests (the diffusing capacity of the lung for carbon monoxide [DLCO; percentage of predicted value] and forced expiratory volume in 1 second per unit of vital capacity [FEV1/VC]) were given before the RT. Radiation plans were available for all patients. For each patient, MLD and V₂₀ (volume of lung receiving at least 20 Gy) were recorded.

Statistical analyses

Patient and tumor characteristics were grouped according to use of ACEIs during RT, and between-group comparisons were made with chi-squared or Fisher's exact tests. For all clinical and dosimetric variables, Cox proportional hazards models were fitted to determine the association of ACEI intake with rates of grade 2 RP in both univariate and multivariate analyses. To coincide with the number of patients in each analyzed group (which correlates directly with the number of events in each group) and thus to minimize the risk of associations that were due to chance, we selected four variables that have been reported to have the greatest influence on RP rates in this analysis: sex (14), smoking status (2), MLD (15), and receipt of concurrent chemotherapy (15), and included them in the model. Results are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Finally, in a supplementary analysis, we evaluated the interaction of sex and MLD with ACEI use to determine if these factors influenced any potential correlations between ACEI and RP. We chose MLD because dosimetric factors are closely related to the risk of developing RP after definitive RT, and we chose sex based on two previous studies that consisted mostly of male patients. The Kaplan-Meier method was used to estimate of freedom from symptomatic (grade 2) RP over time according to MLD, sex, and use or no use of ACEIs, and subgroups were compared with the log-rank statistic. *P* values of 0.05 or less were considered to

indicate statistical significance; all tests were two-sided. Statistical analyses were done with Stata/SE v10.1 software (Stata Corp LP, College Station, TX).

RESULTS

Patient characteristics

The final study population consisted of 413 patients, 65 who had taken ACEIs during definitive RT and 348 who had not. Patient characteristics are listed in Table 1. Median patient age was 66 years (range 34–88 years), and most patients in both groups had stage III disease (81%) and had received concurrent chemotherapy (80%). Forty-nine patients were prescribed ARBs. The most commonly prescribed drugs were lisinopril (given to 50% of patients who took ACEIs), olmesartan and valsartan (given to 61% of patients who took ARBs).

ACEI, other risk factors, and symptomatic RP

A total of 183 patients (44%) experienced symptomatic RP (133 grade 2, 47 grade 3, 0 grade 4, and 3 grade 5). The effects of patient characteristics and concurrent medication use on the risk of grade 2 RP are outlined in Table 2. Twenty-two of 65 patients (34%) taking ACEIs developed grade 2 RP compared with 161 of 348 of patients (46%) not taking ACEIs. This difference was of borderline statistical significance ($P=0.06$). Fifty of 111 patients (45%) who had taken ACEIs or ARBs developed grade 2 RP compared with 133 of 302 of patients (44%) not taking ACEIs or ARB ($P=0.85$). In univariate analysis of other variables, smoking status (having smoked previously or currently) was linked with reduced risk of symptomatic RP, as was MLD >20 Gy, $V_5 >0.65\%$, $V_{20} >0.37\%$, and $V_{30} >0.26\%$ (Table 2).

After adjustment for sex, smoking status, MLD and concurrent carboplatin and paclitaxel chemotherapy, the use of ACEIs was not significantly associated with a reduced risk of symptomatic RP (HR=0.66, $P=0.07$). Only smoking status and MLD remained significant predictors of grade 2 RP (Table 3).

Interactions between MLD, sex, and ACEIs on symptomatic RP

The recommended dose constraint on MLD to the total lung for all patients in this study was <20 Gy. To clarify whether exceeding this dose constraint interacted with ACEI use and grade 2 RP, we compared freedom from grade 2 RP according to whether patients had MLD >20 Gy ($n=298$) or MLD ≤ 20 Gy ($n=115$) (Fig. 2). Interestingly, use of ACEIs reduced the probability of symptomatic RP for those with an MLD of <20 Gy ($P<0.01$, Fig. 2A) but had no effect in the high-MLD group ($P=0.12$, Fig. 2B). We similarly evaluated whether sex interacted with ACEI use and grade 2 RP, as was reported previously and found that among male patients, the use of ACEIs was associated with a lower risk of grade 2 RP ($P=0.04$, Fig. 2C), but no such effect was evident for female patients ($P=0.66$, Fig. 2D).

DISCUSSION

To the best of our knowledge, this is the largest retrospective review, with the most complete set of covariates, reported to date on the possible association between ACEI use and risk of RP in patients with NSCLC after definitive RT. Our pertinent findings can be summarized as follows. First, we found that in an unadjusted (i.e., univariate) analysis, the use of ACEIs seemed to be associated with an absolute risk reduction of 10%-15% (P borderline significant) of symptomatic RP. Second, we found that when adequately adjusting for sex, smoking status, use of concurrent carboplatin and paclitaxel chemotherapy, and most importantly MLD, the strength of this association was reduced. Third, we found that including the related drug class ARBs in the analysis did not improve this correlation, and in fact weakened it, a finding consistent with at least one study assessing this question (8). Finally, we found an interaction between MLD or sex and the effect of ACEIs on RP, possibly indicating that much of the benefit from the use of ACEIs is restricted to male patients, as has been previously suggested by others (7), or that any potential benefit from the use of ACEIs is negated by high lung doses.

Initial interest in the potential relationship between ACEIs and RP in clinical settings arose from the documented ability of some of these drugs to reduce the risk of radiation-induced lung and kidney injury in animal models (16). ACEIs suppress the renin-angiotensin system by reducing the production of angiotensin II, whereas ARBs selectively block the actions of the angiotensin II type I receptor. Angiotensin II, in addition to elevating blood pressure, works to stimulate collagen synthesis and promote the growth of vascular smooth muscle cells. Proposed protective mechanisms of ACEIs include the downregulation of TGF β 1, reduction of pulmonary hypertension, and suppression of the renin-angiotensin system (5). These functions may have important implications for the development of radiation-induced injury (17, 18). Notably, however, all of the preclinical data on this topic were obtained using captopril or single high-dose irradiation (4, 5, 19). In our study, only one of 413 patients used captopril and all patients were given fractionated RT.

From a clinical standpoint, whether ACEIs can reduce RP has been questioned for almost two decades. Wang et al. (6) reported a cohort of 230 patients treated between 1994 and 1997 and most patients (57%) were treated with 2D nonconformal RT. No difference was found in that study in the incidence of RP between ACEI users and nonusers (15% vs. 12%, $P=0.75$). Since that time, two subsequent retrospective clinical studies both showed a benefit from the use of ACEI in reducing RP, which may have reignited interest in this topic. Kharofa et al. (7) reported a group of 162 patients with stage I–III NSCLC, all of whom were male and all treated with three-dimensional conformal RT; 12 of these 162 patients experienced grade 2 RP. All of the 62 ACEI users in that study took lisinopril except for one patient who took captopril, and only one patient among the 62 ACEI users in that study developed symptomatic RP compared with 11 of the 100 nonusers, which was significant in univariate analysis ($P=0.032$). The authors of that study concluded that the incidental concurrent use of ACEIs during thoracic RT was associated with a decreased risk of RP. In the other study (8), 21 of 160 patients had been taking ACEIs (11 ramipril, 7 lisinopril, 2 perindopril, and 1 enalapril), and 27 developed symptomatic RP. The use of ACEIs was associated with a decreased risk of RP in univariate analysis ($P=0.027$) but not

in multivariate analysis ($P=0.648$). Our findings also suggested an association between use of ACEIs and reduction in lung toxicity, but this apparent association was not statistically significant.

In our study, the development of RP was associated with the dosimetric variables MLD, V_5 , V_{20} , and V_{30} , associations that are consistent with previous findings (15, 20). Interestingly, in our study the use of ACEIs seemed to benefit patients receiving low MLD (< 20 Gy) but that benefit disappeared when lung doses were higher. This finding is not surprising given the well-established strong influence of lung dose on RP. We thus hypothesize that the preclinical mechanisms previously noted occur in clinical settings as well, but the effects are probably more minor in that they cannot adequately provide a benefit when the insult to the lungs is substantial.

Although other pharmacologic agents (e.g., statins, anti-inflammatory agents, or inhaled steroids) were not the primary focus of this analysis, we did not find associations between the use of any of these agents and RP. The utility of these agents has not been established in this context, although a limited number of studies have shown potential benefits in reducing RT-related toxicity. One such study showed that use of statins or statins with ACEIs during radical pelvic radiotherapy significantly reduced acute gastrointestinal symptom scores (21). Before that analysis, no clinical reports of RP and statin use had been published. Certainly, the efficacy of these medications in reducing toxicity should be evaluated in further studies that include this as a primary aim.

Notably, smoking was a protective factor for RP in our study, a finding that is consistent with previous clinical reports that smoking reduced the risk of radiation pneumonitis (2). In a meta-analysis reported by Palma et al. (22), smokers were at lower risk of symptomatic pneumonitis in univariate analysis (OR=0.39, 95% CI 0.19–0.80, $P=0.01$). The mechanism underlying this effect is not clear at this time (23), but possible explanations may include a depressed inflammatory response among smokers (24), smoking-induced hypoxia (25), or a downregulated DNA repair capacity among non-smokers with lung cancer, which would increase susceptibility to radiation-induced injury (26).

The Palma meta-analysis (22) also demonstrated that receipt of carboplatin/paclitaxel chemotherapy (as opposed to cisplatin/etoposide) was a risk factor for symptomatic pneumonitis. Given the small number of patients who received cisplatin and etoposide in our study (20 of 413), we could not make this comparison. However, evaluations such as these are certainly important in guiding the choice of chemotherapy regimens for patients with radiation treatment plans that approach lung constraints.

We acknowledge several limitations of our study. First, data were missing or incomplete regarding the duration of ACEI use before and after treatment, the significance of which is unknown. However, in experimental studies, RP in a rat model was prevented even if an ACEI (captopril) was started 1 week after irradiation or if it was discontinued after 5 weeks (5). Second, as noted above, patients in this study had received mostly non-thiol ACEIs, which may have contributed to our negative findings. Third, most patients in our study had stage III NSCLC, which could have masked a specific protective role in earlier-stage

disease. Fortunately, the database we used is prospectively maintained, and more patients with stage I/II disease will be enrolled in the future. Finally, because of practical limitations, we could not evaluate the potential influence of all medications that patients were taking at the time of treatment; interactions among these various medications could be the subject of future analyses, ideally in clinical trials. However, the strengths of this study worthy of note include the fairly homogenous treatment planning, dose prescription, consistent prescription constraints, and definitive RT at a single institution.

In conclusion, this analysis demonstrated that concurrent use of ACEIs was not significantly associated with a reduced risk of symptomatic RP after definitive RT in a large group of patients with NSCLC. We did find in secondary analyses that patients who were male or had an MLD of ≥ 20 Gy may derive some pulmonary protective benefit from use of these drugs. We conclude that evaluations in prospective trials should include use of ACEIs with a specific focus on interaction with lung dose and sex.

Acknowledgments

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References

1. Minami-Shimmyo Y, Ohe Y, Yamamoto S, et al. Risk factors for treatment-related death associated with chemotherapy and thoracic radiotherapy for lung cancer. *J Thorac Oncol.* 2012; 7:177–182. [PubMed: 22134071]
2. Jin H, Tucker SL, Liu HH, et al. Dose–volume thresholds and smoking status for the risk of treatment-related pneumonitis in inoperable non-small cell lung cancer treated with definitive radiotherapy. *Radiother Oncol.* 2009; 91:427–432. [PubMed: 18937989]
3. Vogelius IR, Westerly DC, Aznar MC, et al. Estimated radiation pneumonitis risk after photon versus proton therapy alone or combined with chemotherapy for lung cancer. *Acta Oncol.* 2011; 50:772–776. [PubMed: 21767173]
4. Kma L, Gao F, Fish BL, et al. Angiotensin converting enzyme inhibitors mitigate collagen synthesis induced by a single dose of radiation to the whole thorax. *Radiat Res.* 2012; 53:10–17.
5. Ghosh SN, Zhang R, Fish BL, et al. Renin-angiotensin system suppression mitigates experimental radiation pneumonitis. *Int J Radiat Oncol Biol Phys.* 2009; 75:1528–1536. [PubMed: 19931735]
6. Wang L, Fu X, Clough R, et al. Can angiotensin-converting enzyme inhibitors protect against symptomatic radiation pneumonitis. *Radiat Res.* 2000; 153:405–410. [PubMed: 10761000]
7. Kharofa J, Cohen EP, Tomic R, et al. Decreased risk of radiation pneumonitis with incidental concurrent use of angiotensin-converting enzyme inhibitors and thoracic radiation therapy. *Int J Radiat Oncol Biol Phys.* 2012; 84:238–243. [PubMed: 22300564]
8. Jenkins P, Watts J. An improved model for predicting radiation pneumonitis incorporating clinical and dosimetric variables. *Int J Radiat Oncol Biol Phys.* 2011; 80:1023–1029. [PubMed: 21543165]
9. Siempos II, Kopterides P, Armaganidis A. Additional experimental evidence that statins protect against acute lung injury. *Respir Care.* 2012; 57:331. [PubMed: 22304804]
10. 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. [PubMed: 15963660]
11. Shi A, Zhu G, Wu H, et al. Analysis of clinical and dosimetric factors associated with severe acute radiation pneumonitis in patients with locally advanced non-small cell lung cancer treated with concurrent chemotherapy and intensity-modulated radiotherapy. *Radiat Oncol.* 2010; 5:35. [PubMed: 20462424]

12. Ramella S, Trodella L, Mineo TC, et al. Adding ipsilateral v20 and v30 to conventional dosimetric constraints predicts radiation pneumonitis in stage IIIa–b nsc lc treated with combined-modality therapy. *Int J Radiat Oncol Biol Phys*. 2010; 76:110–115. [PubMed: 19619955]
13. Lopez Guerra JL, Gomez DR, Zhuang Y, et al. Changes in pulmonary function after three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, or proton beam therapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2012; 83:e537–e543. [PubMed: 22420964]
14. Robnett TJ, Machtay M, Vines EF, et al. Factors predicting severe radiation pneumonitis in patients receiving definitive chemoradiation for lung cancer. *Int J Radiat Oncol Biol Phys*. 2000; 48:89–94. [PubMed: 10924976]
15. Kim M, Lee J, Ha B, et al. Factors predicting radiation pneumonitis in locally advanced non-small cell lung cancer. *Radiat Oncol*. 2011; 29:181–190.
16. Moulder J. Pharmacological intervention to prevent or ameliorate chronic radiation injuries. *Semin Radiat Oncol*. 2003; 13:73–84. [PubMed: 12520466]
17. Robbins M, Zhao W, Garcia-Espinosa M, et al. Renin-angiotensin system blockers and modulation of radiation-induced brain injury. *Curr Drug Targets*. 2010; 11:1413–1422. [PubMed: 20583976]
18. Shen XZ, Ong FS, Bernstein EA, et al. Nontraditional roles of angiotensin-converting enzyme. *Hypertension*. 2012; 59:763–768. [PubMed: 22353608]
19. Medhora M, Gao F, Jacobs ER, et al. Radiation damage to the lung: Mitigation by angiotensin-converting enzyme (ACE) inhibitors. *Respirology*. 2012; 17:66–71. [PubMed: 22023053]
20. Zhang X, Sun J, Sun J, et al. Prediction of radiation pneumonitis in lung cancer patients: a systematic review. *J Cancer Res Clin Oncol*. 2012; 138:2103–2116.
21. Wedlake LJ, Silia F, Benton B, et al. Evaluating the efficacy of statins and ace-inhibitors in reducing gastrointestinal toxicity in patients receiving radiotherapy for pelvic malignancies. *Eur J Cancer*. 2012; 48:2117–2124. [PubMed: 22386574]
22. Palma DA, Senan S, Tsujino K, et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys*. 2013; 85:444–450. [PubMed: 22682812]
23. Vogelius IR, Bentzen SM. A literature-based meta-analysis of clinical risk factors for development of radiation induced pneumonitis. *Acta Oncol*. 2012; 51:975–983. [PubMed: 22950387]
24. Bjerner L, Franzén L, Littbrand B, et al. Effects of smoking and irradiated volume on inflammatory response in the lung of irradiated breast cancer patients evaluated with bronchoalveolar lavage. *Cancer Res*. 1990; 50:2027–2030. [PubMed: 2317792]
25. Grau C, Horsman M, Overgaard J. Influence of carboxyhemoglobin level on tumor growth, blood flow, and radiation response in an experimental model. *Int J Radiat Oncol Biol Phys*. 1992; 22:421–424. [PubMed: 1735672]
26. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers--a different disease. *Nat Rev Cancer*. 2007; 7:778–790. [PubMed: 17882278]

Participants	Number
All patients enrolled Jan 1, 2004–Dec 31, 2010; stages I-III NSCLC with detailed medication record	557
↓ Exclude patients registered on institutional protocols	-53
↓ Exclude patients with radiation dose less than 60 Gy	-3
↓ Exclude patients with stereotactic body radiation therapy	-1
↓ Exclude patients with more than one primary lung tumor	-6
↓ Exclude patients without lung CT or PET reevaluation within 1 year after completion of radiation	-43
↓ Exclude patients with missing dosimetric data	-38
Source population	413
Taking ACEIs	65
Not taking ACEIs	348

Fig. 1.
Selection of study participants.

Fig. 2.

Comparison of freedom from grade ≥ 2 radiation pneumonitis (RP) in patients with non-small cell lung cancer who had (A) low mean lung dose (MLD) or (B) high MLD or were (C) male or (D) female, according to whether angiotensin-converting enzyme inhibitors (ACEIs) were used during definitive radiation therapy (RT).

Table 1

Patient Characteristics	No. of Patients (%)		P Value*
	ACEI (n=65)	No ACEI (n=348)	
Sex			0.49
Male	40 (62)	198 (57)	
Female	25 (38)	150 (43)	
Age, years			<0.01
<70	31 (48)	241 (69)	
70	34 (52)	107 (31)	
Race			0.23*
Nonwhite	12 (18)	49 (14)	
White	53 (82)	299 (86)	
Karnofsky Performance Status Score			0.02*
80	52 (80)	231 (66)	
>80	13 (20)	117 (34)	
Clinical Disease Stage			<0.01*
I	10 (15)	31 (9)	
II	10 (15)	27 (8)	
IIIA	32 (49)	130 (37)	
IIIB	13 (20)	160 (46)	
Tumor Histology			0.09
Nonsquamous	32 (49)	211 (61)	
Squamous	33 (51)	137 (39)	
Smoking Status			0.08*
Never	5 (7)	22 (6)	
Previous	53 (82)	247 (71)	
Current	7 (11)	79 (23)	
Radiation Technique			0.19*
3D CRT	7 (11)	29 (8)	

Characteristic	No. of Patients (%)		P Value*
	ACEI (n=65)	No ACEI (n=348)	
IMRT	38 (58)	242 (70)	
Proton therapy	20 (31)	77 (22)	
Radiation Dose, Gy			
60 and <70	36 (55)	197 (57)	0.86
70	29 (45)	151 (43)	
Radiation Fractionation			
Once a day	63 (97)	342 (98)	0.37*
Twice a day	2 (3)	6 (2)	
Gross Tumor Volume, cm³			0.25
<107	34 (52)	164 (47)	
107	26 (40)	173 (50)	
Unknown	5 (8)	11 (3)	
Mean Lung Dose, Gy (GyE for protons)			0.45
20	46 (71)	252 (72)	
>20	19 (29)	96 (28)	
V₅, %			0.63*
0.65	55 (84)	292 (84)	
>0.65	7 (11)	29 (8)	
Unknown	3 (5)	27 (8)	
V₁₀, %			0.78*
0.5	59 (91)	299 (86)	
>0.5	3 (5)	22 (6)	
Unknown	3 (5)	27 (8)	
V₂₀, %			0.17
0.37	49 (75)	288 (83)	
>0.37	16 (25)	60 (17)	
V₃₀, %			0.90
0.26	33 (51)	168 (48)	
<0.26	29 (45)	153 (44)	

Characteristic	No. of Patients (%)			P Value*
	ACEI (n=65)	No ACEI (n=348)		
Unknown	3 (5)	27 (8)		
DLCO, %				0.56
<63	25 (38)	122 (35)		
63	22 (34)	129 (37)		
Unknown	18 (28)	97 (28)		
FEV1, %				0.82
<68	26 (34)	126 (36)		
68	25 (38)	130 (37)		
Unknown	14 (28)	92 (26)		
Concurrent Chemotherapy				0.11
No	18 (28)	66 (19)		
Yes	47 (72)	282 (81)		
Concurrent Carboplatin/Paclitaxel				0.06
No	43 (66)	181 (52)		
Yes	22 (34)	158 (45)		
Unknown	0 (0)	9 (3)		
ARB				0.03*
No	62 (95)	302 (87)		
Yes	3 (5)	46 (13)		
Inhaled Steroid				0.23*
No	57 (88)	289 (83)		
Yes	8 (12)	59 (17)		
Statins				<0.01
No	29 (45)	263 (76)		
Yes	36 (55)	85 (24)		
NSAID				0.89
No	30 (46)	164 (47)		
Yes	35 (54)	184 (53)		

P values are from χ^2 tests unless otherwise noted.

* Fisher's exact test.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; 3D CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; ARB, angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drug

Table 2

Patient Characteristics, Concurrent Medication Use, and Risk of Radiation Pneumonitis

Variable	Grade 2 Radiation Pneumonitis (n=183)			
	No. (%)	HR	95% CI	P
ACEI				
No	161 (88)			
Yes	22 (12)	0.65	0.42–1.02	0.06
Sex				
Male	103 (56)			
Female	80 (44)	1.07	0.80–1.43	0.66
Age, years				
<70	124 (68)			
70	59 (32)	0.91	0.67–1.24	0.54
Race				
Nonwhite	22 (12)			
White	161 (88)	1.32	0.85–2.07	0.22
Karnofsky Performance Status Score				
80	133 (73)			
>80	50 (27)	0.75	0.54–1.03	0.08
Clinical Disease Stage				
I/II	31 (17)			
III	152 (83)	1.29	0.87–1.89	0.20
Tumor Histology				
Nonsquamous	111 (61)			
Squamous	72 (39)	0.93	0.69–1.25	0.65
Smoking Status				
Never	16 (9)			
Previous	136 (74)	0.59	0.34–0.97	0.04
Current	31 (17)	0.41	0.22–0.74	<0.01
Radiation Technique				
3D CRT	11 (6)			
IMRT	133 (73)	1.79	0.97–3.31	0.06
Proton therapy	39 (21)	1.27	0.65–2.48	0.49
Radiation dose, Gy				
<70	105 (57)			
70	78 (43)	0.86	0.64–1.16	0.33
Radiation Fractionation				
Once a day	182 (99)			
Twice a day	1 (1)	0.26	0.04–1.85	0.18
Gross Tumor Volume, cm³				
<107	88 (48)			
107	88 (48)	1.11	0.82–1.49	0.50

Variable	Grade 2 Radiation Pneumonitis (n=183)			
	No. (%)	HR	95% CI	P
Unknown	7 (4)			
Mean lung dose, Gy				
20	124 (68)			
>20	59 (32)	1.47	1.08–2.01	0.02
V₅, %				
0.65	154 (84)			
>0.65	22 (12)	1.91	1.22–3.00	0.01
V₁₀, %				
0.5	163 (89)			
>0.5	13 (7)	1.52	0.86–2.68	0.15
Unknown	7 (4)			
V₂₀, %				
0.37	144 (79)			
>0.37	39 (21)	1.48	1.03–2.09	0.03
V₃₀, %				
0.26	84 (46)			
>0.26	92 (50)	1.45	1.08–1.96	0.01
Unknown	7 (4)			
DLCO, %				
<63	73 (40)			
63	69 (38)	0.93	0.67–1.29	0.65
Unknown	41 (22)			
FEV1, %				
<68	68 (37)			
68	78 (43)	1.16	0.84–1.60	0.38
Unknown	37 (20)			
Concurrent Chemotherapy				
No	32 (17)			
Yes	151 (83)	1.26	0.86–1.85	0.23
Concurrent Carboplatin/Paclitaxel				
No	98 (54)			
Yes	85 (46)	1.08	0.80–1.44	0.62
ARB				
No	155 (85)			
Yes	28 (15)	1.39	0.93–2.08	0.11
ACEI/ARB				
No	133 (73)			
Yes	50 (27)	0.97	0.70–1.34	0.85
Inhaled Steroids				
No	148 (81)			
Yes	35 (19)	1.25	0.87–1.81	0.23

Variable	Grade 2 Radiation Pneumonitis (n=183)			
	No. (%)	HR	95% CI	P
Statins				
No	129 (71)			
Yes	54 (29)	1.04	0.75–1.42	0.83
NSAIDs				
No	85 (46)			
Yes	98 (54)	1.08	0.81–1.44	0.62

Abbreviations: HR, hazard ratio; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitor; 3D CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; ARB, Angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drug

Table 3

Multivariate Cox Proportional Hazards Model for Risk of Radiation Pneumonitis

Variable	Grade 2 Radiation Pneumonitis		
	HR	95% CI	P
ACEI			
Yes vs. No	0.66	0.42–1.03	0.07
Sex			
Female vs. Male	0.97	0.72–1.30	0.83
Smoking			
Yes vs. No	0.56	0.33–0.93	0.03
Mean Lung Dose, Gy			
>20 vs. 20	1.45	1.06–1.99	0.02
Concurrent Carboplatin/Paclitaxel			
Yes vs. No	0.99	0.73–1.33	0.93

Abbreviations: HR, hazard ratio; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitor.