

Prospective Study of the Airways and Pulmonary Parenchyma of Patients at Risk for a Second Lung Cancer

Melissa Means-Markwell,¹ R. Ilona Linnoila,²
John Williams,¹ Pasi A. Jänne,³ Frederic Kaye,²
Kevin O'Neil,¹ and Bruce E. Johnson³

¹Departments of Medicine and Pathology, National Naval Medical Center, ²Cell and Cancer Biology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, and ³Lowe Center for Thoracic Oncology, Department of Adult Oncology, Dana Farber Cancer Institute, and Departments of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

ABSTRACT

Purpose: We conducted our study to compare the number of preneoplastic lesions in the airways and nodules in the pulmonary parenchyma of patients with resected non-small cell lung cancer with the patients whose treatment included chest radiotherapy.

Experimental Design: Patients were eligible if they had successfully resected stage I and II non-small cell lung cancer or advanced stage non-small cell or small cell lung cancer treated with chest radiotherapy with or without chemotherapy and were free of cancer for >2 years. Patients underwent a history and physical examination, white light and fluorescence bronchoscopy, and computerized tomography of the chest. The airway epithelium was examined for preneoplastic histological changes, and the pulmonary parenchyma was examined for the presence of nodules.

Results: Twenty-nine patients at risk for lung cancer were studied between 1997 and 1999. Two patients treated with chest radiotherapy had an area of moderate dysplasia ($n = 1$) and carcinoma *in situ* ($n = 1$), whereas one patient treated with surgical resection alone had an area of mild dysplasia. Six other patients had metaplasia detected in their airway epithelium. Ten of the 13 patients treated with chest radiotherapy had pulmonary nodules compared with 5 of the 13 patients treated with surgical resection alone.

Conclusions: Mild dysplasia, moderate dysplasia, severe dysplasia, and carcinoma *in situ* are unusual in patients with resected lung cancer who have stopped smoking for an extended period of time. Patients with lung cancer treated with chest irradiation may be at higher risk for preneoplastic lesions and pulmonary nodules than patients treated with

surgical resection alone, but additional patients will need to be studied.

INTRODUCTION

Lung cancer is the most common cause of cancer deaths in the United States (1). Efforts to reduce the mortality of lung cancer in the United States and Europe have included screening studies to attempt to identify lung cancer more often when it can be effectively treated with surgical resection. Screening studies with chest radiographs and sputum cytology have thus far been unsuccessful in reducing lung cancer mortality (2–4).

Another approach has been to study early histological changes in the airways of patients at risk for lung cancer to identify patients likely to develop bronchogenic carcinoma. This would allow physicians to treat the lesions locally before the lesions become invasive cancers or to administer agents that could potentially reverse preneoplastic lesions and prevent the development of cancer (chemoprevention agents). The histological changes in the airway epithelium of cigarette smokers that precede the development of lung cancer have been described for >30 years (5–9). Fluorescence bronchoscopy has been developed to help identify these preneoplastic lesions (10–12). The presence of severe dysplasia and carcinoma *in situ* in the airways of patients at risk for lung cancer is associated with the subsequent development of lung cancer (13, 14). However, these preneoplastic lesions detected by bronchoscopy are uncommon, need to be in the proximal airway accessible to visualization and biopsy, and the technique has technical limitations that make large-scale screening programs problematic.

Another screening modality for detecting early lung cancers is CT⁴ of the chest. Adult cigarette smokers screened with CT have their lung cancers detected at an early stage (60–80% stage IA), and most are adenocarcinomas (15–19). A large national trial is ongoing to compare the outcome of subjects screened with CT of the chest with those screened with chest radiographs (20).

One potential way to increase the possibility of detecting preneoplastic lesions is to screen patients who are at high risk for developing lung cancer. Some ongoing trials of fluorescence bronchoscopy use patients who have atypia detected by sputum cytology as entry criteria to increase the proportion of patients with preneoplastic lesions in the airways (21, 22). Another way to potentially enrich the number of preneoplastic lesions is to select a patient population that has already been treated successfully for an initial lung cancer. Patients with surgically resected lung cancer have a 2–3% risk per year of developing a second lung cancer, nearly 10-fold higher than a similar population of adult cigarette smokers (23). Patients with lung cancer treated

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Requests for reprints: Bruce E. Johnson, Director, Lowe Center for Thoracic Oncology, Dana Farber Cancer Institute, Room D1234, 44 Binney Street, Boston, MA 02445. Phone: (617) 632-5314; Fax: (617) 632-5786; E-mail: BEJOHNSON@PARTNERS.ORG.

⁴ The abbreviations used are: CT, computerized tomography; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

with chemotherapy plus chest radiotherapy have an increasing risk of developing lung cancer with the passage of time, going from a 2% risk per year 2 years after treatment to 10% or higher 10 years later (24, 25). In addition, 70% of these lesions are squamous cell carcinomas (23). If increased numbers of preneoplastic lesions are proportional to the risk of developing a second lung cancer, patients with a resected NSCLC should have a higher incidence of preneoplastic lesions than patients who have had a similar exposure to cigarette smoke. In addition, patients with squamous cell carcinoma or those treated with chemotherapy plus chest radiotherapy may be more likely to develop preneoplastic lesions with squamous differentiation, which would, more likely, be visible with fiberoptic bronchoscopy.

There are relatively few patients with regional lung cancer in the United States surviving for ≥ 2 years, one of the proposed populations to be examined in this study. The Surveillance, Epidemiology, and End Results⁵ estimates that there are 18,000 patients with regional NSCLC and 2,000 patients with regional SCLC surviving ≥ 2 years from the start of treatment. The Surveillance, Epidemiology, and End Results designation of regional roughly corresponds to limited stage SCLC and stage III NSCLC. The patients available in our institution for study were mostly patients with limited stage SCLC because of our past research focus on SCLC. Given the paucity of these patients, we also included patients with stage III NSCLC treated with chest radiotherapy. There is extensive information on the contribution of chest radiotherapy and continued cigarette smoking to the increased risk of development of a second lung cancer in patients surviving SCLC and NSCLC (26–29). The type of chemotherapy, doses of chemotherapy, timing and dose of radiation, surgical treatment, and underlying pathology (SCLC versus NSCLC) differs between the proposed groups of patients but has not been documented to have as much impact on the risk of second lung cancers as chest radiation and cigarette smoking. Nonetheless, we believed it was important to find out whether there was a somewhat dramatic increase in preneoplastic lesions in the irradiated patients that corresponded to their increased risk of developing a second lung cancer.

We expected to find a higher frequency of preneoplastic lesions in the airways of patients whose treatment included chest radiotherapy compared with patients treated with surgery alone. The patients also had their pulmonary parenchyma studied to determine whether there were nodules present in this same group of patients who had their airways studied during the same time interval. In this prospective study, our patients have well characterized primary tumors, treatment information, and accurate smoking histories to be able to assess their impact on the number of preneoplastic lesions identified in the airways and pulmonary parenchyma of our patients at risk for the development of lung cancer.

PATIENTS AND METHODS

Study Design. This study was a prospective evaluation of the airway epithelium and parenchyma of patients at risk for

lung cancer. It was conducted after obtaining protocol approval from the Institutional Review Boards of the National Cancer Institute and the National Naval Medical Center in Bethesda, Maryland. The objectives of the study were to determine the number of dysplastic lesions and areas of carcinoma *in situ* in the airways of patients at risk for a second lung cancer using white light and fluorescence bronchoscopy. A second objective was to compare the number of dysplastic lesions and areas of carcinoma *in situ* in the airways of patients with resected tumors with the number of lesions in the patients treated with combined modality therapy (chest radiotherapy with or without chemotherapy) and to evaluate the incidence of peripheral nodules identified by chest CT in the two groups. The impact of cigarette smoking on the number of dysplastic lesions was also assessed.

Patient Population. Patients were eligible if they had successfully resected stage I and II NSCLC or stage III NSCLC or SCLC treated with chest radiotherapy with or without chemotherapy and were alive and free of cancer for > 2 years. Patients were recruited from the Pulmonary Medicine and Medical Oncology Clinics at the National Naval Medical Center and the Center for Cancer Research at the National Cancer Institute. The inclusion criteria were: ≥ 18 years of age; an Eastern Cooperative Oncology Group performance status of 0–2; WBC count of $> 2,000$ and $< 20,000$; and a platelet count of $> 50,000$. Patients were excluded if they had uncontrolled hypertension with a blood pressure in excess of 200/120, unstable angina, bleeding disorder, allergy to lidocaine, administration of photosensitizing drugs within the previous 3 months, chest irradiation within 18 months, yttrium aluminum garnet laser treatment within 1 month, or were pregnant. The patients needed to be willing to undergo bronchoscopy and CT of the chest.

Patient Evaluation. Patients underwent evaluation with a history including information on past and current smoking and physical examination. Laboratory testing included a complete blood count, prothrombin time and partial thromboplastin time, serum β human chorionic gonadotropin determination in women < 50 years of age, and arterial blood gases. A chest radiograph, pulmonary function tests, and CT of the chest were obtained before bronchoscopy. Operative, pathology, and treatment reports were obtained and reviewed.

White Light and Fluorescence Bronchoscopy. Patients determined to be eligible were recruited to the study and provided informed consent. Bronchoscopy was performed using a BF20D fiberoptic bronchoscope (Olympus, Philadelphia, PA). The tracheobronchial epithelial areas were classified using three categories using the system described by Lam *et al.* (10, 11): class I, no visual abnormalities, class II, inflammation, trauma, anatomical anomalies, or metaplasia; class III, changes of moderate or severe dysplasia, carcinoma *in situ*, or invasive carcinoma. The location of class II and III lesions was noted. The examination was then repeated using the fluorescence bronchoscope (LIFE Imaging System, Vancouver, British Columbia, Canada). The class II and III lesions noted on white light bronchoscopy were reinspected under fluorescence. New class II and III areas identified using fluorescence were noted and reexamined under white light bronchoscopy. All lesions categorized as class III images were biopsied under white light bronchoscopy. At least one biopsy was obtained from airway epithelium that was categorized as class I. Patients without areas

⁵ Internet address: www.seer.cancer.gov.

Table 1 Patient characteristics

Characteristic	Number
Gender	
Women	10
Men	19
Age, median (range)	66 (37–79)
Cancer	
NSCLC	22
SCLC	7
Smoking history	
Ex-smoker	26
Current smoker	3
Previous successful treatment for lung cancer	
Surgical resection alone	16
Chest radiotherapy included	13
Chest irradiation ± surgery	1
Chemotherapy + chest radiation	11
Radiation alone	1

of class II and III images had at least two biopsies taken from normal (class I) epithelium. All bronchoscopies, both white light and fluorescence, were videotaped for review.

The biopsy specimens were reviewed by two anatomical pathologists (R. I. L. and J. W.) who were unaware of the bronchoscopy results. They were classified by consensus as showing metaplasia, mild dysplasia, moderate dysplasia, severe dysplasia, carcinoma *in situ*, and invasive cancer by WHO criteria (9). The lesions classified as metaplasia, mild dysplasia, moderate dysplasia, severe dysplasia, and carcinoma were considered preneoplastic lesions. The epithelium classified as moderate dysplasia, severe dysplasia, or carcinoma *in situ* was considered as intraepithelial neoplasia (30, 31).

Statistical Analyses. The sample size was estimated by published information available at the time, assuming that patients with resected lung cancer have moderate dysplasia, severe dysplasia, carcinoma *in situ*, and invasive cancer ~30% of the time, similar to current cigarette smokers. Patients treated with combined modality therapy (chemotherapy plus chest radiotherapy) have approximately two to three times greater risk of a second tumor than patients treated with surgical resection. Therefore, we estimated that 70% of patients treated with combined modality therapy would have moderate dysplasia or worse. Twenty-eight patients would have been needed in each group to detect a difference at the two-tailed $P = 0.05$ level of significance with 80% power. We assumed there would be some imbalance and some inevaluable patients, therefore, the targeted patient sample size was set at 70. The Fisher's exact test and Pearson's χ^2 test were applied to a contingency table to reveal the association between chest radiotherapy and preneoplastic lesions and pulmonary nodules. All P s correspond to two-sided statistical tests.

RESULTS

Patient Characteristics. Twenty-nine patients were entered into the trial between January 1997 and July 1999 (Table 1). The trial was terminated before the completion of the accrual because of the departure of one of the investigators. The majority were men, and the median age was 66 years. All 29 of the patients had smoked cigarettes; 26 were ex-smokers and 3 were

current smokers at the time of their bronchoscopy. The median number of pack-years was 42, with a range of 5–100. The 26 patients stopped smoking cigarettes a median of 7 years (range, 1–26) before the bronchoscopic examination. Twenty-five of the 26 patients stopped smoking ≥ 2 years before participating in the study. Seven patients were treated for SCLC, and 22 were treated for NSCLC (3 with squamous cell carcinoma, 12 with adenocarcinoma, 3 with bronchioloalveolar cell carcinoma, 2 with large cell carcinoma, and 2 with non-small cell, not otherwise specified). Six of the seven patients with SCLC had limited stage disease and underwent combined modality therapy with etoposide cisplatin plus chest radiotherapy. The patient with extensive stage disease was initially treated with chemotherapy, followed by chest irradiation when she relapsed in her chest. Six of the patients had locally advanced stage NSCLC and were treated with combined modality therapy. Four were treated with chemotherapy and chest radiation, one with surgery plus chest radiation, and one with chest radiation alone. Sixteen patients had early stage non-small cell carcinoma and were treated with surgical resection alone.

Fiberoptic Bronchoscopy Findings. Twenty-nine patients met the entry criteria and participated in the study. A single patient with resected early stage NSCLC did not have his airways examined or undergo biopsies because the fluorescence bronchoscope malfunctioned. The 28 patients had their airways categorized as being normal (class I), abnormal but benign (class II), and suspicious for malignancy (class III) by both white light and fluorescence bronchoscopy. Patients were categorized by the most abnormal lesions in their airways. The airways of the patients examined with white light bronchoscopy showed 8 had class I findings and 13 had class II findings. The remaining seven patients had at least one area of class III findings. The airways of the patients examined with fluorescence bronchoscopy showed seven patients had class I findings and one had class II findings. The remaining 20 patients had at least one area of class III findings.

Histological Findings in the Airways. There were 74 biopsies taken from these 28 patients, with 70 having adequate tissue for histological interpretation (Table 2). There were 11 areas of metaplasia, 1 area of mild dysplasia, 1 area of moderate dysplasia, and 1 area of carcinoma *in situ*. The three areas of

Table 2 Histological findings of 70 biopsies from 28 patients at risk for lung cancers

	Dysplasia				CIS
	Normal	Meta ^a	Mild	Mod Sev	
White light bronchoscopy					
Class I	33	7		1	
Class II	18	3	1		
Class III	5	1			1
Total	56	11	1	1	1
Fluorescence bronchoscopy					
Class I	25	5			
Class II	4	0			
Class III	27	6	1	1	1
Total	56	11	1	1	1

^a Meta, metaplasia; Mod, moderate dysplasia; Sev, severe dysplasia; CIS, carcinoma *in situ*.

Table 3 Histological findings of patients at risk for lung cancers

	Dysplasia				
	Meta	Mild	Mod	Sev	CIS
Chest radiotherapy (<i>n</i> = 13)	9	0	1	0	1
Surgical resection (<i>n</i> = 15)	2	1	0	0	0

^a Meta, metaplasia; Mod, moderate dysplasia; Sev, severe dysplasia; CIS, carcinoma *in situ*.

mild dysplasia, moderate dysplasia, and carcinoma *in situ* were from areas of class III identified by fluorescence fiberoptic bronchoscopy. White light had identified the carcinoma *in situ* as class III. The area of moderate dysplasia was identified as class I and mild dysplasia as class II.

There was one area of moderate dysplasia and one area of carcinoma *in situ* in the airway epithelium in 2 of the 13 patients whose treatment included chest radiotherapy, whereas there was a single patient of the 15 patients treated with surgical resection alone who had mild dysplasia (Table 3). The patient with moderate dysplasia in his airway epithelium had a stage III squamous cell carcinoma and was treated with chemotherapy plus chest radiotherapy 3 years before undergoing fluorescence bronchoscopy. The patient with carcinoma *in situ* had a large cell carcinoma and was treated with surgery and chest radiotherapy 7 years before undergoing fluorescence bronchoscopy. The patient with mild dysplasia had been treated with surgical resection alone for a stage I adenocarcinoma of the lung 4 years before undergoing fluorescence bronchoscopy.

Although the study was not powered to detect differences in metaplasia, the preliminary data suggest that metaplasia may be more common in patients treated with chest radiotherapy than in patients treated with surgical resection. Squamous metaplasia was not included as a planned end point because it is not a validated marker of premalignancy. There were nine areas of metaplasia in 6 of the 13 patients treated with chest radiotherapy, including one area of metaplasia in the patient with carcinoma *in situ*. There were two areas of metaplasia in 2 of the 15 patients treated with surgical resection alone, including one area of metaplasia in the patient with mild dysplasia. The differences in the fraction of patients with metaplasia in the airway epithelium of the irradiated patients and those treated with surgical resection approached statistical significance (6 of 13 compared with 2 of 15, respectively; $P = 0.096$ by the Fisher's exact test). There was a significant difference between the number of patients with metaplasia, dysplasia, and carcinoma *in situ* in the airway epithelium of those treated with chest radiotherapy (7 of 13) compared with the 2 of 15 treated with surgical resection alone ($P = 0.02$ by χ^2 test and 0.04 by Fisher's exact test).

The patient with carcinoma *in situ* developed a NSCLC at another site and died from lung cancer 6 months after the bronchoscopy. The patient with moderate dysplasia is alive and free of cancer >3 years after the examination with fluorescence bronchoscopy. The patient with mild dysplasia treated with surgical resection alone was one of the three who continued to smoke cigarettes. This patient underwent a successful resection of a second adenocarcinoma of the lung 32 months after the bronchoscopic examinations. There were no areas of dysplasia

or carcinoma *in situ* identified in the patients who had undergone surgical resection and stopped smoking cigarettes.

CT Findings. Twenty-six of the 29 enrolled patients with information on their airways had a chest CT performed and were available for review. Fifteen of the 26 (58%) patients had nodules with a median diameter of 6 mm (range, 3–20). Twelve patients had a single nodule, one had two nodules, and two had three or more nodules. Five of the seven patients (71%) with SCLC and 10 of the 19 patients (53%) with NSCLC had a CT with detectable nodules. There were nodules in 5 of 10 patients with adenocarcinoma, 1 of the 3 patients with squamous cell carcinoma, both of the patients with large cell carcinoma, 1 of the 3 patients with bronchioloalveolar carcinoma, and one nodule in the patient with non-small lung cancer, not otherwise specified. The patients who did not have CT scans included two patients treated for adenocarcinomas and one patient treated for NSCLC, not otherwise specified. There were 13 patients whose treatment included chest radiotherapy and 13 patients treated with surgical resection alone who had CTs of the chest performed. Ten of 13 patients treated with chest radiotherapy had nodules detected compared with 5 of 13 patients treated with surgical resection alone ($P = 0.05$, χ^2 test).

There was follow-up information available on patients who had nodules >1 cm in diameter, the size in which previous screening studies have recommended a biopsy of the nodule (17, 18). Three patients had nodules of ≥ 1 cm (10, 14, and 20 mm). These three patients either declined additional evaluation or opted for radiographic follow-up. One patient is still alive at last follow-up without evidence of cancer. One patient with the 14-mm nodule is alive 3 years later with the nodule still present. The patient with the 10-mm nodule recurred at a different location and died of his NSCLC 2 years after documentation of the nodule.

Patients with Airway Lesions and Pulmonary Nodules.

The patients with carcinoma *in situ* in the right upper lobe also had an 8-mm lesion in the right infrahilar area. The patient with moderate dysplasia in the bronchus intermedius had a 4-mm lesion in the right upper lobe. The patient with mild dysplasia in the right upper lobe had no nodules detected by CT.

DISCUSSION

The initial proposal in this study was to compare the number of intraepithelial lesions (moderate dysplasia, severe dysplasia, carcinoma *in situ*) in the airways of patients with lung cancer treated with chest radiotherapy with those treated with surgical resection. Despite studying 28 patients with successfully treated lung cancer, only 2 (7%) had intraepithelial neoplasia and a single patient treated with surgery had mild dysplasia. This reduced the power of the study, and the findings are not sufficient to make any conclusions about the differences between the frequency of intraepithelial neoplasia between the two groups. This was much lower than anticipated when we planned the trial but is quite similar to the low incidence of intraepithelial neoplasia in two other populations of successfully treated patients with smoking-related malignancies. Weigal *et al.* (30, 32) detected a 6% incidence of intraepithelial lesions or carcinomas observed in 51 patients with resected lung cancers. There were no intraepithelial lesions detected in the airways of

14 patients with previous lung cancer (11) or head and neck cancer (3) in a study of 39 patients by Kurie *et al.* (33); the most advanced airway lesion detected was mild dysplasia. Our study did not reach its targeted sample size, which reduced the likelihood that the findings would achieve sufficient statistical power to answer our proposed questions. We had considered doubling the accrual to its target sample size of 28 evaluable patients in each group. However, the estimated percentage of moderate dysplasia, severe dysplasia, and carcinoma *in situ* patients with lung cancer treated with chest radiotherapy was 70%, as described in "Patients and Methods," dramatically more than the 15% observed in the 13 patients treated with chest radiotherapy. In fact, had we been interested in detecting a difference of the magnitude actually observed (15% versus 7%), 260 patients in each treatment category would have been required to detect that difference with 80% power and a two-tailed 0.05 significance level. A goal to detect 20% versus 5% would have required 80 of each type. Therefore, rather than continue the current study, we have a study planned comparing patients with resected stage I adenocarcinoma of the lung with patients with stage III adenocarcinoma treated with chest radiotherapy. Patients will also undergo CT scans of their chest to detect and follow pulmonary nodules by criteria published previously (15–18).

A second potential explanation from the small number of intraepithelial lesions is the low proportion of patients in our study with resected NSCLC who have squamous cell carcinoma. The recognized preneoplastic lesions in the airway epithelium is one of squamous cell differentiation (9). Patients with successfully resected squamous cell carcinoma or adenocarcinoma of the lung who develop a second lung cancer are expected to have the same histology 70% of the time (23). Therefore, preneoplastic lesions in the airway epithelium are expected to be more common in patients with resected squamous cell carcinomas. The other study of resected lung cancer patients showed three lesions (two intraepithelial neoplasia and one invasive carcinoma) in 2 of the 20 patients (10%) with previous squamous cell carcinomas and a single lesion in 31 patients with lung cancers other than squamous cell carcinoma that includes 22 adenocarcinomas (3%). Only three of our patients had a squamous cell carcinoma of the lung, therefore, only three of the patients may have had a predisposition to form these preneoplastic lesions in their airway epithelium. We do not have adequate numbers to compare intraepithelial neoplasia in our patients with adenocarcinomas versus squamous cell carcinoma.

The lesions that have been identified in the airway epithelium that are associated with the subsequent progression to lung cancer have included severe dysplasia and carcinoma *in situ*, whereas less advanced dysplasia and areas of metaplasia have not (13, 14). The study was originally designed to compare moderate dysplasia, severe dysplasia, and carcinoma *in situ* and did not include mild dysplasia and areas of metaplasia. However, metaplasia has been used as an end point in some trials of chemoprevention agents for patients at risk for lung cancer (34, 35). Therefore, we have provided the information on metaplasia in this patient population. Despite the absence of these more advanced airway lesions, the frequency of preneoplastic lesions (metaplasia to carcinoma *in situ*) is more common in patients whose treatment included chest radiotherapy than in those

treated with surgical resection alone. To the best of our knowledge, this is the first report of the increased frequency of airway lesions in patients who have been treated with chest radiotherapy compared with patients treated with surgical resection alone.

Another reason for finding relatively few preneoplastic lesions in the airways of our patients is the extended duration in which they have not been exposed to cigarette smoke. Our patients surviving treatment of lung cancer have been followed for extended periods of time (median, 4 years; range, 1–20) from the time of starting treatment, and all but three had quit smoking cigarettes. The impact of smoking cessation on metaplasia and dysplasia has been observed before. Patients were studied in four different randomized, controlled clinical trials comparing the metaplasia and dysplasia in the airways of patients treated with retinoid compounds or anethole dithiolen-thione to placebo (21, 34, 36). The subjects who continued to smoke cigarettes had more metaplasia or dysplasia in their airways than those who had stopped smoking. Therefore, the number of patients with dysplasia and carcinoma *in situ* may be rare because of the absence of continued exposure of the airway epithelium to cigarette smoke for an extended period of time.

We have provided some preliminary information about the presence of pulmonary nodules in patients with resected NSCLCs and those treated with chest radiotherapy. Fifteen of the 26 patients had nodules detected on CT of the chest. These scans were performed before the publications on the nodules in patients at risk for lung cancer because of cigarette smoking (15–19, 23, 37). Therefore, the CT was not performed in an analogous way as might have been done for lung cancer screening. Nonetheless, in our small group of patients, nodules >2 mm were found in more than half of our patients, more than twice the rate of the 23% found in 1000 adults age ≥ 60 years of age with >10 pack-years of smoking (17) and similar to that reported by Swenson *et al.* (15, 16). Once again, the nodules were more commonly detected in the cohort whose treatment included chest radiation than in those treated with surgical resection alone. Study guidelines have proposed that subjects at risk for lung cancer with pulmonary nodules >1 cm should undergo biopsy (15–17). Our study was not designed to follow these patients longitudinally, but we do have information on the outcome of the three patients with nodules >1 cm. We do not have follow-up information on the other nodules, which reduces the significance of our findings.

The numbers reported here are small, and we did not reach our target accrual. Nonetheless, we believe it is important to report this information to allow additional studies of patients at risk for second lung cancers. These patients develop second lung cancer at a rate of 2–10% per year, and 75% of these patients die of their lung cancers within 2 years (23). Strategies to prevent these cancers by using chemoprevention agents have thus far been unsuccessful (28, 29). Identification of early cancers by studying the airway may be unsuccessful if other investigators find such a low incidence of early airway lesions similar to that found in our patient population. We have provided information that patients with no metaplasia, dysplasia, or carcinoma *in situ* in their airways can have pulmonary nodules detected by CT. The low incidence of airway lesions in patients with resected NSCLC may warrant the use of both CT of the lung and

screening airway studies to optimally evaluate patients to find these early lesions.

On the basis of these studies, it becomes evident that it is important to carefully collect the information on cigarette smoking and confirm the low frequency of intraepithelial neoplasia in patients who have discontinued smoking for extended periods of time. The small number of patients with resected squamous cell carcinoma (3) that are reported in our study have not allowed us to comment extensively on the tendency of patients with resected squamous cell cancer to develop preneoplastic lesions compared with those with resected adenocarcinomas. It does seem that it is not common for patients with resected adenocarcinoma who have stopped smoking cigarettes to have preneoplastic lesions in their airways. Additional research will be needed to determine whether there is a difference in the number of preneoplastic lesions in the airways of patients treated with chest irradiation from those with adenocarcinoma.

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