

## EARLY DIAGNOSIS AND INTERVENTION LUNG CANCER: CLINICAL STUDIES

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Lung cancer is the most common fatal malignancy in both men and women in the United States. In 1999, an estimated 171,600 patients will be diagnosed. Because the diagnosis is most commonly made in later stages, including presentations that manifest as distant metastasis, approximately 158,900 deaths will occur in 1999, if the current survival statistics continue. Today, lung cancer is the third most common cause of death in the world. Worldwide, lung cancer was responsible for more than 900,000 deaths in 1990.<sup>1</sup>

Studies examining the efficacy of screening for lung cancer carried out in the 1970s and 1980s have led to a nihilistic attitude regarding the early diagnosis of lung cancer. Easily obtained clinical indices that can be used to identify individuals at high risk for the development of lung cancer were not appreciated at the time of design of the large screening trials. Unfortunately, these trials were carried out in populations that are not at greatly increased risk for lung cancer and may have yielded falsely discouraging results. The purpose of this chapter is to present an approach to early identification and intervention that could dramatically alter the course and outcome of lung cancer today.

### HISTORICAL PERSPECTIVE

The association between chronic lung disease and lung cancer was recognized more than 40 years ago (see also Chapter 20). Advanced emphysema, chronic bronchitis, and chronic tuberculosis antedated the diagnosis of lung cancer in 45 of 86 patients over a 10-year period. More than 90% of these 86 patients had a chronic cough prior to the diagnosis of lung cancer. Ironically, in that era, chest x-rays and sputum cytology screening for lung cancer were advised.<sup>2,3</sup> Later, it was again emphasized that lung cancer commonly accompanied chronic lung diseases such as chronic bronchitis.<sup>4</sup>

On December 4, 1951, the Philadelphia Neoplasm Research Project was initiated to study the natural history of bronchogenic carcinoma in a population of older men by

semiannual chest mini phorofluorograms and a symptom questionnaire. By December 1965, the project was completed. In all, 6,137 male smokers were enrolled. One hundred fifty-six histologically confirmed lung cancers had been identified; 66 on enrollment and 90 after enrollment.<sup>5</sup> Upon completion of this study, the Philadelphia Neoplasm Research Project concluded that early diagnosis of lung cancer was impractical and did not result in reduced mortality.

In the mid-1970s, the National Cancer Institute (NCI) funded three studies, which were conducted at the Johns Hopkins Medical School,<sup>6</sup> the Memorial Sloan-Kettering Cancer Center,<sup>7</sup> and the Mayo Clinic.<sup>8</sup> These studies enrolled men in a screening program using serial chest x-rays and sputum cytologic studies. At the end of these studies, it was again concluded that screening for lung cancer does not reduce mortality from lung cancer. A study of men at high risk in Czechoslovakia also concluded a lack of benefit from semiannual screening.<sup>9</sup>

With the benefit of hindsight, it is now clear that serious deficiencies existed in the design of these studies. All sought to study high-risk smokers, but the association of airflow obstruction with susceptibility to lung cancer was not widely appreciated at the time of design of these studies and was therefore not exploited to define a high-risk group. The entrance criteria for tobacco use were not high enough to guarantee a high risk for lung cancer (only one pack-year of smoking was required before entry in some cases). Women, who are now believed to be of higher susceptibility than men to lung cancer, were not included.

An important shortcoming was that it was believed to be unethical to have an unscreened control population, so none of the studies carried out in the United States had an unscreened control group. The Memorial Sloan-Kettering and Johns Hopkins studies compared yearly with more intensive screening regimens, and the Mayo study compared screening every three months with a recommendation to have yearly screening. It was hoped that the control group (recommended to have yearly screening), would contain a sizable subgroup that did not comply with this recommen-

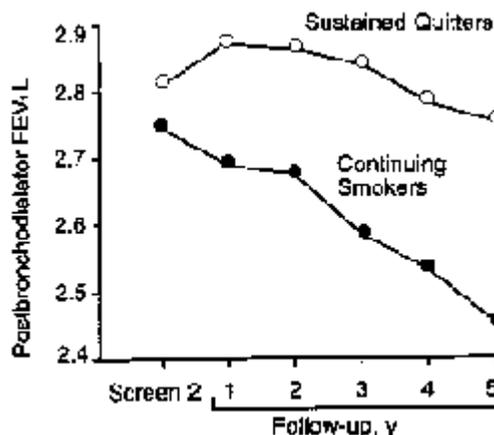
dition, but this subgroup was not as large as hoped. It is important to appreciate that at the time these studies were conducted, the yearly chest radiograph was a standard component of health care. In summary, the current practice of not performing any studies on high-risk smokers or ex-smokers with airflow obstruction, sputum production, or additional exposures to carcinogens such as asbestos or radon daughters has not been shown to be equally efficacious as screening; the question has not been studied.

The results of the Mayo Clinic study have now been revisited.<sup>8</sup> Strauss has concluded that, in fact, early identification did result in improved survival in patients found with early stages of disease. Perhaps the Johns Hopkins study is even more revealing because it showed that many cases of lung cancer that were missed might have been diagnosed using more modern techniques applied to libaried sputum cytology specimens.<sup>11</sup>

The NCI studies resulted in a shift of diagnosis to more early stages of disease, and meaningful improvements were made in resecrebilibry, survival, and fatality of lung cancer. Although overall mortality was not improved by screening, these studies did demonstrate higher 5-year survival rates than expected. Nonetheless, the current dogma is that screening for lung cancer is not worthwhile, and it is not recommended for even large populations of high-risk smokers.<sup>12</sup>

### THE ASSOCIATION BETWEEN CHRONIC AIRFLOW OBSTRUCTION AND LUNG CANCER

The strong association between the presence of airflow obstruction and lung cancer has been known for more than two decades.<sup>13,14</sup> More recent studies have strengthened this association.<sup>15,16</sup> An interesting observation of the Lung Health Study sheds additional light on this relationship. In a sample of middle-aged men and women, over the age of 35, but not yet 60, with only mild degrees of airflow obstruction and with the requirement of smoking at least a pack a day for 10 years (i.e., 10 pack-years), 5,887 patients were followed for 5 years.<sup>17</sup> The main objective of this study was to learn the impact of intervention via smoking cessation and the use of a bronchodilating anticholinergic aerosol on the rate of decline ofventilatory function. In brief, those patients (approximately 22%) who were sustained quitters throughout the 5-year follow-up had a slight improvement in lung function, followed by only a minor decline (Figure 22.1). At the end of 5 years, venrilary function as judged by FEV was only slightly below the mean FEV, levels at Wrollment. By contrast, those patients who continued to smoke had much more rapid rates of decline. One of the "lost interesting features of this study was the cause of death, Presented in Table 22.1. Fifty-seven, or 1%, had died of lung cancer by the end of 5 years. At this writing, another group of patients have emerged with lung cancer in a late



**FIGURE 22.1.** Mean postbronchodilator forced expiratory volume at 1 second (FEV1) for participants in the smoking intervention and placebo group who were sustained quitters (○) and continuing smokers (●). The two curves diverge sharply after baseline. (From Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline in FEV<sub>1</sub>. The Lung Health Study, *JAMA* 1994;272:1,497, with permission.)

follow-up. Now, more than 100 (i.e., approximately 2%), have either died or developed lung cancer. One would have expected that heart attack or stroke might be the most common cause of mortality, but this was not the case, (n = 37). Thus 20 more lung cancer deaths than heart attack and stroke deaths were reported during the follow-up. Unfortunately, no chest x-rays were done during the Lung Health Study to learn whether or not lung cancer was present at the time of enrollment. One can conclude from all of these studies linking airflow obstruction to lung cancer that the increased risk is approximately four- to six-fold, compared to when no airflow obstruction is present, with all other factors including smoking history, occupational exposures, age, sex, and family history taken into consideration.

The new wave of enthusiasm for lung volume reduction surgery has also demonstrated the strong association be-

**TABLE 22.1. THE LUNG HEALTH STUDY: DEATHS WITHIN FIVE YEARS\***

Cause	Special Intervention	Usual Care	Total
Lung cancer	38	19	57
Cardiovascula disease	25	12	37
Other	35	2fi	ss
Total	98	S1	149

\* Randomization 2:1 special intervention to usual care.

tween advanced emphysema and lung cancer.<sup>18</sup> In resected tissues, 6.4% had cancer, of which several were identified only by pathologic examination. Survival at short-term follow-up was excellent.<sup>18</sup>

## RISK FACTORS

By far, the most powerful risk factor in lung cancer is smoking. Approximately 1 in 10 smokers develop bronchogenic carcinoma over a lifetime.<sup>19</sup> Although no safe level of smoking exists, historical tradition has offered the notion that smoking a pack a day for 20 years (i.e., 20 pack-years) or more indicates the populations at highest risk. In general, the year that one starts to smoke and the intensity of smoking over a lifetime magnifies the smoking-related risk.<sup>20</sup> Passive smoking is also an established risk factor for lung cancer.<sup>21</sup>

Certain occupations, such as asbestos mining, those involving asbestos dust exposure, and uranium mining, along with exposure to arsenic, nickel, acrylonitrile, chromium, beryllium, cadmium, chloromethyl ether solvents, and possibly silica, are known occupational risks.<sup>22</sup> Diesel exhaust is considered a risk factor and may explain the increase risk of lung cancer among different types of professional drivers in Denmark.<sup>23</sup> Family history is a definite risk factor, as it is for many organ-associated carcinomas.<sup>14</sup> Consumption of a diet low in fruits and vegetables (possibly because of antioxidant content), may magnify risk.<sup>25</sup> HIV infection may result in lung cancer occurring at a young age, often occurring after a less intense exposure to tobacco than in patients who are not HIV-infected.<sup>26</sup>

## IDENTIFICATION OF ROENTGENOGRAPHICALLY OCCULT LUNG CANCER

### Chest X-rays

Although the chest x-ray is the time-tested method of identifying lung cancer, a reassessment of the outcome of the screening studies has offered renewed hope that case finding with x-rays or screening in high-risk populations may be beneficial. The course and prognosis of cancer so identified has led to only a modest improvement in overall cancer mortality.<sup>27</sup> This sad reality has called for new approaches to the identification of early lung cancer.<sup>27</sup>

### Sputum Cytology

Many years ago, Saccomanno perfected and championed the use of Papanicolaou staining of exfoliated bronchial epithelial cells to identify roentgenographically occult lung cancer. Saccomanno and others studied the evolution and development of progressive stages of dysplasia (mild,

moderate, and severe) as a prelude to carcinoma *in situ* and invasive carcinoma.<sup>28,30</sup> Squamous carcinomas tend to be central and exfoliate early. By contrast, adenocarcinomas, which are peripheral, do not exfoliate quite as readily. Peripheral adenocarcinomas may be more readily identified by newer imaging techniques (see following section). Sputum cytology has been considered the first step in the diagnosis of suspicious pulmonary shadows and nodules, and is less expensive in identifying the presence of malignancy, by far, than fiberoptic bronchoscopy, which is the gold standard for diagnosis today. Bronchoscopic procedures, of course, are appropriate for further confirmation of the histologic type of malignancy and staging. Newer fluorescence-intensified bronchoscopy increases the diagnostic yield in tiny tumors that are difficult to visualize by standard white light bronchoscopy. Sputum cytology is a logical first step in identifying malignancy, which could be further evaluated by invasive techniques.

## RESULTS OF SCREENING FOR EARLY LUNG CANCER

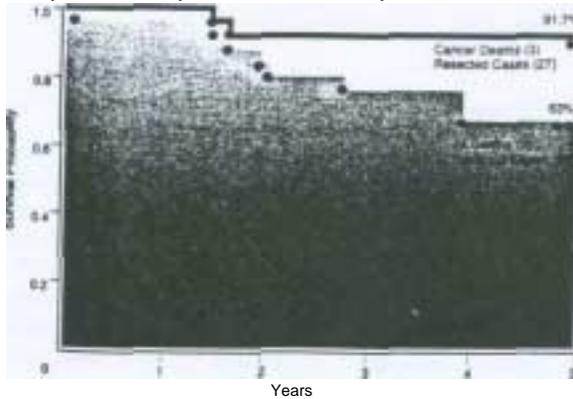
Although early-stage lung cancers clearly have a better prognosis than more advanced stage tumors, this outcome may be partly a reflection of innate tumor biology. In other words, the more indolent tumors may spend more time in early-stage disease than do more aggressive tumors. Intensive screening efforts would then be expected to discover biologically more aggressive tumors at an apparently early Stage, and stage-specific survival would then decrease. Several reports of outcomes from relatively small series in which an effort to diagnose early-stage lung cancer was made demonstrate excellent survival, which would not be the case if screening were ineffective for this reason.

### United States

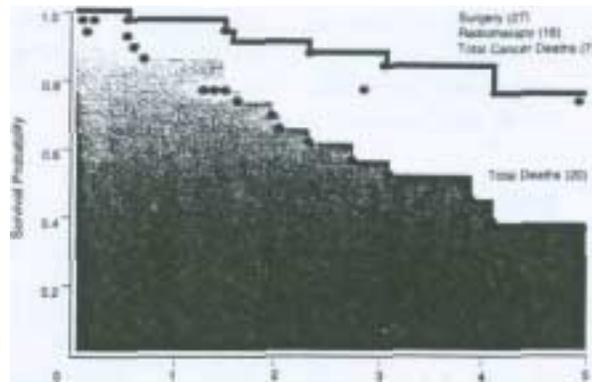
Pulmonologists working in a modest-sized rural community hospital in western Colorado (St. Mary's in Grand Junction) sought to identify cancer based on clinical clues or other risk factors. In this community, 51 consecutive patients with roentgenographically occult lung cancer were identified.<sup>31</sup> Forty-three men and eight women were identified between the ages of 46 and 81 (mean age 64.2); all but two were smokers. Whether or not environmental tobacco smoke could have played a role in the two nonsmokers is not known. Thirty-nine of these patients were smokers with symptoms of cough, increasing dyspnea, family history, or an x-ray lesion that appeared to be a healed scar. Patients with hemoptysis were not included in this series because hemoptysis is a known sentinel sign and symptom for lung cancer. Twelve cancer patients were screened based on occupational risks, with eleven having had significant uranium

mining experience at a time when uranium was mined on the Colorado plateau. One was an asbestos worker.

In this study, sputum cytology revealed either carcinoma *in situ* or invasive carcinoma in some of the patients. Establishing the source of these abnormal cytologic findings by fiberoptic bronchoscopy was the next step. Thirty-one cancers (61%) were found on the first biopsy. Additional biopsies were required for confirmation of cancer, with two bronchoscopies required in eight cases (17%), three in another eight cases (17%), and more than three in three patients. Thus the knowledge of lung cancer, as demonstrated by sputum cytology, urged the physicians in their bronchoscopic approaches to confirmation, preparatory to surgery or other therapies. In this series, 86% were squamous carcinomas, 6% were adenocarcinomas, 4% were large cell carcinoma, and 4% were undifferentiated carcinoma. This histologic destruction reflected the fact that squamous carcinomas are central and tend to exfoliate early. As revealed in the study, sputum cytology does not identify all patients with adenocarcinoma. The cancer stage was *in situ* in 7 (14%), stage I in 38 (74%), and stage II or stage II-A in 2 (4%). Thus only four (8%) patients were at a stage precluding a surgical cure. Twenty-seven of the patients received curative surgical therapy. Their outcome is presented in Figure 22.2. Only three patients had died of cancer at 5 years. Total mortality was only nine patients. Nineteen additional patients were candidates for ablative radiation therapy. Taken together, both surgical and radiation treatments resulted in a much better lung cancer survival rate, with only 9 deaths at 5 years, and total mortality of 21



**FIGURE 22.2.** Survival predictions based on actuarial experience of the 27 patients who received resectional surgery for cure (Kaplan-Meier life table method). Both cancer deaths and deaths from all causes are listed. Circles indicate time of death. Vertical lines indicate survival at the time of original report. (From Bechtel JJ, Kelley WR, Petty TL, et al. Outcome of 51 patients with roentgenographically occult lung cancer detected by sputum cytologic testing: a community hospital program. *Arch Intern Med* 1994; 154:975, with permission.)

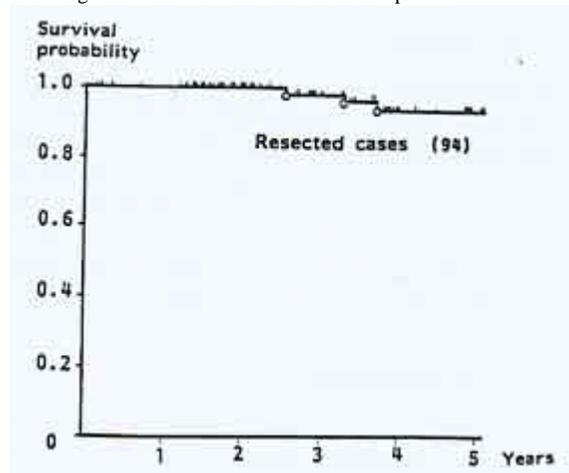


**FIGURE 22.3.** Actual survival in all 46 patients who received treatment with expectation of cure (27 surgery and 19 by radiation; Kaplan-Meier life table method). Both cancer deaths and deaths from all causes are included. Circles indicate time of death. Vertical lines indicate survival observation at the time of original report. (From Bechtel JJ, Kelley WR, Petty TL, et al. Outcome of 51 patients with roentgenographically occult lung cancer detected by sputum cytologic testing: a community hospital program. *Arch Intern Med* 1994;154:975, with permission.)

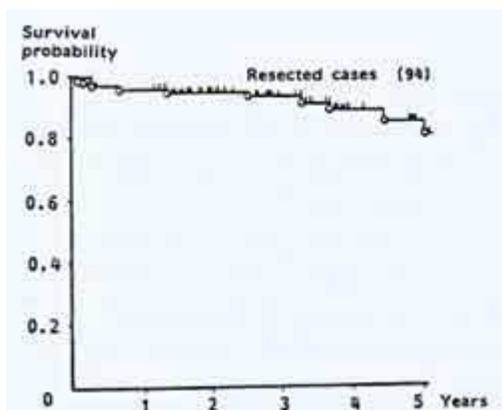
deaths in 5 years (Figure 22.3). This result is far better than in cancers identified either accidentally or on the basis of symptoms, where the overall cancer mortality rate is approximately 85% at 5 years.

### Japan

The results of surgical treatment for roentgenographically occult bronchogenic squamous cell carcinomas has also been reported to be excellent.<sup>300</sup> Ninety-four such patients received surgical resection. The survival over 5 years is presented in Figures 22.4 and 22.5. A total of seven patients



**FIGURE 22.4.** Survival probability of patients with resected roentgenographically occult bronchogenic SCC (time of death from lung cancer).



**FIGURE 22.5.** Survival probability of patients with resected roentgenographically occult bronchogenic SCC (time of death from all causes).

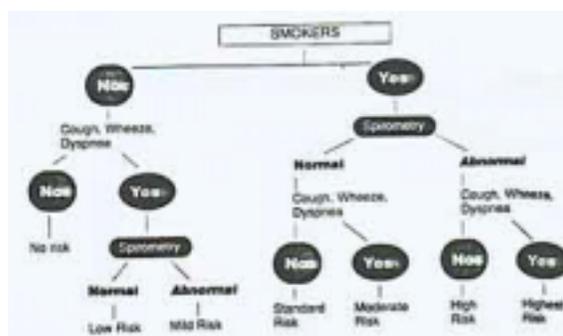
with a subsequent primary cancer had surgical resection with no recurrence after the second operation. Two deaths from lung cancer occurred. These favorable results included an 80.4% survival rate at 5 years, including deaths from all causes, and a 93.5% survival rate considering only lung cancer deaths. Although subsequent primary cancers remained a challenge, the reliability of sputum cytology to identify the presence of roentgenographically occult lung cancer was exceedingly good.<sup>32</sup>

### Scandinavia

The long-term survival of patients with lung cancer from a defined geographic area in Sweden, before and after radiologic screening, showed a much better survival with carcinoma identified with semiannual screening, compared to when it was identified following symptoms.<sup>33</sup> Combined survival at 4 years was 41.7%, compared to 10.3% for those discovered by symptoms ( $P < 0.001$ ). Thus it seems certain that the early identification of lung cancer, either roentgenographically or by sputum cytology, will identify patients with early-stage carcinoma who are suitable for curative therapy, either by surgery or by radiation therapy.

### A PRAGMATIC APPROACH TO SCREENING IN HIGH-RISK POPULATIONS

Because heavy smokers (i.e., those with airflow obstruction) and symptomatic patients are most apt to develop lung cancer, a systematic approach to stratified screening has been proposed.<sup>3</sup> This approach has resulted in the development of two simple algorithms, by which it was proposed that a high yield of lung cancer could be obtained in a targeted



**FIGURE 22.6.** Algorithm to assist in the determination of level of risk of lung cancer of smokers versus non-smokers. Assumes no additional risk; for example, asbestos exposure, uranium mining, chloro methyl ethyl ether exposure, or family history of lung cancer.

population (Figures 22.6 and 22.7). That this approach can result in a relatively high yield of occult lung cancer was shown in a Study of 613 patients, where sputum cytology was obtained at home, with mail-in specimen containers.<sup>35</sup> Five carcinomas *in situ* and six invasive carcinomas, both squamous and adenocarcinoma, were identified (Table 22.2). Three patients with severe atypia can also be considered to have pre- or early-stage carcinoma. Thus the yield in smokers of 30 pack-years or more with airflow obstruction is well above the yield of other screening tests for lethal malignancies such as breast cancer, where the overall yield is approximately 0.23% in women age 50 to 54 to 0.48% in women 75 to 79 years.<sup>36</sup> Interestingly, four more carcinomas have already been identified in the group with only moderate atypia. At this writing, the entire cohort is being followed to identify the final yield that will occur in the targeted population of heavy smokers with associated airflow obstruction.

Peripheral lung cancers, which are most often adenocarcinomas, can be readily identified by spiral CT scans, which



**FIGURE 22.7** Practical diagnostic approach to lung cancer.

**TABLE 22.2. RESULTS OF SPUTUM CYTOLOGY IN HIGH-RISK PATIENTS**

Dysplasia Grade	Number	Percentage
None	72	12.0%
Regular metaplasia	63	11.0%
Mild atypia	309	50.0%
Moderate atypia	155	25.0%
Severe atypia	3	.2%
Carcinoma <i>in situ</i>	5	1.8%
Invasive carcinoma	£	
Total:	613	

From Kennedy TC, Proudfoot SP, Franklin WA, et al. Cytopathological analysis of sputum in patients with airflow obstruction and significant smoking histories. *Cancer Res* 1996;56:4, 673, with permission.

can be completed in 15 seconds with a single breath hold. The dose of irradiation is similar to that associated with mammography. Screening trials for lung cancer utilizing low-dose spiral CT scans are currently underway.<sup>37,38</sup> Recently, a new mobile CT scanner unit has been used in a population-based study that involved mass screening for lung cancer in Japan.<sup>38</sup> Five thousand, four hundred eighty-three people between 40 and 74 years old volunteered. This program was promoted by public announcements by local governments and by leaflets. For comparison, two control groups, from the annual general health survey (n = 10,966), were matched by sex and age within 2 years, and included the smoking habits for smokers of at least 30 pack-years. Of the 5,483 participants, 3,967 underwent CT scans and photofluorography. This group included 64% men and 36% women. Nineteen patients were diagnosed as having lung cancer (0.48%), which is significantly higher than previous standard mass assessments done in the same area. CT missed one case that was found solely on the basis of sputum cytology. Several clinically significant benign lesions were also identified in the study.

Among the 19 patients in whom the workup showed lung cancer, 18 had surgery and one refused surgery but later developed metastasis. The most frequent cell type was adenocarcinoma. Of the 19 patients, 16 were stage I and three were stage IV. It is a fact that the mini-photofluorography had shown no evidence of cancer in 18 of the 19 patients. It should be pointed out that this trial was done in rural Japan where the rate of lung cancer is reported to be low (i.e., only 30 to 50 cases expected per 100,000 in population). The authors found the CT identified almost 10 times as many cancers as were identified by standard mass screening previously done. This study strongly suggests that CT scanning may replace chest x-rays in early case finding or in screening of high-risk populations.

Most recently, the results of the Anti-Lung Cancer Association screening program were presented. From 1975 to 1993, 26,338 examinations with chest x-rays and sputum

cytology were performed, with a detection rate of lung cancer at 0.16%. When low-dose spiral CT examinations were added from 1993 to 1998, 35 lung cancer cases were found in 9,452 (0.37%) examinations. Moreover, this translated to a 3-year survival of 83% from 1993 to 1998 compared to 56% in the former period.<sup>39</sup>

The results of the Early Lung Cancer Action Project (ELCAP) have been reported<sup>40</sup> and are complementary at the Japanese data. ELCAP was designed to evaluate baseline and annual repeat screening by low-radiation-dose computed tomography (low-dose CT) in people at high risk of lung cancer. One thousand symptom-free volunteers, 60 years or older, with at least 10 pack-years of cigarette smoking and no previous cancer, who were medically fit to undergo thoracic surgery were enrolled. Chest radiographs and low-dose CT were done for each participant, and noncalcified pulmonary nodules were investigated using short-term high-resolution CT follow-up for the smallest noncalcified nodules. Noncalcified nodules were detected in 23% of the participants by low-dose CT at baseline, compared to 7% by chest radiography. Malignant disease was detected in 2.7% by CT and 0.7% by chest radiography. Of the 27 CT-detected cancers, 26 were resectable. Biopsies were done on 28 of the 233 participants with noncalcified nodules; 27 had malignant noncalcified nodules and one had a benign nodule. No participant had thoracotomy for a benign nodule. These data point to the utility of low-dose CT in detecting small noncalcified nodules, which could prove to be lung cancer at an earlier and potentially more curable stage. Plans are under way for a multicenter national trial to verify these results.

#### DEVELOPMENT OF MOLECULAR APPROACHES TO EARLY LUNG CANCER DETECTION

Development of new approaches to identify lung cancer in sputum is being pursued. Sputum, bronchial washings, and bronchoalveolar lavage fluid are complex specimens containing a wide variety of soluble and cellular components, only a portion of which are epithelial derived. Novel techniques to derive epithelial cell-enriched specimens from sputum are being developed. Computerized image analysis of Feulgen-stained exfoliated cells has shown significant promise in improving diagnostic capabilities.<sup>41</sup> Encouraging reports of increased sensitivity of monoclonal antibodies for detecting malignant cells in sputum have not been duplicated by additional groups, but further development of this assay is underway.<sup>41-43</sup> Several additional novel markers are under evaluation (see also Chapter 23), including mutation detection targeted at p53 and *ras* genes. In addition, DNA methylation is often aberrant in lung tumors,<sup>43</sup> and a polymerase chain reaction-based method of methylation detection has recently been applied to sputum. Although consid-

erable excitement, has been generated regarding the application of molecular markers to the early detection of lung cancer, none of the tests developed to date are currently ready for large-scale application. Prior to applying any molecular marker to early detection of lung cancer, test characteristics, such as reproducibility (both within a laboratory and between laboratories) sensitivity, and specificity when tested in appropriate disease and control groups, need to be determined.

In addition to early detection, molecular markers have a high potential to achieve clinical application to identify high-risk individuals in whom other screening techniques might be applied for surveillance.<sup>45</sup> Several genetic aberrations have been described in the respiratory epithelial cells of lung cancer patients and current or ex-smokers without lung cancer,<sup>46,47</sup> p53 mutations affecting nonmalignant respiratory epithelial cells have only rarely been described in individuals without lung cancer and might define a group of smokers at extremely high risk for the development of cancer.<sup>48</sup> (see also Chapter 6) Loss of heterozygosity of chromosomes 3p and 9p can be found in most smokers studied to date and might therefore be a less attractive risk marker (see also Chapters 23, 28).<sup>46,47</sup> Either specific combinations or the total number of mutations detectable in respiratory epithelium may be prognostic.

A panel of biomarkers instead of a single marker will likely be required to identify occult lung cancer. The cancer gene marker may be present in exfoliated cells, which appear morphologically normal. This marker is an important new area of outcomes research, which could lead to algorithms that may increase the efficiency and reduce the cost of case finding or screening.<sup>49,50</sup>

### ADVANCED IMAGING TECHNIQUES

Recently, F-fluorodeoxyglucose PET scanning has revealed a high degree of sensitivity and specificity in lung cancer identification,<sup>51,54</sup> with positive predictive values greater than 90% and negative predictive values approaching 100%. The finding of a metabolically active nodule is highly indicative of malignancy.<sup>51</sup> Whole-body PET scanning can be used in the staging of non-small cell cancer<sup>54</sup> (see also Chapter 30).

### ENHANCED BRONCHOSCOPY TECHNIQUES

The best outcome in lung cancer management is treatment when the lesion is discovered in preinvasive stages. However, the intraepithelial neoplastic lesions are somewhat difficult to localize by conventional white light bronchoscopy, particularly if the bronchoscopist is not highly experienced in searching for subtle changes that may indicate lung cancer, as was the case in the Grand Junction Study.

Autofluorescence bronchoscopy was introduced to detect high degrees of dysplasia or in carcinoma *in situ*<sup>5,11,16</sup> (see also Chapters 23, 24). Conventional white light bronchoscopy uses illuminated light that is reflected backscattered absorbed, but it does not induce tissue fluorescence, a process known as *reflectance imaging*. The tissue autofluorescence is not visible to the unaided eye because the intensity is low and obscured by the backscattered light. With suitable instruments, however, the autofluorescence reflected to create an image, which indicates a high likelihood of malignancy.<sup>56</sup> In a recent study, autofluorescence bronchoscopy, when used as an adjunct to standard white light bronchoscopy, enhanced the bronchoscopist's ability to localize small, subtle lesions, which were often malignancies, that were confined to the epithelium (i.e., *in situ* or preinvasive).<sup>57</sup> It is virtually certain that a cure of these lesions with surgery, radiation, and/or laser therapy will be likely. In addition, a novel new therapeutic approach, photodynamic therapy, may also achieve a cure for *in situ* and stage I carcinoma.<sup>58,59</sup> Fluorescent bronchoscopy can be used in surveillance of subsequent carcinomas and sputum markers, either molecular or cytomorphologically, which suggest a second or recurrent lung cancer. Surveillance employing malignancy-associated antigens (MACs) is also under study as a method of detecting small peripheral adenocarcinomas and as an indication of lung cancer recurrence.<sup>60,61</sup>

### A NEW, EXCITING APPROACH TO THE EARLY IDENTIFICATION OF LUNG CANCER

Individual cases of lung cancer must be diagnosed on the basis of clinical suspicion, bolstered by the necessary technology to prove presence and location and to determine the histologic type of malignancy. Suspicion must be based on smoking histories, family histories, occupational exposures, and symptoms. When a high-risk individual is identified (i.e., heavy smoking with any of the following: airflow obstruction, positive family history, additional carcinogenic exposures, or symptoms), systematic studies to identify the presence or absence of lung cancer seem reasonable, given the lack of currently available scientific information that attempts at early identification are not useful in this patient group. The algorithms shown in Figures 22.6 and 22.7, although overly simplistic, may be useful in this regard. Either sputum markers of malignancy using cytomorphology or standard chest x-rays or CT scans will identify the presence of a premalignant or malignant lesion (sputum), or an airway or peripheral abnormality (CT imaging). The next step is to identify the site through white light bronchoscopy or if that modality is unrevealing, with fluorescent endoscopy. When the tumor is located, a biopsy should be performed, and staging should proceed thereafter. The phenomena of MACs may add still another surveillance tool (see also Chapter 23).<sup>60,61</sup> MACs are subtle markers

ations in the size, shape, or texture of the cell nucleus of nonmalignant exfoliated cells that appear to be a result of growth factors produced by nearby lung cancer cells. Their presence may be used in early identification or for surveillance of recurrent lung cancer.<sup>60,61</sup>

Today, the main diagnostic focus should be on early lesions that are amenable to cure. It is distinctly possible that early intraepithelial lesions can be dealt with by photodynamic therapy,<sup>58,59</sup> or other methods such as electrocautery, cryotherapy, or thermoablation, with a YAG laser or brachytherapy. Indeed, the identification of premalignant lesions would expand the possibility of controlled clinical trials in chemoprevention, using the premalignant lesions as endpoints<sup>62,63</sup> (see also Chapter 25).

Thus far, the growing problem of lung cancer, caused primarily by smoking, has eluded prevention, in part because of persistence of transformed epithelial cells lining the airways of aging former smokers. Recent studies have reported that similar numbers of new lung cancer cases arise from former smokers compared to current smokers.<sup>64</sup>

The continued seduction of 3,000 teenagers daily into the bondage of tobacco addiction with advertising financed by a tobacco industry bent on sustaining its economic success unfortunately ensures that lung cancer will remain a major clinical problem for many years, even if all recruitment of new smokers were to Stop immediately. The growing tobacco epidemic has created the most vexing and recalcitrant cancer of our time. With tobacco smoking out of control in large countries such as China, we face a true global disaster. These frightening realities pose an immense challenge to clinicians and scientists who aim to reduce the socioeconomic impact of lung cancer as we approach the new millennium.

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