Screening Strategies for Early Detection of Lung Cancer

The Time Is Now

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CURRENT KNOWLEDGE AND AVAILABLE TECHNOL -ogy could change the outcome of lung cancer. But screening and even case finding in patients at high risk is still not recommended. No major medical organization in the United States recommends any form of screening for lung cancer. For this reason, lung cancer is not diagnosed until it is symptomatic and usually when it is in advanced and incurable stages. Assume that the following facts are true: In the year 2000, approximately 172 000 patients will be diagnosed as having lung cancer, which represents the most common fatal malignancy in both men and women in the United States (based on 1996 data),' and the 5-year survival rate will be only 15%, which is a generous estimate. Simple arithmetic results in 25800 patients who will survive and 146200 patients who will have progressive, rapid, and painful deaths from lung cancer, often with bone and brain metastases. However, the survival rate in early-stage lung cancer, that is, in situ and stage IA, is 60%, which also is a conservative estimate. Thus, if all 172000 patients could be diagnosed at this early stage, this would result in 103200 survivors and 68800 deaths in 2000. Diagnosing and treating lung cancer in the early stages of the disease could save tens of thousands of lives each year.

Historical Perspective

Why does current dogma state that screening for lung cancer is not beneficial? The answer comes from 3 related studies sponsored by the National Cancer Institute (NCI) in the mid-1970s[2,4] and a Czechoslovakian study.[5] These 4 studies used standard chest radiography and sputum cytologic testing to identify persons with lung cancer. Although the resectability and survival rates were higher in at least 1 of the NCI studies,[2] overall mortality did not change.[6] There are many problems with these studies.[2-5] For instance, standard chest radiography, although beneficial in case finding,[7,8] often does not identify early stages of the disease. Also, in the mid-1970s, approximately 50% of the control group received chest radiographs as a part of standard practice.[2,4] Thus, these studies included a control group that was "contaminated" by patients who also had chest radiographs during the study. An annual chest radiograph provides some lung cancer surveillance, albeit crude. In addition, the entry criteria into the NCI studies did not require history of heavy smoking. The criterion of smoking intensity only required the subjects to have consumed 20 cigarettes during the year before study entry. The mean pack-years of smoking was only 20.[2-4]

Moreover, in the Johns Hopkins Lung Project, an analysis of molecular markers for cancer showed that a substantial number of patients determined to be free of cancer actually had evidence of cancer in their expectorated sputum specimens.[9] Thus, this study shows that many cancers that could be detected with modern technology can be missed otherwise.

The Present Era

Recent studies[10,11] using low-radiation, high-resolution computed tomography (CT) have shown that peripheral nodules as small as 3.0 mm can be detected and virtually all of these lung cancers could be resected.[10] Computed tomography is the standard practice for detecting lung cancer in Japan, often by using mobile vehicles with CT scanners to screen for lung cancer in persons living in rural areas, even where smoking prevalence is relatively low." It is well established that CT is far more sensitive and specific than conventional chest radiography in the diagnosis of early peripheral lung cancers, which are usually adenocarcinomas.[10]

Sputum cytologic testing has been successfully used in the United States to identify radiographically occult lung cancer of the central airways, including in a community hospital where the modern method of sputum cytopathologic testing has its roots.[12,13] Lung cancer was diagnosed by sputum cytologic testing in 51 consecutive patients in whom chest radiographic results were normal.[13] Most of these cancers (44/51) were squamous cell carcinomas. These patients were evaluated because of changing symptoms, heavy smoking, or occupational exposures. Forty-six (90.1%) of these patients had early-stage disease that could be treated with surgical intervention or with radiotherapy in an attempt to cure. Actual 5-year survival rate was 54.3% fol-

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See also p 1980.

lowing either surgical or radiotherapy treatment.[14] As expected, some patients had secondary or tertiary carcinomas, which also were identified by sputum cytologic testing in stages during which retreatment was possible. Many ot these patients were cured of their cancer but later died from other causes.

Screening to identify lung cancer in its early stages has been extensively criticized on the basis of lead-time, length-time, and tumor selection biases.[15] The very purpose of screening is to exploit the advantages offered by lead or length time.[16] In other cancers, such as of the breast and prostate gland, treatment in early and even in so-called indolent stages has become the standard of care, thus improving survival. Clinical objectives also should include the detection and cure for lung cancer in its early, less invasive, and probably less virulent stages.'" Extensive evidence indicates that late-stage diagnosis or diagnosis of lung cancer on the basis of symptoms is not the correct approach to this most common fatal malignancy in men and women. New and aggressive approaches to early identification of lung cancer must be adopted.

Like improvements in the radiographic diagnosis of lung cancer, the sensitivity and specificity of sputum cytologic testing has been improved by automated techniques. Also, the search for molecular markers from expectorated sputum cells may make lung cancer screening even more sensitive and specific than it is today.[17]

Case Finding in High-Risk Croups

Nearly 10 years ago, I proposed that lung cancer screening should be performed in patients who are at highest risk.'[8] It is well established that airflow obstruction as measured by spirometry in heavy smokers corresponds to 4 to 6 times increased prevalence of lung cancer compared with patients in whom airflow is normal.[lc1,20] Kennedy et al,[21] in a prospective study of patients who smoked 30 or more pack-years with any degree of airflow obstruction (as defined by a forced expiratory volume in 1 second [FEVi I/forced vital capacity [FVC] ratio of <70% or an FEV[of <80% of predicted normal values), documented that sputum cytologic results were positive for cancer in 1.8% and for severe dysplasia in 0.3% of the patients. A yield of approximately 2.0% of lung cancer diagnoses is huge compared with the 0.5% diagnoses of breast cancer, which Saizmann et al[22] pointed out in high-risk women screened by mammography. In addition, 25.0% of the patients were found to have moderate dysplasia.

A Mayo Clinic study revealed moderate dysplasia in only 2.9% of its patients.[23] The reason for the much higher yield of both cancer and moderate-to-severe dysplasia in the study by Kennedy et al[21] is because of the selection of a high-risk cohort due to heavy smoking and coexistent chronic obstructive pulmonary disease (COPD). A follow-up of patients with moderate dysplasia from this series of patients[2'] has already yielded 4 additional cancers among 41 patients who received bronchoscopy of the 155 patients with moderate dysplasia as detected with sputum cytologic testing (Timothy C. Kennedy, MD, oral communication, May 5, 2000). This follow-up searched for molecular markers of lung cancer in these subjects. These additional squamous cell cancers were all small intraepilhelial lesions, and some were occult or subtle radiographically detected lesions. Three of the cancers were found by both white light and fluorescent bronchoscopy.[2+] The fourth cancer was found only by fluorescent bronchoscopy. Light-intensified fluorescent endoscopy, as compared with white light bronchoscopy, can identify small foci of abnormal fluorescence in which a biopsy should be performed to more accurately detect the presence of cancer.[24] However, bronchoscopy using light-intensified fluorescent endoscopy is not yet widely available.

Other high-risk groups, such as patients with a previous lung cancer, individuals with significant occupational exposure such as asbestos workers, and patients with a strong family history of lung cancer, also would be candidates for screening by CT and sputum cytologic testing.

Positron emission tomography also is not widely available, but in the future, it likely will be valuable to differentiate clearly between benign solitary nodules and those that are probably malignant.[25] Positron emission tomography also will be useful in the staging and the identification of metastatic disease.[25]

Economic Considerations

The cost to screen for early lung cancer and to cure and treat, this disease it is an important consideration. Hillner et al[26] reported that the cost for lung cancer diagnosis and treatment in the present era (1989-1991), when screening is not practiced, is approximately $50000 per patient (1990 dollars). In this study, the 2-year survival rate, in patients so diagnosed, was only 20%. Contrast this rate with a potential rate of 60% or more 5-year survival prediction of early diagnosed lung cancer. The true cost of early diagnosis needs to be established by prospective studies which should determine not only the costs of early identification and treatment but also whether the high end-of-life costs that patients now incur are also found in a cohort of patients with early-stage lung cancer, even if their survival is prolonged.

Lessons From the Lung Health Study

The Lung Health Study, a multicenter, randomized clinical trial of smokers with more than 10 pack-years and who were aged 35 to 60 years, showed that 57 patients (1%) died of lung cancer at the end of 5 years.[2'] Late follow-up data indicated that a total of 227 (3.9%) of the original 5887 patients enrolled in the Lung Health Study developed lung cancer (John E. Connett, MD, oral communication, October 10,1999).

This study was designed to track the course and prognosis of patients with mild-to-moderate stages of COPD and the effect of smoking cessation on the rate of change ofFEVi. Stopping smoking improved FEVi followed by a slight decline in

FEVi in sustained quitters. In patients who continued to smoke, the rate ofFEVi decline was much more rapid. However, only 22% of patients who were randomly assigned to the smoking intervention group (with bronchodilator or placebo) actually succeeded in stopping smoking throughout the 5-year study, compared with 5% of patients who received ordinary care. Many of these patients with histories of heavy smoking would be candidates for yearly surveillance to detect the cytologic or molecular markers of lung cancer. Today, more lung cancer is found in former smokers than in current smokers.[28] Patients with moderate dysplasia also would be excellent candidates for chemoprevention studies, as would patients who were apparently successfully treated for early-stage lung cancer.[29]

Lessons From Japan

A comparison of survival rates has been done in Niigata Prefecture in Japan.[30] Screening for tuberculosis using radiography has been a routine procedure in Japan because of a continuing high prevalence of the disease. During 1963-1977, before lung cancer screening became the norm, the 5-year survival rate was 33.7% for lung cancer cases discovered during tuberculosis radiographic screening.[30] This was a good result in cancer outcome compared with 15% or less survival in the United States at 5 years. A pilot study of screening for lung cancer during 1978-1986 in the same prefecture yielded a 51.8% 5-year survival rate.[30] The lung cancer screening program was expanded to the entire population of the prefecture in 1987 in which sputum cytologic testing was added to radiographic screening. From 1987-1992, the 5-year survival rate increased to 58.4%. In studies of surgery of radiographically occult lung cancer found by sputum cytologic testing, the 5-year survival rate was 80.4% for squamous cell carcinoma.[31]

Critics of lung cancer screening disapprove of the use of 5-year survival curves, but this same yardstick is used as a standard measurement for colon, breast, cervical, and prostate cancers. Why treat survival in lung cancer any differently?

The National Lung Health Education Program

Unfortunately, the great majority of smokers and particularly those with incipient stages of COPD are not seen by pulmonologists or other medical specialists. However, approximately 70% of all smokers do see a physician each year for various reasons.[32] A new national health care initiative, known as the National Lung Health Education Program (NLHEP), has been launched to identify and treat patients with early mild-to-moderate stages of COPD.[33] The NLHEP encourages all primary care practitioners to perform spirometric testing in smokers older than 45 years and in anyone with cough, dyspnea, wheeze, or mucus hypersecretion.[34] The identification of patients with heavy smoking, that is, greater than 30 pack-years and previously undiagnosed airflow obstruction, will provide large numbers of patients who also would be candidates for lung cancer screening.[21]

As learned from the Japanese experience,[30,31] most patients identified with lung cancer by screening will have early stage resectable lesions. Computed tomography will provide a higher yield of detection than standard chest radiography.[10] Follow-up of patients with moderate-to-high degrees of dysplasia will identify even more lesions. Hopefully, this new nationwide effort plus a change of attitude about screening will identify many more patients with lung cancer so a higher cure rate can be expected, compared with the dismal outcome when lung cancer is diagnosed as an incidental finding or on the basis of symptoms, which usually represents advanced and often metastatic stages of disease.

Recent reports following an annual meeting of the American Society of Preventive Oncology argued that modern imaging for tiny, early lung cancers often reveals "indolent cancers,"[35] citing a doubling rate of 1 year. The presenters argued that it would take 8 years for a 5-mm lesion to grow to 3 cm. But who would be comfortable watching a known lung cancer grow over 8 years or even 1 year? At what point would metastasis occur? Spontaneous regression of a proven lung cancer has not been reported.

Conclusion

Now is the time to screen for early-stage lung cancer since it has been shown that lung cancer screening ought to work.[36] By using radiography, screening heavy smokers with airflow obstruction (as determined by spirometry) with sputum cytologic testing for central lesions and CT for peripheral lesions, we can then identify and harvest "the low-hanging fruit."[37] In addition, the cost of curative treatment for early-stage lung cancer can be determined and such effective screening strategies for early detection and treatment of lung cancer should begin to reduce the unnecessary morbidity and mortality of lung cancer.

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