

LUNG CANCER SCREENING

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Lung cancer is the largest cause of cancer death in the United States, and surgical resection of early stage disease is the only treatment that yields high rates of long-term survival. This combination would seem ideal for screening. However, in the 1970s, randomized controlled trials of screening for lung cancer using chest radiographs and sputum cytology demonstrated that, while lung cancer could be detected earlier, at a smaller size and at a more resectable stage, screening did not reduce lung cancer mortality rates (1).

Radiographic chest imaging has advanced substantially since the 1970s. Current scanners can detect lesions in the 1 to 3 mm range using a single breath spiral CT, in contrast to the 1 to 1.5 cm range for chest x-ray. Several large observational studies have demonstrated that annual CT screening of high risk populations yields a substantial number of asymptomatic lung cancers, most at an early stage (2-4). The National Cancer Institute and the American College of Radiology Imaging Network are conducting a randomized trial of CT screening with lung cancer mortality as the endpoint, and it is likely that most organizations that issue screening guidelines will await these results before developing recommendations. Until those recommendations are forthcoming, the practicing physician is in the difficult position of making recommendations to individual patients based on judgments from imperfect existing evidence.

Both the supporters and the opponents of CT screening agree that lung cancer carries an abysmal 85% five-year mortality, and that early stage lung cancer treated with surgical resection has a five-year survival of approximately 80% when detected in the absence of a screening program. They also agree that CT can detect smaller lesions than a chest x-ray, will identify asymptomatic individuals with lung cancer by conventional pathologic criteria, and that the distribution of screen-detected lung cancers is shifted in the direction of early stage disease.

For a screening program to reduce morbidity or mortality it must be accompanied by improved diagnosis and subsequent treatment; however, diagnostic and therapeutic procedures could cause harm if applied to substantial numbers of individuals who turn out to have benign disease. The frequency of a positive finding on the initial CT for screened populations ranges from 20 to 50% (5, 6), depending on the population and geographic location. Higher positivity rates have been reported when a positive finding is defined as *any* abnormality rather than one that requires an evaluation different from that for individuals with a negative scan (ie, a scan at the next annual interval) (7).

Screening programs have developed guidelines for evaluating positive scans to prevent screening from resulting in large numbers of unnecessary invasive procedures (8). These guidelines include follow-up scans to evaluate growth, treatment of some lesions with antibiotics, and further diagnostic evaluations depending on the size and characteristics of the lesion. All programs reporting results to date have very low rates of invasive procedures for benign disease (4, 9, 10). The best programs report 80 to 90% lung cancers when invasive procedures are indicated following the protocol.

For many, the high percentage of early stage disease detected and high five-year survival for early stage disease offer a compelling justification for screening high risk patients. Others argue that data derived from lung cancer detection in the absence of organized screening cannot be used to predict the results of screening asymptomatic individuals. Several biases do exist with screening for any disease (11), but the arguments that finding early stage disease in screening programs may not alter disease outcomes are largely based on two concerns.

One suggests that at the time of screening detection, lung cancers that are going to metastasize have already disseminated, and those that have not yet disseminated are far less likely to do so before they would be detected due to symptoms. If the hypothesis that cancer outcomes are predetermined at diagnosis is true, then screen-detected lung cancers should have outcomes similar to those diagnosed without screening, even though there is a shift to earlier stage cancer, and stage I lung cancers detected by screening would have worse outcomes than those detected in the absence of screening. Data from the existing observational screening studies demonstrate that outcomes for lung cancer detected by screening are better than the experience for lung cancers detected in the absence of screening. However, five-year mortality data have not been published yet, and screen-detected stage I lung cancers have survivals similar to or better than those published for disease detected in the absence of screening (12). Clearly, lung cancer outcomes are not biologically predetermined at diagnosis.

A second concern suggests that many lung cancers detected in screening trials are growing so slowly or are so biologically inert that they would rarely result in death, and lung cancer is being over diagnosed in screening trials. The term “over diagnosis” can be used for detection of lung cancer in individuals who die prior to the point where the cancer would have been detected absent screening. It is also used for the identification of lesions with non-solid or “ground glass” consistency on the scan that have pathologic morphology that varies from atypical adenomatous hyperplasia through low grade bronchoalveolar carcinoma. These lesions have been observed to be stable for long periods of time raising a question as to whether they should appropriately be classified as lung cancers. These lesions raise important questions about their management but have characteristics that can be used to separate them from lesions of greater concern.

The last form of over diagnosis is the identification of a lung nodule which pathologic examination identifies as a typical lung cancer but which has a clinical course more consistent with benign disease with very slow or non-existent growth and without metastatic spread. While this is a theoretical concern, a substantial body of evidence suggests that it is not a real phenomenon. Not all early stage lung cancers are surgically resected; and if a substantial fraction of lung cancers are biologically benign, then these untreated “over diagnosed” cancers should have prolonged survival even without treatment. Multiple examinations of populations with stage I lung cancer not surgically resected demonstrate outcomes that are uniformly grim. In the early Mayo Clinic trial, all non-surgically treated lung cancers were dead by six years (13). The poor outcome for lung cancers not surgically resected occurs with both screen-detected as well as symptom-detected disease (14). While rare lung cancers may have a relatively slow growing or apparently benign course, there is little evidence that this occurs with sufficient frequency to be of concern in the management of early stage lung cancers.

To date there are no studies comparing populations randomized to receive screening with CT or a control condition not including CT screening. Many insist that the only valid evaluation of an intervention is a randomized controlled trial with a mortality endpoint, and it is likely that agencies providing clinical or reimbursement guidelines will wait for such a trial. Others argue that a delay in offering screening to high-risk populations will result in preventable deaths in view of the clear evidence that screening can produce a shift in stage at diagnosis and improved survival. In the absence of clear national standards on lung cancer screening, it will be the responsibility of individual clinicians to review the evidence as it evolves and determine how to best advise their patients.

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