Lung Cancer Screening

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ABSTRACT: Lung cancer is the leading cause of cancer-related death worldwide. Most patients present symptomatically when the disease is often at an advanced stage and prognosis is poor. In contrast, outcomes are significantly better in patients diagnosed at earlier stages, with a 5-year survival for stage I approaching 75%. Screening for lung cancer may detect potentially fatal cases earlier in their disease course, at a stage when a curative surgical intervention is feasible. The objective of this review is to examine the current evidence for lung cancer screening and the clinical effectiveness of screening for lung cancer by using computed tomography. **KEY INDEXING TERMS:** Lung carcinoma; Screening; Sputum cytology; Chest radiograph; Computed tomography. **[Am J Med Sci 2008;335(1):46–50.]**

Lung cancer is the leading cause of cancer-related death worldwide. It is estimated that in 2007, there will be 213,380 new cases and 160,390 lung cancer related deaths in the United States, which is more than breast, colon, and prostate cancer combined during the same period.[1]

Unfortunately, 75% of patients with lung cancer present with symptoms due to advanced disease that is not curable.[2] Furthermore, despite advances in therapy, the 5-year survival rate for all stages combined is approximately 16%.[1] In contrast, outcomes are significantly better in patients diagnosed at earlier stages, with a 5-year survival for stage I disease ranging from 60% to 75%.[3–5] Thus, it seems reasonable to attempt to detect disease earlier in asymptomatic patients when curative resections can be attempted. Theoretically, this approach should reduce the mortality rates from lung cancer. However, the evidence for the effectiveness of lung cancer screening is controversial, and clear-cut recommendations for screening cannot currently be made. This article will review the current data on the effectiveness of lung cancer screening and the biases that can confound the interpretation of these studies.

Chest Radiography and Sputum Cytology in Lung Cancer Screening

Before any discussion of screening using computed tomography (CT), it is worthwhile examining the literature on screening by using chest radiographs. The earliest trials were conducted in the 1960s and 1970s. The Northwest London Mass Radiography Service randomly assigned subjects to either a chest radiograph every 6 months for 3 years or a baseline and end-of-study chest radiograph only. After 3 years, the annual mortality rate was not different between the 2 groups.[6]

In the United States, the Memorial-Sloan Kettering and The Johns Hopkins trials evaluated the additional benefit of sputum analysis to annual chest radiographs. In both studies, participants received annual chest radiographs, with half randomly assigned to dual screening with sputum cytology. Follow-up at 5 and 8 years did not show difference in lung cancer incidence or mortality rates.[7–9] The Mayo Lung Project randomly assigned subjects to a 6-year program of chest radiography and sputum cytology every 4 months versus a control group receiving an annual chest radiograph. More early stage cancers were identified in the screening group. There was no reduction in late stage cancers, and, paradoxically, lung cancer deaths were higher in the screened group after 20 years of follow-up.[10–12]

In Czechoslovakia, patients were randomly assigned to either semiannual screening by sputum and chest radiography or a radiograph at baseline and 3 years.[13] More cases of lung cancer and early stage disease were discovered in the semiannual screening group. Again, no reduction was found in late stage cancer cases or mortality between the 2 groups at 3 and 15 years after enrollment.[14] All of these studies have been criticized for having methodological flaws including being underpowered to answer the question and having the control group contaminated by having undergone the test being evaluated (in this case chest radiographs).[15] Still, the use of chest radiographic screening for lung

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cancer cannot be recommended based on the outcome of these studies.

Lung Cancer Screening Using Chest CT

Low-radiation–dose CT (LDCT) uses low levels of radiation to generate an image. This technique is faster and less expensive than standard helical CT scanning, and it detects almost 3 times as many small lung nodules compared with a chest radiograph. Currently, the only available data are from observational cohort studies that provide valuable information on disease stage distribution and survival of the screened population, but do not provide data on the overall effectiveness of screening.

Trials conducted in Japan included the Anti-Lung Cancer Association (ALCA),[16] Hitachi Employee's Health Insurance Group (Hitachi),[17] and Matsumoto Research Centre (Matsumoto).[18,19] These studies used 10-mm collimation for the CT scans, and in the ALCA and Matsumoto studies, sputum cytology was included in screening. Of 15,050 total participants, 72 lung cancers were detected during prevalence screen (0.4%), 57 of which were stage IA (79.1%). In the 3 trials, a total of 21,762 incidence (annual) screens were reported with 60 (0.2%) new cancers detected. Fifty (83.3%) of these were stage IA. It is important to mention that in Japan screening was available at a younger age, usually 40, and smoking history was not a requirement for participation. The percent of nonsmokers in these trials ranged from 14% to 53%.

In the United States, the Early Lung Cancer Action Project (ELCAP) screened 1,000 asymptomatic volunteers with at least a 10 pack-year history of cigarette smoking with chest radiographs and LDCT.[20] Noncalcified lung nodules were detected in 23% by LDCT and 7% by chest radiography. Malignant nodules were detected in 2.7% by CT versus 0.7% by chest radiograph. Twenty-seven lung cancers were identified and 23 (85%) were stage I. The estimated 5-year survival rate in this group of patients was 60% to 80%.[21]

This was followed by a prospective study of LDCT screening conducted by the Mayo Clinic, which enrolled 1,520 high-risk subjects.[22] One year after baseline scanning, 2,244 noncalcified lung nodules were identified in 1,000 participants (66%). Twenty-five cases of lung cancer were diagnosed (22 were prevalence lung cancers and 3 were incidence lung cancers), and 22 underwent surgical resection. Twelve (57%) of the 21 non–small-cell cancers detected were stage IA at diagnosis. After 5 years of annual CT scanning,[23] a total of 3,356 noncalcified nodules were found in 73.5% of the cohort; approximately 95% of the nodules were benign with clinical follow-up or surgical biopsy. Sixty-eight primary lung cancers were documented in 66 subjects, 34 on annual (incidence) studies and 3 interval lung cancers not detected through annual screening. Of the incidence cancers, 61% were stage I and 33% presented at stage III or IV.

Recently, a large multicenter, multinational, nonrandomized trial denominated the International ELCAP (I-ELCAP) was reported.[24] The I-ECAP screened 31,567 subjects using LDCT.[24] Lung cancer was identified in 484 patients, with 412 stage I disease. Estimated 10-year survival was 80% for all patients regardless of stage and treatment, and 88% for stage I cancer. This study confirmed earlier observations that lung cancers detected by CT screening are very early stage and highly treatable. The study has been criticized because, while survival estimates are reported to 10 years, the median follow-up was only 40 months, and less than 20% of subjects were observed for more than 5 years.[25] In addition, the disease-specific survival rate does not account for the outcome of the subjects not diagnosed with lung cancer, and without follow-up of all participants, the lung cancer mortality rate for the entire population cannot be known.[26,27]

In contrast to the optimistic findings published by the I-ELCAP investigators, Bach and colleagues[28] examined 3 single-arm studies conducted in Milan, Rochester, and Florida that screened 3,246 high-risk subjects with annual CT scans with a median follow-up of 3.9 years. The frequencies of observed new lung cancer cases, lung cancer resections, advanced lung cancer cases, and deaths from lung cancer were compared with the expected numbers based on 2 validated models. There were 144 individuals diagnosed with lung cancer compared with 44.5 expected cases (relative risk [RR], 3.2; 95% confidence interval [CI], 2.7 to 3.8; $P < 0.001$). The rate of lung cancer resection was 10-fold higher, 109 resected compared with 10.9 expected cases that were predicted for that cohort (RR, 10.0; 95% CI, 8.2 to 11.9; $P < 0.001$). There were 42 cases of advanced lung cancer compared with 33.4 expected cases, and 38 deaths, which is what was predicted for that cohort (RR, 1.0; 95% CI, 0.7–1.3; $P = 0.90$). This study showed that screening with LDCT may increase the rate of lung cancer detected and resected but may not reduce the risk of advanced lung cancer or overall mortality from lung cancer. Parenthetically, the survivorship of those stage I patients resected was similar to that seen by the I-ELCAP investigators.

Results from observational CT studies demonstrate that LDCT is capable of detecting early lung cancer in asymptomatic individuals. However, it is still unknown if such detection can reduce lung cancer mortality. For this reason, the National Cancer Institute has instituted the National Lung Screening Trial (NLST).[29] The NLST is a randomized, controlled trial that by 2004 recruited nearly 50,000 current or former smokers and randomly assigned them for screening with chest radiography (the control group) and helical CT scan. Subjects were