Lung cancer is the leading cause of cancer-related death worldwide. At the time of initial presentation, most patients are at an advance stage of disease and have a poor associated prognosis. Those diagnosed and treated at earlier stages have a significantly better outcome with 5-year survival for stage I disease approaching 75%. Ideally a screening strategy for lung cancer would detect disease at an earlier stage and allow for potential surgical cure. The purpose of this review is to examine past and current evidence as it relates to lung cancer screening.

### Introduction

Lung cancer accounts for the largest number of cancer related death worldwide. It is expected that there will be a total of 219,000 new cases of lung cancer in the United States in 2009, accounting for 15% of all cancer diagnoses. An estimated 159,390 deaths from lung cancer, accounting for 28% of all cancer deaths, are expected in 2009.1

At the time of presentation, only 16% of patients are diagnosed with early stage disease with potential for cure by surgical resection. However, the five year survival for those with pathologic stage I non-small cell lung cancer is 58–73% after surgery.2 Unfortunately, the five year survival for all-comers is 15% despite therapy. This significant difference in survivorship makes the identification of earlier staged disease a desirable prospect, which in theory will allow for reduction in mortality from lung cancer. To date, all lung cancer screening tests have failed to show improvement in mortality and recommendations for screening in high risk asymptomatic patients have remained controversial. A review of the data on the effectiveness of various screening techniques available for lung cancer, and the biases that can be problematic in designing a study of lung cancer screening techniques follows.

### Concepts of Screening

The purpose of screening is to identify disease at a stage when a cure is still possible.3 Ideally, the screening test would identify asymptomatic patients allowing for early intervention that will change the course of the disease and result in decreased mortality.4 In screening trials, survival from the time of diagnosis is often reported. However, this can be misleading as this measure is prone to a number of biases, including lead-time bias, length-time bias, and overdiagnosis bias.

Lead-time bias may result in increased disease incidence, seemingly better survival, but no change in mortality, as defined by the proportion of cancer deaths among the screened population.5 For example, if a screen-detected cancer is ultimately fatal at the same timepoint that death would have occurred had it not been detected, the diagnosis is simply made earlier in the screened group without delaying the time of death.

Length-time bias allows the growth rate of the tumor to affect the probability of detecting disease with screening. Rapidly growing and more aggressive tumors produce symptoms that quickly result in a shortened window for screening. If the screening test is not repeated frequently, patients are likely to present with symptoms. For those with slow growing tumors, the reverse is true; there is a longer potential screening period during which patients are asymptomatic, resulting in a higher proportion of indolent tumors detected in the screened group; this creates an apparent improvement in survival while mortality may remain unchanged.4

An extreme form of length-time bias is overdiagnosis bias. This screening bias occurs when very indolent tumors are detected, establishing a higher incidence of disease and improvements in survival and stage distribution, but does not affect mortality.5

The inappropriate comparison of survival and stage distribution can lead to the implementation of screening practices which detect disease earlier, but are not more effective, and may lead to net harm by way of intervention.6 Randomized controlled trials are the most appropriate method for evaluating the effectiveness of a screening test because they eliminate confounding variables. Thus far, there have been no randomized controlled trials that identify a lung cancer screening strategy that reduces disease specific mortality.

### Lung Cancer Screening Trials

**Chest radiography and sputum cytology.** The first trials for lung cancer screening were conducted in the 1960s and 1970s. In 1964, a test group of 29,000 London men was screened with a chest radiograph every six months for three years, while the control group was screened with chest radiograph at the start and end of the trial. Although the test group experienced earlier cancer detection, there was no significant reduction in mortality.7
In the early 1970s, the National Cancer Institute initiated a three-center trial known as the Cooperative Early Lung Cancer Group. The goal of this trial was to evaluate the addition of sputum cytology to chest radiograph in screening for lung cancer. Two of the institutions, Memorial Sloan-Kettering Cancer Center and Johns Hopkins Medical Institutions, randomized male smokers to two groups; the test group received both annual chest radiographs and sputum cytology at four month intervals, while the control group received annual chest radiographs alone.8,9 The third institution, the Mayo Clinic, randomized male smokers to a test group that underwent sputum cytology and chest radiograph every 4 months, and compared mortality to the control group receiving annual chest radiograph alone.10 All three studies failed to show any significant improvement in mortality from lung cancer between the test and control groups. Furthermore, despite extending follow-up and additional 13 years, the Mayo lung project failed to show a reduction in mortality in the treatment arm.11

A similar trial was also conducted in Czechoslovakia in which patients were randomized to semiannual screening with chest radiograph and sputum cytology, or chest radiography at baseline and at three year intervals.12 More lung cancers were discovered at an earlier stage in those screened semiannually, a phenomenon which continues in the screening trials using low-dose CT screening. However, there was again no improvement in mortality between the two groups at three years and with extended follow-up at fifteen years.13

Light-induced fluorescence endoscopy (LIFE). A number of endobronchial treatment modalities including cryotherapy, laser therapy, and photodynamic therapy, have been developed to target small intraepithelial (or preinvasive) neoplastic lesions. Unfortunately, identifying at risk people with these lesions and localizing the endobronchial lesions themselves can be challenging. When occult lung cancer is detected by sputum cytology alone with normal radiographic findings, conventional bronchoscopy is the only way to identify the lesion. One study found it to be successful in merely 29% of cases.14

A difference in fluorescence between normal and neoplastic tissue can be used to enhance the ability of bronchoscopy to identify intraepithelial neoplasia.15-17 In a multicenter trial conducted by Lam and colleagues in 1998, the addition of LIFE bronchoscopy to conventional white light bronchoscopy improved the sensitivity of detecting at least one lesion from 37.3 to 75%, but did not improve the positive predictive value.18 While this modality may be better at localizing tracheobronchial dysplasia, it still must rely on sputum cytology to identify those harboring dysplastic or malignant lesions; a practice that has not been shown to improve overall mortality.

Chest computerized tomography. Low radiation dose computed tomography (LDCT) is faster and less expensive than standard helical CT scanning and has been shown to detect nearly three times the number of small nodules detected by chest radiograph.19 It is reasonable to conclude that the use of LDCT would allow for earlier detection, improved stage distribution and survival of those screened; however, current data available from cohort studies do not provide information on mortality benefit.

In the late 1990s and early 2000, a number of single arm studies were performed in Japan with the aim of evaluating the usefulness of annual screening with LDCT for lung cancer detection.20-23 A trial conducted in Matsumoto, Japan utilized a mobile CT scanner unit to reach the general population, evaluating 5,483 asymptomatic patients aged 40–79 years with LDCT at one year intervals for three years. Sixty surgically confirmed lung cancers were detected with 88% (56/60) found to be stage IA.24 The Anti-Lung Cancer Association Project evaluated 1,611 patients with LDCT at six month intervals; a total of 7,891 examinations were performed and 22 cases of lung cancer detected with 82% found to be stage 1A disease.25 LDCT was also evaluated in a group of patients belonging to the Hitachi Employee Health insurance group as part of annual health examinations. A total of 7,956 patients were evaluated and 41 lesions were confirmed as cancer, with 85% (35/41) found to be stage 1.20

The Early Lung Cancer Action Project (ELCAP) conducted in the United States during this same time period also sought to demonstrate the superiority of LDCT versus chest radiograph in lung cancer screening. A non-comparative design was implemented that screened 1,000 asymptomatic high-risk patients. Non-calcified lung nodules were detected in 23% (233) of patients using LDCT and 7% (68) by chest radiograph. Malignant nodules were found in 2.7% (27) by LDCT and 0.7% (7) using chest radiograph. Twenty seven lung cancers were detected and 26 (96%) were surgically resected, 85% (23/27) of which were stage 1. Importantly, 83% (19/23) were not identified on chest radiograph. The estimated five year survival of these CT-identified malignancies was 60–80%.19

An additional prospective cohort study performed at the Mayo Clinic enrolled 1,520 high risk patients to determine if LDCT would cause a downward shift in staging of lung cancer. One year after baseline screening, 2,244 non-calcified nodules were identified in 1,000 patients (66% of participants). Twenty-five cases (1.6%) of lung cancer were identified and 57% were stage 1A at diagnosis.24

All of the above mentioned trials demonstrated the ability of LDCT to detect lung cancer at an earlier stage than was possible with chest radiograph and sputum cytology. However, with the increased sensitivity of LDCT comes a high rate of detection of benign nodules. This has the potential to create problems with overdiagnosis, patient anxiety, unnecessary surgical interventions, and an increase in morbidity without a resultant decrease in mortality. In order to address these concerns, a group in Spain designed a study to test a protocol that added F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) to LDCT screening.25 The study demonstrated a sensitivity and negative predictive value of 100% for the screening algorithm, suggesting that the addition of FDG-PET minimizes unnecessary biopsies in benign lesions. This notion is further supported by a meta analysis that demonstrated one centimeter or larger pulmonary nodules positive on FDG-PET scan had a high sensitivity (96.8%) and intermediate specificity (77.8%) for malignancy.26

Further efforts were carried out to determine the outcome of patients with clinical stage I cancer detected using annual LDCT.
screening. The International Early Lung Cancer Action Program (I-ELCAP), a large multi-center, international, non-randomized trial, screened 31,567 individuals using LDCT.27 Lung cancer was diagnosed in 484 patients (1.5%), with 412 (85%) found to have stage 1 disease. Estimated ten-year survival was 88% for stage 1 cancer and 92% for those who underwent surgical resection within one month of diagnosis. This study reinforced earlier observations that LDCT is effective in detecting lung cancer at an early stage. It has been criticized, however, because although the survival estimates are reported to ten years, the median follow up was only 40 months with less than 20% of subjects observed for more than 5 years.28 In addition, the outcomes of the other screened subjects were not reported; without this follow up the lung cancer mortality rate for the entire population cannot be estimated.29

In stark contrast to the findings of the I-ELCAP, a prediction model was developed which compared the observed findings of three single-arm screening trials in the U.S and Italy with the predicted cancer outcomes in an unscreened population of smokers. The endpoints included the number of new lung cancer cases, resections, advance lung cancer cases, and deaths from lung cancer. Screening of 3,264 high risk participants over a median of 3.9 years demonstrated that while LDCT increased the rate of lung cancer detected and subsequently resected, there did not appear to be a reduction in the number of advanced cases diagnosed or in the overall mortality from lung cancer predicted in the control group.30 Although compelling, a prediction model is not a substitute for a randomized controlled trial and should be interpreted with caution.

A recent study published the results of a randomized controlled trial conducted in Italy in which 2,472 subjects were randomized to yearly LDCT or to initial chest radiograph and yearly physical exam for a total of 4 years. The subjects had a median follow-up of 33 months, with 60 lung cancers (2.4%) detected in the LDCT group versus 34 (0.6%) in the control group. While more stage I disease was found in the screened group, resection rates were similar in both groups and the number of advanced stage lung cancer was the same. Furthermore, there was no mortality difference between the groups.31 While the authors of this study admit that it was not powered adequately, the results seem to support the previously mentioned prediction model and suggest that the mortality benefit of screening with LDCT may be less than anticipated.

**Serum biomarkers.** Efforts are ongoing to identify serum biomarkers that are elevated in those with lung cancer, and may allow for early detection, risk stratification, prognostication, treatment selection, and monitoring. While progress is being made toward identification and validation of serum biomarkers for lung cancer,32,33 there are still additional studies required before they can be used clinically.

**Ongoing trials.** Control groups and an unbiased outcome measure are needed to make a persuasive case for screening for lung cancer; further, the potential harms of screening must be outweighed by a reduction in lung cancer mortality.34 The most effective way to achieve this is through a randomized controlled trial. To this end, the National Cancer Institute has completed enrollment in the National Lung Screening Trial (NSLT) in which 50,000 former or current smokers were randomized to undergo screening with annual chest radiograph or helical CT scan for a total of three years with an eight year follow up scheduled to end in 2010.35 The trial is powered to detect a 20% reduction in the mortality from lung cancer by screening with helical CT scanning.

In the Netherlands and Denmark, the NELSON trial is underway which is 80% powered to show a reduction in lung cancer mortality of 25% over ten years. Over 20,000 current and former smokers have been enrolled and randomized to screening with CT scanning versus no screening in order to investigate mortality reduction.36 The results of these two studies should provide more conclusive data into the potential benefit of lung cancer screening with minimal bias.

**Current Guidelines for Lung Cancer Screening**

The Society of Thoracic Radiology recommended against mass screening for lung cancer with CT scan in 2001.37 In 2007, the American College of Chest Physicians advised against the use of chest radiographs or sputum cytology in screening for lung cancer outside of clinical trials. In addition, serial LCDTs were not recommended for screening until the results of the NSLT are finalized.38 The United States Preventative Services Task Force concluded that the evidence for screening asymptomatic patients with sputum cytology, chest radiograph, LDCT, or any combination is insufficient and therefore not recommended.39 Finally, the American Cancer Society recommends against lung cancer screening in high risk asymptomatic patients. However, given the increased use of spiral CT and radiographs in smokers it has been recommended that informed decisions be made by those at risk, and that testing be conducted in centers with multidisciplinary specialty groups that allow for diagnosis and follow-up.40

**Key Points for Lung Cancer Screening**

- Screening high risk patients with sputum cytology, chest radiograph, serial CT thorax, LIFE bronchoscopy or any combination of these has not been shown to improve disease specific mortality.
- Currently there are no screening techniques recommended for the detection of lung cancer.
- The National Lung Screening Trial, a well powered, randomized controlled trial, is scheduled for completion in 2010 and will better address mortality reduction from screening with helical CT scanning.

**Conclusion**

Lung cancer is responsible for more cancer deaths worldwide than any other cancer and most often presents at a late stage. This creates a need for a screening strategy that detects lung cancer at an earlier stage and reduces the mortality from this disease. Although the non-randomized cohort studies demonstrate that
screening high risk individuals with CT scanning can detect lung cancer at an earlier stage, there is unfortunately no evidence to support an overall reduction in disease specific mortality. Large scale randomized studies are currently underway to investigate the effect of screening on all-cause and lung cancer specific mortality. Until these results are available, there will be no published guidelines to support the screening of asymptomatic patients outside of well designed research trials.

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