

REVIEW ARTICLE

LUNG CANCER SCREENING

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ABSTRACT

Lung cancer has been the leading cause of cancer related death in developed countries for many years; however, it has more recently become a growing health problem on a global level. Within Pakistan, the first report of the Karachi Cancer Registry in 2000 found lung cancer to be the most common cancer diagnosis among men¹. To reduce the burden of this disease, efforts have been ongoing for years to determine if lung cancer screening can identify disease at an early stage when curative therapy is most effective. The results of the National Lung Screening Trial, (NLST) proved that lung cancer screening by computed tomography (CT) can reduce the mortality of lung cancer in a high-risk population². These results have lead to a renewed interest in lung cancer screening and efforts to resolve questions regarding the most effective way to implement CT screening.

INTRODUCTION

Lung cancer has been the leading cause of cancer related death in developed countries for many years; however, it has more recently become a growing health problem on a global level as the prevalence of tobacco smoking in developing countries has steadily increased. The most recent global statistics, provided by the International Agency for Research on Cancer, report an incidence of over 1.6 million cases of lung cancer. Combined, over 1.3 million men and women died of lung cancer³ in 2008 – the leading cause of cancer death. The number of deaths attributed to lung cancer is expected to continue to rise through 2030 due to smoking trends in developing countries over the past several decades⁴. The most recent report from World Health Organization estimates the prevalence of smoking in Pakistan is 36% among men and 6% among women⁵. The most effective way to reduce the morbidity and mortality from lung cancer is to reduce the amount of tobacco smoking. However even those who have successfully quit smoking continue to have significant risk of lung cancer for many years. An additional approach is to focus efforts on identifying the disease at an early stage to reduce its lethal impact. In developed countries only 15% of lung cancer is diagnoses as stage I disease, when a chance of curable resection is greatest². These factors have lead to consideration of lung cancer screening to improve outcomes through early detection. Originally studies focused on chest radiography, (CXR) with or without sputum analysis. More recently studies have integrated computed tomography, (CT) scans to screen for suspicious nodules. In 2011 a randomized study of reduced-dose CT scans for lung cancer screening in a high-risk population demonstrated an improvement in lung cancer mortality making lung cancer screening tenable for the first time.

Lung Cancer Screening Using Chest Radiograph

In the 1970s several large randomized studies were started in the United States to evaluate the value of CXR and cytology of sputum samples to improve lung cancer mortality in high-risk subjects. These studies enrolled men older than 45 years with significant smoking history and were not suspected of having lung cancer at enrollment. The Johns Hopkins Lung Project and Memorial Sloan Kettering Lung Project had control groups with annual CXRs and investigational groups with added annual cytology examination of sputum samples⁶. The Mayo Lung Project randomized subjects to a control arm of annual CXR with sputum analysis vs. the same studies preformed every four months⁷.

The studies screened patients for 5-8 years and at least 2 additional years of follow-up once screening was complete. These studies routinely demonstrated an increase in lung cancer detected as Stage I disease with increased rates of surgical resection. However all three studies failed to demonstrate an improvement in lung cancer mortality. For example the long-term follow-up of the Mayo Lung Project revealed a lung cancer mortality rate of 4.4 per 1000 person-years vs. 3.9 per 1000 person-years in the control group.

Another large randomized trial of lung cancer screening using CXR, The Prostate, Lung, Colorectal and Ovarian (PLCO) Trial, recently reported on lung cancer mortality outcomes in a high-risk group⁸. Specifically those age 55-74 with 30 pack-years of smoking, if former smokers have quit within 15 years of enrollment. This study examined annual CXR vs. usual care. The CXRs were performed at baseline then annually for a total of 4 exams, the patients were then followed for an additional 6 years. Tumors that were identified during screening studies compared to the

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control arm or after screening had ended, were more commonly stage I disease and adenocarcinoma subtype. Unfortunately this did not improve outcomes. Lung cancer mortality (in 10,000 person years) was 36.1 in the intervention arm vs. 38.3 in the control arm for a RR of 0.94 (CI 0.81-1.10) with no significant improvement seen. The authors point out the dilution effect of the additional lung tumors diagnosed after the screening was complete may have diminished the ability to demonstrate a lung cancer mortality improvement with annual CXR.

Overcoming Bias in Cancer Screening

The original lung cancer screening studies using CXR illustrate the importance of concentrating on the correct endpoints in screening studies. When survival is measured in cancer screening trials, whether randomized or non-randomized, several biases inherent in cancer screening may obscure the outcomes. These include lead-time bias, length-time bias and overdiagnosis (an extreme of length-time bias). Lead-time bias describes the ability of screening to detect cancer earlier than in the non-screening group and improve survival from time of diagnosis without a change in the overall mortality of the patient. In a similar manner, length-time bias refers to the tendency of screening to preferentially detect cases that have a long pre-clinical duration leading to survival advantages that occur when comparing screen-detected to symptom detected cases. Slowly growing tumors have a longer time frame during which they can be identified with a longer time between onset of disease and symptoms. Thus, screening studies will be biased to identify slow growing tumors, an important reason for the high increase in the detection of lung cancers by CT screening⁹⁻¹¹. Overdiagnosis is an extreme of length-time bias where indolent cancers are diagnosed upon screening that may never affect the overall health of the patient. At this time it is not clear if screening studies will lead to overdiagnosis of lung cancer, but increases in the number of lung cancers diagnosed without an improvement in overall mortality were seen in the Mayo Lung Trial leading to worries of overdiagnosis in the screening arm⁷. The primary endpoint of improvement in disease specific mortality through a randomized screening study is important to reduce the effect of lead-time and length-time bias inherent to cancer screening.

Lung Cancer Screening by CT Scan

The initial lung cancer screening studies using CT scans were non-randomized trials. Two of the original trials were performed in Japan with CT scans combined with CXR and sputum analysis.^{9,10} These studies included subjects with minimal smoking history, including never-smokers. The incidence of lung cancer detected in these population studies was low (0.48% and 0.3%) due to the low-risk of the general population studied. However these studies demonstrated that spiral CT scans were feasible as a screening modality and could detect early stage disease that was not seen on CXR. Investigators at the Mayo Clinic performed a large CT screening trial and compared the lung cancer mortality results with those from the Mayo Lung Project that used CXR and sputum for screening, as described above. 1,520 subjects were enrolled with at least 20 pack-years of smoking. These subjects underwent a baseline CT scan with four additional annual scans. There were a total of 68 lung cancers diagnosed; however the lung cancer mortality rate was not significantly less than the previous Mayo Lung Project study, (2.8 vs. 2.0 per 1000 person years $p=0.43$). Over the course of the CT screening trial, 74% of subjects had a non-calcified pulmonary nodule identified, leading to a high false-positive rates and the need for additional follow-up scans. Finally, the Early Lung Cancer Action Program (ELCAP), demonstrated that CT screening scans lead to an increase in the diagnosis of Stage I disease. In ELCAP 85% of those who received a diagnosis of lung cancer had clinical stage I disease¹³ and in this subgroup a 10-years survival rate of 88%. It was also shown that prevalence tumors, those identified on baseline scans, were predominately adenocarcinomas, which have a greater potential for indolent disease. Although the survival rate for those patients with lung cancer detected on CT screening was encouraging, without a control group there is limited ability to account for the effect of lead-time and length-time bias.

Randomized Studies of CT Screening

Dante, an Italian study to determine the effect of screening with low-dose spiral computed tomography (LDCT), was performed with approximately 2400 European men ages 60-75 years with 20 or more pack-years of smoking exposure¹⁴. The subjects were randomized to LDCT annually for 5 scans vs. observation with clinical review by phone. Initial results were published in 2009 after a median follow-up of 33.7 months. During this time 60 patients were diagnosed with lung cancer in the LDCT arm and 34 within the control arm. The lung cancer detection rate was 4.7% in the LDCT arm vs. 2.84% in the control arm. In the LDCT arm 60% underwent complete resection vs. 50% in the control arm. Although the number of lung cancer cases diagnosed at Stage I was higher in the LDCT arm, the number of Stage IIIB-IV cases were identical in both arms. After a median of 3 years of follow-up, 20/60 patients (33%) died of lung cancer in the LDCT arm and 20/34 patients (59%) died of lung cancer in the control arm. Although CT screening found more lung cancer at an earlier stage, the number of patients who died of lung cancer in each arm was identical. The results of this study are limited by a small number of subjects with a short follow-up. As discussed below, the improvement in lung cancer mortality within the NLST was not seen until a follow-up period of over six years. It will be of interest to see if the Dante results also change with longer follow-up.

National Lung Screening Trial (NLST)

The NLST is the first large, randomized study of low-dose chest CT vs. chest radiograph (CXR) in lung cancer screening with a long follow-up interval². The NLST enrolled 53,454 subjects at high-risk for lung cancer. High-risk subjects were defined as those age 55 to 74 years who had at least a 30 pack-year smoking history and, if former smokers, had quit within 15 years of enrollment. Subjects were randomized to reduced-dose CT scans of the chest or CXR upon enrollment then annually for two additional screenings. Patients were then followed for a median of 6.5 years for the primary endpoint of lung cancer mortality.

The compliance to screening between both arms was excellent with 95% in the CT arm and 93% in the CXR arm completing all three rounds of imaging. A positive screening exam was defined as any non-calcified nodule at least 4mm in size or other suspicious findings (adenopathy, pleural fluid etc.). The number of positive screening studies was higher in the CT group (24.2%) than the CXR group (6.9%). Of these a total of 96.4% were false positive results in the CT group vs. 94.5% in the CXR group. 1060 lung cancers were diagnosed in the CT group vs. 941 in the CXR group with a ratio of 1.13 (95% CI 1.03-1.23). Lung cancers diagnosed following a screening CT scan were more likely to be stage I or II and more likely to be adenocarcinoma or bronchioloalveolar carcinoma than those diagnosed by CXR or in the years after screening was complete. Lung cancer mortality in the CT group vs. CXR group was 247 vs. 309 per 100,000 person-years. The relative reduction in lung cancer mortality was 20% (95% CI, 6.8% to 26.7% $P=0.004$). Although previous lung cancer screening studies using CT scans have demonstrated the ability to detect lung cancer at an early stage, lack of randomization to a control arm prevented analysis of the effect on mortality. By randomizing a large number of subjects to a control arm, NLST was able to assess the effect of CT screening on lung cancer mortality for the first time. These results prove that lung cancer screening with low-dose CT scans can impact the number of patients dying from lung cancer, and have lead to a recommendation for lung cancer screening for the first time. Clearly there are many challenges to institute lung cancer screening by LDCT, but NLST provides the needed data to start this discussion.

The large number of false positive screening tests, predominately due to small pulmonary nodules, leads to concerns of excess cost and adverse events from the subsequent diagnostic studies. The appropriate follow-up of indeterminate, pulmonary nodules identified on non-screening CT scans was analyzed in 2005 and lead to the publication of the Fleischner Society Guidelines. These guidelines were based on data from previous CT scan screening studies, such as ELCAP. This analysis was specific to small (under 10 mm) non-calcified solid pulmonary nodules and did not address non-solid or partly solid nodules. Recommendations were based on two patient groups due to smoking history and other known risk factors, (Table I). Guidelines for the management of pulmonary nodules detected on screening CT scans were recently proposed by the National Comprehensive Cancer Network (NCCN). These guidelines are similar to the original Fleischner Guidelines but also accounted for non-solid or partly solid nodules (Table II).

Table I. Fleischner Society Guidelines for Management of Pulmonary Nodules

Nodule size	Low-Risk	High-Risk
< 4 mm	No follow-up	Follow-up CT at 12 mos. If unchanged, no further follow-up
>4-6 mm	Follow-up CT at 12 mos. If unchanged, no further follow-up	Follow-up CT at 6-12mo Then at 18-24 mo. if unchanged
>6-8 mm	Follow up CT at 6-12 mo. Then at 18-24 mo. if unchanged	Follow-up CT at 3-6 mos. Then at 9 -12 and 24 mo. if unchanged
> 8 mm	Follow-up CT at 3, 9 and 24 mo., CECT, PET and/or biopsy	Same as for low-risk

CT – computed tomography, CECT – contrast-enhanced computed tomography, PET- positron-emission tomography

Table II. NCCN Guidelines for Management of Pulmonary Nodules Found on Screening LDCT*

Size Solid or Part Solid		Nodule Size Non-Solid	
<4 mm	None	< 5 mm	LDCT in 12 mos. If stable, annual screening If increased size or more solid, LDCT in 3-6 mo. or excision
> 4-8 mm	LDCT in 6 mos. If unchanged, LDCT 12 mo. If increased, excision		
> 6-8 mm	LDCT in 3 mos. If unchanged, LDCT 6 mo. If increased, excision	5-10 mm	LDCT in 6 mos. If stable, annual screening If increased, excision
>8 mm	PET/CT If low suspicion LDCT 3 mo. If high suspicion, biopsy or excision	> 10 mm	LDCT in 3 mos. If stable, LDCT in 3-6 mo. If increased, excision
Endobronchial nodule	LDCT in 1 mo. If not resolved, bronchoscopy		

*In addition to annual LDCT until age 74. LDCT – low-dose computed tomography, PET/CT- positron-emission tomography/computed tomography

One way to reduce the false positive rate in lung cancer screening is the development and use of additional biomarkers of disease. These may be based on analysis of molecular markers, (in plasma, sputum, exhaled gas, etc.) or biomarkers based on imaging. The Dutch-Belgian lung cancer screening trial (NELSON) was designed to analyze tumor volume doubling time (VDT) as a biomarker to improve the ability to distinguish benign from malignant pulmonary nodules found on CT screening. Although the final ten-year mortality data is not available for the randomized study, data has been published regarding the use of VDT for indeterminate nodules on the 7557 subjects who underwent screening CT scans with 2 years of follow-up. In this study, investigators used change in semi-automated volume measurements of pulmonary nodules found on CT screening as a biomarker of malignancy. Subjects who had indeterminate nodules measuring 50-500mm³ on baseline CT scan had a repeat CT with volumetric measurements performed after a three-month interval. Pulmonary nodules that had a VDT less than 400 days were considered positive and invasive biopsy was recommended. Subjects in the screening arm without a positive finding underwent a second round of CT screening one year after the baseline scan. Using VDT the investigators found the need for follow-up evaluation in those with indeterminate nodules was decreased without reducing the overall sensitivity of the CT screening. The process used to calculate VDT is labor intensive for the radiologist requiring review of the segmentation of each nodule to ensure only tumor was included, not airway, or blood vessel. As segmentation algorithms improve, the hands-on time of the radiologist should decrease. Other biomarkers, including serum autoantibodies, microRNAs, etc. are in development and will hopefully become helpful in the future to further reduce false positive screening tests.

The development of biomarkers, whether imaging based or molecular markers, may also provide insight into the behavior of pulmonary nodules detected upon CT screening to reduce over diagnosis. The ability to accurately predict the indolent nature of some early-stage lung cancers may prevent the unnecessary cost and invasive procedures used to treat a lesion that may never impact the health of the individual if left unidentified. Currently it is not clear if LDCT screening will lead to over diagnosis particularly as NLST clearly demonstrated a benefit in lung cancer mortality with screening. Longer follow-up of the randomized CT screening trials will provide information regarding outcomes of patients with indolent appearing disease, such as non-solid nodules.

The appropriate duration of lung cancer screening with LDCT is not known. There must be balance between continued improvement in lung cancer mortality and the risk of accumulated radiation exposure. As mentioned above, upon analysis of the CXR screening arm of the PLCO study, the authors speculate that a 'dilutional effect' of lung cancer diagnosed following the screening phase of the study may have led to a non-significant change in mortality in the intervention group.⁸ The analysis of NLST included the enrollment period from 2002 – 2004 and follow-up of events until December 2009. Within the NLST screening arm, the baseline scan led to the diagnosis

of 270 lung cancers, the first annual scan 168 and final screening scan 211². At the end of the third round of CT scans, screening was discontinued per protocol without any indication that the risk of a lung cancer diagnosis was diminished among these subjects. The authors also report on lung cancer diagnosis made without a screening test, predominately those diagnosed in the follow-up years after the screening was completed. Within the screening arm, 367 lung cancer diagnoses were made without a screening test, suggesting that ongoing rounds of CT screening may have identified additional lung cancer at an early stage. Because there is no data to determine the optimal duration of CT screening for lung cancer, the National Comprehensive Cancer Network has recommended ongoing, annual screening from ages 55 thru 74¹⁶. Although LDCT scans have reduced radiation dosing, (1.5 mSv) from conventional CT scans (7 mSv), the risk of repeated scans is not well delineated and must be taken into consideration, particularly in a patient population already at high-risk of lung cancer. Radiation-induced cancer risk in individuals under 50 years old is estimated to be higher than the mortality reduction from lung cancer screening¹⁸. At this time there is no data to support LDCT for lung cancer screening in those less than 50 years old.

Summary

The results of NLST proved that reduced-dose CT screening for lung cancer in high-risk population reduces lung cancer mortality. This finding represents the conclusion of many years of investigation into lung cancer screening. However it leaves many questions unanswered, including the best interval, duration, and follow-up of screening LDCT scans. Ongoing analysis of the randomized trials of CT screening, as well as novel imaging techniques and molecular biomarkers, will aid in answering these questions and reducing the amount of futile scans and invasive procedures brought on by lung cancer screening.

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