Several uncertainties need to be addressed before lung cancer screening can be included in standardized clinical care.

Lung Cancer Screening: Advantages, Controversies, and Applications

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Background: Lung cancer is the leading cause of cancer death in the United States. Results from the National Lung Screening Trial (NLST) have shown that low-dose computed tomography (CT) is capable of detecting lung neoplasms in individuals at high risk. However, whether it is advantageous to perform lung cancer screening on these patients is a significant concern, as are the potential adverse outcomes from screening.

Methods: A review of several randomized clinical trials, focusing on the NLST, was undertaken. Adverse outcomes and costs related to lung cancer screening were also examined.

Results: Lung cancer screening using low-dose CT in high-risk individuals reduced lung cancer deaths by more than 20% when compared with those screened by chest radiography. False-positive results were seen in both groups, but the number of adverse events from the screening test and subsequent diagnostic procedures was low.

Conclusions: Lung cancer screening is controversial, but the NLST has demonstrated that such testing may reduce lung cancer deaths in high-risk individuals when performed with low-dose CT rather than chest radiography. Guidelines should be established to not only help identify an appropriate screening population, but also develop standards for radiological testing.

Introduction

Lung cancer is the leading cause of cancer death in the United States.1 The 5-year survival rate after diagnosis is 15.6%,2 which is lower than the survival rate for breast, colon, or prostate cancer.1 Advances in treatment, including surgical, medical, and radiotherapeutic interventions, have provided little improvement in the long-term survival rate of patients diagnosed with primary lung malignancies.1

The link between smoking and lung cancer has been known for decades; however, it was not until the mid-1960s when the US Surgeon General first reported that tobacco smoke was a direct cause of lung cancer.3 Although the rate of smoking has declined in both sexes, millions of individuals in the United States continue to smoke and thus are at a higher risk for this malignancy.2 A high percentage of lung cancer has been seen in individuals who are only casual smokers or those who are former smokers because the risk of lung cancer does not decline for many years following smoking cessation.1

Dorothy Fox, Solitude. Acrylic on canvas, 36” x 36”.

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result, concern has arisen with regard to decreasing lung cancer mortality rates.

For several decades, strategies to reduce lung cancer–related deaths through screening have been evaluated, focusing on chest radiography and sputum cytology. Randomized controlled trials involving chest radiography and sputum cytology have detected early-stage lung cancers, many of which were found to be resectable. However, early-stage cancer detection has not been accompanied by a reduction in mortality, thus implying that screening with these modalities is not beneficial. Approximately 10 years ago, observational studies found that computed tomography (CT) scans may be more efficacious in screening than earlier modalities. In response, the National Cancer Institute initiated the National Lung Screening Trial (NLST) in 2002, which was a randomized clinical trial that screened high-risk individuals with CT scan or chest radiography. The results showed a 20% reduction in mortality rates for those screened using CT.

Although screening with chest CT has been shown to reduce mortality in lung cancer, several other issues should be considered prior to initiating widespread screening as the standard of care: How effective is CT screening in actual practice when compared with a controlled scenario (eg, the NLST)? How cost effective is cancer screening? How will these costs be covered? What adverse events may result from over-diagnosis and further diagnostic testing? These are all aspects that should be considered when developing a framework and guidelines to make lung cancer screening a standardized clinical practice.

**Disease Presentation**

Lung cancer is the most common cause of cancer-related death worldwide. The American Cancer Society predicts that in 2013, approximately 230,000 new cases of lung cancer were diagnosed, along with nearly 160,000 lung cancer–associated deaths in the United States. For some time, lung cancer has been the most common cause of cancer-related death in men. Prior to the turn of the 21st century, it became the most common cause of cancer death in women, with nearly half of all lung cancer deaths occurring in women.

Approximately 95% of lung cancers can be categorized into small-cell lung cancer (SCLC) or non–small-cell lung cancer (NSCLC), a distinction necessary for management, prognosis, and screening efficacy. SCLC is more centrally located, commonly arising in the larger airways such as primary and secondary bronchi, and is an aggressive tumor characterized by rapid doubling time and early metastasis, making it more challenging to detect during the early stages. By contrast, NSCLC is a disease often found in peripheral lung tissue, making it more amenable to detection by screening. Cure rates for early-stage NSCLC following resection and 5-year survival rates are more than 70%, making screening an important practice for possible early detection and decreased mortality rates.

**Screening Population**

Although it would be ideal if all individuals could be screened, it is neither realistic nor advantageous to do so. Therefore, which groups should be screened for lung cancer? While it appears logical to consider screening those who are at the highest risk of developing this class of malignancy, other factors must be considered. For instance, how much has a patient smoked and for how long? Are older persons at a higher risk of developing lung cancer than their younger counterparts, and how should we account for other coexisting lung conditions such as chronic obstructive pulmonary disease or asthma? The purpose of a screening test is to identify the presence of a malignancy in patients before they begin to develop symptoms; therefore, interventions are likely to have a better chance of improving survival rates.

Over the last 15 years, many trials have evaluated various groups of people to determine who would derive benefit, if any, from lung cancer screening. The NLST is the only trial that has shown a decrease in mortality resulting from lung cancer screening.

**National Lung Screening Trial**

In August 2011, results from the NLST were released by the National Cancer Institute. The NLST was a randomized control trial started in 2002 that screened at-risk smokers using either low-dose CT or standard chest radiography. Most of the NLST sites were designated National Cancer Institute centers, and more than 80% were large, multidisciplinary academic centers with more than 400 beds. A total of 5,454 participants enrolled in the study. Eligible participants were identified as current or former smokers who had no personal history of malignancy, those who had smoked the equivalent of one pack of cigarettes a day for a minimum of 30 years, and former smokers who had quit less than 15 years prior to participating in the study and were between the ages of 55 and 75 years. Participants were randomized to receive three annual screening examinations by either low-dose CT or chest radiography. They were then followed for an additional 5 years after the screening examinations were completed. In individuals diagnosed with lung cancer, no subsequent screening tests were performed. In both groups, the screening test was positive if it showed a noncalcified pulmonary nodule 4 mm or larger in diameter or if there were other findings suspicious for cancer. When comparing the two groups after the completion of the three annual screenings, 24% of participants screened with low-dose CT had positive screening results compared with 6.9% of in-
individuals who received chest radiography. Of the group found to be positive, more than 75% of the participants underwent further diagnostic evaluation, either with additional imaging or with invasive and surgical procedures, and more than 90% of the positive results were false-positives in each of the screening groups. Of the group screened with low-dose CT, 1,060 participants had lung cancer, 44 of whom had a negative screening test. In the group screened with chest radiography, 941 individuals had lung cancer, 137 of whom had negative screening tests. In each group, the percentage of stage IA and stage IB lung cancers was highest among cancers diagnosed following a positive screening test. Despite the large number of participants who underwent further diagnostic testing, the authors noted that the additional diagnostic testing resulted in only a small number of adverse events, much lower than expected.

Overall, when comparing the two groups, the detection of lung cancer was 13% greater in the group screened with low-dose CT when compared with those screened with chest radiography. Both screening modalities detected malignancies in earlier stages (IA and IB) but more so in those screened using low-dose CT. Of the malignancies found, adenocarcinoma and squamous cell lung cancers comprised the majority, possibly due the peripheral location of the lesions.

Mortality rates were also analyzed. A total of 356 lung cancer deaths occurred in the group screened using low-dose CT vs 443 deaths in the group screened using chest radiography. The number needed to screen with low-dose CT to prevent one death from lung cancer was 320. In August 2011, the published results of the NLST showed a 20% relative reduction in mortality rates from lung cancer in individuals screened using low-dose CT.

Controversies Regarding Lung Cancer Screening
Results from the NLST demonstrated that low-dose CT screening for lung cancer provided significant reduction in mortality rates among individuals at high risk, but uncertainty still exists regarding the harms of screening and the ability to reproduce these results in the general population. Potential harms to consider include adverse events resulting from further invasive diagnostic testing, costs incurred by screening and additional diagnostic testing, radiation risks to patients from low-dose CT used for screening, the effects of overdiagnosis, and the negative effects that screening may have on smoking cessation.

Complications of Subsequent Diagnostic Procedures
Low-dose CT identifies both benign and cancerous noncalcified nodules, with the former being considered a false-positive result. The NLST researchers reported that more than 90% of the nodules identified in the study were benign, most of which were due to the detection of benign intrapulmonary lymph nodes or noncalcified granulomas. One concern is that, when a nodule is initially detected, further diagnostic testing must be performed to further characterize the nodule. This diagnostic testing includes additional imaging and invasive procedures, either through transthoracic needle biopsy, bronchoscopic fine-needle aspiration, or, less likely, a surgical approach. In the NLST, 1.2% of patients who had a lung nodule but not cancer underwent an invasive procedure such as a needle biopsy or bronchoscopy. Moreover, 0.7% of participants without cancer underwent a thoracoscopy, mediastinoscopy, or thoracotomy. Procedure risks for transbronchial biopsy are reportedly 1% for hemorrhage, 15% for pneumothorax, and 6.6% for pneumothorax requiring a chest tube. Some researchers have expressed concern, specifically for those with moderate to severe chronic obstructive pulmonary disease. These patients are more likely to have surgical complications in the potential screening population. With additional testing comes the risk of additional complications. Per the NLST, complications and deaths arising from further imaging and invasive testing were rare but did occur.

In patients with a benign lung nodule but no malignancy, results from the NLST indicated that a major complication occurred in almost 5 individuals per every 10,000 persons screened. In that same population, death occurred in about 4 individuals per every 10,000 persons screened. Both rates were higher than those screened by chest radiography.

Cost Effectiveness of Screening
Despite the NLST results revealing a 20% reduction on lung cancer mortality, concern still exists regarding the financial demands that lung cancer screening may place on an already strained health care system. The cost of low-dose CT can vary among facilities but currently is around $300 a study. Therefore, it is important to compare CT screening for lung cancer with other more economical modalities, including prevention through smoking cessation programs and basic health maintenance. Another important factor to consider is whether the cancer being detected is in an advanced stage vs an early stage. Detection at an advanced stage will likely require more aggressive treatments and will also impact the quality of life after initial diagnosis, thus influencing the cost effectiveness of screening.

Medical intervention may be evaluated in the form of quality and quantity of life generated by that particular intervention, defined as a quality-adjusted life year (QALY). Cost per QALY is defined as a cost-effectiveness ratio for a particular medical interven-
nodule size, and low-dose CT was compared against chest radiography in high-risk patients. A subsequent analysis of the DANTE trial compares low-dose CT with sputum and chest radiography (2,500 participants). The NELSON trial was specified to maximize diagnostic yield with early results suggesting no difference in mortality rates. However, the study is small and underpowered compared with the NLST.

**Overdiagnosis and False-Positive Results**

Results from the NLST also showed a high number of false-positive results with low-dose CT screening. Overall, positive results were three times higher in those screened with low-dose CT; however, the majority of these results were false-positive due to the presence of benign pulmonary nodules or noncalcified granulomas. Overdiagnosis was also seen in individuals with true-positive results. Many of these positive results would not have been detected if these individuals not been screened with low-dose CT. Some of these positive results were eventually found to be malignant but would not have developed into an advanced illness and would not have been detected or warranted treatment. As a result, overdiagnosis was seen with low-dose CT screening that subjected individuals to invasive procedures and aggressive treatments that they otherwise would not have undergone.

**Lung Cancer Screening Before and After NLST**

Several trials have studied chest radiography for lung cancer screening. The Mayo Lung Project was one of the first trials to evaluate screening with chest radiography and sputum vs usual care and was conducted on men who smoked. The trial had an incidence of lung cancer of 8.3 per 1,000 patients. The study showed a higher detection of early lung cancers in the screening cohort, but ultimately no reduction was seen in mortality rates. The Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) trial used chest radiography at baseline and then annually for 3 years in non–high-risk general population patients vs community patients. A total of 67,038 people were screened: 8.9% had positive results, and 126 were diagnosed with cancer (2.1%). No significant difference was seen in the incidence between the control group and those screened. A subsequent analysis of the PLCO trial by the NLST demonstrated no reduction in mortality when comparing chest radiography screening vs community/usual care. The results of the PLCO trial detection were similar to the previous Mayo Lung Project.

Preliminary results on mortality rates from the ongoing Dutch Belgium Randomized Lung Cancer Screening Trial were reviewed. The trial enrolled 4,000 patients and screened current and former smokers. Follow-up screening was determined based on nodule size, and low-dose CT was compared against no screening/usual care. Thus far, the results reveal an early detection rate of early-stage cancers, but no mortality benefit has been seen. Such results are contrary to the low-dose CT trial. However, this study was underpowered compared with the NLST.

Three randomized trials — the DANTE trial, the Dutch Belgium Randomized Lung Cancer Screening Trial (NELSON), and ITALUNG — are being conducted on either current or former smokers. The DANTE trial compares low-dose CT with sputum and chest radiography in high-risk patients. Preliminary data appear to show higher detection rates with the low-dose CT group than with sputum and chest radiography, with early results suggesting no differences in mortality rates. However, the study is small (2,500 participants). The NELSON trial was specifi-
cally designed to find a 25% reduction in mortality rates with low-dose CT screening. Unlike the NLST or the DANTE trial, the NELSON trial is comparing low-dose CT screening with no screening. Researchers enrolled 7,500 participants to determine the impact of CT screening on smoking cessation and cost. While some preliminary data indicate an incidence of 1.2% in the screening group, no information is available yet on mortality rates.10 The ITALUNG trial is also comparing low-dose CT among patients with screening and those without screening, and preliminary results revealed that about 1.5% of patients received a lung cancer diagnosis after 4 years of screening,21,23 which was similar to the NELSON study. This study was also small (about 4,000 participants), and mortality data are not yet available.

Application of Screening
Although the NLST results did show a decrease in lung cancer deaths with screening with low-dose CT,5 one concern is whether these results can be replicated in usual practice. The participants in the NLST were selected based on age, a minimum pack/year smoking history, and access to a multidisciplinary medical center, and they had close follow-up for the duration of the study.5 The concern of many practitioners is that these conditions cannot be replicated in a large portion of the population.2

Access to health care and affordability issues are still potential barriers to screening for lung cancer with low-dose CT. This may be because patients are uninsured or underinsured or they live in an area where a large multidisciplinary medical center is not easily accessible. Another barrier is that the participants in the NLST were actively involved in the trial, making them more likely to follow-up. Many patients in usual practice are lost to follow-up, which would cause screening with low-dose CT to be less beneficial.2

Concerns also exist about the effect that lung cancer screening may have on smoking cessation rates. Some believe that CT screening could be viewed as a teachable moment for motivating individuals to quit smoking, while others argue that if lung cancer is not detected through screening, then patients may believe that they will not develop cancer and continue to smoke. Such barriers need to be addressed in order for low-dose CT to be applicable to the general population.10

Advancements have been made in radiographic imaging and diagnostic modalities so that once an individual is screened and found to have positive results, management and monitoring the prognosis of the tumor become efficacious. One such advancement is a new computational method called single-click ensemble segmentation, which uses a computer algorithm to segment and assess features of lung cancer tumors. A recent study explained how single-click ensemble segmentation is dependent on one operator to initially place the seed input, making delineation of the lesion more accurate and consistent.24 From the initial seed point, multiple seed points within the tumor area are then automatically generated, allowing measurements of tumor size, shape, and texture to be obtained. This may improve prognostic assessments and reduce workload so that additional patient results can be analyzed.

Conclusions
The National Lung Cancer Screening Trial (NLST) has shown that individuals who benefit most from lung cancer screening using low-dose computed tomography are current or former smokers who have no personal history of malignancy, individuals who have smoked one pack of cigarettes every day for at least 30 years, and former smokers who have quit less than 15 years prior to participating in the study and are between the ages of 55 to 75 years.5 Individuals outside of these demographics have either not been studied or have not been shown to have any decrease in mortality from lung cancer screening.

Lung cancer screening continues to be controversial. Although the NLST did show a 20% reduction in mortality rates in lung cancer–related deaths when individuals were screened with low-dose computed tomography compared with chest radiography, several concerns should be addressed before screening becomes standard care. These uncertainties include the cost effectiveness of screening, the radiation risks, adverse events from additional diagnostic testing, the effects of false-positive results, the ability to reproduce the results of trials in clinical practice, and the effects of screening on smoking cessation rates. Such uncertainties should be further explored.

References