Lung Cancer Screening: A Clinical Review

ABSTRACT:
Lung cancer is a predominant cause of cancer-related morbidity and mortality. Early detection of lung cancer can result in much better outcomes. Thus, there is widespread demand for the development of a screening program to identify lung cancer in chronic smokers. Clinical trials and meta-analyses were compared in order to evaluate the utility of screening interventions. Initial trials using chest radiography and sputum cytology screening did not reveal a significant improvement in mortality outcomes.

The National Lung Screening Trial (NLST) was the first to demonstrate a significant reduction in the relative risk of death among subjects who were screened with low-dose computed tomography (CT) compared to chest radiographs alone (RR 0.8, 95% CI 0.70 to 0.92). The NLST has sparked significant interest because it showed the potential benefit of a useful screening program that could be implemented on a large-scale. With a common goal towards reducing lung cancer-related mortality, clinical trials further exploring CT screening have started globally. The results of these trials, along with further studies, are necessary to determine which patient subgroups will benefit most from screening with low-dose CT.

INTRODUCTION
Lung cancer is the most common cause of cancer-related morbidity and mortality in the world. The highest incidence of lung cancer worldwide is in the United States, where it accounts for almost 6% of deaths annually and the five-year survival rate following diagnosis is only 16%. Similarly, as of 2009, lung cancer was responsible for 25% of cancer-related deaths in Ontario. A major contributor to this dismal survival rate is the difficulty in making a timely diagnosis. Often, lung cancer is asymptomatic until the disease has reached a late stage, at which point the prognosis is grim.

Lung cancer mortality is highly variable based on disease progression at the time of diagnosis. If lung cancer is detected at an earlier stage, surgical intervention has a much higher chance of success. If detected at stage I, five-year survival is approximately 73%. In contrast, detection at stage IV has a five-year survival of less than 9%. Thus, lung cancer screening has been extensively investigated in high-risk individuals in an attempt at earlier detection.

Screening with chest radiographs have been studied at great length in high risk individuals. A meta-analysis looking at nine separate trials assessing the utility of chest radiographs for lung cancer screening, eight of which were randomized controlled trials, included a total of 453,965 subjects. Several of these trials compared outcomes based on screening frequency while others compared screening against no screening. No significant mortality benefit was detected for screening regimens using chest radiography.

Research has been undertaken to determine if the addition of sputum cytology to chest radiography would improve lung cancer detection and survival. Sputum provides the added benefit of obtaining a sample of potentially malignant cells. Several trials across North America and Europe evaluated this screening regimen in high-risk individuals. A meta-analysis reviewed each of these studies, which included a total sample size of over 50,000 individuals. Again, no significant mortality benefit was detected.
Recently, researchers have started exploring low-dose computed tomography (CT) as a possible screening method. The purpose of this review is to provide a thorough overview of the current evidence for CT screening.

METHODS

Data for this review were identified by reviewing the latest expert consensus guidelines on lung cancer screening (Table 1). Bibliographies from the guidelines were also reviewed to identify relevant studies.

CT SCREENING National Lung Screening Trial

Initially prohibited for screening purposes due to excessive radiation, recent advances in radiation dose reduction techniques have allowed for low-dose CT to be performed safely.

The National Lung Screening Trial (NLST) hosted in the United States was the largest study ever performed to explore CT screening for lung cancer. Its primary outcome was lung cancer-specific mortality. In total, 53,454 high-risk individuals, between the ages of 55 to 74, who had smoked at least 30-pack years, or had quit less than 15 years ago were included. Patients with a prior diagnosis of lung cancer or who had previously received a CT scan within the last 1.5 years were excluded.

The study population was randomized into two arms. The screening intervention group was assigned to a total of three low-dose CT scans at annual intervals. The control group did not receive CT scans throughout the trial and instead received three chest radiographs at annual intervals. Baseline characteristics, including smoking history, were similar between the study arms.

Fellowship-trained thoracic radiologists interpreted the results of each scan. Several possible pre-defined findings led to a ‘positive’ screen for suspicion of cancer. Any CT scan or radiograph with a non-calcified node with a diameter of at least 4 mm was considered a positive result. Other possible image findings including lymph node enlargement and pleural effusions were also designated as positive. Individuals with positive results were given further diagnostic follow-up and medical care based on the recommendations of the radiologist and other healthcare providers.

The NLST was stopped early when interim analysis identified that CT screening led to a significant reduction in lung cancer specific mortality (RR=20%; 95% CI, 6.8% to 26.7%; P=0.004). The CT arm resulted in lung cancer death rate of 247 per 100 000 person-years compared to 309 deaths per 100 000 person-years in the control arm. Consequentially, the NLST showed that a screening intervention could lead to measurable improvements in lung cancer-related mortality.

In each of the three screening tests performed on study participants, the low-dose CT arm had a much higher incidence of positive image findings. In the first screen, 27.3% of participants receiving CT scans had a positive result compared to only 9.2% in the chest radiograph arm. Subsequent screens for the next two years showed a similar trend at 27.9% vs 6.2% and 16.8% vs 5.0%. After compiling the results from all three screening tests, an overall 39.1% of participants in the low-dose CT arm had at least one positive result compared to 16.0% in the control arm after three years. Further assessment revealed a positive screen results in a false positive rate of 96.4% in the low-dose CT group and 94.5% in the chest radiograph group. Overall, the rate of false positives was similar in both arms of the trial, but participants in the CT group had true positive test results almost three times as often.

Limitations and Concerns

When interpreting results of the NLST, several limitations must be considered. Image interpretation was performed by thoracic fellowship-trained radiologists. Additionally, lung cancer therapy was performed by highly-specialized surgeons, respirologists, oncologists, and radiation oncologists. If screening were to be implemented in a general community setting, it is unknown how varying proficiency among specialists could affect outcomes. This raises doubt with respect to the reproducibility of the NLST results on a national scale.

Other concerns with the NLST include overdiagnosis and healthy volunteer biases. Overdiagnosis bias refers to the detection and diagnosis of asymptomatic cancers that would not have affected life expectancy. By confirming a cancer diagnosis that would have not have had an impact on mortality outcome, the potential benefits of a screening intervention may be artificially inflated. Healthy volunteer bias is based on the premise that individuals who typically volunteer for clinical studies are usually healthier.

Another limitation associated with CT screening is the high rate of false positives. Elevated false positives lead to more unnecessary diagnostic follow-up that is often invasive and poses its own risks. For example, transbronchial biopsy carries the potential risks of hemorrhage, pneumothorax, and pneumothorax requiring a chest tube. Additionally, the high false positive rate can lead to negative psychosocial consequences including anxiety and depression. Finally, there is the potential for CT screening to lead to radiation-induced cancers. It is estimated that 1.5% to 2% of all cancers in the United States will be attributed to the use of CT scans in the near future. Having continuous screening scans can lead to an excessive cumulative radiation dose.

With any intervention in healthcare, it is critical to consider cost effectiveness to ensure sustainability. Preliminary studies in the American setting have estimated the cost of annual lung cancer screening to be 81,000 United States Dollars (USD) per quality-adjusted life year (QALY) gained. 100,000 USD per QALY is typically considered the threshold for cost-effectiveness in a screening program. Relevant changes pertaining to screening eligibility, frequency, diagnostic thresholds, and follow-up treatments can have a major effect on the cost model. Additionally, studies evaluating the potential cost-efficacy in a public healthcare model, such as the Canadian model, are still required.
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Current Recommendations

Current consensus guideline recommendation statements from various North American medical societies and governmental agencies can be found in Table 1.

Ongoing and Future Trials

In addition to the NLST, there are several other trials assessing the utility of low-dose CT screening for lung cancer.

Table 1

<table>
<thead>
<tr>
<th>Agency or Society</th>
<th>Screening Recommendation</th>
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<tbody>
<tr>
<td>USPSTF(^{17})</td>
<td>The USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.</td>
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<tr>
<td>CancerCare Ontario(^{18})</td>
<td>Screening for lung cancer with LDCT is recommended in high-risk populations defined as persons 55 to 74 years of age with a minimum smoking history of ≥30 pack-years who currently smoke or have quit within the past 15 years and are disease free at the time of screening.</td>
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<td>American College of Radiology(^{19})</td>
<td>The United States Preventive Services Task Force (USPSTF) has issued a recommendation (Grade B) for low-dose computed tomography (CT) lung cancer screening of adults aged 55 to 80 years who have a 30-pack-per-year smoking history and currently smoke or have quit within the past 15 years. The ACR supports this recommendation.</td>
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<td>American Cancer Society(^{20})</td>
<td>The American Cancer Society recommends that clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about lung cancer screening with patients aged 55 to 74 years who have at least a 30-pack-year smoking history, currently smoke or have quit within the past 15 years, and who are in relatively good health.</td>
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<td>American Association of Thoracic Surgeons(^{21})</td>
<td>The American Association for Thoracic Surgery guidelines call for annual lung cancer screening with low-dose computed tomography screening for North Americans from age 55 to 79 years with a 30 pack-year history of smoking. Long-term lung cancer survivors should have annual low-dose computed tomography to detect second primary lung cancer until the age of 79 years. Annual low-dose computed tomography lung cancer screening should be offered starting at age 50 years with a 20 pack-year history if there is an additional cumulative risk of developing lung cancer of 5% or greater over the following 5 years. Lung cancer screening requires participation by a subspecialty-qualified team.</td>
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<tr>
<td>American College of Chest Physicians(^{22})</td>
<td>For smokers and former smokers ages 55 to 74 who have smoked for 30 pack-years or more and either continue to smoke or have quit within the past 15 years, ASCO suggests that annual screening with LDCT should be offered over both annual screening with chest radiograph or no screening, but only in settings that can deliver the comprehensive care provided to NLST participants. For individuals who have accumulated fewer than 30 pack-years of smoking, are either younger than 55 or older than 74, or who quit smoking more than 15 years ago, as well as for individuals with severe comorbidities that would preclude potentially curative treatment and/or limit life expectancy, ASCO suggests that CT screening should not be performed.</td>
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In addition to chest radiographs and CT scans, there have been other proposed imaging modalities that may have potential as a screening intervention such as endobronchial ultrasounds and positron emission tomography. However, there have not been clinical trials exploring the screening utility of these tests.\(^{11}\)

CONCLUSIONS

Current evidence suggests that low-dose CT screening leads to a significant reduction of mortality in high-risk patients. Various North American governmental and non-governmental medical societies have advocated national screening programs. The results of several ongoing trials may resolve the potential limitations of CT screening which would enable implementation of a more widely accepted national screening program.
Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population and Design</th>
<th>Inclusion and Exclusion Criteria</th>
<th>Main Results</th>
<th>Strengths and Weaknesses</th>
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<tbody>
<tr>
<td>NLST9</td>
<td>53,454 RCT Comparison: LDCT vs CXR</td>
<td>Inclusion: • Male and female between 55-74 years old • 30+ pack-year history • Quit smoking &lt;15 years ago • Can lie on back with arms raised over head Exclusion: • Metallic implants in chest or back • History of lung cancer • History of lung removal • Unexplained weight loss of over 15 pounds in the last 12 months • CT Chest in the last 18 months • Participation in another cancer screening trial • Recent hemoptysis</td>
<td>• Significant lung-cancer specific mortality reduction with LDCT compared to the chest radiograph group. RR=20% [95% CI, 6.8 to 26.7; P=0.004]</td>
<td>Strengths: • Large study powered to detect mortality • High adherence rate • High followup rate • Well-defined rigorous inclusion criteria Weaknesses: • Concern over reproducibility • Overdiagnosis bias • Healthy volunteer bias • Using chest radiography as control group limits the ability of this trial to answer the question of whether low-dose CT provides a mortality benefit over no screening</td>
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<td>DANTE7</td>
<td>2,811 RCT Comparison: LDCT vs Usual Care</td>
<td>Inclusion: • Minimum 60 years of age • Males only • Current or former smokers with a 20+ pack-year history Exclusion: • A history of any cancer within the last 10 years • Comorbid conditions with a life expectancy of under 5 years • Inability to comply with any component of the screening or follow-up protocol</td>
<td>• Twenty patients in the LDCT group (1.6%) and 20 controls (1.7%) died of lung cancer • Non-significant difference led authors to conclude mortality benefit from lung cancer screening by LDCT might be much smaller than anticipated</td>
<td>Strengths: • Control arm had no screening, which is an accurate representation of the effects of low-dose CT compared to usual care Weaknesses: • Small study population not powered to detect mortality • Study population male only</td>
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<td>Danish Lung Cancer Screening Trial14</td>
<td>4,104 RCT Comparison: LDCT vs Usual Care</td>
<td>Inclusion: • 20+ pack-year history and currently smoking • Or, former smokers 20+ pack-year history that quit after the age of 50 and &lt;10 years ago • Men or women aged 50-70 • Be able to climb 2 flights of stairs (36 steps) without pausing • FEV-1 at least 30% of normal predicted value Exclusion: • Body weight above 130 kg • Previous treatment for lung cancer, breast cancer, or hypernephroma • History of any cancer within the last 5 years • History of tuberculosis within the last 2 years • Any comorbidity that would shorten life expectancy to under 10 years • CT scan within the last 12 months</td>
<td>• More lung cancers were diagnosed in the screening group [69 vs. 24, p&lt;0.001] • More lung cancers were low stage (48 vs 21 stage I-IIB non-small cell lung cancer [NSCLC] and limited stage small cell lung cancer [SCLC], p=0.002) in screening group • High-stage lung cancer was the same [21 vs 16 stage IIIA-IV NSCLC and extensive stage SCLC, p=0.509] between the two groups • No mortality difference</td>
<td>Strengths: • High followup rate • Control arm had no screening, which is an accurate representation of the effects of low-dose CT compared to usual care Weaknesses: • Overdiagnosis bias • Small study population not powered to detect mortality</td>
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<tr>
<td>Study</td>
<td>Population Size</td>
<td>Study Design</td>
<td>Comparison</td>
<td>Inclusion</td>
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<td>MILD 13</td>
<td>4,099</td>
<td>RCT</td>
<td>Annual LDCT vs Biennial LDCT vs Usual Care</td>
<td>Inclusion: Male or Female smoker with a 20+ pack-year history; Former smoker with 20+ pack-year history that quit &lt;10 years ago</td>
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<td>LUSI 16</td>
<td>Ongoing</td>
<td>RCT</td>
<td>LDCT vs Usual Care</td>
<td>Inclusion: Male or female between the ages of 50-79 and with 'heavy' smoking history</td>
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<td>UKLS 12</td>
<td>32,000 Proposed 4,000 To Date</td>
<td>RCT</td>
<td>LDCT vs Usual Care</td>
<td>Inclusion: Male or female between the ages of 50-75; Target population with 5% risk of developing lung cancer in 5 years selected using Liverpool Lung Project risk prediction model</td>
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<td>NELSON 5</td>
<td>15,822</td>
<td>RCT</td>
<td>LDCT vs Usual Care</td>
<td>Inclusion: Males aged 50-75; Current smokers who smoked more than 15 cigarettes daily for over 25 years or more than 10 cigarettes daily for over 30 years; Former smokers with 10 years or less of cessation, and above criteria</td>
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- Strengths: Improved outcomes, increased accuracy, reduced mortality.
- Weaknesses: Limited sample size, lack of long-term follow-up, potential for overdiagnosis.
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RCT
Comparison: LDCT vs Usual Care

Inclusion
• Male or female between the ages of 55-69
• Current smokers with a 20+ pack-year history
• Former smoker with 20+ pack-year history that quit <10 years ago

Exclusion
• History of previous cancer
• General conditions precluding thoracic surgery
• Inability to give consent

• Not available

Strengths
• Control arm had no screening, allowing for comparison of low-dose CT to usual care

Weaknesses
• Small overall study population, not powered to detect significant mortality benefit

CXR: Chest Radiography; LDCT: Low-dose computed tomography; RCT: Randomized Controlled Trial

References