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Short Communication

Screening for Lung Cancer

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Special Issue on
Lung Cancer

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Lung cancer is the leading cause of cancer related deaths in the United States. The estimated number of lung cancer deaths in 2012 was higher than the total combined number of deaths from breast, prostate and colon cancer. In 2012, according to the published data from the American Cancer Society, a total of 226,160 new cases of lung cancer had been diagnosed with a total death of 160,340 secondary to lung cancer. It was estimated that about 1 person out of 2000 in the US died because of lung cancer in 2012 [1-2].

Smoking is by far the most important risk factor for lung cancer and at least 85% of lung cancers are attributed to smoking [3]. An estimated 45.3 million people, or 19.3% of all adults (aged 18 years or older), in the United States actively smoke cigarettes [4]. This translates into a significant proportion of the American population at a high risk for lung cancer. Unfortunately, around 75% of newly diagnosed lung cancers are incurable at the time of diagnosis [5].

Because of the major morbidity and mortality in lung cancer, screening has been a focus of investigation for decades. The US Preventive Services Task Force (USPTF) [6] recommended an annual Low Dose CT (LDCT) scan for persons at high risk for lung cancer based on age and smoking history. A reasonable choice was to recommend screening for persons 55 to 80 years old with a 30 pack-year or more history of smoking who currently smokes or have smoked within the past 15 years. (B recommendation= high certainty of moderate net-benefit or moderate certainty of considerable net-benefit) In addition, patients undergoing screening should be able to undergo curative surgery if needed without serious comorbidities that might limit their life expectancy (Table 1).

The USPTF emphasized that the highest net benefit for LDCT screening will be in high risk patients for lung cancer in order to avoid unintended consequences such as false-positive results and over diagnosis.

WHAT IS THE EVIDENCE SUPPORTING LDCT SCREENING FOR LUNG CANCER?

Five randomized controlled trials tested the effectiveness of LDCT in the screening for lung cancer

1-National Lung Cancer Screening Trial "NLST"

Funded by the National Cancer Institute, the NLST [7] is the best evidence to date that tested LDCT in lung cancer screening. The NLST enrolled around 50 thousand participants comparing annual LDCT versus single posterior-anterior chest radiograph for three consecutive years. Chest radiograph was chosen as the screening method in the control group rather than conventional care since it was being compared to conventional care in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial [8] at the same time of NLST trial design. In case chest radiography would have shown a benefit, designing the NLST trial with conventional care in the control group would have been less beneficial. Inclusion criteria, was similar to those adopted by the USPTF, which were asymptomatic men and women between the age of 55 and 74, who had a total of 30 pack –year smoking and smoked within the past 15 years. The study was stopped early after a median of 6.5 years of follow up when the reduction in lung cancer mortality achieved 20% (95% CI, 6.8% to 26.7%) in the LDCT group. The lung cancer specific mortality among participants who underwent at least 1 screening test, was 346

Table 1: Lung Cancer Screening Summary.

Who to screen?	**-Patients between age 55 to 80 -At least 30 pack-year smoking history and actively smoking OR quit within past 15 years - Relatively healthy**
How to screen?	-Annual low dose CT scans
Where to screen?	-In an established screening program to ensure compliance and appropriate follow-up
What additional input needed?	-Smoking cessation counseling -Shared decision making between physicians and patients discussing potential benefits versus harm

Table 2: Potential Concerns with Low dose CT screening.

Over diagnosis
False-positive Results
Lead-time Bias
Length-time Bias
Smoking Cessation
False Reassurance
Cost-Effectiveness

deaths out of 26455 participants (1.3%) in the LDCT group compared with 425 deaths out of 26232 participants (1.6%) in the radiography group. The number needed to screen with low-dose CT to prevent one death from lung cancer was 320.

2-The DANTE (Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essay) was a European study that compared LDCT to conventional care [9]. The study included male patients with a history of 20 pack-year smoking or more with no significant co-morbid conditions between the ages of 60 and 74. Each arm in the study had approximately 1200 patients. The intervention group had 4 annual LDCTs. After a median follow-up of 34 months, the relative risk (RR) of lung cancer mortality among the LDCT group was 0.83 (CI, 0.45 to 1.54). All-cause mortality was equal in both groups at 3 years, with an RR of 0.85 (CI, 0.56 to 1.27).

3-The DLCT (Danish Lung Cancer Screening Trial) trial compared LDCT to conventional care [10]. This was a single center study that randomized about 2000 participants to each group. The study included men and women aged between 50 to 70 years, who were current or former smokers with at least 20 pack years of smoking history. Former smokers should have quit after the age of 50 years and have been abstinent for <10 years. Participants had to be able to climb two flights of stairs without pausing. Lung function was measured by spirometry and forced expiratory volume in the first second had to be at least 30% of predicted. Participants with nodules with diameters larger than 15 mm or rapidly growing were referred for diagnostic workup. After a median follow-up of 4.8 years, the RR for lung cancer mortality all-cause mortality was 1.37 (CI, 0.63 to 2.97) and 1.46 (CI, 0.99 to 2.15) in the LDCT group compared to the control group.

4-The MILD (Multicentric Italian Lung Detection) study was another single-center trial that randomized about 4000 participants to three groups comparing annual or biennial LDCT versus no screening [11]. The trial included men and women aged 49 years or older with a history of 20 pack-year smoking or more that smoked within the past 10 years. There was no difference in cancer related mortality or total mortality between across the groups. The lung cancer related mortality and the total mortality hazard ratio was 1.52 (95% CI 0.63–3.65) and 1.39 (95% CI 0.83–2.34) when both LDCT arms were compared to the control group. The follow up periods reported were different between groups (45 months for the combined LDCT group vs. 56 months for the control group).

5- The NELSON (Nederlands Leuvens Longkanker Screenings Onderzoek) trial is the largest ongoing European lung cancer screening study using LDCT. A total of 15,822 participants were enrolled and randomized to either screening with LDCT (7,915) at baseline, 1, 3 and 5.5 years later or no screening (7,907). Inclusion criteria were age 50 – 75 years, smoking history of 15 or more cigarettes per day for 25 years or 10 or more cigarettes for 30 years and either current smokers or history of having quit less than 10 years ago. Patients are expected to have a follow up for 10 years. In this study, CT images are analyzed by semi automated volume measurements software. Final results are not published yet, but preliminary data has shown a favorable lung cancer stage distribution at diagnosis (70.8% stage I) [12].

Risks of LDCT

1-Radiation Exposure: The risk of cancer induced radiation is currently estimated based on models mostly developed from atomic bombing survivors and many studies of medical imaging exposure.

The estimated radiation dose for LDCT per-exam is 1.4 mSv, as reported in the NSLT. However, there are Variations between different centers. Doses at this range is less than half of annual background exposure from living in the United States and less than one quarter of a diagnostic CT scan dose which is about 8mSv. It is estimated that the NLST participants received approximately 8 mSv per participant over 3 years, including both screening and diagnostic examinations (averaged over the entire screened population). Using these information and cancer related radiation models, Beach et al, estimated that one cancer death may be caused by radiation from imaging per 2500 persons screened. As the number needed to screen with LDCT to prevent 1 lung cancer related death is 320, the benefits of LDCT screening outweigh the risk of cancer induced by radiation [13,14].

2-Complications of Diagnostic Procedures: In the NLST trial [7], around 2.5 % of the positive test results required additional diagnostic procedure. The rate of complication from any further intervention was around 0.36% and rate of mortality was 0.035% (<0.15) within 60 days after any invasive procedure.

WHAT ARE THE POTENTIAL CONCERNS WITH LUNG CANCER SCREENING?

- Over diagnosis in screened population (Table 1)

It is a bias that occurs during a screening test where indolent cancer is identified but probably will never affect the patient's overall healthcare or long-term prognosis. Previous chest radiography screening studies identified an over diagnosis rate of about 25% [14], whereas the Mayo screening study [15] showed that around 27% of all cancer detected have a doubling time of >400 days suggesting over diagnosis bias. In the NLST, the probability that any type of lung cancer to be an over diagnosis is 18.5% in the LDCT arm during the 7 year follow up period [16]. Therefore, patients might undergo unnecessary diagnostic interventions and treatment leading to increased cost, morbidity and sometimes mortality in an indolent cancer that might never cause clinical disease.

- False Positive Scans

It is defined as having at least one CT scan with non-calcified nodule that was found later to be non-malignant. High false positive rates were commonly found during screening for lung cancer. In the NLST, around 24.2% of the subjects had at least one positive CT scan during screening and 96.4% of those were false positive [7]. Most subjects were subsequently followed by additional CT scan but few underwent unnecessary diagnostic testing.

- Lead-Time Bias

It refers to early detection of lung cancer before clinical symptoms develop but without changing the life expectancy of patients.

- Length-Time Bias

It refers to the ability to detect indolent tumors during annual LDCT screening much more likely than aggressive rapidly – growing tumors as they move slowly from indolent stage to clinical symptoms.

- Smoking Cessation

One major concern in patients that will undergo annual LDCT screening is smoking behavior. Unfortunately, two major studies did not show any difference in smoking cessation rates between patients assigned to LDCT versus no LDCT [17,18]. Physicians should educate patients about smoking cessation and offer medical as well as psychological therapy if needed.

- False Reassurance

The sensitivity for LDCT to detect lung cancer is between 80 to 100%, with a false negative rate that ranges between 0 to 20% [19-22].Therefore, a formal discussion between physician and patient should be done before committing any patient to long term screening.

- Cost Effectiveness

The number needed to screen in the NLST to save one life is 320 patients [7]. This compares favorably well with screening modalities such as colonoscopy and mammography. However, the actual quality-adjusted life-year gained for LDCT screening might vary from as low as 19,000$ to more than 2,000,000$ depending on patient's smoking status (lower cost for current smokers compared to higher costs for former smokers), screening adherence and diagnostic procedures [23-25].

ESTABLISHING A SCREENING CLINIC

There is no doubt that once LDCT screening is widely endorsed the number of patients with lung nodules will increase dramatically. Therefore, a multidisciplinary team consisting of pulmonologist with special interest in lung cancer, radiologist, thoracic surgeon, nurse and a social worker are needed to initiate screening in high risk patients as well as follow up patients appropriately afterwards. Furthermore, it is recommended that only patients who meet USPTF criteria should undergo screening. A formal discussion between the physician and patient about the benefits, risks and potential uncertainties for LDCT screening should be held before committing anyone to a screening program. In addition, all current smokers should be counseled about smoking and offered therapy or be enrolled in a special program for smoking cessation.

FUTURE DIRECTIONS

An accurate and practical model that can predict the probability that a lung nodule is malignant and that can be used to guide clinical decision making will reduce costs and the risk of morbidity in screening programs. Some models based on patient and nodule characteristics have been developed with encouraging results [26]. Recent advances in genomics, epigenomics, proteomics and metabolomics, have identified potential biomarkers in the blood, urine, exhaled breath condensate, bronchial specimens, saliva and sputum that may help to select the most-at risk population for lung cancer, potentially reducing unnecessary work ups in low risk patients [27].

SUMMARY AND CONCLUSION

LDCT screening reduces mortality in a high risk population as defined by the NLST. Screening through a dedicated clinic or specialized program will probably maximize cost benefit, reduce unnecessary interventions and assure adequate follow-up leading to overall better patients' welfare. Smoking cessation should be an essential part of a lung cancer screening program.

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