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.

### Table 1: Lung Cancer Screening Summary

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

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 2: Potential Concerns with Low dose CT screening.

<table>
<thead>
<tr>
<th>Potential Concerns</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over diagnosis</td>
<td>Exceeds 18.5% of patients (6.3%) in the LDCT group compared with 425 deaths out of 26545 participants (1.3%) in the LDCT group and 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.</td>
</tr>
<tr>
<td>False-positive results</td>
<td>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].</td>
</tr>
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<td>Lead-time bias</td>
<td>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].</td>
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<td>Length-time bias</td>
<td>Lead-time bias 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 &gt;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.</td>
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<tr>
<td>Smoking cessation</td>
<td>Risks of LDCT False-positive scans 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 &gt;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.</td>
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<td>False reassurance</td>
<td>Risks of LDCT 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</td>
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<td>Cost-effectiveness</td>
<td>Risks of LDCT 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</td>
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</tbody>
</table>
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.

REFERENCES


