Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening
Disclosures:
I, like many physicians, receive compensation from the government and their insurance company cronies who completely control how I practice medicine.
Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide.

In 2015, it is estimated that 158,040 deaths (86,380 in men, 71,660 in women) from lung cancer will occur in the United States.

Five-year survival rates for lung cancer are only 16.8%, partly because most patients have advanced-stage lung cancer at initial diagnosis.
- These facts—combined with the success of screening in improving outcomes in cervical, colon, and breast cancers—have been the impetus for studies to develop an effective lung cancer screening test.

- Ideally, effective screening will lead to earlier detection of lung cancer (before patients have symptoms and when treatment is more likely to be effective) and will decrease mortality.
Currently, most lung cancer is diagnosed clinically when patients present with symptoms such as persistent cough, pain, and weight loss; unfortunately, patients with these symptoms usually have advanced lung cancer.
Early detection of lung cancer is an important opportunity for decreasing mortality.
Screening Tests

- Improve outcome.
- Be scientifically validated (e.g., have acceptable levels of sensitivity and specificity).
- Be low risk, reproducible, accessible, and cost effective.
So far, standard yearly Chest X-rays in high-risk individuals has never been shown to reduce a person’s risk of dying from lung cancer.

Thus, Chest X-Ray and sputum cytology are not recommended for lung cancer screening.
Considerable interest has been shown to developing screening tools to detect early-stage lung cancer. Recent data supports using low-dose computed tomography (LDCT) of the chest to screen select patients who are at high risk for lung cancer.
Background

- Lung cancer is the largest contributor to mortality from cancer. The National Lung Screening Trial (NLST) showed that screening with low-dose helical computed tomography (CT) rather than with chest radiography reduced mortality from lung cancer.

- This study describes the screening, diagnosis, and limited treatment results from the initial round of screening in the NLST to inform and improve lung-cancer–screening programs.
At 33 U.S. centers, from August 2002 through April 2004, they enrolled asymptomatic participants, 55 to 74 years of age, with a history of at least 30 pack-years of smoking.

The participants were randomly assigned to undergo annual screening, with the use of either low-dose CT or chest radiography, for 3 years. Nodules or other suspicious findings were classified as positive results.

This article reports findings from the initial screening examination.
Low-dose CT was performed on multidetector helical CT scanners of four or more channels. Single-view posteroanterior chest radiographs were obtained with the use of conventional film or digital radiographic systems.

Technical standards and acquisition variables for both low-dose CT and chest radiographic screening have been published previously.
Results

- A total of 53,439 eligible participants were randomly assigned to a study group (26,715 to low-dose CT and 26,724 to chest radiography); 26,309 participants (98.5%) and 26,035 (97.4%), respectively, underwent screening.

- A total of 7191 participants (27.3%) in the low-dose CT group and 2387 (9.2%) in the radiography group had a positive screening result.

- In the respective groups, 6369 participants (90.4%) and 2176 (92.7%) had at least one follow-up diagnostic procedure, including imaging in 5717 (81.1%) and 2010 (85.6%) and surgery in 297 (4.2%) and 121 (5.2%).
Results

- Lung cancer was diagnosed in 292 participants (1.1%) in the low-dose CT group versus 190 (0.7%) in the radiography group (stage 1 in 158 vs. 70 participants and stage IIB to IV in 120 vs. 112).

- Sensitivity and specificity were 93.8% and 73.4% for low-dose CT and 73.5% and 91.3% for chest radiography, respectively.
The NLST showed a 20% reduction in lung-cancer mortality with low-dose CT versus chest radiography (247 vs. 309 deaths per 100,000 patient-years of follow-up).

In absolute terms, this translated to approximately 3 fewer deaths from lung cancer per 1000 high-risk persons who underwent low-dose CT screening.
Results

- To put this finding into context, the magnitude of benefit is at least as great as that reported for breast-cancer mortality with annual mammographic screening among women 50 to 59 years of age.

- In addition, a 6.7% reduction in the relative risk of death from any cause was observed, although this benefit was explained almost entirely by fewer deaths from lung cancer.
The National Lung Screening Trial (NLST) showed that screening with low-dose CT reduced the risk of death from lung cancer by 20% among persons 55 to 74 years of age who had a smoking history of at least 30 pack-years and were current smokers or were former smokers who had quit within the previous 15 years.
Risks of screening include frequent false positive findings that often require CT surveillance and less commonly lead to invasive biopsy or surgery that reveals benign findings.

Most guidelines recommend that high-risk smokers and former smokers be offered screening with low-dose CT and engaged in a process of shared, informed decision making to weigh the pros and cons and make an individualized choice.
There is concern that the favorable balance between the benefits and harms of screening observed in the idealized conditions of the NLST may be difficult to replicate when lung-cancer screening is introduced in diverse clinical practice settings.

Current smokers should be advised that screening is not a substitute for smoking cessation. Patients with positive screening-test results are more likely than those with negative results to quit smoking, but the effect of participating in a screening program on the rate of smoking cessation is uncertain.
Conclusions

- The NLST initial screening results are consistent with the existing literature on screening by means of low-dose CT and chest radiography, suggesting that a reduction in mortality from lung cancer is achievable at U.S. screening centers that have staff experienced in chest CT.

- Among the findings of the trial is that three annual low-dose CT screens detected more lung cancers, more early-stage lung cancers, and fewer late-stage lung cancers relative to radiography screening, albeit with a slightly lower positive predictive value.
Annual lung-cancer screening of high-risk smokers and former smokers with the use of low-dose CT is at least as effective in preventing death from cancer as annual mammographic screening for breast cancer in women 50 to 59 years of age.

Among high-risk smokers and former smokers, screening with low-dose CT (along with subsequent evaluation and treatment) prevents one of five deaths from lung cancer.

Lung-cancer screening with low-dose CT is not a single test. It is a process that involves annual testing and follow-up of screening-detected abnormalities.

False positive test results occur in approximately one of five low-dose CT screening examinations. Each examination is approximately 20 times as likely to yield a false positive result as it is to reveal lung cancer.

Most false positive results will require follow-up with one or more subsequent CT scans, but a minority (5%) will require evaluation with invasive biopsy or surgery.

Screening for lung cancer with low-dose CT is not a substitute for smoking cessation. Stopping smoking is the most effective way to reduce the risk of death from lung cancer and has other important immediate and long-term cardiovascular and respiratory health benefits.
Chest X-ray dose

Standard dose

Presenter: Jonathan E. Schwartz, MD
Compared to a conventional CT, the low-dose CT scan for lung cancer uses approximately 5 times less radiation. Depending on the size of the patient, a low-dose CT scan will typically deliver 2 – 4 millisieverts of radiation exposure. A conventional CT scan typically delivers between 5-20 millisieverts.
The amount of radiation patients are exposed to during a low-dose CT scan is approximately equivalent to each of the following:

- Receiving 15 traditional X-rays
- Taking 50 cross-country flights
- 6 months of natural background radiation
#### Lung Cancer Screening

**RISK ASSESSMENT**

<table>
<thead>
<tr>
<th>Smoking history&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Radon exposure&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Occupational exposure&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Cancer history&lt;sup&gt;f&lt;/sup&gt;</th>
<th>Family history of lung cancer in first-degree relatives</th>
<th>Disease history (COPD or pulmonary fibrosis)</th>
<th>Smoking exposure&lt;sup&gt;g&lt;/sup&gt; (second-hand smoke)</th>
<th>Absence of symptoms or signs of lung cancer (If symptoms, see appropriate NCCN Guidelines)</th>
</tr>
</thead>
</table>

**RISK STATUS**

- **High risk**
  - Age 55–74 y and
  - ≥30 pack-year history of smoking and
  - Smoking cessation <15 y (category 1)
  - Or
  - Age ≥65 y and
  - ≥20 pack-year history of smoking and
  - One additional risk factor (other than second-hand smoke)

- **Moderate risk**
  - Age ≥55 y and
  - ≥20 pack-year history of smoking or second-hand smoke exposure<sup>g</sup>
  - No additional risk factors

- **Low risk**
  - Age <65 y and/or
  - <20 pack-year history of smoking

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In candidates for screening, shared patient/physician decision making is recommended, including a discussion of benefits/risks.<sup>l</sup>

Lung cancer screening not recommended

Lung cancer screening not recommended

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**Note:** All recommendations are category 2A unless otherwise indicated.

*Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.*

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EVALUATION OF SCREENING FINDINGS

- New nodule at annual or follow-up LDCT
- Suspected infection/inflammation
  - Consider treatment with antibiotics
  - Repeat LDCT in 1–2 mol
- No suspected infection/inflammation
  - Solid or part-solid nodule
    - GGOs/GGNs/NS
  - Multiple GGOs/GGNs/NS

FOLLOW-UP OF SCREENING FINDINGS

- Resolving
- Resolved
- Persistent or enlarging
- Biopsy
- Surgical excision

- Consider annual LDCT screening
  - Annual LDCT screening (see LCS-1)
- Annual LDCT in 3 mol
  - LDCT in 3 mol (See LCS-3 or LCS-4)
- Low suspicion of lung cancer
  - PET/CT
- Lung cancer confirmed
  - Appropriate NCCN Guidelines

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### NCCN Guidelines Version 1.2016 Lung Cancer Screening

#### EVALUATION OF SCREENING FINDINGS

<table>
<thead>
<tr>
<th>Finding</th>
<th>Follow-Up of Screening Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure GGNs ≤5 mm in diameter</td>
<td>Stable, resolving, or resolved</td>
</tr>
<tr>
<td>Multiple GGOs with a dominant lesion</td>
<td>LDCT in 12 months</td>
</tr>
<tr>
<td>Pure GGNs &gt;5 mm in diameter without a dominant lesion</td>
<td>Increase in size &gt;5 mm and/or becomes solid or part solid</td>
</tr>
<tr>
<td>Dominant nodule with part-solid or solid component</td>
<td>LDCT in 8 months</td>
</tr>
<tr>
<td>Persistent or Increase in size &gt;5 mm</td>
<td>Annul LDCT screening (see LCS-3)</td>
</tr>
</tbody>
</table>

#### FOLLOW-UP OF SCREENING FINDINGS

- **Stable, resolving, or resolved**
  - Annual LDCT for 2 years (category 1) and suggest annual LDCT until patient is no longer a candidate for definitive treatment
- **Increase in size >5 mm and/or becomes solid or part solid**
  - LDCT 3–6 months
  - Consider surgical excision
- **No cancer**
  - Consider annual LDCT until patient is no longer a candidate for definitive treatment
- **Cancer confirmed**
  - See appropriate NCCN Guidelines

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Nivolumab, a fully human IgG4 programmed death-1 (PD-1) immune checkpoint inhibitor antibody, demonstrating antitumor activity and durable responses in patients (pts) with solid tumors including melanoma, renal cell cancer and non-small cell lung cancer.
Programmed cell death protein 1, also known as PD-1 is a cell surface receptor that belongs to the immunoglobulin superfamily and is expressed on T cells and pro-B cells.

PD-1 and its ligands play an important role in down regulating the immune system by preventing the activation of T-cells, which in turn reduces autoimmunity and promotes self-tolerance. The inhibitory effect of PD-1 is accomplished through a dual mechanism of promoting apoptosis (programmed cell death) in antigen specific T-cells in lymph nodes while simultaneously reducing apoptosis in regulatory T cells (suppressor T cells).[3]
1. Normal Immune Response

T-cell activation and tumor attack

Presenter: Jonathan E. Schwartz, MD
2. Tumor Immune Evasion

T-cell inactivation through the PD-1 immune checkpoint
3. Normal Immune Response Restored
T-cell reactivation and decreased tumor growth* through PD-1 immune checkpoint inhibition. While having an effect on the tumor, this could also affect normal cells.
Findings from a randomized phase III study indicate that PD-1 immunotherapy is an effective treatment option for patients with non-squamous, non-small cell lung cancer (NSCLC).
Among patients with advanced disease that worsened after receiving platinum-based chemotherapy, those treated with Nivolumab lived on average three months longer than those treated with Docetaxel chemotherapy.

This is the first phase III study to show that immunotherapy is effective against non-squamous cell NSCLC, and appears to be particularly active in patients with PD-L1-positive tumors.

Presenter: Jonathan E. Schwartz, MD
Lung cancer is the most common cancer worldwide, with more than 1.8 million new cases diagnosed in 2012.

It is also the leading cause of cancer deaths in the United States.

NSCLC is the most common form of lung cancer, accounting for 85% of all lung cancers.

More than two-thirds of those are non-squamous cell cancers.
The study randomly assigned 582 patients with advanced non-squamous NSCLC to treatment with Nivolumab or Docetaxel.

Response rates were higher in the Nivolumab group compared to the Docetaxel group (19.2% vs. 12.4%).

Responses also lasted significantly longer in the Nivolumab group (17.1 months vs. 5.6 months, on average).
The median overall survival was 12.2 months in the Nivolumab group compared to 9.4 months in the Docetaxel group.

Of note, in the subgroup of patients with high levels of PD-L1 in their tumor (≥1% cells), the median survival with Nivolumab exceeded 17 months as compared to 9 months for those treated with Docetaxel.
Nivolumab was well tolerated overall, with only one in 10 patients experiencing serious side effects, compared to more than half of patients in the Docetaxel arm.

There was one treatment-related death in the Docetaxel arm and none in the Nivolumab arm.

Due to toxic side effects, 4.9% patients stopped Nivolumab, and 14.9% patients stopped Docetaxel.
The researchers pointed out that patients with higher levels of the biomarker PD-L1 experienced the greatest degree of benefit from Nivolumab.

Overall, patients who received Nivolumab had a 27% lower risk of death compared to those who received Docetaxel.

However, the subgroup of patients with the high levels of PD-L1 had a 41-60% reduction in risk of death, which was not observed in cases of low or undetectable PD-L1 levels.
Earlier this year, the FDA approved Nivolumab as a second-line treatment for advanced squamous NSCL.

Nivolumab could potentially become a new standard therapy for patients with previously treated NSCLC.
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