Lung cancer screening trials: Denmark and beyond

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Lung cancer is the leading cause of cancer death worldwide, with fewer than 15% of patients surviving 5 years after diagnosis, despite advances in treatment during the past 20 years. Lung cancer screening (secondary prevention), in addition to smoking cessation programs (primary prevention), might be the most exciting improvement in methods to reduce lung cancer mortality. The great interest in lung cancer screening was started by the introduction of low-dose multi-detector computed tomography (CT) in the 1990s. The non-randomized International Early Lung Cancer Action Project study ($n = 32,000$)¹ was followed by several randomized clinical trials of high-risk current and former smokers. These included the National Lung Screening Trial (NLST) in the United States ($n = 53,500$),² the Dutch-Belgian screening trial ($n = 15,822$),³ the Danish Lung Cancer Screening Trial (DLCST, $n = 4104$),⁴ and several other collaborating trials in Europe.⁵⁻⁷ Recently, the National Cancer Institute published the report that the NLST gave evidence for a mortality reduction of 20.3% with low-dose CT screening compared with chest radiographic screening and a 7% overall mortality reduction after 3 annual screening rounds and 8 years of follow-up.² The NLST was a very well-performed randomized trial and has convincingly shown for the first time that CT screening, in high-risk subjects, can lead to a substantial reduction in lung cancer mortality and that the screening overall was not detrimental, because a reduction of 7% in general mortality was also observed. These are extremely important findings. The European trials have been smaller, but all have had a control group without any screening performed (usual care) and, therefore, potentially, the difference between the mortality in the CT and control arms could be more pronounced. In addition, the trials were started 2 to 3 years after the NLST and, therefore, have not yet performed a pooling of data and presented a combined mortality analysis. The Dutch-Belgian screening trial and the DLCST are expected to perform a final mortality analysis in 2015 but contemplated a preliminary pooling of data in 2011.

The DLCST is a 5-year prospective randomized controlled screening trial evaluating the effect of annual CT screening for lung cancer. The overall design and baseline results were published in 2009.⁴

METHODS

From October 2004 to March 2006, 4104 men and women were enrolled in the DLCST after recruitment by advertisements in local and regional free-of-charge newspapers, stating the purpose, study design, and inclusion criteria. The trial was funded in full by a governmental grant and was without costs to the participants.

The inclusion criteria were men (55%) and women (45%), aged 50 to 70 years, who were current or former smokers with at least 20 pack-years of smoking history. Former smokers should have quit for no more than 10 years. Lung function was measured by spirometry and forced expiratory volume in 1 second had to be at least 30% of predicted.

The exclusion criteria were a body weight greater than 130 kg, a history of cancer diagnosis and treatment, lung tuberculosis, expected life expectancy of less than 10 years, and chest CT scan received during the past year for any reason.

Randomization was to either a screening group ($n = 2052$) or a control group ($n = 2052$). The screening group received 5 annual, low-dose chest CT scans (1 baseline scan and 4 incidence scans). All came for an annual visit to the screening clinic, at which lung function tests were performed and questionnaires concerning health, lifestyle, smoking habits, and psychosocial consequences of screening were completed.¹ The CT scans were evaluated by 2 experienced radiologists,¹ with volumetric analysis of the detected nodules validated as in the Dutch-Belgian screening trial.⁸ Positron emission tomography scans were used to supplement the radiologic assessment.⁹

RESULTS

The DLCST showed that smoking habits during screening were unaffected by CT screening per se at 1 year of follow-up.¹⁰ Contamination by off-study CT scans in the control group was low (0.04%).¹¹

In the CT screening group, a total of 68 lung cancers were diagnosed. At baseline, the detection rate was 0.8%,⁴ and the incidence rounds had a mean annual detection rate of 0.6% (chi-square test, $P = .492$). Of the 68 cases, 3 were small cell lung cancer (SCLC) and 65 were non-SCLC. Also, 57 (84%) were early stage (stage I–IIIA non-SCLC and limited-stage SCLC) and thus potentially curable, and 11 (16%) were diagnosed in a late stage (stage IIIB–IV non-SCLC and extensive-stage SCLC). One interval cancer was diagnosed 10 months after the third incidence scan.

Significantly more lung cancers were diagnosed in the screening group (chi-square test, 68 vs 24; $P < .001$) and more were low stage (chi-square test, 57 vs 10; $P < .001$). The number of late-stage lung cancers was the same in both groups (chi-square test, 11 vs 14; $P = .640$). The number of new lung cancers remained high during all 4 incidence rounds in the screening group compared with

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the control group ($P < .001$). A high proportion of the screen-detected lung cancers (>75%) were treated by minimally invasive surgery (video-assisted thoracic surgery; data to be published).

CONCLUSIONS

The experience from the lung cancer CT screening trials have shown that CT screening will lead to increased detection of early-stage lung cancer and, consequently, an increased number of early-stage cases will be referred for surgical treatment. Most of these cases will be suitable for minimal invasive treatment. It is important that surgeons prepare themselves for this scenario, to deliver high-quality minimally invasive surgery to their patients, whenever appropriate.

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