Lung Cancer Screening Commentary

The recent early release of the preliminary results of the National Lung Screening Trial (NLST) has generated a great deal of excitement regarding the potential of CT screening to reduce lung cancer mortality among high risk individuals. Although public policy decisions will await a more detailed analysis of the data following publication in peer-reviewed journals, a spirited dialogue about CT screening is already underway. With this in mind, and in the context of these preliminary results, the Journal has invited international leaders in the field of lung cancer screening to share their perspectives regarding the question “Is CT screening for lung cancer ready for prime time?” In this editorial feature, Dr Rob van Klaveren, a principal investigator of the ongoing Dutch-Belgian Randomized Lung Cancer Screening (NELSON) study, and Dr Claudia Henschke, a principal investigator of the International Early Lung Cancer Action Program (I-ELCAP), share their perspectives on this topic.

Is CT Screening for Lung Cancer Ready for Prime Time?

Rob J. van Klaveren, MD, PhD

Lung cancer is a health problem of global proportions and the most important cause of cancer death in the world. Despite intensive research over many years, the prognosis is still very poor, with fewer than 15% of the patients surviving 5 years after primary diagnosis. The best way to control the future incidence of lung cancer is to reduce cigarette smoking (primary prevention). However, even after stopping smoking, long-term smokers remain at high risk of lung cancer. As a result, 80% of all lung cancer cases occur in former smokers today. Lung cancer screening (secondary prevention) might play an important role in reducing lung cancer mortality.

Our current standard of care of no screening is based on two negative lung cancer screening trials conducted in the 1970's in which chest X-ray (CXR) was compared with no screening. The most important reason for the negative outcome of these trials was that they were underpowered. In 1993, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial was initiated to determine whether CXR screening would reduce mortality rates from lung cancer. Final mortality results are only anticipated at the end of 2015.1

With the introduction of low-dose multi-detector computer (CT) technology in the 1990's, interest in lung cancer screening gained enormous momentum. After initiation of the non-randomized International Early Lung Cancer Action Project study (I-ELCAP, n = 30,000),2 several randomized clinical trials have been launched in high risk current and former smokers, including the National Lung Screening Trial (NLST, n = 53,000)3 and the Dutch Belgian randomized lung cancer screening trial (NELSON, n = 15,822).4 In NLST, control arm participants received a CXR under the presumption that the PLCO trial might be positive and CXR screening might be the new standard. In contrast, all European trials, including the NELSON trial, offer no screening to control arm participants.

Recently, the National Cancer Institute announced that the NLST showed evidence for a mortality reduction benefit of 20.3% with low-dose CT screening compared to CXR screening and a 7% overall mortality reduction after 3 annual screening rounds and 8 years of follow-up.5 This magnitude of mortality reduction is unprecedented in the history of lung cancer treatment and a major step forward in lung cancer screening research. Many questions have to be answered, however, before lung cancer screening can be introduced on a large scale. Open questions include the true magnitude of the mortality reduction that can be achieved, the number of screening rounds needed, and the optimal screen interval.

Answers to these questions are essential elements for a proper cost-effectiveness and utility analyses based on which health care decisions will be made by individual countries. Extended follow-up in NLST may show a larger mortality reduction, and modelling studies showed that, depending on the scenarios used, lung cancer mortality reductions may widely vary as compared to no screening. With a NELSON-like screening program (3 rounds with a 1- and 2-year interval), a mortality reduction of 15% after 10 years of follow-up was found, but a 23% mortality reduction with annual screening after 10 years of follow-up.6 Others found a 28% mortality reduction after 5 annual screening rounds and 6 years of follow-up.7 In a comparison between the New York-ELCAP cohort with age, sex and tobacco exposure-matched individuals from two well described cohorts, including the Beta-Carotene and Retinol Efficacy Trial (CARET) and the Cancer Prevention Study II (CPS II), the authors generated an estimated lung cancer mortality reduction for current smokers of 36% and for former smokers of 64% after 2 screening rounds and 4 years of follow-up.8 European randomized trial data will not only be important to assess the mortality reduction as compared to no screening, but will also contribute to the assessment of the optimal screening interval. The intervals used in the NELSON trial are 1, 2 and 2.5 to 3.0 years, and in the Milan MILD trial, people are randomized between a CT dense screening program (annual for 10 years) or 5 screening rounds with a 2 year...
interval. The United Kingdom Lung Cancer Screening Trial (UKLS), planned to be launched soon, will investigate the effect of one single screening round in 32,000 participants. Furthermore, we need information on overdiagnosis in lung cancer screening, development of a risk stratification model for current and former smokers, and further improvement of automated volumetric software for the management of screen detected nodules.

REFERENCES


Is CT Screening for Lung Cancer Ready for Prime Time?

Claudia I. Henschke, PhD, MD

CT screening for lung cancer has been shown to significantly reduce mortality in a high-risk population by at least 20 percent. This conclusion is based on the recently reported National Lung Screening Trial (NLST), a large randomized trial funded by the National Cancer Institute (NCI) contrasting CT screening with chest radiographic (CXR) screening. Beyond demonstrating a mortality reduction, other factors must also be considered prior to instituting a national screening policy.

As demonstrated in the United States and in Europe, guidelines are a critical component of breast cancer screening policy. Guidelines minimize potential harms by providing efficient diagnostic and therapeutic algorithms. This includes what we call the regimen of screening which specifies CT image production, radiation dose, definition of positive result, the diagnostic workup, time to diagnosis, pathologic interpretation, time to treatment and specified treatment along with integration of a smoking cessation program. The need for a multidisciplinary team using agreed upon performance indicators and audits of the performance standards are also important components.

The 1999 publication of the Early Lung Cancer Action Project’s (ELCAP) study results showed the marked superiority of CT screening over chest radiography. The results triggered a strong public demand for information on CT screening and led ELCAP to organize the International Conference on Screening for Lung Cancer. An open invitation was extended to all interested in screening, including representatives from the American Cancer Society (ACS), the NCI and many other international groups and investigators. Public demand also prompted multiple NCI Advisory Board discussions and led the NCI Director to call for a Progress Review Group report that included early detection of lung cancer 3; that many other international groups and investigators. Public demand also prompted multiple NCI Advisory Board discussions and led the NCI Director to call for a Progress Review Group report that included early detection of lung cancer 3; that many other international groups and investigators.

At the First International Conference on Screening for Lung Cancer in October 1999, the consensus among attendees was that pooling data from different institutions should be encouraged. ELCAP was charged with developing the protocol for such collaboration which was unanimously accepted and subsequently used for organizing NY-ELCAP5 and I-ELCAP. The protocol specified common elements in the regimen of screening required for data pooling, but left it to each institution to set its own enrollment criteria as to age and smoking history, thus broadening the knowledge base as to indications for screening. The protocol has been continuously updated at subsequent International Conferences, including development of criteria for emphysisma and cardiovascular disease scores.

The ELCAP design has proven efficient as relevant diagnostic information (eg, proportion of Stage I diagnoses, median tumor size) to assess annual screening can be obtained in two rounds of screening and the initial ELCAP results were confirmed by the NY-ELCAP. Once lung cancer is diagnosed, the prognostic information can be addressed using either experimental or quasi-experimental approaches. The latter was used to estimate the cure rate of 80% (95% CI: 74%-85%) for lung cancers diagnosed by CT screening among the study’s 31,467 participants following the I-ELCAP protocol. In the absence of screening, the cure rate was about 10%. Thus, a substantial gain in the cure rate was demonstrated and the possible biases of the estimate were also addressed. From the Mount Sinai School of Medicine, New York, NY.

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Motivated by the ELCAP results, the NCI started the NLST in 2002 to compare CT with CXR screening. The NCI study used 25,000 high-risk participants for each arm of the trial and provided 3 rounds of screening per arm. CXR screening was the control arm because another randomized trial started in 1993, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), compares CXR with no screening. On November 4, 2010, the NCI reported that the null hypothesis had been rejected as a 20.3% mortality reduction had been reached.

How do we reconcile the difference in the I-ELCAP estimated cure rate of 80% and the NLST mortality reduction estimate of 20.3%? The answer lies in understanding they are measuring very different parameters and even though they appear quite different, they are consistent with each other. Clearly, the two measures are inter-related; there cannot be a reduction in mortality unless some participants with potentially fatal lung cancer had been cured by the early diagnosis provided by the CT screening followed by early treatment. But why the big difference?

I-ELCAP estimated the cure rate which is a quantitative measure that is dependent on the regimen of screening which includes the low-dose CT scan. The NLST tested the null hypothesis of no mortality reduction of the low-dose CT scan when compared with CXR against the alternative hypothesis of a mortality reduction of at least 20% due to the CT scan. The design uses a limited number of rounds of screening and years of follow-up to reduce the time and cost of the trial. Importantly, the magnitude of the mortality reduction for the alternative hypothesis is an arbitrary value that the designers set. Whether a statistically significant difference between the two hypothesis can be found depends on the design parameters, the actual diagnostic workup and treatment that was performed in the trial and of course, the initial low-dose CT scan provided in each round of screening. Once significance is reached, the trial is stopped.

The full mortality reduction provided by CT screening would only be reached if: screening is continuous for many years, probably 10 years; a well-defined, optimal protocol (eg, I-ELCAP) is used; and, the analysis focuses on the appropriate time interval where the maximum mortality rate reduction becomes manifested, some 7 to 10 years after baseline, and a control arm which provides no screening is used. These requirements are illustrated by analysis of a CT screened cohort compared to a cohort with no screening and, likewise for breast cancer and other cancers as well.

The profound difference in the study design needed to provide a quantitative estimate and one used to test of hypothesis is often not fully appreciated, but should be!

REFERENCES