

## Survival of Patients with Clinical Stage I Lung Cancer Diagnosed by Computed Tomography Screening for Lung Cancer

Claudia I. Henschke for the International Early Lung Cancer Action Program Investigators

Research on computed tomography (CT) screening for lung cancer began in the early 1990s upon the introduction of scanners that allowed complete imaging of the chest in a single breath-hold. At that time, we reviewed prior screening trials for lung cancer and decided to develop an alternative approach (1) based on the recognition that screening for a cancer is the study of the pursuit of early asymptomatic-latent diagnosis of the cancer. The purpose of early diagnosis is to provide for early treatment of the cancer, as it is the treatment that serves to potentially prevent the deaths from lung cancer that would have otherwise occurred.

The aim of the diagnostic research is to determine the frequency of finding people with clinical stage I lung cancer, and this can only be assessed in those that undergo screening. Therefore, we screened 1,000 people with high risk of lung cancer in the Early Lung Cancer Action Project (ELCAP) and found that 85% of the diagnoses were achieved in clinical stage I lung cancer (2, 3). This high proportion of clinical stage I lung cancer diagnoses was in marked contrast to the 15% found in the absence of screening. We also compared chest radiography with CT as we had provided both to all participants and found that chest radiography missed 83% of the patients with clinical stage I NSCLC that were identified by CT (2).

Subsequent to our initial publications (1–3), ELCAP has expanded to form the International (I)-ELCAP, which recognized the benefit of data pooling rather than later metaanalysis.<sup>1</sup> The required regimen of screening was developed, which allowed each participating institution to specify its own enrollment criteria.<sup>2</sup> Regular review of the data, updates of the regimen of screening, and pathologic review of the diagnosed cases of lung cancer were done (4).

The I-ELCAP collaboration confirmed the initial ELCAP finding that 85% of patients diagnosed with lung cancer had clinical stage I NSCLC disease. It also showed that the smaller the cancer the more likely it was to be in clinical stage I NSCLC, which highlighted the usefulness of finding latent cancers at small sizes and suggested that tumor diameter serves as a prognostic indicator for curability, perhaps even for micrometastases not detectable by our current techniques. Although this had previously been shown using the SEER data (5–7), registry data underestimate the real benefit of finding small lung cancers. Based on the initial ELCAP results, it was

estimated that CT screening may result in a cure rate between 60% and 80% (2), much higher than the 5% found in the absence of screening.

The aim of the required intervention research in the context of screening is to determine the benefit of early treatment in preventing death from lung cancer. This question requires a comparison, as treatment, different from diagnosis, potentially changes the disease course and the justifiability of screening requires that the early treatment be sufficiently effective compared with later symptom-prompted treatment. In 2006, I-ELCAP reported on the long-term survival of the patients with clinical stage I lung cancer (8). In this latest I-ELCAP report, lung cancer was diagnosed in 484 participants and their estimated 10-year survival rate was 80% (95% confidence interval, 74–85), regardless of stage or treatment. Among 484, 412 patients (85%) had clinical stage I lung cancer. Among these 412, 302 patients with clinical stage I lung cancer underwent prompt resection (within 1 month) and their estimated 10-year rate was 92% (95% confidence interval, 88–95). The comparator cohort for these 302 clinical stage I lung cancer patients who had prompt resection were the eight with clinical stage I lung cancer who received no treatment and who all died of their lung cancer within 5 years. This comparator cohort provides for learning about the frequency of early diagnosed lung cancer deaths but also importantly the timing of these potentially preventable deaths.

Critics of our study design say our estimates of survival are potentially confounded by lead time, length, and overdiagnosis bias of unknown magnitude and thus defy meaningful interpretation (9). But screening for a cancer is supposed to provide for lead time in diagnosis and treatment. A bias is introduced when treatment effectiveness is assessed by comparing relatively short-term survival rates of a treatment with lead time relative to treatment without lead time. But we did not do this (9).

The longer the latent stage for a subtype of the cancer, the more prevalent it is in baseline screening. Cancers diagnosed at baseline thus tend to grow more slowly than the subtype of cancer in general, including when it is diagnosed in the screening's repetitions. Although this fact may call for making a distinction between baseline and repeat screening, it is not a bias in it. Also, cancers are diagnosed later in their latent course at baseline relative to those diagnosed at repeated screenings, without this being said to introduce timing bias. These facts were also reflected in the pathologic findings of the lung cancers diagnosed at baseline and annual screenings (10).

As to overdiagnosis biasing our survival rates, review of the resected specimens by a panel of expert pulmonary pathologists

**Author's Affiliation:** Radiology and Cardiothoracic Surgery, New York Presbyterian Hospital-Weill Cornell Medical Center, New York, New York  
Received 2/6/07; revised 6/4/07; accepted 6/25/07.

**Requests for reprints:** Claudia I. Henschke, Radiology and Cardiothoracic Surgery, Box 586, The New York Presbyterian Hospital-Weill Cornell Medical Center, 525 East 68th Street, New York, NY 10021. Phone: 212-746-2529; Fax: 212-746-2811; E-mail: chensch@med.cornell.edu.

© 2007 American Association for Cancer Research.  
doi:10.1158/1078-0432.CCR-07-0317

<sup>1</sup> International Conferences on Screening for Lung Cancer (www.IELCAP.org).

<sup>2</sup> International Early Lung Cancer Action Program protocol (www.IELCAP.org).

confirmed that all were genuine lung cancer. Of the patients whose clinical stage I lung cancer was resected, the panel found that 95% were invasive lung cancers whereas the remaining 5% were classified as adenocarcinomas of the bronchioalveolar subtype. This latter subtype by definition does not have invasion of the basement membrane but is considered to be a precursor lesion of invasive adenocarcinoma, the mixed subtype. Finally, all those patients with clinical stage I NSCLC who were not treated died within 5 years of their lung cancer.

The traditional approach for evaluation of screening is to perform a randomized screening trial and compare the mortality from lung cancer in the screened cohort to that of the control cohort, in which mortality in such a trial is defined by deaths from lung cancer divided by person-years of screening. Although this approach avoids overdiagnosis bias as it considers only death from lung cancer and not the number of people diagnosed with it, such a trial requires many years of screening, which is very expensive and increases other problems, such as protocol compliance (11). The National Lung Screening Trial<sup>3</sup> uses this traditional approach and provides three rounds of screening, while we have estimated it would require 10 years of screening. There are other concerns, as well, which we have already shown in addressing the controversies resulting from the breast cancer randomized screening trials (11, 12). Alternatively, modeling has been used to estimate the expected deaths in the absence of screening. The article by Bach et al. (13) illustrates such an approach. In their study, an unspecified model for predicting death from lung cancer was applied to three small studies of CT screening for lung cancer. Unfortunately, more than five of the deaths occurred in people with symptoms of late stage lung cancer at the time of enrollment as well as in patients who did not have a systematic approach of follow-up imaging and biopsy, despite

the paper repeatedly stated that the enrollees were asymptomatic and followed a systematic approach. Exclusion of even five of these ineligible people would have resulted in a statistically significant reduction in deaths due to CT screening even in the early years when it is not expected (12).

Are the currently available results on CT screening to date sufficiently effective to justify screening people who are at risk of lung cancer? Compared with mammography screening for breast cancer, the lung cancer detection rate of 1.3% for baseline and 0.3% for annual repeat screening of I-ELCAP participants 40 years of age and older were slightly higher to those of breast cancer of 0.6% to 1.0% for baseline screening and comparable with those 0.2% to 0.4% for annual repeat screening of women 40 years of age and older (8). The cancer detection rate is dependent on the risk profile of the screenees, and the higher the risk the more productive the screening. Thus, as expected, CT screening of the original ELCAP participants who were former and current smokers at 60 years and older (2, 3) was more productive in detecting lung cancer, as the detection rates were 2.7% for baseline and 0.6% for annual repeat screening. The actual cost of the low-dose CT scan is below \$200, and surgery for clinical stage I lung cancer is less than half of late-stage treatment so that using the original ELCAP data and the actual hospital costs for the work-up, we found CT screening for lung cancer to be highly cost-effective (8). Others have also estimated that cost-effectiveness of CT screening for lung cancer for various risk profiles and their estimates are comparable with that of mammography screening (8).

In conclusion, a person at high risk for lung cancer, who is asymptomatic and interested in potentially being screened, should be fully apprized of the implications of screening and of the treatment that may result (14). In light of this, it is reasonable for the individual to choose to be screened by a multidisciplinary medical team with experience in performing such screenings, using a well-defined CT regimen of screening and having appropriate quality assurance procedures in place.

<sup>3</sup> Aberle D. National Lung Screening Trial (<http://www1.umn.edu/eoh/NewFiles/nlstinfo.html>).

## References

1. Henschke CI, Miettinen OS, Yankelevitz DF, Libby D, Smith JP. Radiographic screening for cancer: New paradigm for its scientific basis. *Clin Imaging* 1994;18:16–20.
2. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet* 1999;354:99–105.
3. Henschke CI, Naidich DP, Yankelevitz DF, et al. Early Lung Cancer Action Project: preliminary findings on annual repeat screening. *Cancer* 2001;92:153–9.
4. I-ELCAP Investigators. CT Screening for Lung Cancer: The relationship of disease stage to tumor size. *Arch Intern Med* 2006;166:321–5.
5. Wisnivesky JP, Yankelevitz DF, Henschke CI. The effect of tumor size on curability of Stage I non-small-cell lung cancers. *Chest* 2004;126:761–5.
6. Yankelevitz DF, Wisnivesky JP, Henschke CI. Stage of lung cancer in relation to its size. 1. Insights. *Chest* 2005;127:1132–5.
7. Wisnivesky JP, Yankelevitz DF, Henschke CI. Stage of lung cancer in relation to its size. 2. Evidence. *Chest* 2005;127:1136–9.
8. The International Early Lung Cancer Action Program Investigators. Survival of Patients with Stage I lung cancer detected on CT screening. *N Engl J Med* 2006;355:1763–71.
9. Henschke CI, Smith JP, Miettinen OS. Response to letters to the editor. *N Engl J Med* 2007;356:743–7.
10. Carter D, Vazquez M, Flieder DB, et al. Comparison of pathologic findings of baseline and annual repeat cancers diagnosed on CT screening. *Lung Cancer* 2007;56:193–9.
11. Henschke CI, Yankelevitz DF, Kostis WJ. CT screening for lung cancer. *Semin Ultrasound CT MR* 2003;24:23–32.
12. Miettinen OS, Henschke CI, Pasmantier MW, Smith JP, Libby DM, Yankelevitz DF. Mammographic screening: No reliable supporting evidence? *Lancet* 2002;359:404–5.
13. Bach PB, Jett JR, Pastorino U, Tockman MS, Swensen SJ, Begg CB. Computed Tomography Screening and Lung Cancer Outcomes. *JAMA* 2007;297:953–97.
14. Henschke CI, Austin JH, Berlin N, et al. Minority Report: CT screening for lung cancer. *J Thorac Imaging* 2005;20:324–5.