Ability of Low-Dose Helical CT To Distinguish Between Benign and Malignant Noncalcified Lung Nodules*

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Study objectives: **Low-dose helical CT scanning identifies early stage lung malignancies and also a large proportion of lung nodules of uncertain diagnostic and prognostic significance (*ie*, indeterminate nodules). The sensitivity, specificity, and predictive value of these indeterminate nodules detected by CT scanning as part of a lung cancer screening program is largely unknown. We therefore calculated the sensitivity, specificity, and predictive values of CT-detected lung nodules that were followed up at least 18 months.**

Design: **Single-arm screening trial with longitudinal follow-up.**

Setting: **Rural areas of United States, from 2000 to 2004.**

Participants: **Former and current nuclear weapons workers, ≥ 45 years old, including smokers and never-smokers, with variable exposure to occupational lung carcinogens.**

Interventions: **A total of 4,401 participants were CT scanned for lung cancer with an initial full chest low-dose CT scan, interval CT scans at 3, 6, and 12 months for indeterminate lung nodules (*eg*, nodules not immediately suspicious for lung cancer), and a 18-month, full-chest, low-dose incidence CT scan.**

Results: **We achieved follow-up for a minimum of 18 months for > 95% of 807 participants with indeterminate or suspicious lung nodules. Only 3 of 727 indeterminate nodules were identified as being malignant during the subsequent 18 months. The radiologist's designation of a nodule as suspicious had a sensitivity of 84.2% and a specificity of 96.6%. Given a prior probability of lung cancer of 2.4%, positive and negative predictive values were 37.2% and 99.6%. Overall, we detected 33 primary lung cancers, including 19 stage I cancers, 5 stage II cancers, 7 stage III-IV cancers, and 3 limited-stage small cell cancers.**

Conclusions: **Helical CT scanning detects many indeterminate nodules, but few are malignant. CT scanning has high sensitivity and specificity to detect early lung cancer. The problem of false-positive results in helical CT scanning is limited and can be rationally managed. Current CT follow-up recommendations are supported.** ***(CHEST 2007; 131:1028–1034)***

Key words: CT scan; indeterminate nodules; lung cancer; screening

Abbreviations: CI = confidence interval; ELCD = Early Lung Cancer Detection; PET = positron emission tomography

Recent studies in Japan, the United States, and Italy[1–6] have established that the low-dose helical CT scan can detect early stage lung cancer that is amenable to resection. The large majority (60 to 85%) of lung cancers detected by CT screening were stage I or IIa at diagnosis. These studies occurred at academic medical centers and principally evaluated high-risk populations, defined as people at least 50 or 60 years old who had smoked cigarettes.

A salient problem in the use of low-dose CT scan for early lung cancer detection is the uncertainty that attends the high proportion of participants who have indeterminate nodules (*eg*, nod-

ules not immediately suspicious for lung cancer). Most indeterminate nodules are not malignant, and there is a critical need to avoid potential harm that may derive from excess radiation, anxiety, and invasive workup of false-positive CT findings. Due to this uncertainty, initial CT screening protocols recommended frequent follow-up CT scans.[2,7,8] Indeed, these initial screening protocols echoed recommendations for follow-up of lung nodules detected incidentally during clinical workup (*ie*, nonscreening context).[9–11]

More recently, investigators have factored in nodule size when recommending frequency of follow-up CT scans; Henschke and colleagues[12] no longer recommend any interval scan (*ie*, prior to the annual 12-month scan) for nodules < 5 mm. Similarly, a committee of the Fleischner Society made the same recommendation for small lung nodules (< 5 mm) that are detected in nonscreening settings.[13] However, studies[12,14] that specify the probability that nodules < 5 mm are malignant are few.

Lung nodule morphology viewed on CT scan is a second key determinant of likelihood of malignancy.[12,14–16] Morphologic characteristics that are suggestive of malignancy are well recognized,[15,16] although the CT screening trials completed to date provide little detail about this aspect of detected nodules, especially the relation between size and morphology.

The current study employs frequent CT scans and near complete follow-up of the cohort to provide valuable information about the nature of CT-detected indeterminate nodules. The screening population consists of rural uranium plant workers, with a broader range of lung cancer risk factors than heretofore studied in the United States, including a greater age span, nonsmokers and former smokers who had quit many years previous to examination, and potential occupational exposures to lung carcinogens.

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Materials and Methods

Study Population

The Early Lung Cancer Detection (ELCD) program applied helical CT scanning to 4,401 active or retired workers at three Department of Energy uranium gaseous diffusion plants in Tennessee, KY, and Ohio between 2000 and 2004. Workers were variably exposed to lung carcinogens, including uranium, plutonium, asbestos, nickel, and beryllium.[17] The United Steelworkers (and its predecessor union, the Paper, Allied-Industrial, Chemical, and Energy International Union) was a major collaborator.

Participants were previously screened with spirometry and posteroanterior and lateral chest radiographs. If a chest radiograph showed a lung mass, the participant was referred to the personal physician for diagnosis. Chest radiographs were obtained a mean of 10.1 months (SD, 7.0 months) prior to the initial CT scan.

Eligibility Criteria for Helical CT Scan

Gaseous diffusion plant workers were eligible for helical CT scanning if they met risk criteria (Table 1). Seven people whose lung cancer was first identified by chest radiograph were not eligible for the ELCD program. Institutional Review Boards of Queens College and the Oak Ridge Associated Universities approved the study. All participants signed an informed consent.

CT Scanning Protocol

The CT scanner was a coach mounted (General Electric HiSpeed DX/I; General Electric Medical Systems; Milwaukee, WI) and was operated by one technician. CT scans used a low-dose technique (120 kilovolt peak, 40 to 50 mA; high-frequency reconstruction algorithm). Images were acquired at a pitch of 1.5 with 7-mm collimation, reconstructed at 6-mm intervals. The first 1,248 CT scans were interpreted by radiologists in the target communities. Thereafter, all CT scans were interpreted by thoracic radiologists in New York City.

Nodule Definition

Opacities with a length/width ratio < 3 were considered nodules, permitting differentiation from blood vessels. Lung nodules with uniform or ring calcification were considered benign. Noncalcified nodules with irregular margins, regardless of size were deemed suspicious. Nodules ≥ 3 mm in maximum

Table 1—*Eligibility Criteria for Participation, ELCD Program, 2000–2004*

Participant Age, yr	Criteria
Any	Scarring of lung or pleura related to asbestos/silica, or at least one positive beryllium lymphocyte proliferation test result
45 to 49	Smoked ≥ 20 yr and quit ≤ 15 yr ago; and/or Department of Energy production, maintenance, or laboratory worker ≥ 5 yr and work began ≥ 20 yr previously
≥ 50	Smoked ≥ 10 yr and quit smoking ≤ 15 yr ago; and/or Department of Energy production, maintenance, or laboratory worker ≥ 5 yr