CT Screening for Lung Cancer: Diagnoses Resulting from the New York Early Lung Cancer Action Project[1]

New York Early Lung Cancer Action Project Investigators

Purpose: To evaluate prospectively the diagnostic performance of the New York Early Lung Cancer Action Project (NY-ELCAP) regimen in the diagnosis of early lung cancer at baseline and annual repeat computed tomographic (CT) screenings.

Materials and Methods: Informed consent and institutional review board approval were obtained for this HIPAA-compliant study of baseline and annual repeat low-dose CT screening performed with a common regimen in asymptomatic individuals at 12 institutions in New York State. All 6295 participants were aged 60 years or older, had smoked for at least 10 pack-years, had no prior cancer, had not undergone chest CT in the previous 3 years, and were medically fit to undergo thoracic surgery. Median age was 66 years, and median smoking history was 40 pack-years. The proportion (and 95% exact confidence intervals [CIs]) of subjects with a positive result, as determined by using nodule size; the diagnoses of lung cancer resulting from subsequent work-up; and the distribution by cancer stage and cell type were determined. When relevant, 95% CIs for the proportions were calculated.

Results: Initial CT imaging led to recommendations for further work-up in 14.4% (95% CI: 13.5%, 15.3%) of the 6295 baseline screenings and 6.0% (95% CI: 5.1%, 6.6%) of the 6014 annual repeat screenings. Of 101 patients in whom the diagnosis of lung cancer resulted from baseline screening and three in whom a diagnosis of lung cancer was prompted by symptoms prior to the first scheduled repeat screening, 95 (91.3%) had no clinical evidence of metastases. Of the 20 patients in whom the diagnosis of lung cancer resulted from annual repeat screening, 17 (85%) showed no evidence of metastases. Of the 134 recommended biopsies, 125 (93.3%) resulted in diagnosis of lung cancer or another malignancy, while none of the 24 biopsies performed outside of the recommendation of the regimen resulted in diagnosis of lung cancer.

Conclusion: The NY-ELCAP regimen of screening revealed that annual CT screening for lung cancer resulted in identification of a high proportion of patients with early-stage disease.

[1] The complete list of investigators and affiliations is in the Appendix. From the 2004 RSNA Annual Meeting. Received March 14, 2006; revision requested May 17; revision received June 9; accepted July 7; final version accepted September 1. Supported in part by the City of New York Department of Health and Mental Hygiene; Starr Foundation; Empire Blue Cross and Blue Shield; New York Community Trust; New York State Office of Science, Technology, and Academic Research; the Rogers Family Fund; Weill Medical College of Cornell University; Cornell University; and Academic Medical Development Company. **Address correspondence to** Claudia I. Henschke, PhD, MD, Department of Radiology, New York Presbyterian Hospital–Weill Cornell Medical Center, 525 E 68th St, New York, NY 10021 (e-mail: *chensch@med.cornell.edu*).

Radiology

The goal of cancer screening is to assign a diagnosis before symptoms or overt signs of cancer develop. The screening process begins with baseline screening. This is followed by periodic repeat screening. It is important to distinguish between baseline and repeat screenings. For one, the baseline and repeat screening regimens are different; thus, the diagnostic performance of each regimen may be different with respect to the frequency of positive results and the proportion of patients in whom lung cancer was diagnosed by means of prognostic indicators (eg, cancer stage). Furthermore, the performance properties of repeat screening must be emphasized because it is these repeated rounds of screening that are typical of the entire program, not the first round of baseline screening.

The baseline computed tomographic (CT) screening findings in 1000 high-risk participants in the Early Lung Cancer Action Project (ELCAP) (1) sparked considerable interest in CT screening for lung cancer (2); however, expansion—particularly of repeat screening—was needed (3). This led us to augment the original ELCAP, which was conducted at two institutions in New York, NY, with the New York ELCAP (NY-ELCAP), which involved 12 institutions throughout the state of New York.

NY-ELCAP investigators used the same design to evaluate the cancer screening that had been used in ELCAP (1,4,5). The design makes a sharp distinction between screening per se (the pursuit of an early diagnosis) and the intervention that may be recommended after diagnosis of lung cancer is made. The NY-ELCAP regimen incorporated advances in CT technology and ELCAP findings. Multi–detector row CT scanners replaced single–detector row CT scanners. The number of images obtained increased by an order of magnitude, and this led to the discovery of additional small nodules. Smaller nodules were also identified because images were interpreted on high-resolution monitors instead of film hard copies. Analysis of the ELCAP experience (6–10) led to refinements in the screening regimen that enabled us to avoid unnecessary work-up, particularly at baseline screening. Thus, the purpose of our study was to evaluate prospectively the diagnostic performance of the NY-ELCAP regimen in the diagnosis of early lung cancer at baseline and annual repeat CT screenings.

Advances in Knowledge

- The results from baseline and repeat screening are different.
- The proportion of screenees with a positive screening result and diagnosis of stage I cancer depends on the screening regimen (criteria of positive results and work-up of patients with a positive result).

Materials and Methods

Empire Blue Cross and Blue Shield, New York City, the state of New York, the Starr Foundation, and the New York Community Trust all contributed funds to the Academic Medical Development Company for this study. The authors controlled all data and information submitted for publication.

The Screened Cohort

Beginning in June 2000 and lasting through February 2003, 6295 asymptomatic volunteers aged 60 years or older who had a smoking history of at least 10 pack-years, had no history of cancer (other than nonmelanotic skin cancer), had not undergone chest CT in the past 3 years, and were considered fit enough to undergo thoracic surgery were enrolled in NY-ELCAP. Recruitment was achieved by informing the physicians at each institution about the project and by running newspaper, radio, and television announcements. Consent was obtained from all patients for baseline and annual repeat screenings. The study protocol was compliant with the Health Insurance Portability and Accountability Act and approved by the institutional review board at each institution. Patients were screened at Weill Medical College of Cornell University, which was the coordinating center (n = 1337); State University of New York at Stony Brook (n = 791); Maimonides Medical Center (n = 707); Roswell Park Cancer Institute (n = 623); State University of New York, Upstate Medical University (n = 569); North Shore–Long Island Jewish Health System (n = 567); Columbia University Medical Center (n = 547); Mount Sinai School of Medicine (n = 455); Memorial Sloan-Kettering Cancer Center (n = 305); New York Medical College (n = 230); Our Lady of Mercy Medical Center (n = 133); and State University of New York, Downstate Medical Center (n = 31).

Of the 6295 participants, 3221 (51.2%) were women, 5480 (87.1%) were white, 460 (7.3%) were black, 211 (3.4%) were Hispanic, 102 (1.6%) were Asian, and 42 (0.7%) were American Indian, Pacific Islander, or other. At admission, median patient age was 66 years and median smoking history was 40 pack-years; 2082 (33.1%) patients were current smokers, 763 (12.1%) had a history of asbestos exposure, and 1298 (20.6%) had a family history of lung cancer.

Of the 6295 participants, 45 died of causes other than lung cancer prior to annual repeat screening, 147 had medical reasons—including diagnosis of lung cancer (n = 21) or another type of cancer (n = 6)—for not returning for repeat screening, and 96 moved out of the area. Of the remaining 6007 participants, 5134 underwent the first annual repeat screening examination (7–18 months after baseline screening). Of

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Abbreviations:
ELCAP = Early Lung Cancer Action Project
NY-ELCAP = New York ELCAP

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these 5134 subjects, 880 underwent additional annual repeat screening, which resulted in a total of 6014 annual repeat screenings. Of the 5134 participants who underwent annual repeat screening, 2631 (51.2%) were women, 4557 (88.8%) were white, 338 (6.6%) were black, 141 (2.7%) were Hispanic, 64 (1.2%) were Asian, and 34 (0.7%) were American Indian, Pacific Islander, or other. At the time of repeat screening, median age was 67 years, median smoking history was 41 pack-years, 1337 patients (26.0%) were current smokers, 667 (13.0%) had a history of asbestos exposure, and 1077 (21.0%) had a family history of lung cancer.

Initial Imaging

In four institutions, baseline and repeat screenings were performed with multi–detector row CT scanners at 120 kVp and 40 mA, with a pitch of 1.5 (as defined by the International Electrotechnical Commission) and collimation of 1.25 mm. In seven institutions, baseline and repeat screenings were performed with single–detector row CT scanners at 120 kVp and 40 mA, with a pitch of 2.0 and collimation of 10 mm. In the remaining institution, baseline screening was performed with a single–detector row helical CT scanner, whereas repeat screening was performed with a recently installed multi–detector row CT scanner. The technical parameters used in these examinations were the same as those used in the other single– and multi–detector row CT examinations.

In all CT examinations, contiguous images were obtained from the thoracic inlet to the adrenal glands during a single breath hold (15–20 seconds). Intravenous contrast material was not used. The scans were electronically sent to the coordinating center on a daily basis via the Web-based ELCAP management system (11).

Interpretation of Initial CT Images

The images from the initial CT examination in the baseline and repeat rounds of screening were interpreted at each site by a radiologist (7–25 years of experience in the interpretation of thoracic CT images) who was aware that these images were obtained during baseline or repeat screening, and his or her interpretation was transmitted to the coordinating center via the ELCAP management system. In ELCAP (1,3), multiple images were viewed on film hard copies; however, in NY-ELCAP, radiologists viewed images on a high-resolution monitor at typical window and level settings and scrolled through the images one by one. For repeat screenings, images were displayed side-by-side with the corresponding images obtained at baseline screening or more recently. For the purpose of assessing nodule and lymph node sizes, however, the settings were standardized and were the same as those used in ELCAP: The window width and level settings, respectively, were 1500 HU and −650 HU for lung nodules and 350 HU and 25 HU for lymph nodes. A second central interpretation was performed at the coordinating center by one of three chest radiologists (C.I.H., D.I.M., and D.F.Y., with 20, 20, and 15 years of experience, respectively), all of whom had 8 years of experience interpreting low-dose screening CT images, without knowledge of the results of the on-site interpretation. The on-site radiologist received the independent central interpretation via the ELCAP management system. Discrepancies (if any) were highlighted, and the on-site radiologist used this information to revise his or her interpretation. For the purposes of this report, the final consensus interpretation was defined as that made by one of the three central-interpretation radiologists after review of the second on-site interpretation.

The radiologists' first concern was to identify all noncalcified nodules, including parenchymal and endobronchial nodules, that were visible on the CT images. The elusiveness of a precise definition of a nodule on CT images was recognized by MacMahon et al (12); however, previously, a nodule was defined as a nonlinear round opacity in ELCAP (1). A nodule was classified as noncalcified if it was *(a)* less than 5 mm in diameter and appeared noncalcified in its entirety (attenuation of the nodule was less than that of the ribs on images obtained with bone and lung window settings); *(b)* 5–20 mm in diameter and wholly noncalcified or the edge of the nodule was spiculated (to any extent), even when it had calcifications of a classic benign pattern (central, lamellated, or popcorn); or *(c)* larger than 20 mm in diameter and any part of it was noncalcified. Nodules were considered benign if they were classified as calcified with these criteria or if they contained sufficient fat to be classified as hamartomas.

For each noncalcified nodule that satisfied the above criteria, location (lobe and distance, in millimeters, to costal pleura), size (length and width, in millimeters), and consistency (solid, part solid, or nonsolid) were documented. Size was addressed in terms of diameter, which was defined as the average length and width of the nodule on the image with the largest cross-sectional area. Consistency was considered solid if the nodule obscured the entire lung parenchyma within the nodule, part solid if it obscured part of the lung parenchyma within the nodule, and nonsolid if it did not obscure the lung parenchyma within the nodule (6). The term *subsolid nodule* was used to indicate a nodule that was part solid, nonsolid, or both.

Positive Result

For baseline screening, the definition of a positive result on the initial CT examination was based on knowledge gained in ELCAP (1,6–10). The result was considered positive if radiologists identified at least one *(a)* solid or part-solid noncalcified nodule at least 5 mm in diameter or *(b)* nonsolid noncalcified nodule at least 8 mm in diameter.

The result was considered semipositive if the radiologists identified *(a)* noncalcified solid or part-solid nodules that were all smaller than 5 mm in diameter or *(b)* nonsolid nodules that were all smaller than 8 mm in diameter (ie, nodules were too small to be considered positive findings). On the basis of analysis of ELCAP results (7), we concluded that no further evaluation was required until repeat screening 1 year after initial baseline imaging.

For annual repeat screening, the definition of a positive result remained

the same as that in ELCAP (3): Any newly identified noncalcified nodule (thus growing in size since prior screening), regardless of size or other features. The definition of growth was updated to account for nodule consistency: Any enlargement of the entire nodule, growth of the solid component of a part-solid nodule, or development of a solid component in a previously nonsolid nodule that was visually identified by the radiologist was considered a sign of growth.

When a single–detector row CT unit was used, a positive result was considered tentative. Thereafter, nodules were immediately examined by using CT with a 1-mm collimation. As in ELCAP, in NY-ELCAP, the result from the latter examination was the basis for the final classification as positive or negative according to the criteria given previously.

Work-up after a Positive Result

As in ELCAP (1), in NY-ELCAP, the work-up recommended after a positive result was identified depended on the diameter of the relevant nodules (9).

In the baseline round, for nodules 5–14 mm in diameter, one option was to perform CT 3 months after the initial CT examination. Another option was to immediately perform positron emission tomography (PET). If the nodule showed signs of growth or if PET findings were positive, biopsy was performed; otherwise, the work-up stopped. For nodules 15 mm in diameter or larger (regardless of whether they were solid, part solid, or nonsolid), another option was to perform biopsy immediately. Ideally, fine-needle aspiration biopsy would be performed. If this option was unavailable, patients were examined with video-assisted thoracoscopy, bronchoscopy, or a combination of these techniques, with bronchoscopy recommended primarily in patients with endobronchial lesions. In patients suspected of having an infection, physicians could prescribe a 2-week course of antibiotics and perform CT 1 month later. If the nodule showed no resolution or growth, biopsy was to be performed; otherwise, work-up stopped. Repeat CT screening was to be performed 12 months after initial CT in all participants for whom work-up stopped or biopsy did not result in a diagnosis of lung cancer.

In repeat rounds, if all nodules were smaller than 3.0 mm in diameter, CT was to be performed 6 months later; however, if the diameter of the largest nodule was larger than 3.0 mm but smaller than 5.0 mm, CT was to be performed 3 months later. If growth was identified, biopsy was to be performed immediately; however, if no growth was seen in any of the nodules, work-up stopped. If at least one noncalcified nodule was 5.0 mm in diameter or larger, an immediate 2-week course of broad-spectrum antibiotics was recommended and followed by CT 1 month after initial CT. If the relevant nodules had completely or partially resolved, work-up stopped. If any nodule showed growth or no resolution, options for further evaluation were immediate biopsy or PET. If PET findings were positive, biopsy was to be performed. If PET findings were indeterminate or negative, CT was to be performed 3 months later. If CT revealed nodule growth, biopsy was to be performed; otherwise, work-up stopped. Repeat CT screening was to be performed 12 months after initial CT in the prior screening examination in all participants for whom work-up stopped or biopsy did not result in a diagnosis of lung cancer.

Radiologists visually assessed nodule growth and focused on the image that showed the largest cross-sectional area of the nodule. Growth of nodules smaller than 15 mm in diameter was based on the radiologist's measurement. When the radiologist was uncertain about growth, the nodule was assessed with automated nodule volumetry at the coordinating center and considered to be growing if its volume increased by more than 10% per month (13–15).

For further work-up in patients with a positive result, the imaging equipment used and specifications for its use followed the standard practice in place at the institution where the examination was performed. Biopsy was performed in accordance with the standard practice in place at the institution where it was performed. NY-ELCAP provided the initial CT examination for the baseline round and one repeat screening CT examination at no charge; thereafter, participants with noncalcified nodules that showed no growth on the initial CT images of the first annual repeat round were followed up according to the usual standard of care at that institution.

Rule-in Diagnosis after Biopsy

Biopsy specimens were submitted to experienced pathologists for independent interpretation. The cytology specimens were reviewed by a cytologist (M.F.V.) with 18 years of experience. The lesion was classified as malignant if malignant cells were seen, as atypical if cytologic findings were suspicious for either adenocarcinoma with bronchioloalveolar features or atypical adenomatous proliferation, as benign if a specific benign diagnosis could be made (eg, hamartoma, granulomatous disease, fibrosis, or normal lymph node), or as indeterminate. Histologic specimens were reviewed in accordance with a defined protocol (16,17) by a five-member panel of pulmonary pathologists with 20–37 years of experience (D.C., E.B., A.G., M.N., W.T.) who assigned the consensus diagnosis according to the World Health Organization criteria published in 2004 (18).

A rule-in diagnosis of lung cancer was classified as a baseline screening diagnosis if it resulted from work-up prompted by a positive finding at baseline screening, regardless of when the diagnosis was actually made. Diagnoses were also classified in this way if the result was semipositive in that it called for repeat CT evaluation 1 year later. If the result of initial baseline CT was negative and diagnostic work-up was prompted by suspicion-raising symptoms (or an incidental finding) before the scheduled first annual repeat screening, it was classified as an interim diagnosis in the baseline round, regardless of when the diagnosis was made. Analogous attributions were applied in the context of repeat-screening rounds.

To document interim diagnoses of

lung cancer in baseline and annual repeat screening rounds, each patient enrolled in the study who did not return for repeat screening was contacted 1 year after initial repeat screening or the most recent screening. If the patient could not be contacted either directly or through relatives, the referring physician was contacted. If these steps failed to provide the needed information, death records were reviewed.

Characterization of Patients in Whom Lung Cancer Was Diagnosed

Each patient in whom lung cancer was diagnosed was characterized in terms of the disease stage and cell type and also by the nodule consistency and size. Clinical TNM classification was based on the CT and PET (if applicable) findings obtained closest in time to when biopsy was recommended. Staging was problematic when no lymph node metastases were detected but more than one cancer was diagnosed in the same lobe or in a different lobe. When there are no detectable lymph node metastases and the cell types of cancers are the same, the classification is supposed to be T4N0M0, T1N0M1, or T2N0M1 depending on whether the lesions are in the same or different lobes, not T1N0M0 or T2N0M0 (19). Only when the cell types are different should the lesions be classified as separate primary cancers. However, adenocarcinoma is a very common type of lung cancer; therefore, the likelihood of finding the same cell type is high, even with separate primary cancers. Thus, patients with multiple adenocarcinomas (all smaller than 30 mm in diameter) without lymph node metastases were classified as if they had stage I lung cancer (20).

The type of intervention, its results, and its timing after diagnosis of lung cancer were documented by the principal investigator at the participating institution. This investigator also documented patient deaths that occurred within 30 days of the intervention.

Adherence to the Screening Regimen

Once a patient was deemed eligible for the study and had signed the consent form, all relevant information was entered into the Web-based ELCAP management system (11). This system served to document findings and guide actions from initial patient contact, to scheduling baseline and repeat screenings, to follow-up of patients in whom lung cancer was diagnosed. It also enabled central review of adherence to the protocol in terms of completeness and consistency of collected data and provided a means for electronic transmission of images to the coordinating center for central interpretation and nodule volumetry.

While the protocol yielded recommendations for diagnostic work-up, decisions as to how to proceed in the event of a positive result at initial CT screening were up to each participant's referring physician. The actual diagnostic procedures and findings were recorded.

Statistical Analysis

Point estimates of the proportion of participants *(a)* with a positive finding; *(b)* with lung cancer, according to cell type; and *(c)* considered to have clinical stage I lung cancer were determined for baseline and repeat screenings. The frequency of biopsy recommendation and the resulting diagnoses were obtained separately for baseline and repeat screenings. Two-sided 95% exact confidence intervals of the proportion of patients with a positive finding and the proportion of patients in whom stage I lung cancer was diagnosed were derived with the Statistical Analysis System, version 8.0 (SAS Institute, Cary, NC).

Results

Positive Result

Of the 6295 participants, 906 (14.4%; 95% confidence interval: 13.5%, 15.3%) had a positive result of the initial baseline CT examination (Table 1). A semipositive result was obtained in 1722 participants (27.4%; 95% confidence interval: 26.3%, 28.5%).

Of the 6014 instances of annual repeat screening, the result was positive in 361 examinations (6.0%; 95% CI: 5.4%, 6.6%) (Table 1). The rate of pos-

Table 1

Positive and Negative Results of Initial CT in the Baseline and Annual Repeat Cycles of Screening

Screening Cycle and Nodule Consistency	Diameter of the Largest Relevant Nodule						Negative Result	Total
	<3 mm	3–4 mm	5–9 mm	10–14 mm	≥15 mm	Any Diameter		
Baseline cycle								
Solid	· · ·	· · ·	607	69	58	734	· · ·	· · ·
Part solid	· · ·	· · ·	29	18	26	73	· · ·	· · ·
Nonsolid	· · ·	· · ·	45	39	15	99	· · ·	· · ·
Any consistency	· · ·	· · ·	681 (10.8)	126 (2.0)	99 (1.6)	906 (14.4)	5389 (85.6)	6295 (100.0)
Annual repeat cycles								
Solid	31	88	87	34	25	265	· · ·	· · ·
Part solid	0	6	7	4	7	24	· · ·	· · ·
Nonsolid	1	5	37	21	8	72	· · ·	· · ·
Any consistency	32 (0.5)	99 (1.6)	131 (2.2)	59 (1.0)	40 (0.7)	361 (6.0)	5653 (94.0)	6014 (100.0)

Note.—Data are numbers of patients. Data in parentheses are percentages.

itive results at initial repeat CT screening was highest in the institution that had upgraded from a single–detector row CT unit to a multi–detector row unit for the repeat screenings.

Diagnostic Work-up of Participants with a Positive Result

Baseline round.—Immediate additional work-up was recommended for the 906 participants with positive findings. For the 1722 participants with semipositive findings, repeat screening 12 months later was recommended.

Of the 906 participants with a positive result, 502 underwent additional diagnostic work-up before the first annual repeat screening, 325 underwent only the first annual repeat screening, and 79 underwent no additional diagnostic work-up in this study. Immediate biopsy was recommended in 43 participants because of the large size of the nodule (≥15 mm in diameter). Biopsy was performed in 39 participants; four refused to undergo this procedure. Lung cancer was diagnosed in 36 participants; metastatic colon cancer, in two; and a benign lesion (inflammation), in one (Table 2). Immediate biopsy was performed in four other participants with smaller (10–14 mm in diameter) nodules because of prominent spiculations and in one other participant because of an endobronchial lesion. A diagnosis of lung cancer was made in all five participants. Immediate PET was recommended in 20 participants and performed in 18. PET findings were positive in nine participants, and subsequent biopsy resulted in a diagnosis of lung cancer in all nine (Table 2). Another 116 of the participants with a positive result of initial baseline CT returned within 2 months of screening. Biopsy was recommended in 31 of these participants because the nodule(s) did not decrease after antibiotic therapy or the nodule(s) showed signs of growth. Biopsy was performed in 24 participants and resulted in a diagnosis of lung cancer in 22, atypia in one, and inflammation in one (Table 2). Another 287 participants underwent CT 3–6 months after initial baseline CT, and biopsy was recommended for 15 of them because of interim nodule growth. Biopsy was performed in 13 of these participants and resulted in a diagnosis of lung cancer in 11 and atypia in one; findings were indeterminate in one (Table 2). Finally, 325 participants underwent work-up as part of repeat screening only. Of these participants, 22 were recommended for biopsy because of nodule growth. Of the 12 participants who underwent biopsy, 11 received a diagnosis of lung cancer and one had indeterminate diagnosis (Table 2).

Among the 1722 participants with a semipositive result, 1453 (84.4%) returned for the recommended work-up as part of their first annual repeat screening, 48 (2.8%) returned later, and 222 (12.9%) underwent no additional work-up in the study. Biopsy was recommended for nine participants and performed in eight; it resulted in a diagnosis of lung cancer in seven of them and granuloma in one (Table 2).

Repeat round.—In annual repeat screening rounds, 151 of the 361 participants with a positive result of the initial CT examination underwent additional diagnostic work-up before the next

Table 2

Biopsy Recommendations, Actual Biopsies, and Resulting Diagnoses at Baseline and Annual Repeat Screening

Screening Cycle and Basis for Biopsy Recommendations	Biopsy Recommended	Biopsy Performed	Biopsy Result				
			Lung Cancer	Atypia	Metastasis	Benign	Indeterminate
Baseline cycle							
Initial CT							
Size	43	39	36	0	2	1	0
Appearance and location	5	5	5	0	0	0	0
PET	9	9	9	0	0	0	0
No decrease in 1–2 months	31	24	22	1	0	2	0
Growth in 3–6 months	15	13	11	1	0	0	1
Growth at first annual repeat screening	20	11	10	0	0	0	1
Growth at additional screening	2	1	1	0	0	0	0
Growth of semipositive lesions at first annual repeat screening	9	8	7	0	0	1	0
Any recommendation for biopsy in baseline cycle	134	110	101	2	2	3	2
Annual repeat cycles							
Newly seen lesion	10	10	10*	0	0	0	0
No change or growth in less than 2 months	10	8	7*	0	0	1	0
Growth in 3–6 months	5	4	3	0	0	0	1
Growth at additional screening	6	2	2	0	0	0	0
Any recommendation for biopsy in annual repeat cycles	31	24	22	0	0	1	1

Note.—Data are numbers of patients.

* One case of lymphoma included.

Table 3

Distribution of Patients with Screening and Interim Diagnoses of Lung Cancer in the Baseline and Annual Repeat Cycles

Screening Cycle and Consistency	Diameter of Malignant Nodule				Interim Diagnosis of Lung Cancer	Total	No Lymph Node Metastases
	<5 mm	5–14 mm	≥15 mm	Any Diameter			
Baseline cycle							
Solid	2	32	37	71	3	74	65 (88)
Part solid	0	7	11	18	0	18	18 (100)
Nonsolid	1	10	1	12	0	12	12 (100)
Any consistency	3	49	49	101	3	104	95 (91.3)
Annual repeat cycles							
Solid	1	11	4	16	0	16	13 (81)
Part solid	0	0	0	0	0	0	· · ·
Nonsolid	0	4	0	4	0	4	4 (100)
Any consistency	1	15	4	20	0	20	17 (85)

Note.—Data are numbers of patients. Data in parentheses are percentages.

scheduled annual repeat screening. Another 44 participants underwent additional work-up as part of further repeat screening only. The remaining 166 participants had no further diagnostic work-up as part of this study.

In the 361 participants with positive results, immediate biopsy was recommended for 10 participants, each of whom had a growing nodule larger than 5 mm in diameter. Biopsy was performed in all 10 of them and resulted in a diagnosis of lung cancer in nine and of lymphoma in one (Table 2). Immediate PET was recommended for four participants, all of whom underwent this procedure. None of these examinations resulted in a positive PET finding; thus, none of the participants was recommended for biopsy. Another 65 participants with a positive result returned within 2 months of screening; biopsy was recommended for 10 of them because the nodule(s) did not resolve after antibiotic therapy or because the nodule(s) showed signs of growth. Biopsy was performed in eight of these participants and resulted in a diagnosis of lung cancer in six, B-cell lymphoma in one, and a benign lesion (pneumonia) in one (Table 2). Another 70 participants underwent CT 3–6 months after initial CT screening. Biopsy was recommended for five of them because of interim nodule growth. Four of these participants underwent biopsy, which resulted in a diagnosis of lung cancer in three; diagnosis was indeterminate in one (Table 2). Another 44 participants underwent work-up for annual repeat screening only. Six of them were recommended for biopsy because of interim nodule growth. Only two participants underwent biopsy, which resulted in a diagnosis of lung cancer in both participants (Table 2).

Biopsies

Of the 134 recommended biopsies, 102 were positive and eight were semipositive in the baseline round, whereas 24 were positive in the repeat round. A diagnosis of lung cancer (n = 121) or another malignancy (lymphoma, n = 2; metastases, n = 2) was made in 125 (93.3%) participants. Findings were suspicious for malignancy in two (1.5%) participants (Table 2).

Biopsy was performed against the protocol recommendation in 22 participants with positive findings and in two participants with semipositive findings. There was no evidence of growth, positive PET findings, or failure to respond to antibiotic therapy. None of the biopsies revealed malignancy, and only one biopsy resulted in a diagnosis of atypical bronchioalveolar proliferation.

Lung Cancer Diagnoses

Baseline round.—Of the 101 patients in whom a diagnosis of lung cancer resulted from initial baseline screening, 98 had cancer in a parenchymal nodule and three had cancer in an endobronchial nodule. All but two of the 101 nodules were resectable when recommended for biopsy. Of the 101 patients, 89 (88.1%) had no clinical evidence of lymph node metastases (ie, all 30 patients in whom cancer manifested as a subsolid nodule and 62 [87%] of the remaining 71 patients in whom cancer manifested as a solid nodule) (Table 3). Cancers that manifested as solid nodules (n = 71) were seen about twice as frequently as were those that manifested as subsolid nodules (n = 30). The cancer manifested as the largest noncalcified nodule in all but two patients. In both of these patients, a smaller nonsolid nodule grew while the larger nodule, which was also nonsolid, did not. On the initial baseline CT images, the median diameter of the cancer was 14 mm; it was 15 mm for cancers that manifested as solid nodules, 17 mm for cancers that manifested as part-solid nodules, and 9 mm for cancers that manifested as nonsolid nodules.

In addition to the 101 screening diagnoses, three diagnoses were prompted by symptoms before the first scheduled repeat screening. None of the patients in whom these diagnoses were made had clinical evidence of lymph node metastases. In all three patients, the abnormality could be identified retrospectively on the initial CT images obtained 2, 10, and 11 months earlier. (One lesion was located in the left main bronchus, one was in the right middle lobe,

and one was in the right posterior segmental bronchus.) The carcinoma types and TNM status were mucoepidermoid carcinoma (T3N0M0), small cell carcinoma (T2N2M0), and poorly differentiated non–small cell carcinoma (T1N2M0); two lesions were resected, and one was treated with chemotherapy.

Of the 104 patients in whom lung cancer was diagnosed as a result of baseline screening or prompting of symptoms prior to the first scheduled annual repeat screening session, 95 (91.3%) had no clinical evidence of lymph node metastases when recommended for biopsy.

Repeat round.—In all of the 20 patients in whom the diagnosis was made at annual repeat screening, cancers manifested in parenchymal nodules and were resectable when recommended for biopsy. Of these 20 cases, 17 (85%) had no clinical evidence of lymph node metastases (Table 3). All three cases with lymph node metastases were small cell carcinomas. Cancers that manifested as solid nodules (n = 16) occurred four times more frequently than those that manifested as subsolid nodules (n = 4), with the latter all being nonsolid. On the initial CT images, the median diameter of the cancer was 8 mm both for cancers that manifested as solid nodules and for those that manifested as nonsolid nodules. All diagnoses were prompted by screening findings; none was prompted by symptoms before the next scheduled repeat screening session (Table 3).

Delay in Diagnosis

Of the 121 patients in whom biopsy was performed as a result of baseline or repeat screening findings, 84 underwent biopsy in a timely fashion in that biopsy was performed within 6 months of the initial CT examination that yielded a positive result. Biopsy was delayed by 7–60 months in 37 patients with positive baseline or repeat screening results. None of these patients had evidence of lymph node metastases when biopsy was recommended; however, all nodules had grown by the time biopsy was performed. Of the 10 cancers that manifested as nonsolid or part-solid nodules, none showed evidence of lymph node metastases when resection was finally performed. However, of the 27 cancers that manifested as solid nodules, 15 showed no evidence of lymph node metastases, while 12 showed progression in the stage of the disease—two spread within the same lobe only, one spread within the same lobe and to other lobes, six spread to ipsilateral lymph nodes, and three spread to ipsilateral and distant lymph nodes and to other organs.

Treatment and Cell Type

In the 121 patients in whom lung cancer was diagnosed, 97 (80.2%) nodules were ultimately resected. No deaths occurred during surgery. Another 20 patients underwent chemothrapy, radiation therapy, or both. Four patients refused treatment. Lobectomy was not performed in patients with benign disease. In patients with resected cancers, 88 lesions were classified as clinical stage I lung cancer and, at resection, 81 were found to be pathologic stage I lung cancer.

At baseline and repeat screening, adenocarcinoma (65.4% and 35%, respectively) was the carcinoma most frequently seen; squamous cell carcinoma (13.5% and 30%, respectively) and small cell carcinoma (6.7% and 30%, respectively; Table 4) followed. Only adenocarcinoma manifested as a part-solid or nonsolid nodule, while all other cell types manifested as solid nodules.

Discussion

The results of NY-ELCAP supplement the results of ELCAP (1,3,10) and indicate that annual CT screening for lung cancer results in the identification of a high proportion of patients with early-stage lung disease. Almost all diagnoses of lung cancer were screening diagnoses as opposed to interim diagnoses; the per-

Table 4

Frequency Distribution by Cell Type for Consensus Diagnosis in Baseline and Annual Repeat Screening Cycles

	Baseline Screening			Annual Repeat Screening		
Carcinoma Cell Type	Solid	Part Solid	Nonsolid	Solid	Part Solid	Nonsolid
Adenocarcinoma	38	18	12	3	0	4
Non–small cell carcinoma	6*	0	0	0	0	0
Adenosquamous carcinoma	1	0	0	0	0	0
Squamous cell carcinoma	14	0	0	6	0	0
Mucoepidermoid carcinoma	1*	0	0	0	0	0
Neuroendocrine						
Typical carcinoid	3	0	0	0	0	0
Atypical carcinoid	1	0	0	1	0	0
Large cell	3	0	0	0	0	0
Small cell, combined	7*	0	0	6	0	0
Total	74	18	12	16	0	4

Note.—Data are numbers of patients.

* Includes one interim diagnosis.

centages of diagnoses that were screening diagnoses were 97% and 100% in baseline and annual repeat screening rounds, respectively. A high proportion of patients had no clinical evidence of metastases when biopsy was recommended in the baseline and repeat screening rounds (91% and 85%, respectively). The median tumor diameters at baseline and repeat screening rounds were 14 mm and 8 mm, respectively.

We refer to the frequency distribution of the diagnoses of lung cancer by stage and size as the diagnostic distribution that results from the screening regimen. It is the regimen and the adherence to it that determines this diagnostic determination, not the risk profile of the participants. This distinction is important, as the diagnostic distributions that result from different screening regimens can be compared, regardless of the risk profile of the enrollees. The fact that the diagnostic distribution by stage and size in NY-ELCAP was similar to that in ELCAP (1,3) and in another two studies that had enrollees with different risk profiles (21,22) was not surprising, as these studies followed either the original or the updated screening regimen. The studies conducted in Japan (23–25) had similar results. The proportion of patients with stage I cancer was somewhat lower in two other studies (26,27) in which the authors used a different screening regimen, even though they were encouraged and aided by the ELCAP investigators.

The NY-ELCAP findings showed the benefit of updating the screening regimen since the original ELCAP study (1). In particular, our findings showed the importance of updating the definition of a positive result to accommodate the finer collimation provided by multi–detector row CT and the improved potential for interpretation with high-resolution monitors, which resulted in the identification of many more small nodules in baseline and repeat screenings. As expected from a prior analysis of ELCAP (7), the updated definition of a positive result reduced the percentage of participants who needed further work-up in the baseline round from 41% to 14%, even in geographic regions with endemic fungal diseases. The diagnostic implication of nodule consistency (solid, part solid, or nonsolid) identified by the ELCAP investigators (6) was also confirmed. Furthermore, recommended biopsies enabled us to identify malignancy in 93.3% of cases, while none of the biopsies performed against recommendations resulted in a diagnosis of lung cancer. No lobectomies were performed in patients with benign disease, and no deaths resulted from surgery. Thus, the recommendations turned out to be successful in terms of the avoidance of undue invasive procedures and the associated complications and cost. Delay in the recommended diagnostic work-up, however, detracted from the full benefit of CT screening, as tumor size and stage increased. Thus, it is critical that the referring physicians and screenees are fully informed about the value of choosing and adhering to an optimal screening regimen.

Potentially detracting from the apparent benefit of CT screening is the possibility that an appreciable proportion of patients with stage I lung cancer represents an overdiagnosis of lung cancer. In NY-ELCAP, we protected against overdiagnosis by determining the amount of growth prior to biopsy, particularly in smaller nodules. In fact, growth had to be demonstrated to be considered a positive result in repeat screening. Moreover, the diagnoses of lung cancer were reviewed by experts in pathology and confirmed to be genuine lung cancers according to the 2004 World Health Organization criteria. Finally, the fact that the lesions in patients in whom diagnosis or treatment was delayed demonstrated further growth and progression is further evidence against the possibility of overdiagnosis (28).

The study design is efficient in that it requires only two rounds of screening (baseline screening followed by one annual repeat screening) to enable physicians to adequately determine the diagnostic distribution, as demonstrated by our findings. The quantitative validity of the approach does not require that all study participants return for repeat screening; rather, it requires only that symptom-prompted diagnoses of lung cancer made before the next scheduled repeat screening round are identified among those patients who do not return for repeat screening, as was done in this study.

One limitation of this study was that study participants were not required to undergo diagnostic work-up at the same institution where screening was performed, as this work-up was not paid for as part of the study but was provided as part of a patient's usual health care. While this does not affect the validity of the study as the actual work-up findings were documented, the results do not show what could have been achieved had the protocol been followed perfectly; rather, they show what was actually achieved given the study guidelines and the extent to which they were followed, as well as the management system and central inputs. The lower prevalence of lung cancer that resulted from baseline screening in NY-ELCAP as compared with that in ELCAP (1.6% vs 2.7%), which had the same enrollment criteria, may have been due to the lower median age (66 years vs 67 years) and lower smoking exposure (40 pack-years vs 45 pack-years) in NY-ELCAP, a sampling variation, or a combination of these factors.

The high proportion of stage I lung cancer diagnoses has been validated in this multi-institutional setting. This proportion appears to be highly predictive of the long-term survival rate, as shown in a larger study (29) which included the diagnoses of lung cancer made in NY-ELCAP. In this study, the estimated 10-year survival rate was 80%, regardless of cancer stage and treatment. The benefit of CT screening is thus considerable, as this rate is in sharp contrast to the dismally low 5% cure rate reported by the American Cancer Society (30), as shown by the estimated number of new patients (n = 172 570) in whom lung cancer is diagnosed and the number of deaths (n = 163 510) that occur in the absence of screening. Furthermore, patients in whom a diagnosis of stage I lung cancer was made and who underwent prompt resection had an even higher estimated 10-year survival rate of 92%.

Appendix

NY-ELCAP Investigators: Claudia I. Henschke (principal investigator), David F. Yankelevitz, and Dorothy I. McCauley (Weill Medical College of Cornell University); Matthew Rifkin and Edward S. Fiore (State University of New York at Stony Brook, NY); John H. M. Austin, Gregory D. N. Pearson, and Maria C. Shiau (Columbia University Medical Center, New York, NY); Samuel Kopel (Maimonides Medical Center, Brooklyn, NY); Donald Klippenstein, Alan Litwin, and Peter A. Loud (Roswell Park Cancer Institute, Buffalo, NY); Leslie J. Kohman and Ernest M. Scalzetti (State University of New York, Upstate Medical University, Syracuse, NY); Arfa Khan and Rakesh Shah (North Shore-Long Island Jewish Health System, New Hyde Park, NY); David S. Mendelson (Mount Sinai School of Medicine, New York, NY); Robert T. Heelan and Michelle S. Ginsberg (Memorial Sloan-Kettering Cancer Center, New York, NY); Terence A. S. Matalon (New York Medical College, Valhalla, NY); and Peter H. Wiernik (Our Lady of Mercy Medical Center, Bronx, NY). Coordinating Center at Weill Medical College of Cornell University: Claudia I. Henschke (principal investigator), Nasser Altorki, Ali Farooqi, Yolanda Faustini, Daniel M. Libby, Dorothy I. McCauley, Olli S. Miettinen (also McGill University), Jamie Ostroff (also Memorial Sloan-Kettering Cancer Center), Mark W. Pasmantier, Anthony P. Reeves (also Cornell University), James P. Smith, Madeline F. Vazquez, David F. Yankelevitz, Rowena Yip, Kimberly K. Agnello, Arin L. Kramer, and Jennifer M. Hess. Pathology Review Panel: Darryl Carter, chairman (Yale University School of Medicine, New Haven, Conn); Elizabeth Brambilla (Institut Albert Bonniot, University Joseph Fournier, Grenoble, France); Adi Gazdar (University of Texas Southwestern Medical Center, Dallas, Tex); Masayuki Noguchi (Institute of Basic Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan); and William D. Travis (Memorial Sloan-Kettering Cancer Center, New York, NY).

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