The Pittsburgh Lung Screening Study (PLuSS)

Outcomes within 3 Years of a First Computed Tomography Scan

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Rationale: The role of computed tomography (CT) screening for lung cancer is controversial, currently under study, and not yet fully elucidated.

Objectives: To report findings from initial and 1-year repeat screening low-radiation-dose CT of the chest and 3-year outcomes for 50- to 79-year-old current and ex-smokers in the Pittsburgh Lung Screening Study (PLuSS).

Methods: Notified of findings on screening CT, subjects received diagnostic advice from both study and personal physicians. Tracking subjects for up to three years since initial screening, we obtained medical records to document diagnostic procedures, lung cancer diagnoses, and deaths.

Measurements and Main Results: 3,642 and 3,423 subjects had initial and repeat screening. A total of 1,477 (40.6% of 3,624) were told about noncalcified lung nodules on the initial screening and, before repeat screening, 821 (55.6% of 1,477, 22.5% of 3,642) obtained one or more subsequent diagnostic imaging studies (CT, positron emission tomography [PET], or PET-CT). Tracking identified 80 subjects with lung cancer, including 53 subjects with tumor seen at initial screening. In all, 36 subjects (1.0% of the 3,642 screened), referred for abnormalities on either the initial or repeat screening, had a major thoracic surgical procedure (thoracotomy, video-assisted thoracoscopic surgery [VATS], median sternotomy, or mediastinoscopy) leading to a noncancer final diagnosis. Out of 82 subjects with thoracotomy or VATS to exclude malignancy in a lung nodule, 28 (34.1%) received a noncancer final diagnosis. Forty of 69 (58%) subjects with non-small cell lung cancer had stage I disease at diagnosis.

Conclusions: Though leading to the discovery of early stage lung cancer, CT screening also led to many diagnostic follow-up procedures, including major thoracic surgical procedures with noncancer outcomes.

For 2008 in the United States, the American Cancer Society predicted 215,020 new lung cancer diagnoses and 161,840 lung cancer deaths (1). From 1996 to 2003, only 16% of new lung cancer cases were localized stage at diagnosis and amenable to surgical cure (1).

In the United States, lung cancer death is more common than breast, prostate, and colorectal cancer death combined (1). Improvements in 5-year relative survival have been small for

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The role of computed tomography (CT) screening for lung cancer is controversial, currently under study, and not yet fully elucidated.

What This Study Adds to the Field

Though assisting in the discovery of early stage lung cancer, CT screening also leads to many diagnostic follow-up procedures, including major thoracic surgical procedures with noncancer outcomes.

lung cancer (13% and 16% for cases diagnosed in 1975–1977 and 1996–2003, respectively), particularly when compared with the substantial improvements seen for breast, prostate, and colorectal cancer (1).

Screening for early detection is currently recommended for breast, prostate, and colorectal, but not lung cancer (2). New technologies, primarily low-radiation-dose imaging with multi-detector helical computed tomography (CT), has revived interest in lung cancer screening. CT clearly detects smaller lung tumors at earlier stages than conventional chest X-ray (3–8). Because of lead-time bias, length-time bias, and over-diagnosis (9), conclusions regarding the effects of screening on lung cancer mortality must await results from randomized controlled trials ongoing in the United States (10) and Europe (11–13). Two recent analyses of single-arm cohort studies (14, 15) point to the uncertainty and associated controversy created by the absence of results from randomized control trials. In one analysis, an international collaboration, 85% of CT-detected lung tumors were clinical stage I (15). Moreover, persons with clinical stage I CT-detected lung cancer had favorable 10-year survival (15). From these observations, the investigators concluded that annual CT screening can detect curable lung cancer in a manner capable of preventing 80% of lung cancer deaths (15). In contrast, comparing outcomes observed in three large studies of CT screening to predictions from two validated risk models, the second analysis concluded that CT screening increases lung cancer diagnosis and lung cancer resection without decreasing advanced lung cancer or lung cancer death (14). In addition to over-diagnosis (screen-detection and treatment of clinically insignificant or indolent lung cancer), CT screening frequently detects benign abnormalities (generally, nonmalignant noncalcified lung nodules) that can lead to anxiety, costs, and unnecessary procedures (16, 17).

With a focus on major thoracic surgical procedures with noncancer outcomes, we report findings from initial and 1-year repeat screening computed tomography (CT) of the chest and 3-year outcomes for 50- to 79-year-old current and ex-smokers in

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the Pittsburgh Lung Screening Study (PLuSS), the largest single-institution CT lung cancer screening study reporting to date.

METHODS

Subjects

Between January 2002 and April 2005, the PLuSS used advertisements and mass mailings to recruit volunteers with the following characteristics: (1) age 50 to 79 years; (2) no personal lung cancer history; (3) non-participation in concurrent lung cancer screening studies; (4) no chest computed tomography (CT) within 12 months; (5) current or ex-cigarette smoker of at least one-half pack per day for at least 25 years, and, if quit, quit for no more than 10 years before study enrollment; and (6) body weight less than 400 pounds. Individuals were not excluded because of symptoms.

Baseline activities included completing a risk factor questionnaire, collecting peripheral blood samples, forced expiratory spirometry conducted and analyzed in accordance with American Thoracic Society standards (18, 19), low-radiation-dose CT screening, and physician referral for noncalcified lung nodules. Follow-up activities included repeat CT screening after 12 months and active surveillance for lung cancer-related endpoints. Occurring between March 2002 and September 2005 and between March 2003 and November 2006, respectively, subjects received the initial and 1-year repeat CT at study expense.

Of 9,386 persons assessed by telephone for study eligibility, we excluded 4,352 (46.4%) for reasons related to age ($n = 84$), lung cancer history ($n = 60$), participation in other lung cancer screening studies ($n = 1,043$), recent chest CT ($n = 120$), cigarette smoking history (duration or dose; $n = 1,439$), duration quit ($n = 1,600$), and body weight ($n = 6$) (exclusions applied in sequential fashion). Of 5,034 eligible persons, 1,279 (25.4%) did not accept an enrollment visit and 113 (2.2%) enrolled, but did not return for CT screening. The remaining 3,642 persons, the study population, completed the initial CT screening a median 53 days (range, 2–604 d) after the initial telephone contact. Among eligible persons ($n = 5,034$), CT screening occurred more frequently in men than women (74.6 vs. 70.2%), more frequently in ex-cigarette smokers than current cigarette smokers (76.7 vs. 69.7%), and more frequently in younger than older persons (72.5, 73.9, and 66.5% in 50- to 59-, 60- to 69-, and 70- to 79-yr-old persons, respectively). Otherwise, CT-screened and unscreened eligible persons were similar with respect to age started smoking, duration of cigarette smoking, and duration quit (among ex-smokers).

Screening CT Imaging Protocol

The lung cancer screening protocol used a single-breath-hold, helical, low-dose technique (40–60 mA, 140 kVp) to obtain axial images reconstructed with a high spatial frequency (lung) algorithm at contiguous 2.5-mm intervals. One of two study radiologists (CRF and SNF) used standard lung windows (1,496/–555) to view images (2.5 mm section thickness) on a PACS monitor display system (Stentor; Radiology Informatics Business Group of Phillips Medical Systems, Foster City, CA). Radiologists adjusted window width and level, as appropriate, to detect calcification in nodules and to evaluate mediastinal structures.

Protocol for Primary Interpretation of the Initial Screening CT

A single study radiologist identified and characterized lung nodules according to size, presence and type of calcification (complete, central target, speckled, or peripheral), attenuation (solid, nonsolid, or mixed), border characteristic (smooth, spiculated, or lobulated), and lobar location. The radiologist used the axial image showing the nodule to its fullest extent to measure maximum nodule diameter and nodule diameter perpendicular to this maximum. Analyses averaged these two diameter measurements to obtain a summary measure of nodule size, the average diameter. The category of calcified nodule included all completely calcified nodules and nodules (≤ 2.0 cm average diameter) with central target or lamellate calcification. Procedures further divided noncalcified nodules into low (< 0.5 cm average diameter or 0.5–0.9 cm average diameter with nonspiculated border) and moderate or high lung cancer suspicion categories (0.5–0.9 cm average diameter with spiculated border or ≥ 1.0 cm average diameter). Finally, the interpret-

ing radiologist used subjective criteria to classify larger noncalcified nodules (≥ 1.0 cm average diameter) into moderate and high lung cancer suspicion categories. The initial CT study received a preliminary summary nodule interpretation (low, moderate, or high lung cancer suspicion) based on the rating of the most suspicious nodule. The radiologist used a locally developed computer database application (programmed in Microsoft Office Access 2003) to enter visual CT findings. The application used pre-programmed algorithms to map the visual findings into lung nodule ratings and summary interpretations, as defined above and summarized in Table E1. Intended to encompass less than 5%, 5 to 50%, and greater than 50% pre-biopsy lung cancer probabilities, respectively, we conceived the low, moderate, and high lung cancer suspicion categories to guide referral recommendations and subsequent diagnostic activity.

Protocol for Primary Interpretation of the Repeat Screening CT

The primary interpretation of the repeat screening CT also included a direct visual comparison of initial and repeat CT images. Specifically, a single study radiologist relocated each noncalcified lung nodule noted at baseline and applied subjective criteria to interpret temporal change according to a forced-choice format (suspicious change vs. no significant change vs. partial resolution vs. complete resolution), with suspicious change defined as increase in size or density of a pre-existing nodule. The radiologist also identified and characterized noncalcified lung nodules, visible on repeat CT images, but not enumerated at baseline. The radiologist used the same forced-choice format to report temporal change in nodules, first identified on the repeat CT images, but visible, in retrospect, on the initial CT images.

A computer algorithm, programmed into our Access database application, assigned the moderate lung cancer suspicion rating to every noncalcified lung nodule that either first appeared on repeat CT or showed suspicious change from baseline. The radiologist was allowed to use subjective criteria to assign a high lung cancer suspicion rating to nodules in this category. The algorithm assigned the low lung cancer

TABLE 1. SUBJECTS SCREENED WITH HELICAL COMPUTED TOMOGRAPHY, ENTRY CHARACTERISTICS

	N	%
Enrollment age, yr		
50–59	2,088	57.3
60–69	1,201	33.0
70–79	353	9.7
Cigarette smoking status		
Current smoker	2,192	60.2
Ex-smoker	1,450	39.8
Cigarette dose intensity duration, pack-years		
<20	118	3.2
20–39	1,180	32.4
40–59	1,316	36.1
60–79	660	18.1
80+	368	10.1
Lung disease*	908	24.9
Family history†		
Lung cancer	653	18.0
Other cancer	1,564	43.2
No cancer	1,405	38.8
Airflow obstruction‡		
None	2,085	57.3
GOLD I	493	13.5
GOLD II	828	22.7
GOLD III–IV	234	6.4

* Doctor diagnosis of chronic bronchitis, emphysema, or asthma.

† Hierarchical mutually exclusive categories based on self-reported history of cancer (other than nonmelanoma skin cancer) in parent, sibling, or half-sibling. Family history information is missing in 20 subjects.

‡ No airflow obstruction = $FEV_1/FVC \geq 70$ percent; GOLD I = $FEV_1/FVC < 70$ and $FEV_1 \geq 80$ percent predicted; GOLD II = $FEV_1/FVC < 70$, $FEV_1 < 80$ percent predicted, and $FEV_1 \geq 50$ percent predicted; GOLD III–IV = $FEV_1/FVC < 70$ and $FEV_1 < 50$ percent predicted. Airflow obstruction is missing in two subjects.

suspicion rating to nodules showing no significant change between initial and repeat CT. The repeat screening received a preliminary summary nodule interpretation (low, moderate, or high lung cancer suspicion) based on the rating of the most suspicious nodule.

Secondary Review Procedures

By protocol, a committee that included study radiologists, pulmonologists, and other investigators met in conference and reviewed all CT studies with preliminary moderate or high suspicion nodule interpretations and some low suspicion CT studies with larger (≥ 0.5 cm) nodules. Using subjective clinical criteria and the totality of findings present on all available CT studies, the committee reached consensus regarding a final summary nodule interpretation (no, low, moderate, or high lung cancer suspicion).

Follow-up Recommendations

For each screening CT study, the investigators prepared a written report containing detailed radiologic findings and final summary interpretations. The subject and one personal physician received the written report, by mail, along with a cover letter and explanatory information. Based on the final summary nodule interpretation, written materials advised physician-directed diagnostic follow-up for persons with moderate to high lung cancer suspicion and interval diagnostic CT follow-up for persons with low lung cancer suspicion. Subjects could also receive a recommendation for physician-directed diagnostic follow-up for central airway abnormalities, thoracic lymph enlargements, or other clinically significant incidental findings.

To coincide with the postal delivery of written reports, a nurse practitioner telephoned every subject with any CT finding that generated a follow-up recommendation. The nurse practitioner summarized relevant CT findings and referral recommendations and described follow-up options, options that could include either a consultation visit with the study pulmonologist (D.O.W.) or a no-fee physician office visit with the principal investigator (JLW). Again, based on the final summary nodule interpretation, the investigators generally advised thoracoscopy with excisional biopsy or mediastinoscopy for persons with high suspicion; additional diagnostic imaging studies (thoracic CT, positron emission tomography [PET], or PET-CT) after no greater than 3-month delay for persons with moderate suspicion; and interval periodic thoracic CT for persons with low suspicion, in accordance with published guidelines. During the first year of our study, we advised repeat CT in 6 months for persons with only small (< 0.4 cm) low suspicion nodules and repeat CT in 3 to 6 months for persons with larger (≥ 0.4 cm) low suspicion nodules. After the first year, we responded to evolving opinion regarding the management of small CT screen-detected nodules (4, 8, 20, 21) and began to recommend annual repeat CT screening for persons with only micro-nodules (< 0.4 cm) and 6-month CT follow-up for persons with larger (≥ 0.4 cm) nodules.

Tracking/Surveillance of Study Endpoints

To document diagnostic events and outcomes, the nurse practitioner maintained telephone contact with persons who had received a follow-up recommendation. At annual intervals, the investigators used brief telephone interviews and/or mailed questionnaires to update the vital and cancer status of study subjects and to ascertain interval lung biopsy procedures. Follow-up was 99%, 98%, and 80% complete at the 1-, 2-, and 3-year time points, respectively. Using information obtained over the telephone and signed consents, the investigators identified, acquired, and reviewed relevant medical records, including images and reports from imaging studies (thoracic CT, PET, or PET-CT), biopsy procedure reports, pathology reports, and death certificates.

Focusing on clinical indications and outcomes, one author (D.O.W.) reviewed the assembled medical records of (1) every subject who received a lung cancer diagnosis and (2) every subject with a follow-up recommendation who subsequently experienced an invasive diagnostic procedure. The same author and a certified tumor registrar independently staged every lung cancer case and met in conference to reconcile disagreements. We report only lung cancer diagnoses and invasive diagnostic procedures that occurred within 2 years of the repeat CT or, for persons without repeat CT, within 3 years of the initial CT.

Human Studies

The institutional review board for the University of Pittsburgh approved the research.

RESULTS

Subject Characteristics

The 3,642 subjects with initial CT screening included 1,872 men and 1,770 women, 7.1% nonwhite race or Hispanic ethnicity, mean age 59 years, 42.7% 60+ years of age, median 47 pack-year cigarette smoking history (33–62 pack-year inter-quartile range [IQR]), 14% self-reporting any prior history of chest CT, and median 1.8% (1.0–3.4% IQR) calculated 5-year incident lung cancer risk (22). Table 1 distributes subjects according to age, cigarette smoking status, pack-years, personal history of lung disease, family cancer history, and pulmonary function.

Findings at Initial CT Screening

We referred 1,477 subjects (40.6% of 3,642; Table 2) because of the finding of one or more noncalcified lung nodules at the initial CT screening. Among those screened, 856 (23.5%) had one noncalcified nodule and 621 (17.1%) more than one. Forty (1.1%) and 182 (5.0%) were referred because of high and moderate lung cancer suspicion, respectively (Table 2).

Compliance with Repeat CT Screening

Within 365 days of the initial CT screening, 36 persons (17 men and 19 women) were diagnosed with primary lung cancer and an additional 14 persons died (11 men and three women). Of the remaining 3,592 subjects eligible, 3,423 (95.3%) complied with repeat screening. Compliance with repeat screening was similar among men (95.8%) and women (94.7%; $P = 0.12$). Median time elapsing between initial and repeat CT screening was 385 days (371–406 IQR).

Lung Nodule Findings on Repeat Screening CT

Reevaluation at repeat CT screening of 2,497 noncalcified nodules seen at baseline showed suspicious change in 81 (3.2%), no change in 1,930 (77.3%), partial resolution in 276

TABLE 2. NUMBER OF INITIAL COMPUTED TOMOGRAPHY SCREENINGS, SUBSEQUENT DIAGNOSTIC IMAGING STUDIES, AND REPEAT COMPUTED TOMOGRAPHY SCREENINGS, ACCORDING TO REASON FOR REFERRAL, LEVEL OF LUNG CANCER SUSPICION, AND DIAMETER OF THE LARGEST NONCALCIFIED LUNG NODULE

Initial or Repeat CT Screening Result	Initial Screening*	Imaging Studies†	Repeat Screening‡
Any suspicious nodule	1,477	1,070	1,450
High or moderate suspicion	222	333	224
High suspicion	40	76	18
Moderate suspicion	182	257	206
Low suspicion	1,255	737	1,226
largest nodule ≥ 0.5 cm	487	380	563
largest nodule < 0.5 cm	768	357	663
Lymph node or airway abnormality§	49	52	6
Significant incidental finding	82	19	50
Any reason	1,608	1,141	1,506

Definition of abbreviation: CT = computed tomography.

* N = 3,642 subjects had an initial CT screening.

† Includes chest CT, PET, or PET-CT completed between initial screening and repeat screening or within 365 days of initial screening, for subjects without repeat screening.

‡ N = 3,423 subjects had a repeat CT screening.

§ Thoracic lymph node enlargement and/or central airway mass, filling defect, or occlusion in the absence of noncalcified lung nodules.

(11.1%), complete resolution in 192 (7.7%), and calcification in 18 (0.7%). Using a hierarchy (suspicious change, no change, partial resolution, complete resolution, and calcification) to classify persons with more than one nodule, repeat CT screening in 1,386 subjects with one or more noncalcified baseline nodules showed suspicious change in 75 (5.4%), no change in 1,110 (80.1%), partial resolution in 108 (7.8%), complete resolution in 82 (5.9%), and calcification in 11 (0.8%). Of 358 noncalcified nodules first seen on repeat CT, but visible in retrospect on initial CT, 66 (18.4%) showed suspicious change, 284 (79.3%) no change, and 8 (2.2%) partial resolution. The same hierarchical classification of 302 subjects with one or more noncalcified nodules first seen on repeat CT, but visible in retrospect on initial CT, showed suspicious change in 64 (21.2%), no change in 232 (76.8%), and partial resolution in 6 (2.0%). Finally, 339 noncalcified nodules were visible in 256 subjects (7.5% of 3,423) on the repeat CT, but not on the initial CT.

We referred 1,450 subjects (42.4% of 3,423) because of new or changed nodules, 18 (0.5% of 3,423) and 206 (6.0% of 3,423) with high and moderate lung cancer suspicion, respectively (Table 2). In a subgroup of 1,928 subjects without reason for referral after initial screen, we referred 231 (12.0%) because of new nodules, including 2 (0.1%) and 92 (4.8%) with high and moderate lung cancer suspicion, respectively (*see* the online supplement). The online supplement contains a detailed account of repeat CT screen results in other subgroups defined according to results on the initial screen.

Diagnostic Imaging

In the interval between initial and repeat CT (or within 365 d of initial CT for persons without repeat CT), tracking procedures documented 1,070 diagnostic imaging studies (thoracic CT, PET, or PET-CT; Table 2) in 821 (55.6% of 1,477) persons referred because of a noncalcified lung nodule seen at initial CT. One-hundred ninety-three (193; 86.9%) of 222 subjects referred because of a high or moderate suspicion nodule received 333 diagnostic imaging studies and 628 (50.0%) of 1,255 subjects referred because of a low suspicion nodule received 737 studies ($P < 0.0001$, 86.9 vs. 50%). Three hundred nine (309; 40.2%) of 768 subjects referred because of small (< 0.5 cm) low suspicion nodule received 357 diagnostic imaging studies and 319 (65.5%) of 487 subjects referred for larger (≥ 0.5 cm) low suspicion nodule received 380 diagnostic imaging studies ($P < 0.0001$, 40.2 vs. 65.5%).

Diagnostic Events

We identified 36 subjects (1.0% of 3,642) who were referred for abnormalities on either the initial or repeat screening and who subsequently received a noncancer diagnosis after a major thoracic surgical procedure. Classified according to the most invasive procedure, these 36 subjects included nine with thoracotomy, 21 with video-assisted thoracoscopic surgery (VATS), two with median sternotomy, and four with mediastinoscopy. The two median sternotomy procedures were performed to remove a thymic cyst and a bronchogenic cyst seen on initial CT. The four mediastinoscopy procedures were performed to evaluate abnormal PET in the mediastinum (one subject) or to evaluate enlarged lymph nodes seen on initial CT (three subjects, including two diagnosed with sarcoidosis).

The group of 30 subjects with thoracotomy or VATS included 28 subjects with lung resection to exclude malignancy in a lung nodule (Table 3), 1 subject with thoracotomy with emphysematous bleb resection to treat spontaneous pneumothorax, and 1 subject with VATS wedge resection to diagnose interstitial lung disease. The 28 subjects with thoracotomy or VATS lung resection to exclude malignant lung nodule constituted 0.8% (95%

TABLE 3. THORACOTOMY OR VIDEO-ASSISTED THORACOSCOPY IN THE SETTING OF COMPUTED TOMOGRAPHY LUNG CANCER SCREENING

Clinical Outcome	Thoracotomy or VATS		P Value [‡]
	Primary Lung Cancer* (N = 54)	Noncancer Diagnosis [†] (N = 28)	
Procedure			0.0006
Lobectomy	20	3	
Segmentectomy	15	3	
Wedge resection	17	22	
Thoracoscopic biopsy of hilar mass	2	0	
Surgical approach			0.2328
Thoracotomy	24	8	
VATS	30	20	
Role of clinical investigator			
Seen by clinician, procedure recommended		3	
Seen by clinician, procedure not recommended		8	
Not seen by clinician		17	
Diagnosis			
Primary lung cancer			
Non-small cell carcinoma	51		
Neuroendocrine carcinoma	2		
Small cell carcinoma	1		
Noncancer			
Fibrosis/inflammation		7	
Bronchiolitis		5	
Granuloma		5	
Pneumonitis/pleuritis		4	
Intrapulmonary lymph node		3	
Hamartoma		2	
Histoplasmosis		1	
Bronchiectasis		1	

Definition of abbreviation: VATS = video-assisted thoracoscopy.

* Thoracotomy or VATS for primary lung cancer diagnosed within 2 years of a repeat screening or, for subjects without repeat screening, within 3 years of an initial screening.

[†] Medical referral for any abnormality on an initial or repeat screening and thoracotomy or VATS to exclude malignant lung nodule (completed within 2 yr of a repeat screening or, for subjects without repeat screening, within 3 yr of an initial screening) with resultant diagnosis other than cancer.

[‡] Statistical significance (exact test) of the difference between the group with primary lung cancer and the group with noncancer diagnosis.

confidence interval [exact binomial; CI], 0.5–1.1%) of 3,642 screened subjects and 1.6% (95% CI, 1.1–2.3%) of 1,726 subjects with a referral recommendation for noncalcified nodule on either initial or repeat CT. These 28 subjects received non-lung cancer diagnoses of limited or no clinical significance (e.g., fibrosis, bronchiolitis, pneumonitis, intrapulmonary lymph node, etc.; Table 3). Notably, these 28 subjects typically underwent thoracotomy or VATS against the primary recommendation or without the advice of clinical investigators attached to the CT screening program (Table 3). Out of 80 subjects with primary lung cancer diagnosed within 2 years of the repeat screening or, for subjects without repeat screening, within 3 years of the initial screening (Table 4), we identified 54 subjects who had thoracotomy or VATS for either the diagnosis or treatment of lung cancer (Table 3). Therefore, in the setting of CT screening, we observed 28 and 54 subjects who experienced thoracotomy or VATS with benign and lung cancer outcomes, respectively (a ratio of 1 to 2).

Cancer Outcomes

Eighty subjects (2.2% cumulative incidence; 95% CI, 1.7–2.7%) had primary lung cancer diagnosed within 2 years of the repeat screening or, for subjects without repeat screening, within 3 years

TABLE 4. PRIMARY LUNG CANCER EVENTS* IN THE SETTING OF COMPUTED TOMOGRAPHY LUNG CANCER SCREENING

	Tumor Seen on Initial CT		All
	Yes	No	
Small cell lung cancer	1	10 [†]	11
Limited	0	5	5
Extensive	1	5	6
Non-small cell lung cancer	52	17 [‡]	69
Stage I	31	9	40
IA	23	5	28
IB	8	4	12
Stage II	2	1	3
IIA	1	1	2
IIB	1	0	1
Stage III	15	6	21
IIIA	11	2	13
IIIB	4	4	8
Stage IV	4	1	5

Definition of abbreviation: CT = computed tomography.

* Primary lung cancer diagnosed within 2 years of a repeat screening or, for subjects without repeat screening, within 3 years of an initial screening.

[†] Includes two subjects without a referral from either the initial or repeat CT screening.

[‡] Includes one subject without a referral from either the initial or repeat CT screening.

of the initial screening. Table 4 distributes these subjects according to manner of detection (primary tumor reported or not reported on the initial CT as an abnormality in need of diagnostic follow-up), cell type (small cell or non-small cell), and diagnostic stage. Notably, 40 (58.0%; 95% CI, 45.5–69.8%) of 69 non-small cell lung cancer cases and 31 (59.6%; 95% CI, 45.1–73.0%) of 52 non-small cell lung cancer cases with manifestations visible at initial screening were early stage (stage I).

Tracking of subjects referred for abnormalities seen on initial or repeat CT identified nine subjects with cancer diagnoses other than primary lung cancer (two Hodgkin's disease, two lymphoma, and five cancers metastatic to lung).

DISCUSSION

Low-radiation-dose helical CT hopes to reduce lung cancer mortality through early detection. In a high-risk cohort (n = 3,642; mean age 59 yr, median 47 pack-year cigarette smoking history, and 43% with airflow obstruction; Table 1), we report findings from initial CT followed by repeat CT 1 year later and clinical outcomes observed within 3 years of initial screening. Follow-up showed lung cancer detected at early stage (Table 4), though at the cost of frequent referral for CT-related abnormalities (Table 2).

As shown in Table 2, we delivered a follow-up recommendation to 1,477 subjects (40.6% of 3,642) with noncalcified nodules on an initial CT. The initial CT identified 40 (1.1%) subjects with high suspicion and 182 (5.0%) subjects with moderate suspicion nodules, representing $\geq 50\%$ and 5 to 50% expectation of lung cancer on biopsy, respectively. Estimates of the prevalence of one or more noncalcified nodules on initial screening CT include 23.3% in New York (4), 26.3% in Japan (6), 43% in Germany (3), and 51% in Minnesota (8). Most nodules seen on an initial screening CT are benign. In agreement with Swensen and co-workers (20), 2,416 of 2,497 (96.8%) noncalcified lung nodules seen on our initial CT showed no change, partial or complete resolution, or calcification, when re-examined 1 year later, a behavior implying benign etiology.

The appearance of new nodules on repeat CT is another property of screening that complicates management. In our study,

339 noncalcified nodules, not visible on the initial CT, appeared in 256 of 3,423 subjects on repeat CT, representing a 7.5% 1-year risk of new nodule.

Potential harms from false-positive nodules include financial and emotional costs, as well as morbidity and mortality, associated with diagnostic intervention. We documented 737 diagnostic imaging studies (CT, PET, or PET-CT) during the first year of follow-up in 628 of 1,255 (50.0%) subjects with low suspicion nodule. In the subset with only small (< 0.5 cm) low suspicion nodules, we documented 357 studies in 309 of 768 (40.2%) subjects.

Twenty-eight (34%) of 82 subjects with thoracotomy or VATS procedures for known or suspected lung cancer ended in a non-cancer diagnosis, a result somewhat better than typical practice, where 50% of thoracic surgical procedures to exclude malignancy in a lung nodule do not find cancer (23, 24). Even after taking account of subjects who obtained thoracotomy or VATS against the primary recommendation of study clinicians (Table 3), the frequency of resection for benign nodules, as observed under our protocol, is higher than generally desired. Because the 3-year follow-up was not yet complete, our analysis may underestimate the true frequency of thoracotomy or VATS ending in noncancer diagnoses.

In 3 of 28 instances (Table 3) of lung resection for benign nodule, a study pulmonologist (D.O.W.) recommended the procedure, triggered, in two instances, by falsely positive PET and, in the third instance, by appearance of a new nodule on repeat CT. In eight instances, subjects elected lung resection, despite the study pulmonologist's primary recommendation in favor of continued observation with serial imaging. The remaining 17 subjects did not consult with the study pulmonologist before accepting lung resection. Fourteen of 17 had lung resection after the initial screening. When characterized according to our criteria for lung cancer suspicion and the I-ELCAP diagnostic algorithm (15), we found three subjects with moderate-high lung cancer suspicion who were I-ELCAP qualified for immediate biopsy, seven subjects with moderate-high lung cancer suspicion who were I-ELCAP qualified for 3-month CT, and four subjects with low cancer suspicion who were I-ELCAP qualified for repeat CT screening in 1 year. Therefore, our results show a high frequency of thoracotomy or VATS without cancer and an apparent community bias toward aggressive intervention with biopsy for persons with indeterminate lung nodule. Observing 12% of 522 subjects having a biopsy within 1 year of a positive screening CT, Pinsky and colleagues also describe an apparent community bias toward biopsy (17). These results argue for strict adherence to diagnostic guidelines, in combination with informed decision making, when managing persons with nodules detected on screening CT. Although validated evidence-based guidelines are lacking, consensus guidelines are evolving to provide a framework for managing findings detected on screening CT (4, 8, 15, 21).

Forty (50%) of 80 subjects with primary lung cancer diagnosed within 3 years of initial CT were stage I non-small cell lung cancer (Table 4). Though representing a higher percentage of early stage disease when compared with the general population (1), the stage distribution we observed is less favorable than that reported by other investigators (3–8, 14, 15), but similar to the 53% value reported by the Lung Cancer Screening Research Group (25). Potential explanations include: (1) selection factors favoring enrollment of minimally symptomatic as opposed to completely asymptomatic at-risk subjects, and (2) variable practices with respect to diagnostic intervention and/or staging.

We present results from the largest single-institution study of CT lung cancer screening in current and ex-cigarette smokers.

Our results include detailed information about diagnostic imaging studies and invasive procedures that emanate from CT screening.

Conclusions

CT detects many indeterminate lung nodules, as well as early stage lung cancer. Diagnostic imaging studies and invasive procedures associated with CT screening incur costs, health risks, and anxiety that adversely affect quality of life. Our results indicate a tendency, in our community, toward overly aggressive diagnostic evaluation, including thoracotomy and VATS lung resection of CT screen-detected lung nodules. These results underscore the importance of adhering to diagnostic algorithms for managing CT screen-detected nodules.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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