Screening for Lung Cancer with Low-Dose Spiral Computed Tomography

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Studies suggest that screening with spiral computed tomography can detect lung cancers at a smaller size and earlier stage than chest radiography can. To evaluate low-radiation-dose spiral computed tomography and sputum cytology in screening for lung cancer, we enrolled 1,520 individuals aged 50 yr or older who had smoked 20 pack-years or more in a prospective cohort study. One year after baseline scanning, 2,244 uncalcified lung nodules were identified in 1,000 participants (66%). Twenty-five cases of lung cancer were diagnosed (22 prevalence, 3 incidence). Computed tomography alone detected 23 cases; sputum cytology alone detected 2 cases. Cell types were: squamous cell, 6; adenocarcinoma or bronchioalveolar, 15; large cell, 1; small cell, 3. Twenty-two patients underwent curative surgical resection. Seven benign nodules were resected. The mean size of the non-small cell cancers detected by computed tomography was 17 mm (median, 13 mm). The postsurgical stage was IA, 13; IB, 1; IIA, 5; IIB, 1; IIIA, 2; limited, 3. Twelve (57%) of the 21 non-small cell cancers detected by computed tomography were stage IA at diagnosis. Computed tomography can detect early-stage lung cancers. The rate of benign nodule detection is high.

Keywords: carcinoma; non-small cell lung; cytology; smoking; tomography, x-ray computed

In the United States, lung cancer is the most common fatal malignancy for both men and women. Approximately 175,000 new cases are diagnosed each year, of which 75–80% are non-small cell lung cancer. It is estimated that 1 in 18 women and 1 in 12 men will develop bronchogenic carcinoma in their lifetimes. More than 50% of patients will have distant metastases at diagnosis and only 20–25% will be localized and potentially resectable for cure (1).

The number of deaths from lung cancer exceeds the total combined number of deaths from the next three most common causes of death from cancer: breast, colorectal, and prostate cancers. Screening is recommended for each of these three cancers, and there has been a significant improvement in 5-yr survival over the past 25 yr. Lung cancer survival has not improved.

In the 1970s, the National Cancer Institute supported three mass-screening programs involving the Johns Hopkins University School of Medicine, Memorial Sloan-Kettering Cancer Center, and Mayo Clinic (2–4). No mortality difference was observed between the screened and the control groups (5), even with extended follow-up through 1996, even though 48% of cancers in the screen arm were early-stage cancers (stages 0, I, and II) (6). As a result of these and other studies, no organizations recommend screening (7).

Investigators have only recently considered the use of low-dose computed tomography for screening (8–14). These studies have suggested that screening with spiral computed tomography can detect lung cancers at a smaller size (less than 2 cm in diameter) and earlier stage (85–93% stage I) as compared with chest radiography and current clinical practice.

It is unclear whether smaller nodules represent earlier-stage disease and whether detection at an earlier stage improves mortality rates. It is also unclear whether screening with computed tomography creates problems related to overdiagnosis, unnecessary surgical procedure expense, morbidity, and mortality.

To further examine these questions, a study protocol was developed to test the hypothesis that screening with low-dose, fast spiral chest computed tomography in patients at high risk for lung cancer would result in a significant downward shift to stage IA and IB tumors at diagnosis, as compared with previous chest radiograph-based studies (2–6) and current clinical practice (1).

METHODS

Participants were enrolled into the study after written informed consent in response to local and regional television and newspaper coverage that carried information regarding the general outline of the study and eligibility requirements as well as funding of the National Institutes of Health grant. Participants were asymptomatic men and women 50 yr of age or older. Participants had to be current or past (quit less than 10 yr ago) cigarette smokers. A history of cigarette smoking at least 20 pack-years was necessary for entrance into the study. Ineligible were those with a history of any cancer within 5 yr other than nonmelanomatous skin cancer, cervical cancer *in situ*, or localized prostate cancer. Only mentally competent patients considered healthy enough to undergo pulmonary resection (i.e., patients without congestive heart failure or, in the judgment of the registered-nurse study coordinator, disabling dyspnea at the time of enrollment) were entered into the study. Any patient with a serious illness that decreased life expectancy to less than 5 yr was excluded. This protocol was approved by the Mayo Foundation Institutional Review Board and by the National Cancer Institute.

All participants agreed to undergo a prevalence computed tomography scan and three annual incidence scans. Annual induced sputum samples were obtained for immediate cytologic analysis. Blood was obtained from each participant and stored for subsequent DNA analysis. Spirometry (forced expiratory volume in 1 s) was performed on each participant.

All scans were performed on a multislice spiral computed tomography scanner (LightSpeed Model QX/i, General Electric Medical Systems, Inc., Milwaukee, WI) using the following technique: 5-mm slice width with 3.75-mm reconstruction interval; HS mode; pitch (ratio of table travel per rotation to total beam width), 1.5; exposure

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time, 0.8 s/rotation; table feed, 30 mm/rotation (37.5 mm/s); 120 kVp; and 40 mA. Effective radiation dose was 0.65 mSv (65 mrem). Follow-up computed tomography was performed at numerous institutions; the technique used was not dictated by the study protocol. It is our understanding that most, if not all, medical centers use standard-dose chest computed tomography with thin sections (1–3 mm) for nodule analysis.

All computed tomography images were viewed in cine-mode formats at a computer workstation by one of four investigator radiologists (T.E.H., S.J.S., G.L.A., A.M.S.). Images were viewed at standard lung, soft tissue, and bone windows.

The location and size of each uncalcified nodule were tabulated. A nodule was considered to be uncalcified if it did not contain benign-pattern calcification (diffuse, central, laminated, chondroid). All nodules identified in the baseline year were considered prevalence nodules. All nodules identified on the first annual computed tomography examination were considered incidence nodules regardless of whether they were present in retrospect on the baseline examination.

Computed tomography reports and a letter from a pulmonologist (J.R.J., D.E.M.) were sent to each participant and his or her physician (as designated by the participant). Nodule management recommendations were made to the attending physician based on an untested, internally developed management algorithm for indeterminate lung nodules (Figure 1).

RESULTS

From January 20, 1999, to December 15, 1999, 1,520 participants were enrolled and underwent the baseline prevalence computed tomography scan. Enrollment was denied to 421 applicants because they did not meet the eligibility criteria. The reasons for ineligibility were insufficient smoking history, 198; not interested in study after informed consent, 84; history of cancer within 5 yr, 37; congestive heart failure, 18; age, 31; enrollment in a conflicting research study, 4; respiratory insufficiency, 7; and miscellaneous health or personal situations, 42. Of the 1,511 living participants, 1,464 (97%) have returned for the first of their three annual incidence scans, which were performed within a 1-mo window on either side of their 1-yr anniversary. The 1,520 participants comprised 785 men and 735 women; 1,508 (99%) were white and 12 were African American, Native American, or Hispanic. Of the 1,520 participants, 742 (49%) were previous Mayo Clinic patients; the remaining patients were new to Mayo Clinic. All were 50 yr old or older (mean age, 59 yr; range, 50–85 yr). Sixty-one percent were current smokers; 39% were former smokers. The median number of pack-years was 45 (range, 20–230 pack-years).

Nine participants died after enrollment. One of the nine deaths was related to lung cancer (small cell lung cancer). Other causes of death were heart disease (three participants), laryngeal cancer, esophageal cancer, pancreatic cancer, lymphoma, and suicide. The man who committed suicide had a 2-mm lung nodule not thought to be cancer and a 4-cm abdominal aortic aneurysm. None of the nine deaths was related to surgery for either benign or malignant nodules.

One or more uncalcified prevalent lung nodules were prospectively identified in 782 participants (51%). The nodules were distributed in size and number as follows: < 4 mm: 307 (39%); 4–7 mm: 391 (50%); 8–20 mm: 76 (10%); > 20 mm: 8 (1%).

During interpretation of the first annual incidence scan, additional nodules were retrospectively diagnosed on the baseline scan in 375 (26%) of 1,464 participants. In 231 participants (62% of these 375 participants), the diameter of the retrospectively identified nodules was less than 4 mm, in 137 (37%) it was 4–7 mm, and in 6 (2%) it was 8–20 mm.

A total of 2,053 nodules were present on the prevalence scan. On the first annual incidence scan, 195 (9%) had resolved, 36 (2%) had been surgically removed (some patients had more than one nodule removed per operation), 86 (4%) had increased in size, 79 (4%) had decreased in size, and 1,657 (81%) were stable.

Of the 1,464 participants, 191 (13%) had incidence nodules detected on their first annual scan that were not present in ret-

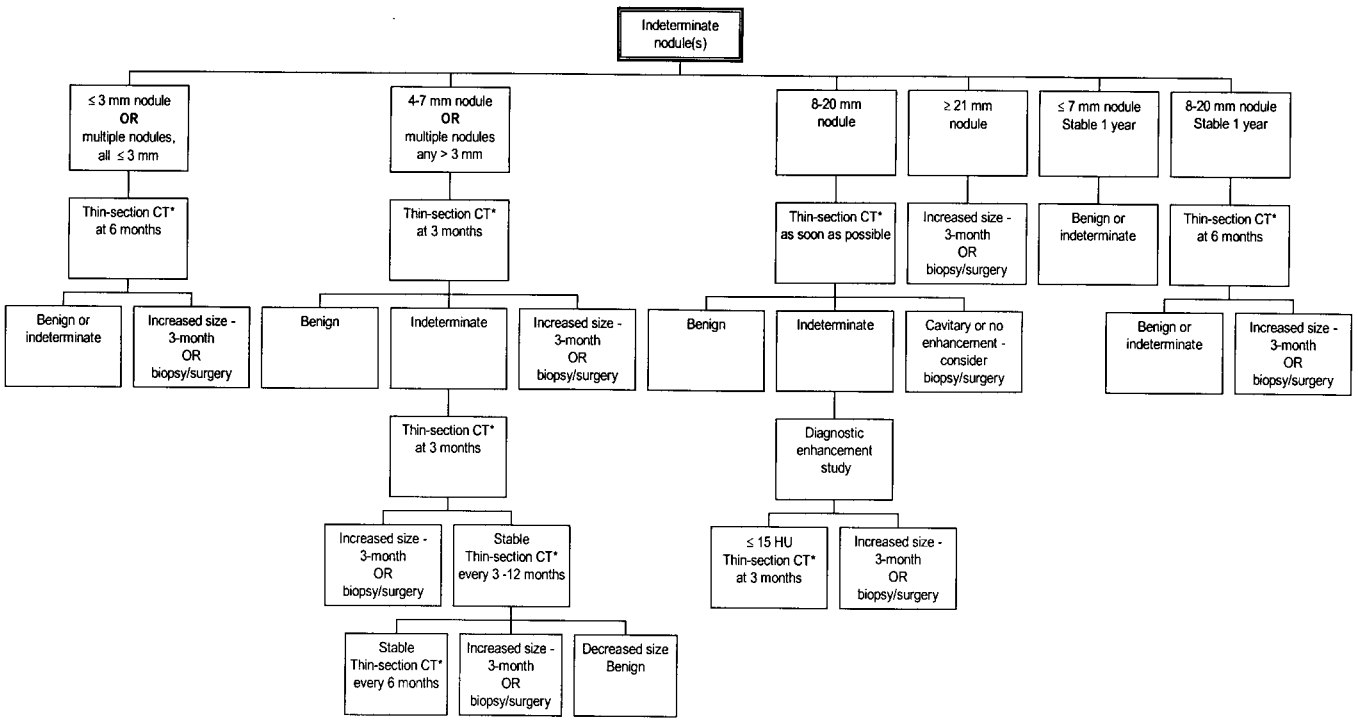

Figure 1. Study group recommendation for follow-up spiral computed tomography (CT). Recommendation is based on the size of the largest nodule. HU, Hounsfield unit. *Slice thickness of 1 to 3 mm.

rospect on the baseline scan. In 70 participants (37% of these 191 participants), the diameter of these incidence nodules was less than 4 mm, in 102 (53%) it was 4–7 mm, in 16 (8%) it was 8–20 mm, and in 3 (2%) it was more than 20 mm.

A total of 2,244 uncalcified prevalence and incidence lung nodules have been identified. In 1,000 (66%) of 1,520 participants, one or more lung nodules have been identified. In addition, 31 participants at baseline and 10 at the first annual scan had more than six nodules. We did not record the number of nodules if it was more than six.

To date, we have documented 25 primary lung cancers (1.7% of 1,464 participants; 1.1% of 2,244 nodules): 22 were non-small cell carcinomas, and 3 were limited-stage small cell carcinomas (Table 1 and Figure 2); 22 were prevalence lung cancers, and 3 were incidence lung cancers; 23 were diagnosed with computed tomography alone, and 2 (1 prevalence and 1 incidence) were diagnosed with sputum cytology alone. The incidence small cell cancer detected by sputum cytology alone was present in retrospect on computed tomography. By cell type, 6 cancers were squamous cell, 15 were adenocarcinoma/bronchioloalveolar carcinoma, 1 was large cell, and 3 were small cell. The mean size of the non-small cell lung cancers detected by computed tomography was 17 mm.

Potentially curative pulmonary resection was performed in 22 participants, pulmonary lobectomy in 20, segmentectomy in 1, and wedge excision in 1. The postsurgical cancer stage was IA in 13 participants, IB in 1, IIA in 5, IIB in 1, IIIA in 2, and limited small cell in 3. Seven patients underwent removal of a benign disease, 6 with a wedge excision, and 1 with a lobectomy. Five of the 7 patients had radiologic evidence of nodule growth. The diagnoses (1 patient had 2 nodules) were inflammatory changes, 2 patients; granuloma, 2; hamartoma, 1; scarring, 1; pulmonary embolus, 1; and squamous metaplasia, 1. All remaining nodules are being managed with observation at 3-, 6-, or 12-mo intervals and are considered radiologically indeterminate. Although we have recommendations for every nodule based on size, decisions regarding management are in the hands of the attending local physician and the patient and are not dictated by the study protocol.

Of the 1,520 participants enrolled, 210 (14%) had incidental nonpulmonary computed tomography findings of significance (Table 2). Ancillary nonpulmonary computed tomography findings were considered clinically "significant" if they required further evaluation (e.g., adrenal mass) or had substantive clinical implications (e.g., renal cell carcinoma). These included 2 bronchial carcinoid tumors, 4 renal cell carcinomas, 3 breast cancers, 2 lymphomas, 2 gastric tumors, and 1 pheochromocytoma. One patient with a small pancreatic adenocarcinoma was identified in retrospect.

Chest radiographs were not prospectively studied. Nine of the 21 participants with cancers detected by computed tomography had a chest radiograph within 1 mo of the computed tomography scan on which the cancer was detected. On five of the nine radiographs, the cancer was prospectively identified.

DISCUSSION

The prevalence and first incidence year results of our prospective cohort trial indicate that computed tomography can identify small and early-stage lung cancers. The mean size of the non-small cell lung cancers detected by computed tomography was 17 mm. Most (57%) of the non-small lung cancers detected by computed tomography were stage IA. The 5-yr survival rate after resection of stage IA non-small cell lung cancer ranges from 62% to 82% (15–23).

Low-dose computed tomography screening for lung cancer offers the possibility of reducing mortality through early detection. It is clearly unproven, and existing data do not justify its widespread use in the general population beyond scientific studies. Potential for bias exists in phase II (single-arm) studies. From our data, it is not clear whether there has been a stage shift. The relatively high percentage of stage IA non-small cell

TABLE 1. TWENTY-FIVE PRIMARY LUNG CANCERS FOUND ON SCREENING WITH COMPUTED TOMOGRAPHY ALONE OR SPUTUM CYTOLOGY ALONE

Case Number	Cell Type	Cancer Stage	Nodule Type	Nodule Diameter (*mm*)
1	Large cell neuroendocrine	IIA	Prevalence	9
2	Squamous cell	IA	Prevalence	11
3	Adenocarcinoma	IA	Prevalence	14
4	Adenocarcinoma	IA	Prevalence	20
5	Adenocarcinoma	IIA	Prevalence	15
6	Adenocarcinoma	IIIA	Prevalence	31
7	Squamous cell	IIIA	Prevalence	48
8	Bronchioloalveolar	IA	Prevalence	21
9	Adenocarcinoma	IA	Prevalence	11
10	Squamous cell*	IA	Prevalence	5
11	Adenocarcinoma	IA	Prevalence	15
12	Adenocarcinoma	IIA	Prevalence	13
13	Squamous cell	IA	Prevalence	10
14	Small cell carcinoma	Limited	Prevalence	12
15	Small cell carcinoma	Limited	Prevalence	55
16	Adenocarcinoma	IA	Prevalence	7
17	Bronchioloalveolar	IA	Prevalence	11
18	Adenocarcinoma	IA	Prevalence	20
19	Adenocarcinoma	IA	Prevalence	14
20	Adenocarcinoma	IA	Prevalence	8
21	Bronchioloalveolar	IB	Prevalence	12
22	Small cell carcinoma*	Limited	Incidence	4
23	Squamous cell	IIA	Incidence	36
24	Squamous cell	IIB	Incidence	8
25	Bronchioloalveolar	IIA	Prevalence	16

* Found on screening by sputum cytology alone.

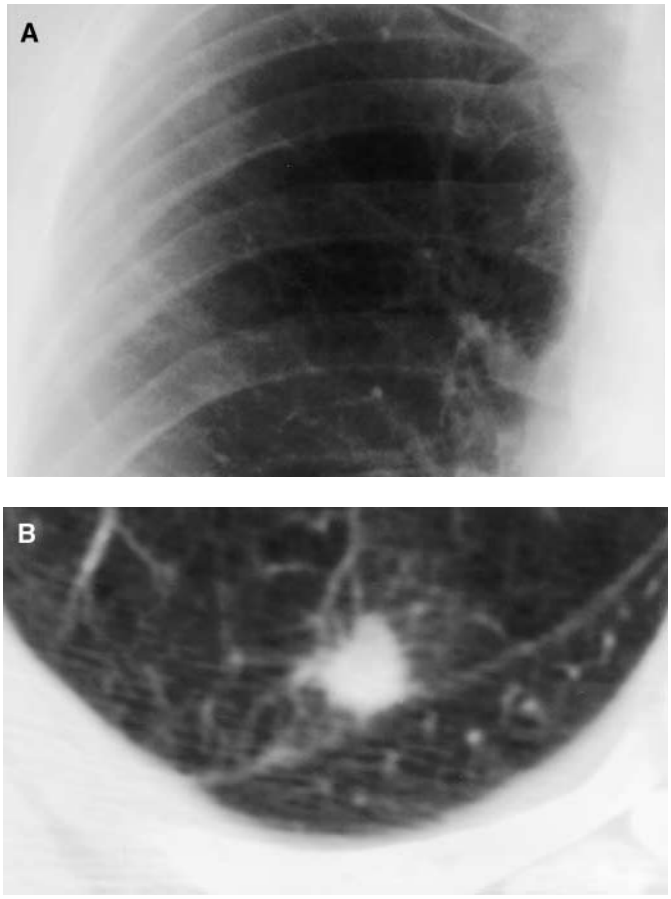

Figure 2. Fifty-six-year-old man with a stage IA prevalence adenocarcinoma (case no. 16 in Table 1). (*A*) Focused view of chest radiograph in the region of cancer does not demonstrate evidence of a nodule. (*B*) Low-dose spiral computed tomography shows a 7-mm adenocarcinoma.

lung cancers detected with computed tomography could reflect any combination of selection, length, overdiagnosis, and lead-time biases. To demonstrate a stage shift, one must show not only an increase in early-stage disease but also a concomitant decrease in late-stage disease. Furthermore, our study is biased by the exclusion of patients with a history of cancer and those not healthy enough to undergo lung resection. Further study is needed to confirm the role that these biases may have in the promising results we and others have observed.

False-Positive Rates

After 2 yr of study, we have found 2,244 uncalcified lung nodules in 66% of our 1,520 screened participants. We estimate that approximately 98% of these are falsely positive findings (1–14). Assuming that our 13% incidence rate of indeterminate lung nodules continues, almost all patients will have at least one false-positive examination result after only a few years of screening. Henschke and coworkers (11) found nodules in approximately 25% of screened participants, but they used computed tomography techniques (10-mm–thick sections and film [not workstation] viewing) that should allow detection of fewer small nodules (24). They also studied a population that may be expected to have a lower prevalence of fungal granulomas. However, none of the 2,244 lung nodules was calcified on 5-mm sections, and we do not have evidence from this study that a large proportion were granulomas. In fact, only two of the eight benign nodules removed were granulomas.

TABLE 2. OTHER COMPUTED TOMOGRAPHY FINDINGS IN 210 PATIENTS SCREENED FOR LUNG CANCER

Finding	Number
Renal cell cancer	4
Indeterminate renal mass	33
Renal calculi	24
Bronchial carcinoid	2*
Tracheal nodule	7
Lobar collapse	2
Bronchiectasis	11
Breast cancer	3
Breast nodule	17
Atrial myxoma	1
Abdominal aortic aneurysm	51
Pericardial effusion	9
Pleural effusion	4
Pulmonary artery calcification	1
Lymphoma	2
Spine metastasis	1
Adrenal mass	35
Pheochromocytoma	1
Gastric tumor	2

* One atypical.

Radiologically indeterminate benign lung nodules are considered a falsely positive finding of lung cancer. False-positive results are a significant concern. After several annual screening examinations with computed tomography, almost all of the patients in our cohort will need one or more follow-up examinations with computed tomography for indeterminate nodules or ancillary findings. The potential harm includes financial and emotional costs. The morbidity and mortality associated with radiation, biopsy, and surgical procedures must be considered. Morbidity and mortality considerations are particularly disconcerting in cases of benign lesions and overdiagnosed cancers. Clinicians currently lack the ability to determine which cancers will be lethal and which ones are the result of overdiagnosis (6, 25). "Overdiagnosis" includes cases of slow-growing, relatively indolent lung cancers (e.g., some cases of bronchioloalveolar and adenocarcinoma) that a patient dies with and not from. The issue of competing risks (e.g., heart disease, stroke, chronic obstructive pulmonary disease) is an important consideration that must be analyzed in the context of the overall efficacy of this screening examination.

In both the United States and Europe, approximately half of the patients undergoing surgical biopsy of an indeterminate lung nodule subsequently received a diagnosis that the nodule was benign (26–29). A benign biopsy rate of 50% would be extraordinarily costly and carry with it morbidity and mortality that would preclude use of this screening technique. In our series, seven participants underwent surgical biopsy of indeterminate lung nodules that subsequently were diagnosed as benign. Our proposed lung nodule management algorithm (Figure 1) is designed to expedite surgery for lung cancer and minimize intervention for benign nodules (30–33). However, a substantial concern is that surgery for benign nodules could dramatically increase when this screening technique is released into practice.

Twenty-six percent of participants had nodules that were missed on the baseline scan. This is a high false-negative rate. Although most of these nodules were quite small, it may be an inherent problem with human observation (34). We did not measure intraobserver or interobserver variability. This is a limitation of our study and an important issue in radiologic screening procedures. Computer-aided detection programs may be helpful in lowering the false-negative rate. Periodic screen-

ing, perhaps on an annual basis, will mitigate the downside of missing relatively small and slow-growing cancers.

Incidental Findings

Fourteen percent of our participants had incidental nonpulmonary findings of clinical significance (Table 2). It is possible that these findings enhance the potential value of computed tomography screening for lung cancer. Some of the findings we defined as clinically significant led to potentially life-saving surgery or chemotherapy because of early detection, when the patient was asymptomatic. These findings included aortic aneurysm, renal cell carcinoma, bronchial carcinoid, breast cancer, gastric cancer, pheochromocytoma, and lymphoma. (Note that we excluded all bronchial carcinoids from the lung cancer list.) It is also possible that for some individuals, incidental findings only add cost, anxiety, and even morbidity and mortality. Low specificity and high cost for evaluation of false-positive cases are important issues that clearly require further study.

In this cohort, we are exploring the possibility of using computed tomography to screen systematically for signs of heart disease (coronary artery calcification) (35), stroke (carotid artery calcification) (36), emphysema (presence and quantification) (37), osteoporosis (quantitative computed tomography bone mineral densitometry) (38), and risk of cardiovascular disease, non-insulin–dependent diabetes mellitus, and hypertension (visceral fat ratio) (39). Low-dose computed tomography has the potential to be used as a comprehensive screening tool for many of the most common causes of death.

Conclusion

Given the data from single-arm studies performed in Japan and the United States, it is plausible that earlier detection of lung cancer by computed tomography may result in decreased mortality. Earlier detection of lung cancer does not necessarily translate into decreased mortality, however. We raise concerns regarding a very high false-positive rate. The observed low specificity of this proposed screening examination could render it prohibitively expensive. Determination of improved disease-specific mortality and cost effectiveness will likely be needed for computed tomography to be widely accepted and reimbursed as a screening technique in lung cancer. This should require a prospective randomized controlled study.

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