

# COMPUTED TOMOGRAPHY SCREENING FOR LUNG CANCER

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For the past 20 years, major organizations in the United States have recommended against screening for lung cancer. These recommendations were based on the results of the randomized trials performed in the 1970s, which did not show a reduction in mortality of the screened group compared with the control group.<sup>9, 20, 36</sup> Based on these results, Eddy<sup>1, 2</sup> concluded that physicians should not perform annual chest radiographs of their high-risk patients because it is equivalent to screening. Based on these results and their interpretations, prominent national organizations such as the National Cancer Institute, American Cancer Society, and American Medical Association recommended that screening for lung cancer, whether using chest radiography or sputum cytology, not be performed.

Despite these almost universal recommendations not to deploy radiographic screening for lung cancer even in high-risk individuals in periodic health examinations, many physicians did not agree with these recommendations and continued to do so.<sup>3</sup> Justification for these screening practices by clinicians is based on many factors, including the knowledge that: (1) Lung cancer is the malignancy accounting for most deaths in the United States. (2) The overall cure rate is approximately 10% and has not improved significantly since the 1950s, despite advances in surgery, chemotherapy, and radiation oncology. (3) Early stage lung cancer is curable, as high as 70% and even higher for early stage IA. And (4) the cost of treating incurable lung cancer is significantly higher than treatment of curable lung cancer.

At the heart of the controversy is that the results of the randomized trials were inconsistent with the almost universal acceptance that lung cancer can be cured only if detected early. Further, Flehinger<sup>6</sup> and Sobue<sup>32</sup> showed that unresected stage I lung cancers have a uniformly dismal 5-year survival rate. In addition, there is no doubt that screening detects lung cancer at an earlier stage than it typically is diagnosed by symptoms.

The development of CT scan technology reopened the lung cancer screening debate. Computed tomography scan screening for lung cancer certainly meets all the criteria required for an appropriate screening test. First and perhaps most importantly, the disease for which the screening is being done should have a significant prevalence in the population being studied and be a significant health risk for those afflicted with it. Lung cancer is the leading cause of cancer death in men and women and one of the most lethal of all cancers. Second, there must be an advantage to detect the disease at an earlier stage than at a later or symptom-related stage and there is a well-established survival advantage for early stage lung cancer. Third, the screening test must be relatively safe and sufficiently sensitive to detect these early cases without too many false-positive results. Certainly, the chest radiograph and CT scan are rapid and painless tests without side effects. The radiation dose of low-dose CT scanning approaches that of a chest radiograph. The question of the number of false-positive results of CT scan screening for lung cancer is addressed in this report. Fourth, the cost of the screening test and the subsequent tests

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needed for diagnosis must be acceptable to society as typically measured by cost per life-year saved. Because the cost of CT scanning is somewhat higher than the cost of a chest radiograph and the cost of earlier intervention is lower than the cost of late intervention, the prospects for cost-effective screening seem to be good.

This report focuses on the published results of the baseline and annual repeat CT scan screening of the Early Lung Cancer Action Project (ELCAP) and those of others that address some of the aforementioned issues—in particular, that of the number of false-positive results and required subsequent diagnostics, and the costs of these tests.

Because screening for lung cancer constitutes, at present, an actively evolving topic with respect to all of its principal elements—the screening test(s), the diagnostic workup of screening positives, intervention on early cancer, and identification of suitable candidates for screening—this article also describes the authors' ongoing efforts toward international collaboration and pooling of data to obtain timely consensus on this rapidly evolving area of medical technology and its requisite evaluation to establish the knowledge base of future practice.

### ASSESSING EFFECTIVENESS OF CHEST RADIOGRAPHIC SCREENING

The evidence on chest radiographic screening is based predominantly on the Mayo Lung Project. This project enrolled approximately 10,000 volunteers (5000 in each of the two randomized arms) because this number of participants was necessary to detect a 50% mortality difference between the two groups. Although the ideal contrast for the assessment of screening effect in a randomized, controlled trial (RCT) would have been a comparison of screening with no screening, it was believed this could not be done ethically. Instead, the contrast used in the Mayo Lung Project was screening every 4 months, compared with the recommendation for annual screening. In the execution of the study itself, this contrast was diluted further because only 70% of those in the screening arm completed the 6-year program and 50% of those in the control arm followed the advice of the Mayo clinic and had annual screening.<sup>8-10</sup>

As a result of the study, it was found that the chest radiograph detected only 29% of the cancers in stage I and that the study did not have enough power to detect a smaller, albeit significant, mortality advantage.<sup>7</sup> Flehinger and colleagues<sup>5,7</sup> estimated that the mortality advantage of chest radiographic screening ranged between 0% and 13% and that a randomized trial to demonstrate such a mortality difference would have required more than double the number of subjects and more than 20 years.

Mortality rates were used as the endpoint for the Mayo Lung Project rather than the previously used rates of resectability and stage distribution

because the former was not subject to bias—lead-time, length sampling, and overdiagnosis. The mortality rates were calculated using the cumulative mortality over an average of 9 years—6 years following the inception of the screening program and 3 years of follow-up. To assess the maximum effect of the screening test, these 9 years are not equally relevant. First, it is not reasonable to assume that screening would reach its maximum effect within the first year of screening and even more questionable that it would remain effective once screening was discontinued.

In reporting the mortality rates for the Mayo Lung Project, the authors did not adjust for the contrast dilution that occurred as a result of the contamination of the screening and control groups, nor did they reflect a more appropriate interval for assessment of the maximum screening effect. Miettinen<sup>21</sup> reanalyzed the mortality rates. He believed the more appropriate interval to assess the maximum screening effect was from the period of 3 to 7 years after completion of the baseline screening because "this interval represents a compromise between one that is narrow enough to indeed address the full effect, and one that is wide enough to show a meaningful number of deaths from the disease." Using this more appropriate interval for the mortality rates in addition to well-accepted statistical adjustments for the lack of compliance with the screening and control arms, Miettinen found that the Mayo Clinic study results were consistent with a mortality improvement attributable to radiographic screening that may be as high as 43%. The evidence of the Mayo Lung Project therefore should be interpreted more appropriately as "no direct evidence for (screening)" rather than direct evidence against screening.

### EARLY LUNG CANCER ACTION PROJECT

Inspired by the enhanced potential of computed tomographic (CT) scan in screening for lung cancer, the authors initiated ELCAP in 1992. Its purpose was to assess the usefulness of annual CT scan screening.<sup>11-13</sup> The authors' review of the previous studies of lung cancer screening had led to the conclusion that resection of screen-detected early stage lung cancer commonly is curative, and that this already had been demonstrated beyond question. The real questions remaining to be answered therefore were whether the diagnostic shift toward smaller and earlier stage lung cancers provided by CT scanning and the resultant gain in curability would be large enough to make screening cost-effective, given suitable specifications of the screening regimen and its recipients.

Accordingly, the first-order aim in the authors' original ELCAP study and its subsequent sister projects was to focus on the most promising regimen of early (presymptomatic) diagnosis of lung cancer and to determine how early the diagnoses may be achieved. This focus is a matter of de-

termining the distribution of the diagnosed cases according to indicators such as stage and size and then refining the distribution by other prognostic indicators, such as cell type and tumor growth rates. This diagnostic distribution must be determined separately for baseline and for postbaseline diagnoses, and, for the latter, it again must be considered separately for interim (symptom-prompted) and screen-prompted diagnoses. It was understood that assessment of the resultant gain in curability requires longer follow-up.

### Early Lung Cancer Action Project Enrollment

Enrollment into ELCAP was confined to a cohort of 1000 persons (522 at Cornell University Medical College and 478 at New York University Medical Center), 60 years of age or older with a history of at least 10 pack-years of cigarette smoking and no history of cancer (other than nonmelanotic skin cancer) and fit to undergo thoracic surgery. Baseline screening, initiated in 1993, was completed in 1998. Of the 1000 persons at high risk for lung cancer enrolled, 46% were women (54% men), with median age of 67 years and median pack-years of smoking of 45.<sup>11</sup>

Among the 1000 subjects enrolled at baseline, 841 underwent the first repeat screening 6 to 18 months after the baseline screening.<sup>13</sup> All were asymptomatic at the time. These 841 have had 343 additional repeat screenings within 6 to 18 months of the previous screening, a total of  $841 + 343 = 1184$  "annual" screenings. Among the 159 subjects who did not have a repeat screening 6 to 18 months after baseline screening, 30 were treated as ineligible because of diagnosis of lung cancer resulting from baseline screening; another five were known to be alive but ineligible because of diagnosis of malignancy other than lung cancer; and yet another five were known to have died of causes other than lung cancer before the first repeat screening could have taken place. Two were treated as ineligible because of symptom-prompted diagnosis of lung cancer. Among the remaining 117, when approached for repeat screening, 111 had a clear reason other than diagnosis of lung cancer for forfeiting the repeat screening: six were too ill because of illnesses other than lung cancer, four said their physicians did not recommend repeat screening, 77 refused for reasons of their own, and another 24 had moved.

### The Screening Test—Baseline and Annual Repeat

Baseline and repeat-screening low-dose CT scan images were obtained using a HighSpeed Advantage scanner (GE, Milwaukee WI) at 140 kVp, 40 mA, 2:1 pitch with a collimation (slice thickness) of 10 mm. The images, covering the entire lung

region, were acquired in a single breath-hold at end-inspiration following hyperventilation, and they were reconstructed with overlapping 5-mm intervals. In instances in which the baseline or a subsequent screen led to the detection of nodules that, at the time of the repeat screening, had not yet proved to be benign, the standard-dose "diagnostic" CT scan was used in lieu of the low-dose CT scan.

The images obtained at baseline and annual repeat screening were viewed at lung and mediastinal windows (width, 1600 HU; level, -650 HU; width, 325 HU; level, 25 HU, respectively). Images initially were read on film, with 12 images per film, but once viewing monitors became available, the readings were done on them, viewing the images one at a time, using maximum magnification. In addition, when reading the annual repeat screenings, comparison with prior images was done with side-to-side viewing. Two dedicated chest radiologists—each blinded to the reading of the other—read the images. The respective findings with regard to the presence and number of nodules were recorded separately and then discussed, and the consensus findings were documented for the study. When the two readers could not reach a consensus, the case was presented to a third expert reader, and the adjudicated reading became the final one.

For all instances of nodules found at baseline or annual repeat screening, defined characteristics of the relevant nodules were recorded. Size (length and width), location (lobe), texture (pure ground-glass, other), and calcification (benign, other) were recorded. A nodule was classified as noncalcified if it did not show "benign pattern of calcification."<sup>11,13</sup> Size was defined as the average of length and width, and texture as pure ground-glass, if the nodule did not obscure the lung parenchyma and had no solid component; otherwise, the nodule was classified as "other."

A positive test result at baseline was defined as the presence of one to six noncalcified nodules. If no noncalcified nodule was identified, the result was classified as negative. Instances of more than six noncalcified nodules, diffuse bronchiectasis, or ground-glass opacities were classified as diffuse disease.

On annual repeat screening, note was taken of each newly detected noncalcified nodule. For each newly detected noncalcified nodule, the determination was made whether it was visible in retrospect upon review of the previous screening. If it was visible and there had been no interim growth, no further diagnostic tests were recommended. For those with newly detected noncalcified nodules that had grown (because they were not visible on the previous screening or because, although visible, they were smaller), further workup with a diagnostic CT scan, including high-resolution CT (HRCT) scan of the nodules, was recommended. On HRCT scan, again, the nodule was considered noncalcified if no benign calcifications could be identified using the previous definition. If the di-

agnostic CT, and HRCT scans affirmed the presence of one to six newly detected noncalcified nodules with interim growth, the result of the screening test was classified as positive; otherwise, negative.

Recommendations were made for the workup of positive results of baseline and annual repeat screening. It was not a requirement for the validity of ELCAP that these recommendations be followed, however, as long as the final diagnosis became firmly established. The decision regarding how to proceed therefore was left to the referring physician, and the actual workup was recorded. If malignancy was diagnosed and resectable, lobar resection was coupled with complete mediastinal lymph node dissection and labeling of all lymph node stations, and the deflated lung was palpated for any additional nodules. All cytologic and histologic findings from any biopsy or surgical procedure were documented.

### Diagnostic Workup of Baseline Positives

For cases in which noncalcified nodules were detected on the baseline low-dose CT scan, additional deployment of a standard-dose, diagnostic CT scan of the chest with HRCT scan of the nodule(s) was recommended for management purposes. For all nodules detected on HRCT scanning, the nodule characteristics specified earlier were documented. If the HRCT scan demonstrated benign calcifications not identified in the low-dose CT scanning, in terms of extent and distribution, in a nodule with smooth edges whose size was less than 20 mm, the nodule was considered to be benign.

If those criteria were not met by all of the noncalcified nodules detected in the subject, the ELCAP protocol recommended further workup according to the size of the nodule:

- a. For noncalcified nodules 5 mm or less in size (average of length and width), follow-up by HRCT scan 3 months later; given no growth, again at 6, 12, and 24 months. If no growth was noted over 2 years, the nodule was considered to be benign.
- b. For noncalcified nodules 6 to 10 mm in size, case-by-case assessment of the possibility of obtaining a biopsy using percutaneous transthoracic CT scan-guided fine-needle aspiration or video-assisted thoracoscopic biopsy procedures. For instances in which biopsy was not appropriate, follow-up for growth, as described earlier.
- c. For noncalcified nodules 11 mm or more in size, biopsy according to current standards of care, by fine-needle aspiration, video-assisted thoracoscopy, bronchoscopy, or a combination of these.

### Diagnostic Workup of Annual Repeat Positives

For all instances of a positive result on annual repeat screening, the recommended initial phase

of the diagnostic workup was a course of broad-spectrum oral antibiotics, followed by HRCT scanning 1 month after the initial scan, to assess change(s) in the size(s) of the nodule(s). If the nodule(s) had resolved completely, no further workup was recommended. If the resolution was incomplete and all of the nodules were initially 5 mm or less in size, follow-up HRCT scans was recommended 3 months later. So long as no further growth could be documented, follow-up HRCT scans at 6, 12, and 24 months were recommended. When growth was identified in these small nodules, biopsy was recommended. The same schedule of follow-up was recommended for pure ground-glass opacities as long as no solid component appeared; upon such appearance, biopsy was recommended. For all other instances of incomplete resolution following antibiotics, immediate biopsy was recommended, using percutaneous CT scan-guided transthoracic fine-needle aspiration or video-assisted thoracoscopy procedures. Moreover, all histologic findings from biopsy were documented.

In each case of diagnosed malignancy, the initial HRCT scan and the repeat HRCT scan (which followed the course of antibiotics, if applied) were used to determine the respective volumes of the tumor.<sup>39, 40</sup> These volumes, together with the time between the HRCT scans, were used to calculate the doubling time of the tumor.<sup>39, 40</sup>

### Documentation of Symptom-prompted (Interim) Diagnoses

The screening-induced "diagnostic shift" (to smaller sizes and lower stages at diagnosis) ultimately refers, as was noted, to all diagnoses of lung cancer under the regimen of screening. It therefore was the authors' concern to identify and document all relevant "interim" cases of diagnosed lung cancer prompted by symptoms and to pool these with the cases diagnosed on the prompting of screening.

Relevant for this purpose are cases in subjects who had a previous negative result of the screening test and for whom the diagnosis of lung cancer was the reason that the next screening was not done within 18 months. Among the 159 subjects who did not undergo an annual repeat screening, two had documented symptom-prompted diagnoses of lung cancer. An interim diagnosis of lung cancer was excluded by information provided on all the remaining subjects except for six with whom no contact could be made, directly or indirectly through their relatives and referring physicians.

### Baseline Results

Among the 1000 subjects, low-dose CT scanning identified 233 as having one to six noncalcified nodule(s); in only 33 of these subjects was the

**Table 1. RESULTS OF THE BASELINE AND ANNUAL REPEAT SCREENING**

Number of Subjects With:	Baseline	Annual Repeat
1-6 Noncalcified nodules	23% (233/1000)	2.5% (30/1184)
1-6 Noncalcified nodules after antibiotics	n/a	1.4% (16/1184)
Malignancy	12% (27/233)	44% (7/16)

nodule(s) also apparent on chest radiography. Chest radiography found 68 subjects with one to six noncalcified nodule(s), among whom fewer than half (29) actually had a nodule on low-dose CT scanning. The remaining 35 subjects had false-positive chest radiography-detected nodules in that they were not real pulmonary nodules but merely apparent nodules caused by a confluence of shadows.

Among the 233 subjects with one to six noncalcified nodule(s) found on low-dose CT scanning, 27 (12%) had a nodule-associated malignancy (Table 1; Figs. 1, 2). Among the 68 subjects with one to six noncalcified nodule(s) found on chest radiography, only 7 (10%) were found to have a malignancy—that is, 20 (74%) of the CT scan-detected malignancies were not seen on chest radiography. On the other hand, all of the chest radiographic-detected malignancies were detected on low-dose CT scans.

Among the 27 malignancies found in noncalcified nodules detected on low-dose CT scans, the size was 2 to 5 mm for one, 6 to 10 mm for 14, 11 to 20 mm for eight, and greater than 20 mm for four (Table 2). Of the CT scan-detected malignancies, 23 (85%) of the 27 malignancies were stage I, of which 83% (19 of 23) were missed on chest radiographs.

Pathologically, one of the nodule-associated ma-

lignancies was classified as an atypical carcinoid, one as a squamous cell carcinoma, three as mixed squamous-adenocarcinoma, three as bronchioalveolar carcinoma, two malignancies (in one lobe) were found in one person, one of them classified as adenocarcinoma and the other as bronchioalveolar carcinoma, and the remaining 18 were classified as adenocarcinoma.

**Annual Repeat Screening Results**

In the 1184 annual repeat screenings, low-dose CT plus HRCT scanning resulted in 30 instances of one to six newly detected and growing nodules, representing a rate of 2.5% (30 of 1184) (see Table 1). The rate was, as expected, essentially the same for the first repeat screening and for the subsequent ones. In the 28 instances in which a 1-month HRCT scan could be obtained, the nodule(s) had resolved fully in 12, among them seven in which the recommended course of antibiotics had been used. The remaining 16 instances required further diagnostic workup that, thus far, has led to eight biopsies with seven resulting in the diagnosis of cancer (Fig. 3).

For the six non-small cell malignancies, the median size was 7 mm, and all but one were of stage IA (see Table 2). The exception was a 5-mm adenocarcinoma with mediastinal lymph-node metastases (levels 2 and 4), therefore representing stage IIIA. The single small cell carcinoma was of limited stage. Three of the seven malignancies were larger than 10 mm in size and all were definitely visible (in retrospect) on the previous screening. Of the four measuring 10 mm or less, only one (or perhaps none) was visible on the previous screening. Calculated doubling time for each of the malignancies ranged from 30 to 170 days, with a median of 100 days.

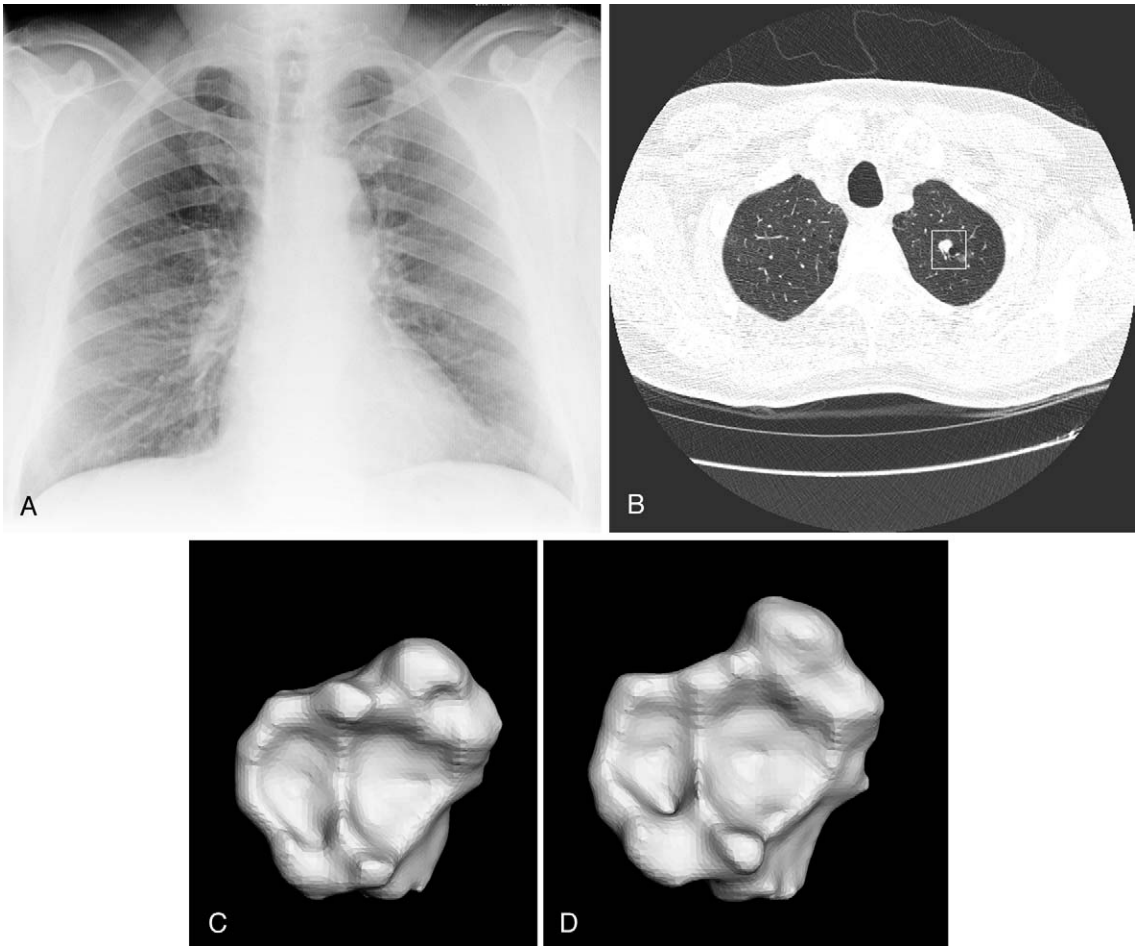
In two additional instances, the diagnosis of lung cancer was prompted by symptoms before the scheduled repeat screening. Both of these cancers were endobronchial. Upon re-examination of previous low-dose CT scanning 6 months earlier, one, a small-cell carcinoma (limited stage), showed no abnormality; the other, a squamous cell carcinoma (stage IIB), showed narrowing and irregularity of the left main bronchus at the site upon re-examination of the low-dose CT scan 5 months earlier. All seven non-small cell malignancies (six screen-detected, one symptom-detected) were deemed resectable.

**Table 2. DISTRIBUTION OF MALIGNANCIES BY SIZE AND STAGE ON BASELINE AND ANNUAL REPEAT SCREENING**

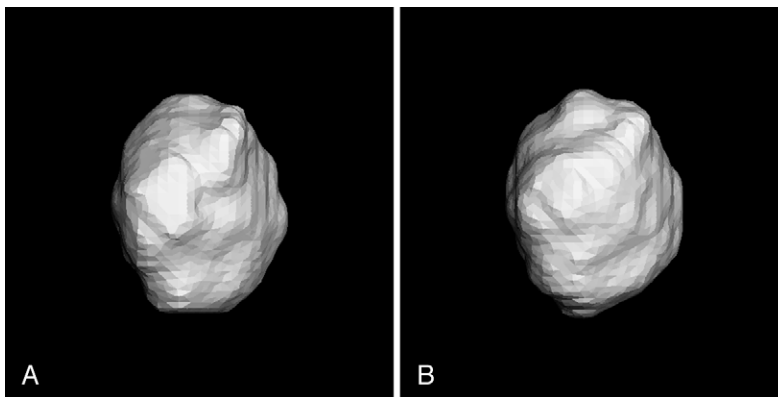
	Stage	Nodule Size on Low-Dose CT Scan				Total
		2-5 mm	6-10 mm	11-20 mm	20-45 mm	
Baseline	IA	1	12	8	1	22
	IB	0	0	0	1	1
	II	0	1	0	—	1
	III	—	1	—	2	3
	All Stages	1	14	8	4	27
Annual Repeat	IA	2	1	2	—	5
	IB	—	—	—	—	—
	II	—	—	—	—	—
	III	1	—	—	—	1
	All Stages	3	1	2	—	6

**Summary of Early Lung Cancer Action Project Results**

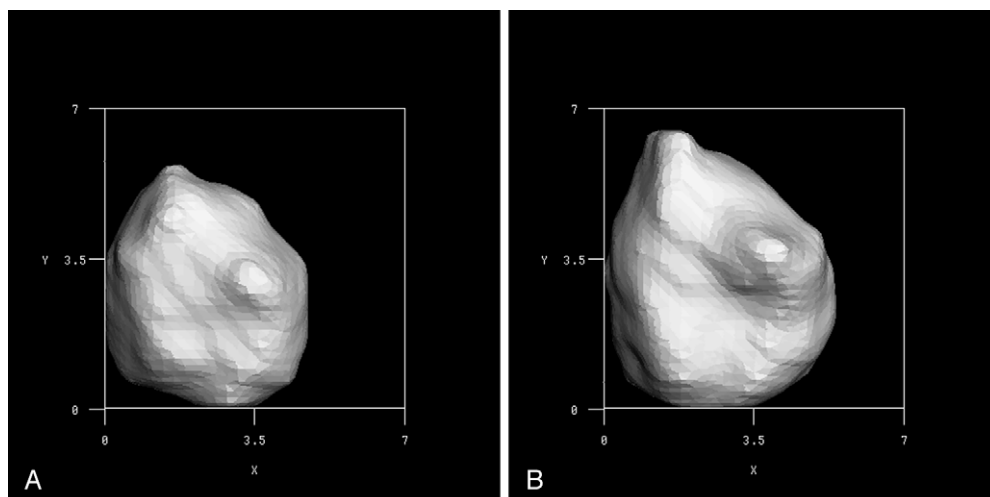
The authors' results confirmed that, relative to traditional chest radiography, CT scan-based screening markedly enhances the detection of lung cancer at earlier and more curable stages relative to what is known to prevail in the absence of screening. It was confirmed, as expected, that the



**Figure 1.** A, Chest radiograph of a male smoker taken at the same time as a baseline screening CT scan (not shown), which showed a solitary noncalcified nodule measuring 5 mm in the left upper lobe. B, Diagnostic CT scan was done following baseline screening. To assess growth, repeat diagnostic CT scan was performed 130 days later (not shown). A three-dimensional surface rendering of the nodule in the CT scan at baseline (C) and 130 days later (D). The change in volume was consistent with malignancy, the nodule was biopsied, and the diagnosis of adenocarcinoma was made.



**Figure 2.** Repeat CT scan of a benign nodule (A) shows no evidence of growth over 218 days (B) as seen in the three-dimensional surface rendered images of the nodule.



**Figure 3.** Three-dimensional surface rendering of a 4-mm nodule found in the left upper lobe on annual repeat screening (A) and 33 days later (B). Growth was consistent with malignancy. Because of severe emphysema in the left upper lobe, no percutaneous needle biopsy was performed so that after the growth assessment, the patient went directly to surgery.

authors' experience with annual repeat screening was different from that with baseline screening, notably with respect to the number of false-positive results of the screening test.<sup>11,13</sup> Positive results on annual repeat screening were much less common (3% versus 23%). The nodule-associated malignancies on annual repeat screening were, as also was anticipated, typically stage IA and small even for that stage. Although more than 80% of the malignancies were stage IA on baseline and annual repeat, the median size was considerably smaller on annual repeat (8 mm versus 15 mm). The EL-CAP recommendations also minimized biopsies on benign nodules.

Translation of the diagnostic distribution of the malignancies found on the annual repeat screening to its estimated corresponding overall rate of curability under screening requires information regarding the stage- and size-specific rates of curability. The 5-year survival rate of stage IA non-small cell malignancies less than 10 mm, detected by CT scan, has been reported to exceed 90%,<sup>27,30</sup> suggesting a curability rate of these malignancies in excess of 80%. Curability of the screen-detected, small, but later stage non-small cell and limited stage small cell malignancies is still to be quantified.

Because the authors' results and inferences mainly pertain to very small lesions, the question of overestimation on the grounds of potential "overdiagnosis" is likely to arise. In the context of screening by traditional radiography, however, it is good to appreciate that evidence clearly shows absence of overdiagnosis in the context of stage I cases.<sup>11,13</sup> But because the CT scan-detected lesions are distinctly smaller, the concern remains legitimate; indeed, it was a concern of the authors. In an effort to avoid the problem, the authors naturally have been careful with the pathologic (cyto-

logic and histologic) criteria for diagnosis of malignancy; beyond this, they had interim growth in all cases of small malignancies, and this was supplemented by documentation of further growth before biopsy.

The authors continue to be comfortable with the interval of 1 year between screenings. As was noted, the screen-detected nodule-associated malignancies showed a substantial diagnostic shift toward earlier stages and smaller sizes, and there has not yet been a single instance of symptom-prompted interim diagnosis of nodule-associated malignancy. The fact that there were two symptom-prompted interim diagnoses of lung cancer, neither nodule-associated, but endobronchial instead, serves as a reminder that CT scan screening for lung cancer might well deserve to be supplemented by cytologic screening of sputum samples with a view to earlier detection of centrally located endobronchial cancers.<sup>37</sup>

Even if a given regimen of CT scan screening for lung cancer serves to raise the overall rate of curability for lung cancer among the screenees, this does not in and of itself justify the use of that regimen of screening. It needs to be applied on indications such that the prospect of early diagnosis and its associated curability translate to a gain in life expectancy sufficient to justify the cost of the "screening"—that is, of the screening test together with the result-contingent definitive diagnostics. The issues here are somewhat complex, but it is evident that, with suitable specifications of the screening and its recipients, the cost of life-years saved can be as low as \$10,000 or even less.<sup>22</sup> Review of the costs of the ELCAP program indicate that the cost per life-year saved is approximately \$2500,<sup>38</sup> well below that for existing programs of screening for breast cancer<sup>26</sup> or cervical cancer,<sup>4</sup> which are more than \$30,000 per life-year

saved and well below the benchmark of \$50,000 used in the United States.

## RESULTS OF OTHER COMPUTED TOMOGRAPHIC SCAN SCREENING STUDIES FOR LUNG CANCER

Computed tomographic scan screening was introduced in Japan in 1993, in the context of an ongoing screening program using chest radiography, the Anti-Lung Cancer Association program at the National Cancer Center in Tokyo.<sup>17</sup> In 1996, Sone and colleagues<sup>33-35</sup> used a mobile unit to perform population screening in Matsumoto, Japan. In both of these projects, the frequency of stage IA among the cancers detected on annual repeat screening was more than 80%.<sup>15</sup>

The ELCAP investigators have helped to set up other screening programs throughout the world by providing the ELCAP protocol, forms, grant applications, advice, and training before the publication of their baseline results. Between 1996 and today, 919 high-risk subjects have entered ELCAP-type screening at the University of Muenster, Germany; 600 in Hadassah Medical Center in Jerusalem, Israel; 600 at Moffitt Cancer Center in Tampa, Florida; and 1520 at the Mayo Clinic in Rochester, Minnesota.<sup>15</sup> Details of the Mayo Clinic CT scan screening project have been described by Jett.<sup>16</sup> Each of these screening projects has varied its screening eligibility criteria somewhat from the original ELCAP and therefore provides additional information regarding the frequency of detected malignancies by age, smoking habit, and other risk indicators.

It is anticipated that the frequency of stage IA lung cancers may vary in these projects for the baseline screening based on the asymptomatic or symptomatic status of the subjects and random variation. The frequency of stage IA lung cancer on annual repeat screening should depend on the diagnostic workup protocol and should be comparable for all spiral CT scanners. This seems to be the case.<sup>15</sup>

## FUTURE EFFORTS

Because there is widespread interest in further development of screening programs throughout the world and rapid advances in technology, screening for lung cancer constitutes an actively evolving topic with respect to all of its principal elements—the screening test(s), the diagnostic workup of patients with positive screening results, intervention in cases with early cancer, and identification of suitable candidates for screening. To this end, the authors have developed an International Early Lung Cancer Action Program (I-ELCAP), an outgrowth of the original ELCAP experience, that provides for international collaboration to obtain rapid consensus on this rapidly evolving area of medical technology and its requisite evaluation toward the knowledge base of future practice by pooling of the data. A detailed new protocol has been developed so that other investigator groups

can initiate research projects and use the ELCAP web-based management and data-recording system and its associated teaching files.<sup>14</sup>

This protocol provides for flexibility regarding the indications for screening and intervention subsequent to the diagnosis of lung cancer while it precisely specifies the regimen of early diagnosis to ensure the poolability of the data across the different institutions. The diagnostic distribution achieved by the regimen of early diagnosis will be ascertained for each of the relevant diagnostic and prognostic categories (e.g., stage, size, cell type). For each of these, the broad aim is to determine case-fatality rates without and with intervention (in the absence of competing causes of death), together with the respective timings of fatal outcomes. These fatality rates also will provide the category-specific proportions of overdiagnosis, curability rates for progressive cases, and the time lags to deaths preventable by early intervention. As a by-product of the flexibility regarding the indications for screening, the I-ELCAP protocol will provide the frequency of screen-detected lung cancers over a wide range of indications for screening.

Underpinning the I-ELCAP efforts is the concept that screening is the pursuit of early diagnosis followed by early intervention. It should be understood, however, that there is another, contrasting outlook with respect to assessment of screening for cancer that leads to an RCT contrasting screening with no screening.<sup>19, 28, 29</sup> These two differing outlooks are not a result of methodologic differences, but, rather, they flow from a divergence in the concept of what screening is—whether the pursuit of early diagnosis (to be followed by early intervention aimed at reduction of fatality) or an intervention in itself (intended to reduce cause-specific mortality).

The RCT outlook considers screening to be an intervention and focuses on cause-specific mortality, a muddled concept at best, with many inherent problems.<sup>18, 23-25, 31</sup> As stated by Sobue,<sup>31</sup> “disease-specific mortality rate tends to be affected by the intervention itself and therefore, needs careful interpretation.” Review of the previous RCT for lung cancer for assessment of traditional radiography—the Mayo Lung Project—illustrates the difficulties encountered in performing RCT to determine reduction in the cause-specific mortality attributable to protocol nonadherence<sup>10, 31</sup> and differential ascertainment of the cause-specific mortality in the screened and unscreened groups.<sup>19</sup>

In contrast, the I-ELCAP protocol focuses on early, presymptomatic diagnosis of lung cancer. Its first-order aim is to determine how early the diagnoses are achieved. Early diagnosis then leads to early intervention and long-term follow-up provides the resulting outcomes. The latter for small tumors is not yet fully proved but promises to be far superior to the now dismal fate of most patients with lung cancer.

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