

***International Early Lung Cancer Action Program:  
Enrollment and Screening Protocol***

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## **Overview**

The International Early Lung Cancer Action Program (I-ELCAP) has as its broad research objective the advancement of knowledge for early diagnosis and treatment of lung cancer. Details of the specific aims and the theoretical basis for the research are given elsewhere.

The participating institutions need to commit themselves to at least one repeat screening (while more is desirable for precision), and follow-up of at least 10 years of all diagnosed lung cancer cases. It is critical for validity of the I-ELCAP database that each institution is committed to fully document the initial and all subsequent screenings for as long as the screenings on that person continue, and to transmit the documentation to the I-ELCAP database. It is also critical to identify and document all instances of interim diagnosis of lung cancer among the screenees, as well as reasons for discontinuation of the screenings.

The treatment interventions can be chosen by each institution. However, each participating institution must be committed to document, for each diagnosed case of lung cancer, not only the timing and nature of the intervention(s) (if any) but also the prospective course in respect to manifestations of metastases.

The development of a protocol has been a concern of the ELCAP (Early Lung Cancer Action Project) Group for more than a decade (1-5), and updates have been made in the framework of the International Conferences (4) organized by this Group and in their resultant international consortium on screening for lung cancer, I-ELCAP. The research program of I-ELCAP is guided by a common protocol (5, 6) and its approach to long-term follow-up (7, 8). The most recently updated version of the protocol is presented below – with the understanding that the pathology aspects of the screening in the I-ELCAP are guided by a separate protocol specific to it (9, 10).

In the framework of the I-ELCAP protocol, there is opportunity for the conduct of related *ancillary studies*: various non-CT initial tests can be deployed parallel with the low-dose CT test. This provides an opportunity for studying their relative merits for one and their value as add-ons for another. Such tests might be based on ‘biomarkers’ among others. Similarly, various treatment options for early lung cancer can be studied.

## **Admissibility for collaboration**

The admissibility criteria for an institution to collaborate in the I-ELCAP are as follows:

1. It is committed to implement the regimen of early diagnosis specified below, including at least one repeat screening.
2. It submits to the I-ELCAP database the institutional documents approving the screening and participation in the I-ELCAP, is committed to conform to the stated requirements, and is amenable to I-ELCAP database auditing of compliance with those requirements.
3. It is committed to provide the I-ELCAP database with each successive instance of baseline screening, and to fully documenting this and also all repeat screenings.
4. It is committed to identify, and to document, each instance of interim diagnosis of lung cancer, including its symptoms/signs (if any).

5. It is committed to document the reason(s) for discontinuation of screening.
6. It is committed to document the timing and nature of the intervention(s), if any, in each instance of diagnosed lung cancer, including in interim-diagnosed cases.
7. It is committed to follow and document each diagnosed case of lung cancer, interim-diagnosed cases included, until manifestations of metastases, death (its cause), or otherwise, for at least 10 years.
8. It is committed to deploy the ELCAP web-based management system for CT screening for lung cancer, and in this framework to submit all the research data – and images as well as pathology specimens (their digital counterparts) – to the I-ELCAP database.
9. It is committed to conform to all other policies of the I-ELCAP, notably those concerned with quality assurance (below).

It deserves note that among the contributors to I-ELCAP could very well be the studies performing randomized controlled trials (RCTs) contrasting CT screening with either no screening or some other type of screening. The relevant contributions would derive from the CT screening arm of such a trial. Of course, all of the requirements above would have to be satisfied.

### **Indications for screening**

As screening is for asymptomatic persons, needed is documentation of the symptom profile, specifically current presence/absence of potential manifestations of lung cancer which include worsening cough, hoarseness, hemoptysis, and unexplained loss of weight. Symptomatic persons are ineligible for enrollment.

Indications for subject participation may vary, notably as to age and smoking history as these can be set by each participating institution, and those indications must be specified. The person must also be willing to undergo repeat screening on schedule.

### **Regimen of screening**

In this protocol, ‘screening’ refers to the entire process of the pursuit of early, rule-in diagnosis of lung cancer. Thus, it only begins with the initial CT test. A positive result of this test is followed by further diagnostics, possibly including biopsy and pathologic assessment of the specimen.

It is understood that there may need to be occasional exceptions to the protocol. Each site is fully responsible for performance of the CT scans and the interpretation, and workup recommendations. In those cases for which protocol recommendations are not followed, it is important to document the reasons for this and to record all results of the alternative workup.

### *Image production*

In this regimen, the initial imaging is the same in baseline and repeat screenings. As there are a large variety of CT manufacturers and models, the following are general guidelines for the image production. Scans should be acquired on multi-detector-row scanners with 4 or more rows. Scans should be acquired so that images can be reconstructed at 1.25 mm or less. There is no specific definition of “low-dose,” although historically most screening protocols have used scan parameters of

120-140 kVp and 30-100 mAs. We currently suggest that scans be obtained at 120 kVp or lower and 40 mAs or lower. Collimation and pitch also affect dose, and these should be set to allow for the lowest dose, while maintaining acceptable image quality. It may be useful to reconstruct the images using both a standard and high-resolution kernel. Scan parameters may also be adjusted to allow for higher doses on large patients. In addition, new dose reduction techniques are being made available by scan manufacturers, and these may also be used, providing that acceptable image quality is maintained.

Images should be acquired in a single breath from the lung apices through the lung bases. The use of contrast material is not involved. For the workup of lung abnormalities that have been identified, typically the same low dose parameters can be used.

### *Reading of images*

The resulting images are read by a radiologist at the site. The reader is aware that the images derive from the initial CT for early diagnosis of lung cancer, and also is informed of whether they are from baseline or repeat screening. The reader views the images as they are displayed in a high-resolution monitor at their typical window and level settings, scrolling through the images one at a time. For the purposes of assessing the size of a nodule or that of a mediastinal abnormality, however, the following settings are used: lung window width 1500 and lung window level -650, and mediastinal window width 350 and mediastinal window level 25.

For a number of screenings, a second, ‘central’ reading is done for quality assurance and teaching purposes, without knowledge of the results of the first, site reading. The site radiologist receives the ‘central’ reading report, with discrepancies, if any, highlighted. In case of a discrepancy, the site radiologist may find it necessary to change the site report; and in this event, the updated report is also submitted to the central facility, where a record is kept. The site radiologist sends the final report to the subject and to his/her referring physician. The quality of the scan and its interpretation is solely the responsibility of the site.

In both baseline and repeat screening, the reader’s first concern with the images from the first, low-dose test is to identify all *non-calcified* nodules visible in them. A nodule is manifest as a focal non-linear opacity, whether the nodule be solid, part-solid, or nonsolid (the latter two corresponding to ‘ground-glass opacity’), located in the parenchyma or endobronchially. A nodule is classified as non-calcified if it fails to meet the usual criteria for benign, calcified nodules. Thus, a nodule less than 5 mm in diameter is non-calcified if all of it appears less dense than the ribs (on bone and lung windows); a nodule 5-20 mm in diameter is non-calcified if most of it is non-calcified (by that criterion) and/or the calcification does not correspond to a classical benign pattern (complete, central, lamellated, popcorn) and/or the edge is spiculated (to any extent); and a nodule over 20 mm in diameter is non-calcified if any part of it is non-calcified (by the criterion above).

The reader documents each of the nodules that even alone would have made the result positive. Specifically, as for each of these nodules, the reader documents the location, size, consistency (‘solid,’ ‘part-solid’ or ‘nonsolid’), presence of calcifications, edge and presence of spiculations. A nodule is classified as part-solid if it has patches within it that completely obscure the lung parenchyma, and non-solid if none of the lung parenchyma in it is completely obscured (11). In making the distinction between part-solid and nonsolid nodule, blood vessels within the nodule, despite their appearance as solid components, are not regarded as solid components.

Nodule diameter is the average of length and width. Length is measured on a single CT image that shows the maximum length; width, defined as the longest perpendicular to the length, is measured on the same CT image. In I-ELCAP research these measures will ultimately be replaced by computer-based assessments of volume.

The reader also documents other findings in the chest, including those in the mediastinum (12), heart (13), soft tissues, and bones. Mediastinal masses can occur anywhere in the mediastinum, including in the thymus, heart, and esophagus; and a mass in the neck, such as the thyroid, may extend into the mediastinum. Such mediastinal and soft tissues masses are documented as to location and size. The reader also documents findings in the liver and adrenal glands as to location and size.

Each coronary artery is identified (main, left anterior descending, circumflex, and right). Evidence of calcification in each artery is documented as none, minimal, moderate, or severe, scored as 0, 1, 2, and 3, respectively (13). Minimal calcification was defined if less than 1/3 of the length of the entire artery showing calcification, moderate as 1/3-2/3, and severe as more than 2/3 showing calcification. With 4 arteries thus scored, each subject received a CAC score in the range from 0 to 12.

The extent of emphysema is identified and classified as none, mild, moderate, or severe, each being scored 0 to 3, respectively. Mild emphysema is defined by having no discrete areas of decreased CT attenuation but splaying of blood vessels suggesting parenchymal expansion or having occasional discrete areas of decreased attenuation; moderate emphysema if discrete areas of decreased attenuation can be identified involving less than half of the lung parenchyma; and, severe emphysema if discrete areas of decreased attenuation can be identified involving more than half of the lung parenchyma. Each subject receives an emphysema score in the range from 0 to 3.

### *Screening frequency*

When application of the regimen at baseline does not lead to the diagnosis of malignancy, repeat screening is scheduled for a preset time subsequent to the initial, low-dose test at baseline. Whereas the protocol calls for annual repeat screening, each institution is free to choose the timing of the repeat screening. In reality, however, practicality leads to variation in this preset interval. Such variations do not threaten the validity of the study, so long as they arise from compelling circumstantial matters (and thereby are as though randomly assigned) and these would provide an opportunity to study the implications of different intervals to repeat screening (in the regimen) as for the resultant diagnostic distribution.

If Stage I, II or IIIA malignancy is diagnosed, screening may be continued with the original schedule.

### *Baseline screening*

At *baseline* the result of the initial CT is positive if at least one solid or part-solid nodule 5.0 mm or more in diameter or at least one nonsolid nodule 8 mm or more in diameter is identified in lung parenchyma (11). When non-calcified nodules are identified but all of them are too small to imply a positive result, the result is semi-positive and calls for CT 12 months after the initial one at baseline (14). If none of the noncalcified nodules meet the criteria for a positive or semi-positive result or the test is negative, a repeat CT is to be performed 12 months later.

When the result is positive, further diagnostic work-up concerns all nodules which even alone would have made the result positive. However, the work-up is different according to the size of the largest nodule.

For solid and part-solid nodules 5 mm but less than 15 mm in diameter, and for nonsolid nodules 8 mm but less than 15 mm in diameter, there are two options. The preferred option (A) is to perform another low-dose non contrast CT 3 months later; if it shows growth at a malignant rate (see growth assessment), biopsy is recommended; if there is no growth or partial or complete resolution, the workup stops. If the nodule is solid and greater than 10 mm in diameter or the solid component of a part-solid nodule is greater than 10 mm in diameter, then another option (B) is to perform PET scan and if the result is positive, biopsy is recommended, while if negative or indeterminate a low-dose CT 3 months later is performed and acted on as specified in option A. When multiple nodules are present and occult infection or inflammation is a possibility, an added option (C) is a course of a broad-spectrum antibiotic with anaerobic coverage followed by low-dose CT 3 months later (15) and the result is acted on as specified in option A.

For nodules 15 mm or larger in diameter (whether solid, part-solid, or nonsolid), two additional options are available. If the nodule appearance is highly suggestive of lung cancer, immediate biopsy is one option (D). As occult infection is a possibility, option (E) is a course of an antibiotic with anaerobic coverage followed by low-dose CT 1 month later (15); if the CT shows no resolution or growth at a malignant rate (see growth assessment), biopsy is recommended. If there is partial or complete resolution on CT, the workup stops.

If a solid endobronchial nodule is identified, a low-dose non-contrast CT scan is performed within 1 month. At the time of the follow-up CT scan, the participant is asked to cough vigorously several times. If the nodule is still present, the participant is referred for pulmonary consultation, and if necessary, bronchoscopy.

For all individuals in whom the diagnostic work-up was stopped or the biopsy did not lead to a diagnosis of lung cancer, repeat CT 12 months after the initial baseline CT is to be performed.

### *Repeat screening*

On *repeat* screenings, again, the reader's first concern with the initial CT is to identify all non-calcified nodules, but now *regardless of size*, and with special regard for the nodule(s), if any, that produced a semi-positive result on the initial CT at baseline. The focus, among these, is on those nodules that are showing *growth* since the previous screen, of overall size or the size of the solid component if previously part-solid, or appearance of a solid component if previously nonsolid. To determine whether growth has occurred, the reader compares the current images with the corresponding previous ones, displayed side-by-side.

On repeat screening, the result of the initial, low-dose CT test is positive if at least one non-calcified nodule with interim growth is identified, whether newly seen or seen in retrospect but not previously identified. If the test is negative, a repeat CT is to be performed 12 months later.

The documentation of the repeat-screen nodules of record -- ones that even alone would have made the test result positive -- is analogous to that at baseline, except that this documentation is supplemented by the corresponding characterization of the nodule in the previous screen. The further diagnostic workup depends on the size and consistency (nonsolid, part-solid or solid) of the nodule(s) of record.

If all the non-calcified newly identified nodules that are solid or part-solid and less than 5 mm in diameter, low-dose non contrast CT at 6 months, respectively after the prior one, is to be performed; any nodule with further growth at a malignant rate (see growth assessment) is biopsied. If no further growth is seen in any of the nodules or they have completely or partially resolved the workup stops. If all the newly identified nodules are nonsolid and less than 8 mm, then a repeat CT 12 months later is to be performed.

If at least one of the newly identified noncalcified nodules, either solid or part-solid, is 5 mm in diameter or larger, or nonsolid and 8 mm in diameter or larger, the preferred option (A) is an immediate course of a broad-spectrum antibiotic with anaerobic coverage followed by low-dose CT 1 month after the prior low-dose test. If it shows growth (see growth assessment), biopsy is recommended; if there is complete or partial resolution, the workup stops. If the nodule is unchanged, then there are two options (B) and (C). Option (B) is to perform a low-dose CT 3 months after the initial CT and if it shows growth, biopsy is recommended, otherwise the workup stops. Option (C), preferably for solid nodules 10 mm or larger part-solid nodules whose solid component is 10 mm or larger, is to perform PET scan and if the PET result is positive, immediate biopsy is done while if it is indeterminate or negative, low-dose CT 3 months after the initial CT is performed. If the nodule shows growth on this follow-up CT, biopsy is recommended, otherwise the workup stops.

If a solid endobronchial nodule is identified, a low-dose non-contrast CT scan is performed within 1 month. At the time of the follow-up CT scan, the participant is asked to cough vigorously several times. If the nodule is still present, the participant is referred for pulmonary consultation, and if needed, bronchoscopy.

For all individuals in whom the work-up was stopped or the biopsy did not lead to a diagnosis of lung cancer, repeat CT 12 months after the prior baseline or repeat CT is to be performed.

#### *Assessment of growth*

Growth of the nodule is defined as enlargement of the entire nodule and/or of the solid component of a part-solid nodule and/or the development of a solid component in a nonsolid nodule on the follow-up CT after the initial annual repeat CT. Short-term assessment of growth, based on CT images, includes consideration of the measurement error and whether nodule volume doubling rate is consistent with malignancy. Volume doubling rates are based on measuring the change in nodule volume from two time separated scans. The time between these two scans must be sufficiently long for a significant detectable change in volume to occur.

The initial low-dose CT scan is used for the initial nodule measurement. All subsequent CTs of the nodule(s) are again performed, ideally with the same scanning parameters that were used to acquire the initial images. The use of contrast material is not involved.

Conservative criteria for a significant percent change in the nodule diameter or growth of the solid component in part-solid nodules are: a) for nodules < 5 mm in diameter, it should be at least 50%; b) for nodules 5 - 9 mm in diameter, it should be at least 30%; c) for nodules  $\geq$  10 mm in diameter, it should be at least 20%. The time between the serial CT scans to observe these changes is given in the baseline and repeat screening sections of this protocol. A very rapid growth rate in the relevant time period is more suggestive of an infection than a malignancy and in this case a course of antibiotics followed by CT 1 month later is to be performed.

Computer assisted growth rate is still a topic of research, and there will likely be variation among the different software that is currently available. These guidelines have been developed as a result of the evaluation of our in house software, and may differ from others, including those that are commercially available. With careful technical and clinical quality review as outlined below, the results of computer analysis are useful in guiding the workup. In this assessment, the screening site has access to having an analysis performed using the web-based research tools (16-20).

When using any computer assisted software, the radiologist must be satisfied with the quality of the CT images and the computer segmentation results as ultimately it is clinical judgment that determines whether growth has occurred. The computer scans and the segmentation should be inspected for image quality (e.g., motion artifacts) and for the quality of the segmentation. The radiologist should visually inspect both nodule image sets side-by-side to verify the quality of the computer segmentation for each image that contains a portion of the nodule. The segmentations should also be examined for extreme errors such as when a vessel is segmented as part of a nodule in one scan but not in the other. Scan slice thickness should not exceed one-third of the nodule size. Also, use of automated algorithms when there is variation in the scanning parameters, in particular, different collimation, should be interpreted with caution.

### *Communication of results*

The early-diagnosis regimen is to be communicated by the physician to each subject. If, however, the subject or his/her physician refuses to follow the recommended regimen, the actual work-up must be carefully documented using the web-based management system.

### *Biopsy*

As the biopsy procedure, CT-guided percutaneous transthoracic fine-needle aspiration is preferred, as this is a 1-hour, minimally invasive, outpatient procedure. If this is not feasible, ultrasound or other guided bronchoscopic biopsy is an option. Video-assisted thoracoscopic (VAT) biopsy can be used; however, use of this procedure requires a stronger suspicion of malignancy than does fine-needle aspiration. It is recommended that prior to VAT, PET scan when feasible is performed and if indeterminate or negative, further growth of the nodule should be assessed by CT. The images of the resulting cytology and histology specimens are also entered into the web-based management system.

The biopsy specimens are described and classified into standard diagnostic categories. Digital images of the cytology and histology slides are submitted for independent reading by the Cytology and Pathology Panels. The diagnosis of these panels is used as the final diagnosis for study purposes, and it is documented on the study forms in the I-ELCAP database.

### **Classification and characterization of diagnosed cancers**

A diagnosis (rule-in) of lung cancer is classified as a baseline screen-diagnosis if it results from work-up prompted by a positive result of the initial CT on baseline, regardless of when the diagnosis actually is achieved. It is classified in this way also if the result was 'semi-positive' in the sense of calling for a repeat CT 12 months later -- on the grounds that at least one non-calcified nodule was identified but none met the size criteria for a positive result. If the result of the initial CT at baseline is negative and the diagnostic work-up is prompted by suspicion-raising symptoms (or an incidental finding) before the scheduled first annual repeat screening, it is classified as an interim-diagnosis in the baseline cycle, again regardless of when the diagnosis is achieved. Analogous attributions are applied in the context of repeat-screening cycles.

Each diagnosed cancer is characterized according to indicators of how early and otherwise significant the cancer is – all of this bearing on the prognostic issues. Initially the descriptors are defined on a-priori grounds, as specified in the section below. Ultimately, once enough outcome information is available, the descriptors of prognostic relevance can be selected on the basis of the accrued data.

Principal among these descriptors/indicators is the *clinical stage* of the disease at diagnosis. Clinical Stage I, for purposes of I-ELCAP research, is defined by no manifestations of lymph node metastases in the hila, mediastinum, supraclavicular or axillary regions, nor distant metastases in adrenals, liver, spleen, bones, or soft tissues visible in the chest CT and no signs of metastases on PET scan, if available. The presence/absence of lymph-node and distant metastases (N and M status) is assessed on the most recent CT scan at the time of diagnosis, and also from a PET scan, if available. The person is still classified as being of clinical Stage I as long as these imaging studies do not demonstrate evidence of lymph node or distant metastases (N0M0) even when there is more than 1 adenocarcinoma, all less than 30 mm in diameter (6). Monitoring and quality assurance is directed to this aspect of the Program.

Closely related to the clinical stage of the disease is the *size* of the tumor, notably within Stage I. Quality assurance in respect to this descriptor of the diagnosed malignancies is internal to the I-ELCAP database, as the study data from the images are available for central measurement. Two measurements of size can be used. One of these has to do with the ‘diameter’ involved in the present regimen of early diagnosis presented above: the ‘diameter’ is the average of the nodule’s length and width. In the analyses, however, an alternative to this may also be used: the nodule volume determined automatically using available software.

Closely related to size is, in turn, the tumor’s *volume doubling rate*. This rate is critical to the early-diagnostic regimen, particularly for tumors less than 10 mm in diameter, and is also presumably quite significant prognostically. This doubling rate can also be derived centrally – and on the basis of automated volumetry.

From the pathology data and diagnoses, eminently important is the distinction between lung cancer cell types, most notably small-cell and non-small-cell types (21). Other descriptors of prognostic significance may be added, especially if data-analysis affirms their relevance. The study data are, again, derived centrally – by the Pathology Panel.

It is hoped that prognostic characterization of the diagnosed cancers can also, in the not too distant future, be in part based on ‘biomarkers’ of the cancer’s degree of aggressiveness. Pursuit of this goal is part of the research aims of I-ELCAP.

### **Intervention policy**

When lung cancer has been diagnosed by the experimental regimen of early diagnosis, that diagnosis creates a situation not inherently one of medical research but of medical practice. The I-ELCAP protocol (of research) naturally does not dictate decisions of practice. However, since the concern in the Program is to learn from the treatment intervention practices, close documentation of the intervention(s) is required. Also important to carefully document is the occurrence of any complications of the intervention(s), notably surgical death (within 30 days) and other serious complications.

The pathologic stage of the cancer in terms of presence/absence of lymph-node involvement and

respective station (N and M status) and intrathoracic extension (M) is based on the surgical findings which are documented. Representative pathology slides are sent for review by the Pathology Panel according to the pathology protocol (10).

In the framework of the I-ELCAP there is opportunity to study the relative merits of *alternative interventions*. With select subtypes of lung cancer diagnoses, some institutions may wish to participate in randomized controlled trials (RCTs) designed to address the relative merits of different therapeutic interventions. RCTs on prevention options are also possible, studies directed, for example, to chemoprevention of recurrence.

The choice of intervention, including the decision whether to intervene, naturally is dependent on individualized prognosis under whatever action is considered. To develop new knowledge for the individualization of prognosis, ancillary studies on the role of biomarkers are encouraged among I-ELCAP participants.

### **The ELCAP Management System**

For the purposes of I-ELCAP, there is web-based interactive system to guide the actions, and to document these actions and various findings, from the initial contact to schedule the baseline screening to the end of the follow-up of at least 10 years of a diagnosed case of lung cancer (22). The system is accessed from any computer connected to the Internet at the participating institution. It presents the context-relevant data form and thereby provides for immediate data entry, at the initial contact and at each subsequent encounter. Not only does it guide the actions in any given encounter, but it also schedules the next one. All of the information is automatically transmitted to the institution's data repository. The system monitors protocol conformity as well as completeness and consistency of the data at the time of its entry.

The system also provides for electronic transmission of CT images (using standard DICOM protocols) and digital pathology 'slides' to the institution's repository. This allows for central reading, including the automatic assessment of nodule volumes and rate of growth. At the same time, each participating institution has with high-speed computer access to its own data.

The system assures confidentiality and reliability. In the transmission, secure scripts are used. Unique passwords are required for access to particular segments of the central database. Accessing the data from each institution involves built-in encryption to maintain security over the Internet (ssh2 and SSL for web access). Identification of the subject is available only to the participating institution, as only the system-assigned code-identifier is available in the I-ELCAP database.

### **Quality assurance**

In I-ELCAP, quality assurance is a central concern. It begins with application of the criteria for data-contributing institutions' admissibility for collaboration (above), and it is served by the built-in management system described above. Additional elements in it are the I-ELCAP database's activities. These include, but are not limited to: central reading of images for teaching purposes, the training of site coordinators as to the I-ELCAP database, and monitoring of their performance – and recommending corrective actions, as needed.

A team of professionals consisting of radiologists, pulmonologists, thoracic surgeons, oncologists, and pathologists working together and meeting regularly has proven to be the most important contribution to assurance of quality in implementing the protocol with efficiency and safety. Such a multi-disciplinary team should be formed and serve at every I-ELCAP site.

Qualifications of the radiologists in the participating institutions consist in board-certification and if possible subspecialization in chest imaging. They have continual access to the electronic teaching files imbedded in the management system and are encouraged to visit the I-ELCAP database center for training sessions provided by its chest radiologists who are highly experienced in the use of CT in the various phases and situations involved in early diagnosis of lung cancer (cf. Regimen of Early Diagnosis, above). This training is concentrated in the time before an institution begins its subject enrollment and it is also available subsequently as needed. The first 100 baseline CTs submitted by a site are also read at the I-ELCAP database. The site receives each central report together with a discrepancy report and is asked to prepare the final report using the central input. After completion of the first 100 baseline CT scans, a report of the results are sent to the site and a conference call is scheduled to discuss the results and any other questions and concerns. A similar process occurs after the next 100 and after 500 baseline CTs are completed. For the radiologists, review of I-ELCAP teaching files (electronically available by the web-based management system) and participation in the International Conferences on Screening for Lung Cancer are required.

As for the pathologists in the participating centers, information regarding the preparation and reading of cytology and histology specimens is provided by the pathology protocol (10). In addition, an outside panel of pathology experts, the Pathology Panel and Cytology Panel, review the pathology specimens (below).

Qualifications of the site pathologist consist of board-certification in pathology and, if possible, subspecialization in chest pathology. These qualifications are supplemented, as needed by on-site training at the I-ELCAP database with pathologists who are experienced in the pathology readings of specimens obtained in the context of the I-ELCAP protocol. They can also participate in the reviews that are held by the Pathology and Cytology Panels. Quality assurance is provided by comparisons of the site readings with those of the Expert Cytology Panel and Expert Pathology Panel. For the pathologists, review of I-ELCAP teaching files (electronically available by the web-based management system) and participation in the International Conferences on Screening for Lung Cancer are recommended.

The study coordinators of the participating institutions are trained by the senior supervisor of the coordinators as to the I-ELCAP database.

If issues arise that cannot be resolved by conference calls, site visits to the participating institution are made to better assess the issue. The site will be provided a reasonable period of time to accomplish any remedial actions.

### **Outcome determination**

Every effort will be made by the I-ELCAP sites to assure complete 10-year follow-up of the diagnosed cases of lung cancer. The beginning of this is documentation of all information that serve to identify the patient over time including the Social Security number in the US (or equivalent internationally). And where the local efforts fail, assistance in locating the person or identifying his/her death will be given, as well as in documenting whether manifestations of metastases have occurred and the cause of death.

## **Workup of ancillary findings**

The following recommendations for thymic masses, cardiac calcifications and emphysema may be modified as additional data accrue in I-ELCAP.

### **1. Thymic masses**

Based on the frequency and natural course of thymic masses identified in baseline and annual repeat screenings for lung cancer (12), the following work-up recommendations are made: If the mass is less than 3.0 cm in diameter on baseline CT, follow-up CT one year later is recommended. If the thymic mass is greater than 3.0 cm or shows growth on the follow-up CT, then further workup according to standard practice is recommended.

### **2. Cardiac calcifications**

If the cardiac calcification score is greater than 6, a referral to a cardiologist, with special focus on preventive cardiology is recommended.

### **3. Emphysema**

If emphysema is present and previously unrecognized, pulmonary function test and consultation with a pulmonologist are recommended.

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