

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

PI: Claudia I. Henschke, PhD, MD
Weill Medical College of Cornell University
New York, New York

December 5, 2007

Overview	1
Admissibility for collaboration	1
Indications for screening.....	2
Regimen of screening.....	2
Image production	
Image reading	
Screening frequency	
Baseline screening	
Repeat screening	
Assessment of growth	
Biopsy	
Characterization of diagnosed cancers...	7
Intervention policy.....	8
ELCAP Management System.....	9
Quality assurance.....	10
Outcome determination.....	11
Workup of ancillary findings	11

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 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 Coordinating Center. 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 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 is 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 in at least one repeat screening.
2. It submits to the Coordinating Center the institutional documents approving the screening and participation in the I-ELCAP, is committed to conform to the stated requirements, and is amenable to Coordinating Center auditing of compliance with those requirements.
3. It is committed to ‘register’ with the Coordinating Center each successive instance of baseline screening, and to fully documenting this and also all repeat screenings, indication included.

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 Coordinating Center.
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 Coordinating Centers of 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, hemoptysis, and unexplained loss of weight. Symptomatic persons are ineligible for enrollment.

Some indications for subject participation may vary and are determined by each participating institution. However, those indications must be specified, notably as to age and smoking history. 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.

Image production

In this regimen, the initial imaging is the same in baseline and repeat screenings. A multi-slice helical CT scanner (4 or more rows) is used, at a low-dose setting (120 kVp, 40-80 mA, and slice thickness of 1.25 mm or less) using the lowest possible pitch to acquire contiguous images in a single breathhold from the thoracic inlet to the adrenal glands. The use of contrast material is not involved. Any CT required for further diagnostic work-up is acquired using the

same low-dose setting.

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, 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.

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 or sub-solid (the latter corresponding to 'ground-glass opacity'), parenchymal or endobronchial. 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).

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 be replaced by computer-based assessments of volume.

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.

The reader also documents other findings in the chest, including those in the mediastinum (12), heart (13) and soft tissues. Mediastinal masses can occur anywhere in the mediastinum, including in the thymus, heart, and esophagus; and a mass in the neck, such as in 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. 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.

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 anywhere between 6-18 months. 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 III malignancy is diagnosed, screening is 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, or in an endobronchial location when solid. When non-calcified nodules are identified but all of them are too small (< 5 mm) 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 met 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 nodule size.

For nodules less than 15 mm in diameter, there are two options. One option (A) is another CT at 3 months; if it shows growth, biopsy is performed, otherwise the workup stops. Based on our experience, this is the preferred option. If the nodule is solid, greater than 10 mm in diameter, and spiculated, then another option (B) is to perform PET scan; if the result is positive, biopsy is performed, if negative CT 3 months after the initial CT is done and acted on as specified in option A. When multiple nodules are present and occult infection or inflammation is a possibility, an added option (D) is a course of an broad-spectrum antibiotic with anaerobic coverage followed by CT 3 month after the initial CT (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 (C). As occult infection is a possibility, another added option (D) is a course of an antibiotic with anaerobic coverage followed by CT (15); if the CT shows no resolution, biopsy is performed. If there is partial resolution on CT, another CT 3 months after

the initial, low-dose test is performed and interpreted as in option B above. If there is full resolution, the workup stops.

For a nodule on which a CT 3 months after the initial CT is performed, growth 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.

For all cases 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 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 work-up is, again, different according to the size of the nodule(s) of record.

If all the non-calcified nodules are less than 3 mm in diameter, or if the largest nodule is more than 3 mm but less than 5 mm in diameter, CT at 6 or 3 months after the prior one, respectively is to be performed; any nodule with further growth at a malignant rate (see below) is biopsied. If no growth is seen in any of the nodules or they have completely or partially resolved the workup stops.

If at least one of the noncalcified nodule is 5 mm in diameter or larger, an immediate course of a broad-spectrum antibiotic with anaerobic coverage followed by CT 1 month after the repeat, low-dose test is option (A). Another option (B) is CT at 1 month after the repeat, low-dose test. If resolution is complete, the work-up stops; if there is partial resolution, CT 3 months after the initial, low-dose test is one option. If the nodule is solid, greater than 10 mm in diameter, and spiculated, then another option (C) is to perform PET scan; if the PET result is positive, immediate biopsy is done. If the PET result is indeterminate or negative, CT 3 months after the initial CT is performed.

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 screening is to be performed.

Assessment of growth

The initial CT is the basis of the initial size measurement. All subsequent CTs of the nodule(s) are again performed at the same low-dose setting (kVp, mA), collimation and pitch used to acquire the previous images of the nodule(s).

The CT images are obtained at maximum resolution (specified field of view and image matrix which can be preset on the scanner) and they are reconstructed using a high-resolution algorithm. The initial images are taken well above the nodule and the final ones well below it, to ensure that the entire nodule is covered by this set of images (which is critical for accurate assessment of growth). The localization of the nodule(s) prior to obtaining the CT images is done using low-dose CT imaging. The use of contrast material is not involved.

Short-term assessment of growth, based on CT images, includes consideration of whether the rate of growth is consistent with malignancy. In this assessment, the screening site has access to collaboration from the Coordinating Center, upon electronic image transmission provided for by the web-based management system of the I-ELCAP (16-20). Computer assisted growth rate is still a topic of research, and there will likely be variation among the different software that is currently available. With careful technical and clinical quality review as outlined below, the results of computer analysis are useful in guiding the workup. The radiologist must be comfortable with all aspects of the CT images and the computer segmentation results. The following guidelines have been developed as a result of the evaluation of our in house software, and may differ from those commercially available.

Computer growth rate estimates are made by measuring the change in lesion volume from two time separated scans. The between scan interval must be large enough for a significant detectable change in volume to occur.

1. It is vital that all computer segmentations are examined for extreme errors such as when a vessel is segmented as part of a nodule in one scan but not in the other. Furthermore, 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.
2. The acquisition parameters of the serial CT scans being compared need to be the same or as close as possible. Scan slice thickness should not exceed one-third of the nodule size. (Do not rely on automated algorithms when there is more than a 2 to 1 difference in the slice thickness).
3. The computer scans and the segmentation should be inspected for image quality (e.g., motion artifacts).
4. Conservative criteria for a significant volume change per month are: a) for nodules < 5 mm in diameter, the volume change should be at least 30%; b) for nodules 5 - 10 mm in diameter, the volume change should be at least 20%; c) for nodules > 10 mm in diameter, the volume change should be at least 10%. The time between the serial CT scans to observe these changes as might occur in cancers is given in the baseline and repeat screening protocol.
5. 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.

Biopsy

As the biopsy procedure, CT-guided percutaneous transthoracic fine-needle aspiration should be used, as this is a 1-hour, minimally invasive, outpatient procedure. If this is not feasible, 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 is performed and if 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 slides are submitted to the Coordinating Center for independent reading by the Pathology Panel. The diagnosis of this panel is used as the final diagnosis for study purposes, and it is documented on the study forms at the Coordinating Center.

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 this regimen, the actual work-up must be carefully documented using the web-based management system.

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, 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). Continual 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 Coordinating Center, as the study data from the images are, as has been noted, derived centrally. Two measurements of size are deployed. 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 will also be used: the nodule volume determined automatically using the software that has been developed at Weill Cornell.

Closely related to size is, in turn, the tumor’s *growth rate*. This growth 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 growth rate will also be derived centrally – and on the basis of automated volumetry.

From the pathology data and diagnoses, eminently important is the distinction between small-cell and non-small-cell cytologic 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 the 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 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 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 so long as all of them are less than 30 mm in diameter (6).

In the framework of the I-ELCAP there is opportunity to study the relative merits of *alternative interventions*. With select subtypes of diagnosis, 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, the Weill Cornell team has developed a 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 (or Coordinating Center). 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 at the Coordinating Center. 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 at the Coordinating Center. This allows for central reading, including the automatic assessment of nodule volumes and rate of growth. At the same time, the Coordinating Center provides each participating institution with high-speed computer access to its own data as well as its images and pathology 'slides.'

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 to the Coordinating Center.

Quality assurance

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

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 Coordinating 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 Coordinating Center. 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 baseline CTs. 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 is 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, I-ELCAP has organized a central Pathology Panel and a central Cytology Panel of experts for the central reading of the 'slides' (below).

Qualifications of the site pathologist consist in board-certification in pathology and, if possible, subspecialization in chest pathology. These qualifications are supplemented, as needed by on-site training at the Coordinating Center 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 central 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 is recommended.

The study coordinators of the participating institutions are trained by the senior supervisor of the coordinators at the Coordinating Center during extensive visits to the Coordinating Center.

If issues arise that cannot be resolved by conference calls, the Coordinating Center will arrange a site visit to the participating institution to better assess the issue. The site visit team typically will consist of representatives from the Coordinating Center and some of the other participating institutions. 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, the Coordinating Center will assist in locating the person or identifying his/her death, as well as in documenting whether manifestations of metastases have occurred and the cause of death.

Workup of ancillary findings

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, another CT one year 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 3, a referral to a preventive cardiologist is recommended.

References

1. Henschke CI, Miettinen OS, Yankelevitz DF, Libby D, Smith JP. Radiographic screening for cancer: New paradigm for its scientific basis. *Clin Imag* 1994;18:16-20
2. Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, et al. Early Lung Cancer Action Project: Overall Design and Findings from Baseline Screening. *Lancet* 1999; 354:99-105.
3. Henschke CI, Naidich DP, Yankelevitz DF, McGuinness G, McCauley DI, Smith JP, Libby D, Pasmantier M, Koizumi J, Flieder D, Vazquez M, Altorki N, Miettinen OS. Early Lung Cancer Action Project: Initial results of annual repeat screening. *Cancer* 2001;92:153-159
4. Program and Consensus statements. International Conferences on Screening for Lung Cancer. Website: www.IELCAP.org
5. Henschke CI, Yankelevitz DF, Smith JP, Miettinen OS. Screening for lung cancer: the Early Lung Cancer Action Approach. *Lung Cancer* 2002;35:143-148
6. I-ELCAP protocol (Website: <http://www.IELCAP.org>).
7. Henschke CI, Wisnivesky JP, Yankelevitz DF, Miettinen OS. Screen-diagnosed small Stage I cancers of the lung: Genuineness and Curability. *Lung Cancer* 2003;39:327-30
8. International Early Lung Cancer Action Program Investigators. Survival of patients with Stage I lung cancer detected on CT screening. *N Engl J Med* 2006; 355: 1763-71.
9. Vazquez M, Flieder D, Travis W, Carter D, Yankelevitz D, Miettinen OSM, Henschke CI. Early Lung Cancer Action Project Pathology Protocol. *Lung Cancer* 2003; 39:231-232
10. Vazquez M, Flieder D, Travis W, Carter D, Yankelevitz D, Miettinen OSM, Henschke CI. Early Lung Cancer Action Project Pathology Protocol. (Website: <http://www.IELCAP.org>).
11. Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley D, Miettinen OS. CT screening for lung cancer: Frequency and significance of part-solid and nonsolid nodules. *AJR* 2002;178:1053-1057
12. Henschke CI, Lee I, Wu N, Farooqi A, Yankelevitz DF, Khan A, Altorki NK, ELCAP and NY-ELCAP Investigators. CT Screening for Lung Cancer: Prevalence and Incidence of Mediastinal Masses. *Radiology* 2006; 239:581-590
13. Shemesh J, Henschke CI, Yip R, Yankelevitz DF, Shaham D, Miettinen OS, Detection of Coronary Artery Calcification by Age and Gender on Low-dose CT Screening for Lung Cancer *Clinical Imaging* 2006; 30:181-185
14. Henschke CI, Yankelevitz DF, Naidich DP, McCauley DI, McGuinness G, Libby DM, Smith JP, Pasmantier MW, Miettinen OS. CT screening for lung cancer: Suspiciousness of nodules according to size on baseline scans. *Radiology* 2004;231:164-8

15. Libby DM, Wu N, Lee JJ, et al. CT screening for lung cancer: the value of short-term CT follow-up. *Chest* 2006; 129:1039 – 1042
16. Yankelevitz DF, Gupta R, Zhao B, Henschke CI. Repeat CT Scanning for Evaluation of Small Pulmonary Nodules: Preliminary Results. *Radiology* 1999;212:561-566
17. Yankelevitz DF, Reeves A, Kostis W, Zhao B, Henschke CI. Determination of malignancy in small pulmonary nodules based on volumetrically determined growth rates: Preliminary Results. *Radiology*. *Radiology* 2000; 217:251-256
18. Kostis WJ, Reeves AP, Yankelevitz DF, Henschke CI. Three-dimensional segmentation and growth rate estimation of small pulmonary nodules in helical CT images. *IEEE Transaction on Medical Imaging*. 2003; 22: 1258-74
19. Reeves A, Chan A, Yankelevitz D, Henschke C, Kessler B, Kostis WJ. On measuring the change in size of pulmonary nodules. *IEEE Transaction on Medical Imaging* 2006; 25:433-450
20. Kostis WJ, Yankelevitz DF, Reeves AP, Fluture SC, Henschke CI. Three-dimensional volumetric measurement of pulmonary nodules: reproducibility and time to follow-up CT. *Radiology* 2004; 231:446-452
21. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC Press, 2004
22. Reeves AP, Kostis WJ, Yankelevitz DF, Henschke CI. A web-based data system for multi-institutional research studies on lung cancer. Radiologic Society of North America Scientific Session. November 2001