Eur Respir J 2003; 21: Suppl. 39, 45s–51s
DOI: 10.1183/09031936.03.00405103

European Respiratory Journal
ISSN 0904-1850

Guidelines for the use of spiral computed tomography in screening for lung cancer

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Guidelines for the use of spiral computed tomography in screening for lung cancer. C.I. Henschke, D.F. Yankelevitz, D.I. McCauley, D.M. Libby, M.W. Pasmantier, J.P. Smith. ©ERS Journals Ltd 2003.
ABSTRACT: Screening should be considered in lung cancer, more than any other cancer. Not only is the disease highly fatal, essentially incurable, when diagnosed on the prompting of symptoms and/or clinical signs, but its occurrence is also highly concentrated in identifiably high-risk persons.

The degree of usefulness of computed tomography (CT)-based screening for lung cancer must be thought of in reference to a particular, presumably optimal, regimen of pursuing early stage diagnosis. This is an algorithm that begins with the initial test ("screening CT") and ends in either discontinuation of the diagnostic pursuit or in diagnosis of lung cancer.

A carefully developed, extensively pilot tested and critically reviewed, updated protocol for CT-based screening for lung cancer is presented here. Its implementation is addressed, together with quality assurance. Finally, the associated curability rate for lung cancer is addressed in the light of what is known or can be surmised from evidence already available. However, recommendation for or against screening requires further information. Principally, the patients risk for lung cancer (in the near future) and the patients life expectancy (when spared of death from lung cancer). These two factors influence when, if ever, to begin screening, and if it is initiated, when to discontinue it. Finally, cost-effectiveness of the screening program should also be considered.
Eur Respir J 2003; 21: Suppl. 39, 45s–51s.

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Keywords: Computed tomography
diagnosis
lung cancer
needle biopsy
screening

Received: July 9 2002
Accepted after revision: November 5 2002

Screening should be considered in lung cancer, more than any other cancer. Not only is the disease highly fatal, essentially incurable, when diagnosed on the prompting of symptoms and/or clinical signs, but also its occurrence is highly concentrated in identifiably high-risk persons. Even pre-computed tomography (CT) radiographical screening allowed for an earlier diagnosis and when nonsmall cell cancer was diagnosed in stage 1, resection was curative in most cases [1]. With CT screening, the prospects are much brighter, as most of the diagnoses are achieved not only in stage I, but also when the tumour is still <10 mm in diameter [2–8]. Therefore, there cannot be any reasonable question about the usefulness of CT-based screening for lung cancer and about whether its associated early treatment can be curative in instances in which post-symptomatic treatment would fail. The question is merely quantitative, *i.e.* to what extent does CT-based screening for lung cancer enhance the curability of the disease by earlier intervention due to earlier diagnosis.

The degree of usefulness of CT-based screening for lung cancer must be thought of in reference to a particular, presumably optimal, regimen of pursuing early latent-stage diagnosis. This algorithm begins with the initial test ("screening CT") and ends either in discontinuation of the diagnostic pursuit or in diagnosis of the disease [8]. Integral to the regimen′s definition is the time interval between its successive repeat applications. In CT-based screening for lung cancer, the regimen′s components are principally radiological (CT-based assessments of growth rate and CT-guided fine-needle aspirations), with the final element in the process leading to early diagnosis being pathological.

The diagnosis that the regimen is designed to achieve (the presence of latent cancer) is presurgical, typically involving a cytological rather than a histological specimen, even though the postsurgical diagnosis may be better informed on account of intraoperative observations and the availability of histological specimens. However, it is the presurgical and not the postsurgical diagnosis that determines the intervention.

While the most immediate purpose of early diagnosis is to allow for early intervention, the intervention is not part of the concept of screening and thus of the screening regimen [8].

No radiological facility should accede to, much less actively market, CT screening for lung cancer without a set of prerequisites being satisfied. The facility should adopt of an optimal regimen and a protocol defining it. The facility should also be competent in its application, both radiological and pathological. Moreover, competent surgery for screen-diagnosed cases must be available and accessible. With such readiness

to screen and to act on its resultant diagnoses, the team must also be able to counsel potential patients on the implications of screening; first and foremost on the degree to which it can provide for enhanced curability of lung cancer through earlier intervention. Finally, screening for lung cancer should not be offered without also offering suitable information to promote cessation of smoking, when indicated [9].

A carefully developed, extensively pilot tested and critically reviewed, updated protocol for CT-based screening for lung cancer is presented here first. Then, its implementation is addressed together with quality assurance. Finally, its associated curability rate is addressed in the light of what is known or can be surmised from evidence already available. All of this is supplemented by delineation of what else needs to be known.

The screening regimen

The development of a protocol for CT-based screening for lung cancer has been a concern of the Early Lung Cancer Action Project (ELCAP) Group for a decade [10, 11] and modifications have been made in the framework of the International Conferences [12] organised by this group and in their resultant international consortium on screening for lung cancer [13]. The latter consortium, the International Early Lung Cancer Action Program (I-ELCAP), has adopted a common protocol [11] and has subsequently updated it. This updated protocol, as of June 2002, is presented below (with the understanding that the pathological aspect of the screening in the I-ELCAP is guided by a separate protocol).

In this regimen, the initial low-dose test (involving "screening CT") is identical at both baseline and repeat screenings. A multi-slice helical CT scanner (General Electric (GE) Lightspeed, Milwaukee, WI, USA; Siemens Volume Zoom, Erlangen, Germany; or equivalent) is preferably used, at a low-dose setting (GE: 120 kVp, 40 mA with 6:1 pitch, 1.25 mm slice thickness and 0.5 s rotation; Siemens: 120 kVp, 20 mA with a 7:1 pitch at 1 mm slice thickness and 0.5 s rotation). In a single breathhold, contiguous slices from the thoracic inlet to the adrenal glands are obtained. The use of contrast material is not involved.

Although multi-slice scanners are preferable, as they provide higher-resolution images in the initial low-dose test and thus simplify the subsequent work-up, single-slice helical (spiral) CT scanners may be used, again at a low-dose setting and obtaining the images at the thinnest possible collimation and lowest pitch, even if the attainment of this collimation requires two breathholds.

The resulting images are read by a radiologist at the site. The reader is aware that the images derive from the initial low-dose test for early diagnosis of lung cancer and whether they are from baseline or repeat screenings. The reader views the images as they are displayed on a high-resolution monitor at their typical window and level settings with maximal magnification, scrolling through the images one at a time. For assessing size, however, the following settings are used: lung window width of 1500 and lung window level of -650, mediastinal window width of 350 and mediastinal window level of 25.

For a predetermined number of screenings, a second central reading is performed, 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 discrepancies, the site radiologist may find it necessary to change the site report; 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 the referring physician.

At both baseline and repeat screenings, the reader's first concern with the images from the first low-dose test is to identify all noncalcified nodules visible. A nodule is manifest as a focal nonlinear opacity, whether the nodule is solid or subsolid (the latter corresponding to ground-glass opacity) [14]. A nodule is classified as noncalcified if it fails to meet the usual criteria for benign, noncalcified nodules [15]. Thus, a nodule <5 mm in diameter is noncalcified if it appears uniformly less dense than the ribs (on bone and lung windows); a nodule 5–20 mm in diameter is noncalcified if <50% of it is calcified (calcification does not correspond to a classical benign pattern (complete, central, lamellated, popcorn)) and/or the edge is spiculated (to some extent at least); and a nodule >20 mm in diameter is noncalcified unless it is completely calcified. Diameter is the average of length and width.

At baseline, the result of the initial low-dose test is negative if there are no non-calcified nodules, all noncalcified nodules are $\leqslant 3$ mm in diameter or there are more than six noncalcified nodules with the largest one <5 mm in diameter. Therefore, the result is positive if there are one to six, or more than six, noncalcified nodules with the largest one $\geqslant 5$ mm in diameter.

When a single-slice scanner is used with a collimation >5 mm, a positive result of the initial low-dose test is only tentative. High-resolution CT (HRCT) imaging should then be carried out on the one to six largest nodules that made the initial result tentatively positive, except in the following cases: 1) when all nodules are $\leqslant 3$ mm in diameter, in which case the definitive result is taken to be negative; 2) when all nodules are >3 mm but <5 mm in diameter, in which case the HRCT images are obtained either immediately or 6 months after the initial low-dose test; and 3) when recommending antibiotics, in which case the HRCT images are obtained 1 month after the initial low-dose test. The criteria for noncalcified nodules given above are applied to these HRCT images and, based on this classification, the result of the initial test is definitively negative or positive as defined above.

HRCT images, whether obtained on a single-slice scanner (see above) to verify the tentative result of the initial test or on a multi-slice scanner for further work-up (detailed below), are consistently obtained at the same dose setting (kVp, mA) and 1 mm collimation through the entire nodule, at the lowest possible pitch in a single breathhold. 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 images are obtained at maximum resolution (GE: targeted field of view of 9.6 cm; Siemens: 10 cm) and they are reconstructed using a high-resolution algorithm. The localisation of the nodule(s) prior to obtaining the HRCT images is done using low-dose CT imaging. The use of contrast material is not involved.

The reader documents whether the result of the initial low-dose test is negative or positive; and if positive, the reader also documents each of the one to six noncalcified nodules, or the six largest nodules where there are more than six of them in total (and the largest one $\geqslant 5$ mm in diameter). For each nodule, the reader documents the location, size, whether solid, part-solid or nonsolid, presence of calcifications and edge type. A nodule is classified as part-solid if it has patches within it that completely obscure the lung parenchyma and nonsolid if none of the lung parenchyma is totally obscured [14]. In making the distinction between part-solid and nonsolid, blood vessels within the nodule, despite their appearance as solid components, are not regarded as solid components.

On repeat screenings, the reader's first concern with the initial low-dose test is once again to identify all noncalcified nodules; however, the main focus is now on the ones that have grown in size (overall size if solid or the size of the solid component if subsolid) since the previous screen. To determine whether growth has occurred, the reader compares the current images with the corresponding previous images.

On repeat screening, the result of the low-dose test is classified as negative or positive using the same criteria as at baseline, with the exception that all noncalcified nodules with interim growth, regardless of size, are tallied. With this same proviso, the documentation of repeat-screen nodules of record is analogous, except that this documentation needs to be supplemented by the corresponding characterisation of the nodule in the previous screen.

When the result of the initial test is negative, whether at baseline (by baseline criteria) or on repeat screening (by repeat screening criteria), the pursuit of early diagnosis stops and the next screening test is scheduled for a time 12 months later (even if the current one is a repeat screen not 12 months after the previous screen).

When the result is positive, further work-up immediately ensues. At baseline, the work-up varies according to the size of the largest nodule of record (defined above) (figs. 1 and 2), as follows. 1) If the nodule is <5 mm in diameter, then an HRCT, limited to the nodules of record, is performed 6 months after the initial low-dose test, and if there is no growth in any of the nodules the work-up stops. If growth is manifest, then fine-needle aspiration is immediately carried out. 2) If the nodule is 5–9 mm in diameter, then HRCT, limited to the nodules of record, is performed 3 months after the initial low-dose test, and if there is no growth in any of the nodules but there are some remaining the HRCT is repeated 6 months after the initial test. If none of the nodules remain at 3 months or no growth is manifest in any of the remaining nodules at 6 months, then the work-up stops. If growth of any of the nodules is manifest at either 3 or 6 months, then fine-needle aspiration is immediately carried out. 3) If the nodule is $\geqslant 10$ mm in diameter, then immediate action on the nodules of record in this size range ensues, while smaller nodules, if any, are worked up according to 1) or 2) above, whichever applies.

For the large nodules, there are two options as follows. 1) Perform HRCT (particularly useful for relatively small nodules having a benign appearance, such as hamartoma or focal pneumonia), limited to the nodules, 1 month after the initial low-dose test. In the interim, a 2-week course of broad-spectrum antibiotics may be used. Further work-up depends on the HRCT result: for the nodules that show complete resolution, the work-up stops; nodules showing growth require immediate fine-needle aspiration; nodules showing partial or no resolution (but no growth) may, depending on whether their appearance is suggestive of malignancy, lead to immediate fine-needle aspiration, immediate positron emission tomography (PET) scanning or repeat HRCT at 3 months after the initial low-dose test. For nodules found to be negative on PET scan or showing no growth on repeat HRCT, the work-up stops. Nodules found to be positive on the PET scan or showing growth on repeat HRCT require an immediate fine-needle aspiration; and if the result is negative (benign-specific), then work-up stops, or if the result is negative (nonspecific), HRCT is repeated in 6 months after the initial low-dose test. At 6 months, for nodules showing no growth, the work-up stops; nodules showing growth require a surgical biopsy. 2) Immediate fine needle aspiration, notably if the nodule is relatively large or has an appearance suggestive of malignancy.

When the regimen at baseline does not lead to the diagnosis of malignancy, repeat screening is scheduled, as stated previously, for a time 12 months subsequent to the initial low-dose test at baseline. Similarly, if malignancy is not diagnosed in the first repeat screening, the second repeat screening is scheduled to follow 12 months after the first one, *etc*. Also, if stage I or II malignancy is diagnosed, screening is continued with the original schedule.

At repeat screening, a positive result of the low-dose test routinely leads to an immediate 2-week course of broad-spectrum antibiotics, followed by an HRCT of the nodules of record at 1 month after the initial low-dose test. Further work-up depends on the HRCT result in respect to resolution or growth of the nodules of record on repeat screening (defined above). If all of these nodules have completely resolved, then the work-up stops. Otherwise, the first concern is to identify the nodules still showing growth since the previous screen (13 months before), thus updating the nodules of record. Among these, any nodule $\geqslant 5$ mm in diameter is immediately biopsied. For the remaining nodules of record (if any), the HRCT is repeated at 3 months after the initial low-dose test. Given complete resolution of all nodules, the work-up stops. Any nodule showing growth (over the 2 months) is immediately biopsied. If there are any remaining

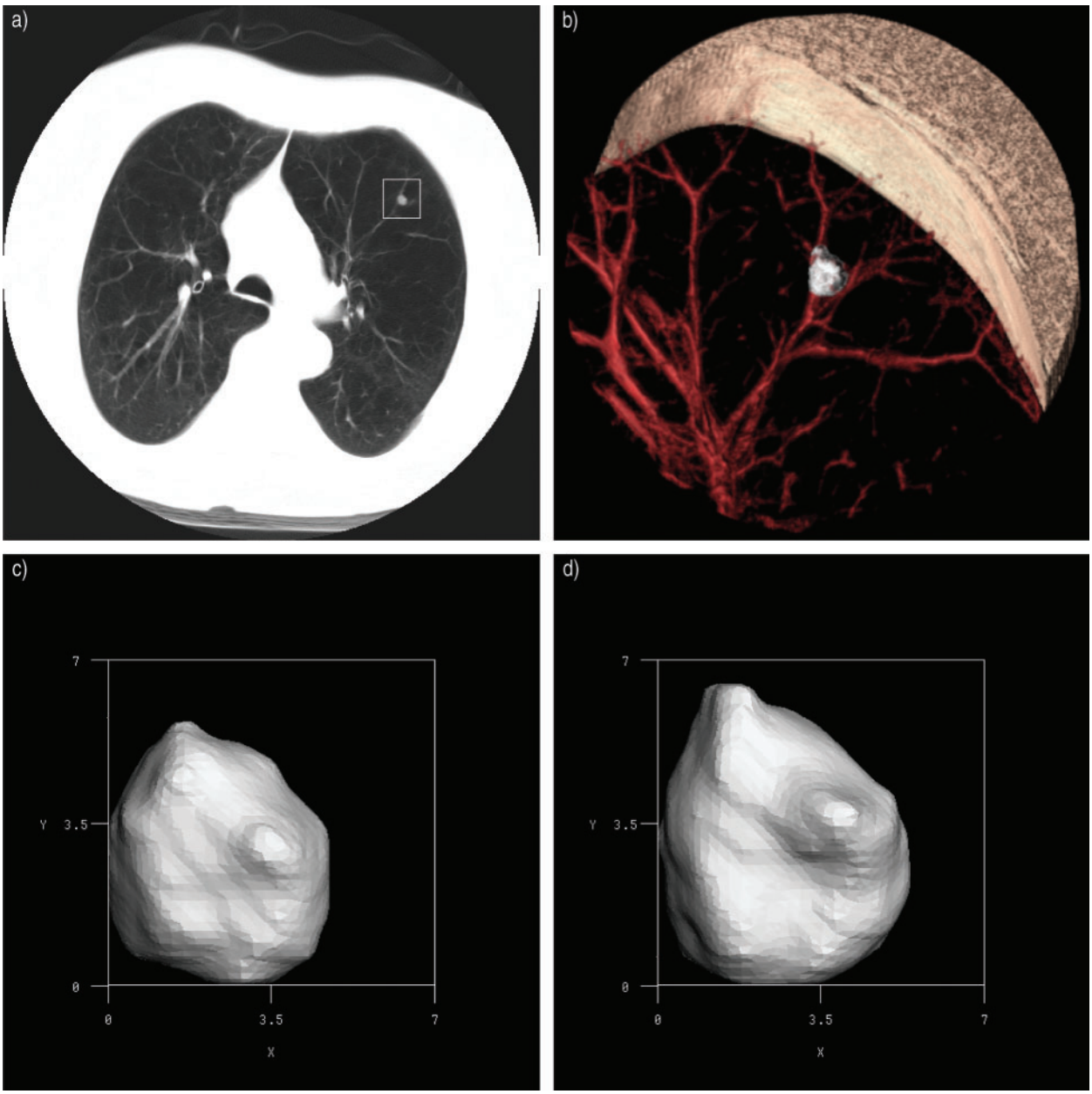

Fig. 1. – A 5-mm pulmonary nodule detected on repeat screening. a) Nodule (in box) shown in left upper lobe. b) Result of three-dimensional segmentation to delineate the volume of the nodule (white) from the attached vasculature and bronchi (red). The nodule volume (c) was compared to that measured on a subsequent high-resolution computed tomography scan taken 1 month later (d). The nodule doubling time was estimated to be 74 days, consistent with malignancy. The nodule was subsequently resected and proven to be malignant on histological examination.

nodules of record, the HRCT is repeated 6 months after the initial low-dose test. The result is dealt with as it was at 3 months, including scheduling for another HRCT, only in this instance at 12 months; and if need be, yet another HRCT is scheduled at 24 months. With any one of these successive HRCTs, the assessment of growth is based on the comparison with the HRCT at 1 month.

The short-term assessment of growth, based on HRCT images [16, 17], includes consideration of whether the rate of growth is consistent with malignancy. In this assessment, the screening site can collaborate with the central facility, following electronic image transmission by the web-based management system of the I-ELCAP.

CT-guided percutaneous transthoracic fine-needle aspiration should be preferably used for the biopsy procedure, as it is a 1-h outpatient procedure. If this is not feasible, video-assisted thoracoscopic biopsy can be used; however, use of this procedure requires a stronger suspicion of malignancy than for those undergoing fine-needle aspiration. The images of the resulting cytology and histology specimens are also entered into the web-based management system.

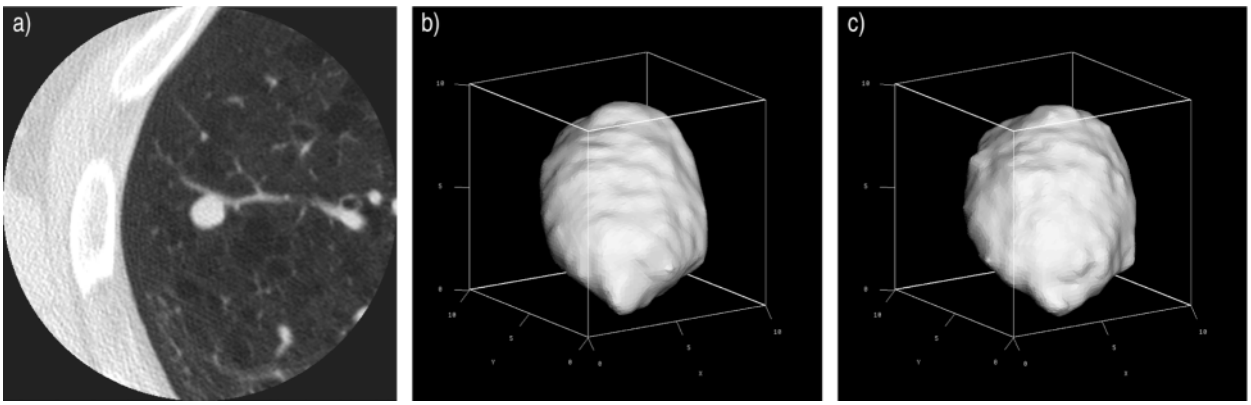

Fig. 2. – An 8-mm pulmonary nodule detected on baseline screening. a) High-resolution computed tomography (CT) of nodule in right upper lobe. The nodule volume (b) was compared to that measured on a subsequent high-resolution CT scan taken 6 months later (c). The nodule doubling time was estimated to be >3,000 days, clearly indicating stability and likely benignity.

The web-based management system calls for documentation of all actions and findings, including those that may not accord with the protocol.

Protocol implementation

The screening coordinator at the site provides information about the available screening to each potential patient and schedules the initial low-dose test for baseline screening [18]. The screening coordinator provides information about the nature, as well as the benefits and risks, of the screening regimen, with particular attention to the radiation dose and its carcinogenic effects. This information may be provided, in part at least, through brochures given with the consent form. The coordinator obtains all contact information when scheduling the initial low-dose test and detailed information pertaining to the indication and contraindications in an interview just before the test is administered. The coordinator performs data entry and scheduling of the follow-up appointments, including repeat screenings. Weekly or bi-weekly, all new enrolments and forthcoming appointments are reported to the radiologist(s), with particular attention to scheduled invasive procedures, to ensure coordinated communication and follow-up.

The technologist at the site prepares and positions the patient on the CT table and obtains the images in the manner prescribed by the protocol, whilst making sure that the patient is comfortable.

The radiologist at the site reads the images from the initial low-dose test and those from subsequent tests, and supervises the entry of the test results into the management system. The same radiologist is also responsible for communicating the results to both the referring physician and the patient. The radiologist is in charge of regular weekly or bi-weekly meetings with the coordinator and other relevant personnel to ensure that communication of the results and recommendations to the referring physician and patient has occurred.

When there is a negative result at the initial test (at baseline and on repeat screening), the radiologist communicates with the referring physician and separately with the patient, stating the result and recommending that the patient should return in 1 yr for the next screening, specifying the date and enclosing an appointment card. If the test result is positive, then the written report is sent to the referring physician, but a phone call is also made to the physician (as per American College of Radiology Communications Standards). The management system is used to document the contacts and follow-up.

Each month, the site physicist ensures, and documents, that the CT number for air and water, as well as distance accuracy, are at acceptable levels (*i.e.* CT number of water is 0 +/- 10 HU, that of air between -1000 and -985 and the distance accuracy within 2 mm for actual linear distance of 100 mm). Image quality (low-contrast detection, high-contrast spatial resolution, distance accuracy) and average dose (MSAD) are documented for both low-dose and standard-dose scannings with each scanner used for screening, and the MSAD measurement is ensured to be in accordance with the American Association of Physicists in Medicine standards [19, 20]. These measurements are documented in quality control logs and they are reviewed at least quarterly by the local quality control coordinator and physicist. Service to correct performance outside of specified parameters is documented and provided to the physicist prior to continuing screening studies. Each month, the physicist ensures, and documents, the scanner measurement accuracy using an anthropomorphic lung phantom with nodules of known size, using the low-dose and standard-dose techniques [18].

Quality assurance

Qualifications of the radiologist should consist of board certification in radiology, together with subspecialisation in chest radiology, supplemented by on-site training at a centre experienced in applying the I-ELCAP protocol and that centre′s recognition of readiness to practice CT screening for lung cancer [18]. The required continuing education should consist of a review of I-ELCAP teaching files (electronically available by the web-based management system),

participation in the International Conferences on Screening for Lung Cancer [12], and comparisons of the site readings with the central reading reports.

For the CT technologist, qualifications consist of certification by the American Registry of Radiologic Technologists or equivalent, and training as well as experience in CT image acquisition, as in the I-ELCAP protocol.

The medical physicist is qualified when certified by the American Board of Radiology or equivalent in radiological physics or its diagnostic subspecialty, and should pursue continuing education in diagnostic physics according to the American College of Radiology Standards for Continuing Medical Education.

A qualified CT screening coordinator is trained to understand the screening protocol and to provide the necessary information to potential patients, to schedule activities and to use the reports provided by the management system to ensure appropriate follow-up of each patient.

Even though I-ELCAP is motivated by concerns for collaborative research, in addition to providing useful care, the quality assurance built into it is no more ambitious than that which befits good practice [8]. As outlined above, quality assurance begins with the qualifications of the key personnel, including their continuing education [18]. I-ELCAP′s web-based management system is an integral part of quality assurance, as it guides adherence to the protocol at every step of the screening regimen, *i.e.* what to do, what to record and scheduling. It also allows for image transfer to a central facility and communication through its internal messaging system, as well as for receiving reports on central readings and identifying problems with data entry. Monitoring of quality is carried out by the central facility using site visits as well as reviewing the data and images routinely and instantaneously flowing to the central facility.

Effectiveness and utility

When helping a patient to decide whether to have screening for lung cancer, the clinician needs to be able to answer two closely related questions.

The first question concerns the regimen′s effectiveness in producing its intended result; not whether it is effective but how effective it is. As the aim of the regimen is early diagnosis, the question is how early is lung cancer diagnosed under the screening regimen? The first baseline screen is different from the subsequent repeat screens. Thus, the effectiveness question is specific to the diagnoses after the baseline screen, *i.e.* to the repeat screen and interim diagnoses combined. It is also specific to nonsmall cell diagnoses, as the prospect of enhanced curability by earlier intervention is currently confined to this type of cancer. This question of effectiveness also refers to the time period during which the screening regimen is adhered to. Conversely, it is reasonable to presume that the effectiveness does not vary over the successive cycles of repeat screening.

Therefore, using these terms, what can be said about the effectiveness of the I-ELCAP regimen? On annual repeat, it typically provides for diagnosis at tumour diameter <10 mm, the majority of all cases (some 80%) being stage IA at diagnosis [3, 5, 7, 8]. As the screening regimen is thus quite effective at attaining early diagnosis, its effectiveness may have considerable utility in providing for cure through early intervention; but to what extent? In stage I cases of nonsmall cell cancer, detected using experimental screening a quarter-century ago, ~60% of tumours typically ~20 mm in diameter at diagnosis were curable by resection [1, 21, 22]. For the distinctly smaller stage I cases diagnosed under the I-ELCAP regimen, a curability rate of 70% can thus be estimated [23]. If curability is confined to stage I cases of nonsmall cell cancer, then the 70% curability rate would apply to the majority of the lung cancer cases diagnosed under the I-ELCAP regimen (after the baseline screen, while the screening continues). This compares very favourably with 5–15% curability with no screening.

Further considerations

Recommendation for or against screening requires further patient information. The two considerations that have critical bearing on indication for screening include: the patient′s risk of lung cancer (in the near future) and the patient′s life expectancy (when spared of death from lung cancer). These two factors influence when, if ever, to begin screening, and if screening is initiated, when to discontinue it [24]. The time from lung cancer diagnosis to death from cancer, preventable by early intervention, should also be considered. Finally, cost-effectiveness of the screening programme should be judged [24–26].

For now, the question of whether to recommend lung-cancer screening needs to be addressed on a background of reliable beliefs. Some authorities and institutions think that the utility of CT screening for lung cancer is unknown, even qualitatively, and that resolution of this issue requires a very large, very expensive, long-term study. Specifically, a randomised controlled trial (RCT), comparing CT screening with more traditional radiographical screening, earlier deemed useless [27], is now being considered. The object of the trial would be to test, inconclusively perhaps, whether CT screening reduces mortality from lung cancer when used in lieu of traditional radiographical alternatives.

In so far as this authoritative view indeed does come up, the pursuit of practice decision begins with choosing between the following two outlooks. 1) The outlook presented here. CT screening obviously allows for earlier diagnosis of lung cancer (usually quite early in stage IA) and it is already known that earlier interventions, provided for by screening, have enhanced effectiveness in preventing death. Therefore, it is known that CT screening for lung cancer provides an increased curability, a reduced case-fatality rate and reduced mortality in any screened population at risk of the disease. No one is so unclear about the relative merits of early and late intervention as to suggest an RCT contrasting the two, or about otherwise

delaying intervention in the context of early diagnosis of the disease. 2) The alternative outlook. Individual deductive reasoning by practitioners, founded on strong grounds as well as on formally correct deductions from these, as in the outlook above, must be rejected in favour of evidence from an RCT, even if the context is something other than intervention research, as in the context of screening research here. With this outlook one needs to find a way not to be discouraged by the previous RCT experiences and their associated controversies, in the context of breast cancer screening in particular.

If the latter outlook is adopted, everything presented here is irrelevant, for now at least, as the time when computed tomography screening for lung cancer is officially sanctioned is many years away. Even if this time does arrive, decisions about screening will have to be made without the randomised controlled trial having provided any quantitative information about the fatality-rate reduction and thus about the curability gain provided for by the screening [28].

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