ELSEVIER
SAUNDERS

Thorac Surg Clin 14 (2004) 53–59

THORACIC
SURGERY
CLINICS

State-of-the-art screening for lung cancer: (part 2): CT scanning

David Yankelevitz, MD*, Claudia I. Henschke, PhD, MD

Department of Radiology, Weill Medical College, Cornell University, 525 East 68th Street, New York, NY 10021, USA

Starting in 1993 two groups independently began exploring the use of CT scans as the initial test in screening protocols for lung cancer. These groups were the National Cancer Center in Tokyo, Japan [1] and the Early Lung Cancer Action Project (ELCAP) at Weill Medical College of Cornell University [2].

The Japanese group had an active clinical screening program using chest radiography. They introduced CT for an additional cost of $350 in 1993. The patients' ages ranged between 38 and 83 and most had a 20 pack-year smoking history, although smoking history was not required. The results of 1369 baseline screens and 2088 semiannual repeat screens were reported by Kaneko et al [1]. Among the 3457 screens, positive findings were present in 20% (701) of patients, and 15 of these subjects had malignant results. The overall yield of CT was 0.43% (15/3457) compared with 0.12% (4/3457) with chest radiography.

At Weill Medical College, a prospective study called ELCAP was started in 1992. Starting in 1993 1000 high-risk subjects aged 60 and older who had at least a 10 pack-year smoking history were enrolled for baseline and annual repeat screening. The median age at enrollment was 67 and the median pack-years smoked was 47. Baseline results were published in 1999 [2], and annual repeat results were published in 2001 [3]. At baseline, 23% (233) of patients had an abnormality, of which 27 were found to be malignant, which yielded an overall rate of 2.7% (27/1000), of which 0.7% (7/1000) were seen on chest radiography. On annual repeat 2.5% of patients had an abnormality, of which seven were found to be malignant, yielding an overall rate of 0.6% (7/1184). Chest radiography was not performed for the repeat studies.

Starting in 1996 a third study, also in Japan, compared CT with chest radiography [4]. Using a mobile CT unit, Sone et al [4] performed baseline screening on 5483 individuals from the general population in Japan aged 40 to 74 years; 3967 also had miniature flourophotography. They found that 5% (279/5483) had a positive result, and the malignancy rate was 0.48% (19/5483) on CT compared with 0.3% on chest radiography. A follow-up report on the results of their annual repeat screening using only CT showed that 3.8% (309/8303) had a positive result and that the malignancy rate was 0.41% (34/8303) [5]. An additional follow-up through 2001 showed that for baseline screening the malignancy rate was 0.51% (40/7847) and on annual repeat screening it was 0.4% (40/10,045) [6].

These studies demonstrated that CT screening for lung cancer was superior to the chest radiograph in detecting lung cancer. They also showed that a positive result on baseline screening was more common than on repeat screening. In the ELCAP study, which had the highest median age and smoking history, the lung cancer rate was also the highest, confirming that age and smoking history are key risk indicators of lung cancer.

Since these early studies several other groups have reported their results. None of them used chest radiography. These studies were done at University of Muenster in Muenster, Germany [7], Japan [8], and, more recently, in the Mayo Clinic in Rochester Minnesota [9] and Milan, Italy [10]. The Mayo group reported that screening with sputum cytology and CT

* Corresponding author.
E-mail address: dyankele@med.cornell.edu (D. Yankelevitz).

1547-4127/04/$ – see front matter
doi:10.1016/S1547-4127(04)00035-0

scanning found that on baseline screening 76% of non–small-cell lung cancer was stage I. On annual repeat screening this proportion was 55%. The Milan group found 55% that of their baseline cancers were stage I, whereas 100% of the annual repeat cancers were stage I. These studies showed a consistent pattern of finding a high proportion of early-stage cancers on baseline screening and annual repeat screening.

Screening regimen

To study CT screening for lung cancer meaningfully, a regimen needs to be described, including specification of the type of scanner, the scanning protocol, the definition of a positive result, and the workup of the positive result (both for baseline and annual repeat). It is important to think of screening as the pursuit of early diagnosis with a view toward early treatment. In this way screening is not merely the application of a single test. In the case of CT screening for lung cancer, CT is merely the initial test. Without considering the regimen of subsequent diagnostic tests that follow, the results of the initial test are not meaningful. Entirely different results will be found following the initial test when different algorithms for workup are used. Thus, there is a need to specify the entire regimen. Each feature of the regimen is important. The ELCAP protocol for the diagnostic workup is updated to incorporate increasing knowledge about screening and technologies advances as they occur [11].

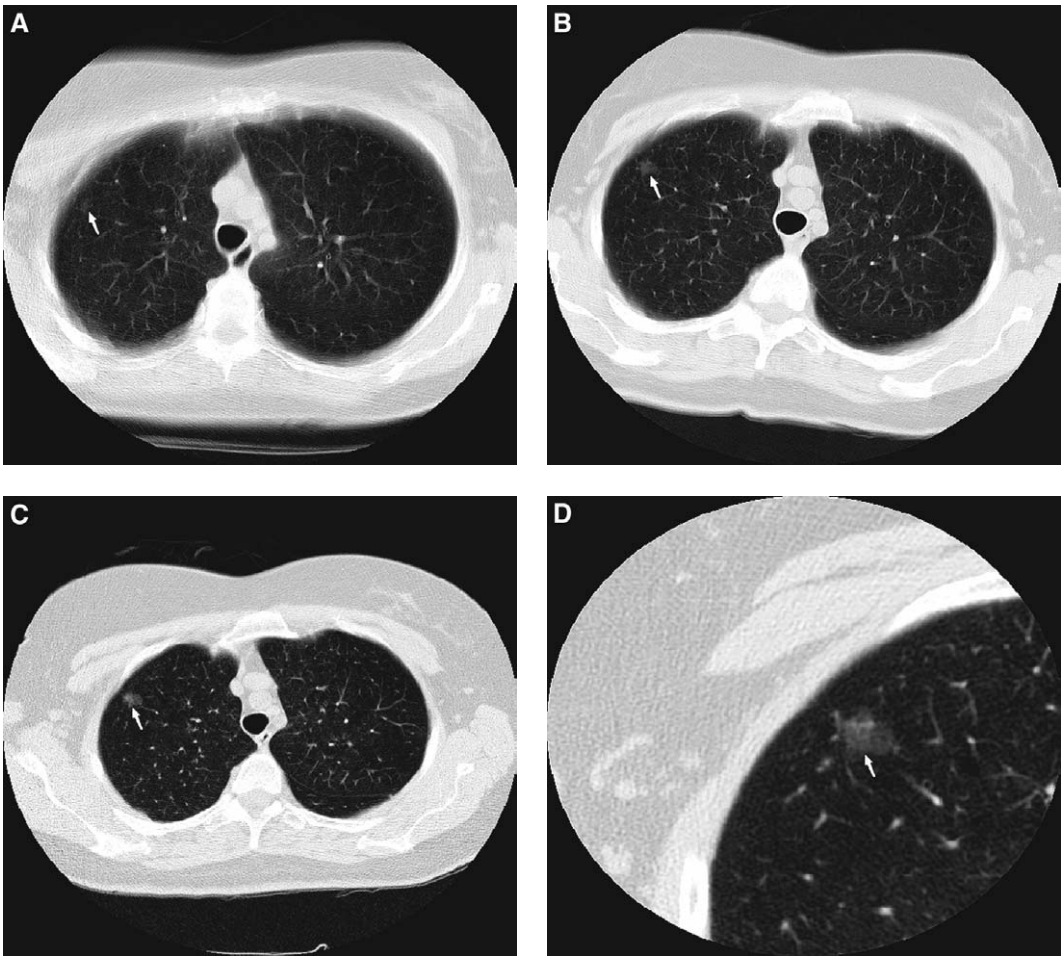

Fig. 1. Starting in 1993 CT screening was performed using a 10 mm slice thickness. With advances in technology, thinner slices were obtained while covering the same volume in a single breath-hold. Effect of slice thickness on visibility of a stable nodule: (*A*) 10 mm slice thicknesses. (*B*) 5 mm slice thickness. (*C*) 2.5 mm slice thickness. (*D*) 1.25 mm slice thickness.

As for the initial CT, technological advances have come at a rapid pace. In 1993, when the initial CT screening studies began, images were obtained with a 10 mm slice thickness. At that time only single slice scanners existed. To scan the entire chest in a single breath hold, a 10 mm thickness was necessary. With the advent of multislice scanners, this practice has changed dramatically. With the constraint of scanning the entire chest in a single breath, slice thickness has decreased progressively from 10 mm to 5 mm to 2.5 mm to current standards of 1.25 mm (Fig. 1). The newest generation of scanners even allow for protocols using a 0.675 mm slice thickness. The basic principle is that use of thinner slice images allows for the detection of smaller nodules. This trend toward thinner slices will continue; there are now prototype units that can produce images with 0.1 mm resolution. Nevertheless, along with the improved resolution comes the additional burden of having the radiologist interpret many more images per scan. Currently, more than 300 images are obtained for each study when using these thinner section images. While this increase has become a concern for the radiologist, it has opened the door for computer-assisted techniques, which perform much better with higher-resolution images. Computer-assisted techniques include techniques that are used to measure the volume of pulmonary nodules so that growth rates can be determined and techniques that allow for automated nodule detection (Fig. 2) [12].

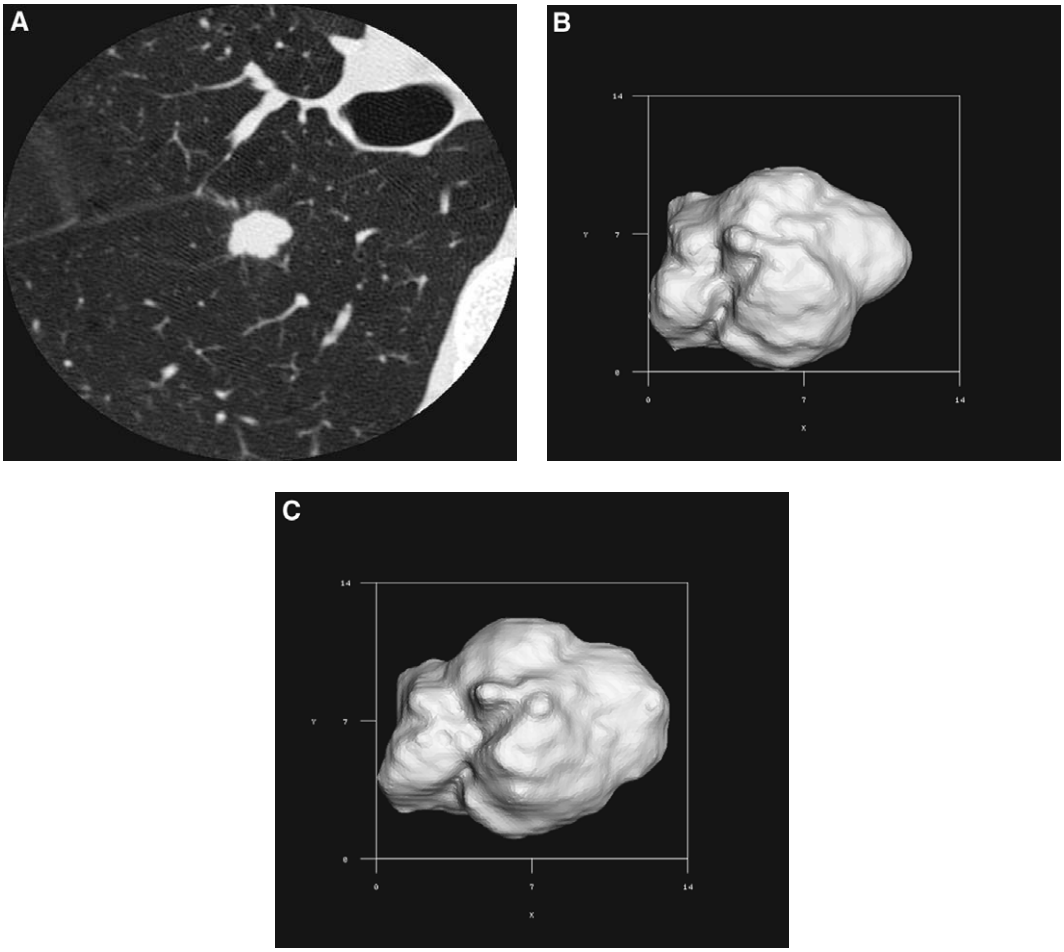

Fig. 2. (*A*) A 10 mm nodule was identified on CT. (*B*) Three-dimensional volumetric reconstruction was performed on the initial CT data. (*C*) One month later. The nodule has grown during this short interval. An increase in volume was 22% has been determined by use of an image processing technique, corresponding to a malignant growth rate.

Diagnostic distribution

On the first baseline screen, it is expected that more cancers will be found than on any single repeat screening cycle. It is assumed that the malignancies reported on baseline screening were those found in nodules detected on the baseline screening, even though the actual diagnosis of malignancy might be made as much as several years later.

The diagnostic distribution is summarized by the relevant prognostic categories, defined as determinants of the long-term outcome of these cases. For lung cancer, these categories include stage, size, and histology. Given this definition it can be expected that the diagnostic distribution will be differ from baseline screening compared with annual repeat screening. An additional important consideration is that with each round of annual repeat screening the diagnostic distribution should remain relatively constant [13], which is of great importance because with a large enough population of patients being studied, the distribution of cancers can be determined with two rounds of screening. It also means that the results of each round of annual repeat screening can be pooled to learn the actual diagnostic distribution with greater confidence. An additional consideration in regard to the diagnostic distribution relates to the relative risk of the population being studied. It can be expected that for a given risk there will be a different overall frequency of detected cancer; however, it can also be expected that even though the overall frequency of cancers might be different, the proportion of the various subtypes should remain the same. In other words, in a high-risk population compared with a low-risk population, many more cancers might be detected with a particular regimen of screening; however, the proportion of stage I cancers will remain constant. Ultimately, this method allows for pooling of data from various sources, providing that the same regimen of screening is followed, which has been an underlying principle in the ongoing International Early Lung Cancer Action Project (I-ELCAP) study, in which approximately 35 institutions around the world have agreed to follow the same protocol and pooling of data. To date, approximately 25,000 cases are in the pooled database [6].

False-positive diagnosis

The issue of false-positive diagnosis has been brought up as a concern in regard to CT screening for lung cancer. One group reported that up to 99% of the nodules identified represent false-positive findings [14], but this is a misleading number. This group defined screening cases with nodules less than 4 mm in diameter as being negative results, yet a high proportion of their false-positives included these 4 mm or smaller nodules [15]. Thus, they interpreted scans as being negative when they contained false-positive findings.

A rational definition of a positive result of screening is to provide for sufficient sensitivity to not miss too many of the cancers while not having too many false-positive findings. For instance, one would not consider the result of a stool guiac study to be positive if a single red blood cell was found; rather, there is some threshold at which the study is considered to be positive. Similarly, in regard to CT screening there is some small size threshold where every person being scanned will have at least one nodule. Its size can be less than 1 mm, but it would not make sense to call each of these nodules false-positives because they occur so frequently as to be noncontributory in terms of discriminating between subjects who have or who do not have the target illness. In regard to screening, the definition of a false-positive result becomes a bit more complex because screening for lung cancer can be thought of as a year-to-year process. It is envisioned that when a person enrolls in a screening program they will come back for an annual repeat study. Under these circumstances, a person who has a small nodule, say less than 5 mm on baseline screening, might simply be told to return for annual repeat screening without any intervening workup. The reason for this might be that in nodules this small it might be so difficult to make a diagnosis in less than 1 year because growth determinations or other diagnostic tests are so inaccurate that it is impractical to pursue each of these nodules. Nevertheless, the nodules cannot be ignored. The patients are merely told to return for their routinely scheduled annual repeat study; they can, thus, be thought of as perhaps representing a different type of positive finding but not a false-positive finding in the sense of leading to additional workup.

The ELCAP group reviewed their results recently and found that on baseline screening it was not practical to obtain a diagnosis of cancer in less than 1 year for nodules smaller than 5 mm [16]. ELCAP's current definition of a positive result of baseline screening does not include subjects whose largest nodule is less than 5 mm [11]. Using this definition they have been able to reduce the number of subjects who have positive baseline screening results to below 15%.

It is also important to distinguish between the findings of baseline screening and annual repeat screen-

ing. While a nodule less than 5 mm on baseline screening does not prompt additional workup in the new ELCAP protocol, a 5 mm nodule found on annual repeat screening that was not present on the prior study does prompt immediate further workup. In this situation one now has the additional information that because the nodule was not present previously, it now is, and therefore it is growing. The growth of a nodule from being invisible to visible in the range of 3 to 5 mm in 1 year is suggestive of a malignant growth rate and needs to be thought of differently than a nodule that is of a similar size and only found on baseline screening, in which no additional information regarding its growth rate is available.

Curability of early lung cancer

While CT screening for lung cancer provides for early diagnosis (especially when compared with waiting for symptom prompting), the ultimate goal is to allow for early treatment. Thus, the issue in regard to the benefit of lung cancer screening relates to answering two component questions. First, how frequently does a particular regimen of screening lead to early diagnosis? Second, how curable are those cancers? When these component issues have been understood, the benefit in terms of reducing death from lung cancer can be derived.

Critical to the concept of curability of lung cancer is learning what proportion of lung cancers are genuine cancers and not overdiagnosed ones. A genuine cancer is one that would lead to death in the absence of intervention. It is not reasonable to think in terms of curing a cancer if in the absence of treatment it was not fatal.

For traditional radiography, a great deal has been learned in regard to issues of genuineness and curability of screen detected lung cancer. Flehinger et al studied this issue directly in the chest radiography screening studies performed as part of the National Cancer Institute Cooperative Early Lung Cancer Detection Project (Mayo Lung Project, New York Lung Project at Memorial Sloan-Kettering Cancer Center, and the Johns Hopkins Lung Project) [17]. When focusing on 45 untreated cases that were stage I, they showed that 5-year fatality rates in the absence and presence of treatment were 90%, which implies that at least 90% are genuine with at most 10% being indolent. Among the cases of stage I cancer that underwent treatment (resection), the corresponding fatality rate was only 30%. Therefore, the overall curability rate for the genuine lung cancers was (90−30)/90, or 67%. Because cases of unresected malignancies might be understaged, Flehinger extended her evaluation to include patients who had suspected mediastinal metastases and found qualitatively similar results.

In further support of these data, a recently published review of screen-detected cancers in stage I in two of these studies (the Mayo Lung Project and the New York Project) found that they fit the profile of genuine (ie, fatal if not treated) cancers. The study

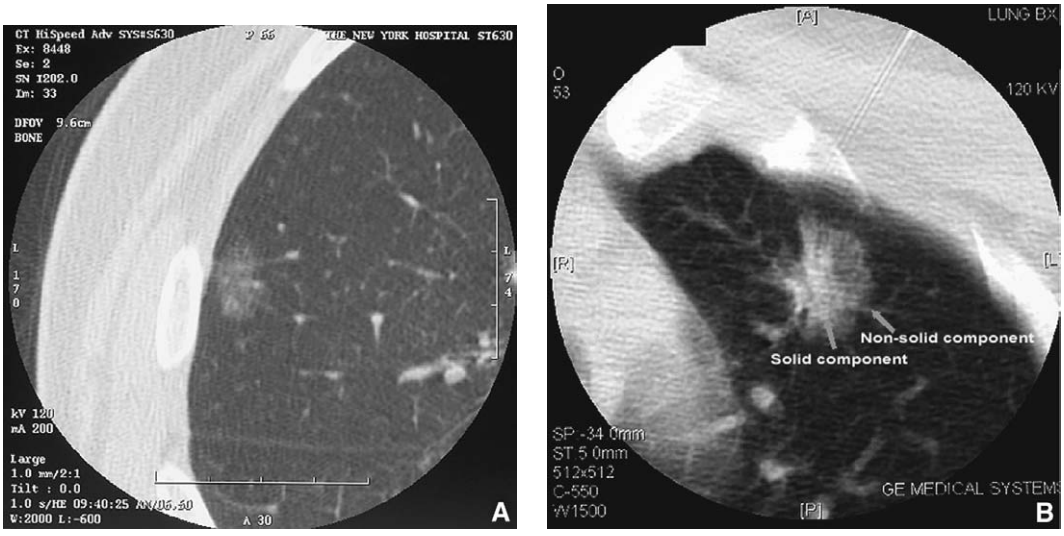

Fig. 3. Subsolid nodules. (*A*) Nonsolid nodule contains no solid elements. The lesion does not completely obscure the underlying parenchyma, and vessels can still be identified. (*B*) Part-solid nodule, which contains solid and nonsolid elements.

evaluated the growth rates of these tumors and found that they were typical of those found in usual clinical practice [18].

In the context of radiographic screening (even at 4-month intervals), stage I diagnosis was achieved in only 29% of the cases [19]. With CT-based screening the proportion has increased markedly. It is now approximately 80%. This shift to a higher frequency of early diagnosis should translate to improved curability because the tumors diagnosed under CT screening are smaller than those found with radiography. An important remaining question to be answered in the context of CT screening is the proportion of stage I lung cancers that are not genuine. This is a more serious concern in regard to CT screening because a new class of lung cancers has now been described called subsolid nodules [20]. Subsolid nodules include the nonsolid and the part-solid nodules (Fig. 3). While they are seen primarily on baseline screening, there is strong evidence to suggest that some of the nonsolid ones are indolent, as manifested in their relatively slow growth rates, their appearance nearly restricted to baseline screening, and the near 100% absence of fatality when they are actually resected [21,22]. Future studies on this topic should help clarfiy the overall proportion of these lesions that are indolent, thus allowing for understanding the overall curability the CT screen-detected lung cancer.

Summary

There have been dramatic improvements in technology in the past decade. In conjunction there have also been advances in our clinical knowledge that have led to changes in the screening regimen. These changes are expected to continue in the future as CT scanners continue to improve and knowledge about screening accumulates, and computer-assisted techniques are expected to play an ever more important role. This dynamic process will lead to continued improvements in the diagnostic distribution of lung cancers detected under CT screening.

References

[1] Kaneko M, Eguchi K, Ohmatsu H, Kakinuma R, Naruke T, Suemasu K, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology 1996;201(3):798–802.

[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(9173):99–105.

[3] Henschke CI, Naidich DP, Yankelevitz DF, McGuinness G, McCauley DI, Smith JP, et al. Early lung cancer action project: initial findings on repeat screenings. Cancer 2001;92(1):153–9.

[4] Sone S, Takashima S, Li F, Yang Z, Honda T, Maruyama Y, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet 1998;351(9111):1242–5.

[5] Sone S, Li F, Yang ZG, Honda T, Maruyama Y, Takashima S, et al. Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. Br J Cancer 2001;84(1):25–32.

[6] International Collaboration to Screen for Lung Cancer. Proceedings of the International Conferences on Screening for Lung Cancer. New York, NY. Available at: http://ICScreen.med.cornell.edu. Accessed December 1, 2003.

[7] Diederich S, Wormanns D, Semik M, Thomas M, Lenzen H, Roos N, et al. Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. Radiology 2002;222(3):773–81.

[8] Nawa T, Nakagawa T, Kusano S, Kawasaki Y, Sugawara Y, Nakata H. Lung cancer screening using low-dose spiral CT: results of baseline and 1-year follow-up studies. Chest 2002;122(1):15–20.

[9] Swensen SJ, Jett JR, Hartman TE, Midthun DE, Sloan JA, Sykes AM, et al. Lung cancer screening with CT: Mayo Clinic experience. Radiology 2003;226(3):756–61.

[10] Pastorino U, Bellomi M, Landoni C, De Fiori E, Arnaldi P, Picchio M, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. Lancet 2003;362(9384):593–7.

[11] Protocol I-ELCAP. Available at: http://icscreen.med.cornell.edu/ielcap.pdf. Accessed December 1, 2003.

[12] Yankelevitz DF, Reeves AP, Kostis WJ, Zhao B, Henschke CI. Small pulmonary nodules: volumetrically determined growth rates based on CT evaluation. Radiology 2000;217(1):251–6.

[13] Henschke CI, Miettinen OS, Yankelevitz DF, Libby DM, Smith JP. Radiographic screening for cancer. Proposed paradigm for requisite research. Clin Imaging 1994;18(1):16–20.

[14] Swensen SJ. CT screening for lung cancer. AJR Am J Roentgenol 2002;179(4):833–6.

[15] Contemporary Screening for the Detection of Lung Cancer. Available at: http://acrin.org/pdf_file2.html?file=protocol_docs/A6654protocol.pdf. p. 29. Accessed December 1, 2003.

[16] Henschke CI, Yankelevitz DF, Miettinen OS. CT screening for lung cancer: suspiciousness of nodules at baseline according to size. Radiology 2003; [in press].

[17] Flehinger BJ, Kimmel M, Melamed MR. The effect of surgical treatment on survival from early lung can-

cer. Implications for screening. Chest 1992;101(4): 1013–8.

[18] Yankelevitz DF, Kostis WJ, Henschke CI, Heelan RT, Libby DM, Pasmantier MW, et al. Overdiagnosis in chest radiographic screening for lung carcinoma: frequency. Cancer 2003;97(5):1271–5.

[19] Fontana RS, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm JR. Lung cancer screening: the Mayo program. J Occup Med 1986;28(8):746–50.

[20] Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley D, Miettinen OS, ELCAP Group. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol 2002;178(5):1053–7.

[21] Aoki T, Nakata H, Watanabe H, Nakamura K, Kasai T, Hashimoto H, et al. Evolution of peripheral lung adenocarcinomas: CT findings correlated with histology and tumor doubling time. AJR Am J Roentgenol 2000;174(3):763–8.

[22] Noguchi M, Morikawa A, Kawasaki M, Matsuno Y, Yamada T, Hirohashi S, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. Cancer 1995;75(12):2844–52.