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Guidelines for Management of Small Pulmonary Nodules Detected on CT Scans: A Statement from the Fleischner Society[1]

Lung nodules are detected very commonly on computed tomographic (CT) scans of the chest, and the ability to detect very small nodules improves with each new generation of CT scanner. In reported studies, up to 51% of smokers aged 50 years or older have pulmonary nodules on CT scans. However, the existing guidelines for follow-up and management of noncalcified nodules detected on nonscreening CT scans were developed before widespread use of multi–detector row CT and still indicate that every indeterminate nodule should be followed with serial CT for a minimum of 2 years. This policy, which requires large numbers of studies to be performed at considerable expense and with substantial radiation exposure for the affected population, has not proved to be beneficial or cost-effective. During the past 5 years, new information regarding prevalence, biologic characteristics, and growth rates of small lung cancers has become available; thus, the authors believe that the time-honored requirement to follow every small indeterminate nodule with serial CT should be revised. In this statement, which has been approved by the Fleischner Society, the pertinent data are reviewed, the authors' conclusions are summarized, and new guidelines are proposed for follow-up and management of small pulmonary nodules detected on CT scans.

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Until now, it has been the accepted standard of practice to regard all noncalcified pulmonary nodules as potentially malignant lesions that require close monitoring until proved stable over a period of 2 years (1,2). This approach was adopted prior to the widespread use of computed tomography (CT) and was based on the observation that a substantial proportion of noncalcified nodules that were detected at chest radiography turned out to be lung cancers. These nodules were almost all larger than 5 mm in diameter, and most were in the 1–3-cm range.

Since the introduction of helical CT in the early 1990s and multi–detector row CT in the late 1990s, the detection of focal rounded pulmonary opacities ("nodules") as small as 1–2 mm in diameter has become routine. In fact, the majority of smokers who undergo thin-section CT have been found to have small lung nodules, most of which are smaller than 7 mm in diameter (3). However, the clinical importance of these extremely small nodules differs substantially from that of larger nodules detected on chest radiographs, in that the vast majority are benign. This issue has been highlighted in several recent publications on CT screening for lung cancer, and the positive relationship of lesion size to likelihood of malignancy has been clearly demonstrated (4,5).

The only current guidelines in the radiology literature for management of small nodules are those that have been developed in the context of lung cancer screening programs (6–8). However, subjects who undergo lung cancer screening in most countries are selected on the basis of age, substantial smoking history, absence of serious comorbid disease, and willingness to participate in all necessary follow-up imaging and intervention. Also, these programs tend to take an aggressive approach to follow-up and early interven-

tion, with a view to achieving the highest possible cure rate while gaining further insight into the behavior and characteristics of small malignant lesions. Therefore, patients whose nodules are detected incidentally during the course of CT performed for other reasons should not necessarily be treated in the same way as subjects in a screening program. Nonetheless, although CT screening has not as yet been proved to help reduce mortality from lung cancer, these programs provide an important source of information for determining the optimal management of "incidental" nodules detected in other situations.

Our intent in this position statement is to provide practical guidelines for the management of small pulmonary nodules that are detected during the course of CT examinations performed for purposes other than lung cancer screening. We recognize that this issue is complex and difficult to reduce to a simple algorithm. We also realize that the definition of a pulmonary nodule is itself elusive, and that not all focal opacities qualify as nodules. Yet, we believe that there is a practical need in the medical community for guidance in this area.

BACKGROUND

Available data indicate that fewer than 1% of very small (<5-mm) nodules in patients without a history of cancer will demonstrate malignant behavior (ie, detectable growth or metastases over a period of 2 or more years) (5,7,9). Nonetheless, multiple follow-up examinations over a 2-year period are commonly performed when such nodules are detected incidentally. Guidelines for the management of the solitary pulmonary nodule were published in 2003 by the American College of Chest Physicians (2) and in a review in by Ost and colleagues in the *New England Journal of Medicine* (1). However, neither of these articles specifically addressed the issue of the very small nodule that is detected as an incidental finding on a CT scan. Ost and colleagues concluded by recommending CT follow-up at 3, 6, 12, 18, and 24 months for all "low-probability" indeterminate nodules (ie, nodules with a low likelihood of being cancer), regardless of size (1). The American College of Chest Physicians recommendation for management of indeterminate solitary nodules was similar, with the proposal for 3-, 6-, 12-, and 24-month CT follow-up intervals, also without any specified lower size limit for a

nodule that would qualify for this protocol (2).

The rationale for recommending serial follow-up studies for all indeterminate small nodules is that some of them will turn out to be cancers and that early intervention will provide an opportunity for cure. The "downside" of this policy includes potential morbidity and mortality from surgery for benign nodules and other false-positive findings, poor utilization of limited resources, increased health care costs, unnecessary patient anxiety, loss of credibility for radiologists who may seem to recommend excessive numbers of CT scans with little benefit, and increased radiation burden for the affected population. The radiation issue is particularly important in younger patients and must be taken into account in determining appropriate follow-up strategies (10–13).

There remains a growing need to reexamine the radiologic approach to small nodules, particularly when CT is performed for indications other than screening. Several fundamental issues need to be considered before an imaging strategy is recommended. Since the decision to perform follow-up studies relies on size, lesion characteristics (eg, morphology), and growth rates (typically described as doubling time), an understanding of these features and their relationship to malignancy should dictate further evaluation. In addition, the patient's risk profile, including age and smoking history, needs to be integrated into the diagnostic algorithm.

Nodules Detected on CT Scans

During the past 5 years, new information regarding the morphology, biologic characteristics, and growth rates of small lung cancers has become available from CT lung cancer screening programs throughout the world. Selected studies are summarized below as representative of the present state of knowledge in this area.

Henschke et al (9) published the initial results from the Early Lung Cancer Action Project CT screening project in 1999. They enrolled 1000 asymptomatic smokers or ex-smokers with at least 10 pack-years of cigarette smoking who were aged 60 years or older. Screening CT studies were performed with 10-mm collimation. The investigators found noncalcified nodules in 23% of subjects and malignant nodules in 2.7%. All detected nodules were subjected to thin-section

CT. If the nodule did not exhibit unequivocally benign characteristics (benign pattern of calcification, smooth margins, and size less than 20 mm), it was followed up with thin-section CT at 3 months and subsequently at 6, 12, and 24 months in the absence of change. Only one cancer was less than 5 mm in diameter at the time of detection in the baseline (10-mm-collimation) study. The results of the repeat screening were reported in 2001. Seven new cancers were detected at the repeat screening; three of these were 5 mm in size (defined as the average of the length and width in that study); all the other proved cancers were larger (8).

Swensen et al (7) reported the results of the Mayo Clinic Lung Cancer Screening Trial after completion of three annual low-dose CT examinations in 1520 smokers. The subjects were aged 50 years or older and had a smoking history of 20 pack-years or more. Two years after baseline screening, 2832 noncalcified pulmonary nodules had been identified in 1049 (69%) participants. Thirty-six lung cancers were diagnosed with the aid of CT (2.6% of participants, 1.4% of nodules): 26 at baseline (prevalence) and 10 at subsequent annual (incidence) CT examinations. Thirty-two (80%) of these cancers were larger than 8 mm, and only one was smaller than 5 mm at the time of detection. Two cancers were detected by using sputum cytology, and there were two interval cancers.

Benjamin et al (14) reported the results of a retrospective review of 334 nonscreening cases in which a lung nodule or nodules were detected that were less than 10 mm in their long axis and for which follow-up CT was recommended. These nodules were identified from 3446 consecutive chest CT studies performed at their institution. Among patients with a nodule, 87 patients had "definitive" follow-up results (2 years without change or biopsy). Nodules in 10 (11%) of these patients were malignant. Nine of these cases were metastases from known primary tumors, and one turned out to be a metastasis from an occult primary tumor. This high incidence of metastases is a reflection of the patient population that was used for this study, in that 56% of the included patients had a known primary tumor. The authors of that article suggested that the malignancy rate in small nodules in patients without a known neoplasm may be as low as 1% and that follow-up may not be necessary in such cases.

Nodule Size

On the basis of analysis of information from the ongoing Mayo Clinic CT Screening Trial, Midthun et al (4) reported that fewer than 1% of very small (<5-mm) nodules in patients without a history of cancer were malignant. They indicated a likelihood of malignancy of 0.2% for nodules smaller than 3 mm, 0.9% for those 4–7 mm, 18% for those 8–20 mm, and 50% for those larger than 20 mm.

Henschke and colleagues (5) recently addressed the issue of optimal follow-up intervals for nodules smaller than 5 mm in diameter. They performed a retrospective review of a total of 2897 baseline screening studies performed between 1993 and 2002 in order to identify those subjects with noncalcified nodules that, at initial detection, were (a) smaller than 5 mm in diameter and (b) 5–9 mm in diameter. In accordance with the screening program guidelines, indeterminate nodules were rescanned at 3-, 6-, and 12-month intervals, while some in the 5–9-mm range that had particularly suspicious morphology were recommended for biopsy. On the basis of the results of these follow-up studies and biopsies, the authors determined that when the largest noncalcified nodule was smaller than 5 mm in diameter (378 patients), a follow-up study in 12 months would have resulted in no case of delayed diagnosis, compared with more aggressive short-term follow-up. However, when the largest nodule was 5–9 mm in diameter, approximately 6% of cases (all of which were malignant) showed interval nodule growth detectable on 4–8-month follow-up scans. Therefore, they recommended that patients with nodules no larger than 5 mm in diameter on a baseline screening CT scan should be referred for repeat annual screening in 12 months time, with no interval scans. This recommendation differs only slightly from the current protocol for the ongoing National Lung Screening Trial, in which patients with nodules smaller than 4 mm in diameter are recommended to return for screening after 12 months, without interval scans or other work-up. Note that these recommendations refer to high-risk subjects who have enrolled in a screening program.

A further practical issue arises in the follow-up to detect interval growth of very small nodules. Comparison of current and previous scans can be performed by using hard copy with manual measurement, soft copy with electronic cali-pers, or software that performs auto-mated volumetric measurement of the nodule (15). The minified display used for hard copy makes accurate measurement of subcentimeter nodules virtually impossible. Even with a state-of-the-art soft-copy display and electronic calipers, substantial inter- and intrareader variations in two-dimensional measurements have been documented (16). Revel and colleagues (16) determined that two-dimensional measurements obtained with electronic calipers were unreliable as a basis for distinguishing benign from malignant solid nodules in the 5–15-mm size range. Limited studies (15,17) that have been performed with automated three-dimensional analysis suggest that such systems can be considerably more accurate and consistent than unaided radiologists in determining interval changes in small nodules. However, Kostis and colleagues (18) have shown that even sophisticated automated volume-measurement methods are susceptible to errors due to motion artifacts or segmentation problems, particularly in the case of very small nodules.

Growth Rate

Hasegawa et al (19) reported an analysis of the growth rates of small lung cancers detected during a 3-year mass screening program. They classified nodules as ground-glass opacity, as ground-glass opacity with a solid component, or as solid. Mean volume doubling times were 813 days, 457 days, and 149 days, respectively, for these three types, all of which were significantly different. In addition, the mean volume doubling time for cancerous nodules in nonsmokers was significantly longer than that for cancerous nodules in smokers. The mean volume doubling time was also significantly longer for nodules not visible on chest radiographs (presumably a function of their smaller average size and/or their lesser average opacity). These data further support the use of extended follow-up intervals for small nonsolid or partly solid nodules, even in high-risk patients. Authors of a number of other series (20,21) have confirmed similar findings and have estimated the median tumor doubling times, assuming a constant growth rate to be in the 160–180-day range. Authors of all of these reports, however, recognize wide variations, and in one study 22% of tumors had a volume doubling time of 465 days or more (21). Note that a 5-mm nodule with a doubling time of 60 days will reach a diameter of 20.3 mm in 12 months, whereas a similar nodule with a doubling time of 240 days would reach a diameter of only 7.1 mm in the same period.

Relative Risk

Sone et al (22) reported the results of a CT screening program carried out in Japan in 1996–1998 that enrolled 5483 subjects. They found an equal prevalence (0.5%) of lung cancer in smokers and nonsmokers, although the death rate from lung cancer in smokers in Japan is approximately four times higher than that in nonsmokers (23). This discrepancy may be explained by an overdiagnosis bias, as many of these slow-growing cancers in nonsmokers might never have been detected or become symptomatic if the subjects had not been screened. It is unclear how many of the nonsmokers in this study may have been affected by second-hand smoke and whether this phenomenon, or underreporting of smoking by screening subjects, might account for the relatively high lung cancer mortality in nonsmokers in Japan compared with that in the United States (24).

The relative risk for developing lung carcinoma in male smokers was about 10 times that in nonsmokers reviewed in the eight prospective studies reviewed for the 1982 report of the Surgeon General on "The Health Consequences of Smoking" (25). For heavy smokers, the risk was 15–35 times greater (25,26). Despite initial evidence suggesting an increased risk of lung cancer in women compared with that in men with an equal smoking history, this has not been confirmed in more recent studies (27–30).

A history of lung cancer in first-degree relatives is also a notable risk factor, and strong evidence for a specific lung cancer susceptibility gene has been discovered recently (31,32). Other established risk factors include exposure to asbestos, uranium, and radon (33–35). However, cigarette smoke remains the overwhelmingly dominant culprit.

Several large screening programs are continuing, and we will learn more from these studies in the next several years. Although the available data are still incomplete, certain tentative conclusions can be drawn at the present:

1. Approximately half of all smokers over 50 years of age have at least one lung nodule at the time of an initial screening examination. In addition, approximately 10% of screening subjects develop a new nodule during a 1-year period (36).

2. The probability that a given nodule

is malignant increases according to its size (4,5). Even in smokers, the percentage of all nodules smaller than 4 mm that will eventually turn into lethal cancers is very low (<1%), whereas for those in the 8-mm range the percentage is approximately 10%–20% (4,7,8,37).

3. Cigarette smokers are at greater risk for lethal cancers, and malignant nodules in smokers grow faster, on average, than do those in nonsmokers (19,25,26). Also, the cancer risk for smokers increases in proportion to the degree and duration of exposure to cigarette smoke (38).

4. Certain features of nodules correlate with likelihood of malignancy, cell type, and growth rate. For instance, small purely ground-glass opacity (nonsolid) nodules that have malignant histopathologic features tend to grow very slowly, with a mean volume doubling time on the order of 2 years (19). Solid cancers, on the other hand, tend to grow more rapidly, with a mean volume doubling time on the order of 6 months. The growth rate of partly solid nodules tends to fall between these extremes, and this particular morphologic pattern is highly predictive of adenocarcinoma (39–41).

5. Increasing patient age generally correlates with increasing likelihood of malignancy. Lung cancer is uncommon in patients younger than 40 years and is rare in those younger than 35 years (42). At the other end of the age scale, although the likelihood of cancer increases, surgical intervention carries greater risks. Also, the likelihood of a small nodule evolving into a cancer that will cause premature death becomes a lesser concern as comorbidity increases in a person and predicted survival decreases with advancing years.

Management Approach

A number of investigators have already raised serious concerns about current management strategies for the indeterminate small nodule, particularly after encountering an overwhelming number of such abnormalities on CT scans (7,14,36). In the study by Henschke et al (5) described earlier, the authors found no cancers in patients in whom the largest noncalcified nodule was less than 5 mm in diameter on the initial scan (zero of 378 patients). Thus there was no advantage in performing short-interval follow-up for nodules smaller than 5 mm in their study, even in high-risk patients.

Therefore, we recommend altering the existing recommendations, which indicate that every indeterminate nodule, regardless of size and morphology, should

Recommendations for Follow-up and Management of Nodules Smaller than 8 mm Detected Incidentally at Nonscreening CT

Nodule Size (mm)*	Low-Risk Patient†	High-Risk Patient‡
≤4	No follow-up needed§	Follow-up CT at 12 mo; if unchanged, no further follow-up‖
>4–6	Follow-up CT at 12 mo; if unchanged, no further follow-up‖	Initial follow-up CT at 6–12 mo then at 18–24 mo if no change‖
>6–8	Initial follow-up CT at 6–12 mo then at 18–24 mo if no change	Initial follow-up CT at 3–6 mo then at 9–12 and 24 mo if no change
>8	Follow-up CT at around 3, 9, and 24 mo, dynamic contrast-enhanced CT, PET, and/or biopsy	Same as for low-risk patient

Note.—Newly detected indeterminate nodule in persons 35 years of age or older.
* Average of length and width.
† Minimal or absent history of smoking and of other known risk factors.
‡ History of smoking or of other known risk factors.
§ The risk of malignancy in this category (<1%) is substantially less than that in a baseline CT scan of an asymptomatic smoker.
‖ Nonsolid (ground-glass) or partly solid nodules may require longer follow-up to exclude indolent adenocarcinoma.

be subjected to a minimum of four or five follow-up CT examinations before being designated benign and the patient being reassured (1,2). As summarized above, data from ongoing CT screening programs with multidetector CT with 5-mm collimation indicate that approximately half of all smokers over 50 years of age have at least one lung nodule on the initial scan (36). In addition, approximately 10% of screening subjects develop a new nodule over a 1-year period, and about 12% can be expected to have one or more additional nodules that were missed on the original scan (36). Assuming similar demographics, approximately 20% of patients who have a nodule detected on CT scans can be expected to have at least one new nodule detected during the currently recommended 2-year minimum follow-up period, which will in turn mandate another series of follow-up CT studies with similar opportunities for new nodules to be detected during the additional follow-up period. Therefore, strict application of the existing recommendations would result in multiple follow-up studies over 2 or more years for a large proportion of all patients who undergo thoracic CT.

In the case of nodules larger than 8 mm, additional options such as contrast material–enhanced CT, positron emission tomography (PET), percutaneous needle biopsy, and thoracoscopic resection can be considered (43–46). Because these approaches depend greatly on available expertise and equipment and have limited applicability to nodules in the subcentimeter range, we have chosen not to offer detailed recommendations in

this regard. Rather, we have elected to focus on the issue of follow-up imaging of smaller nodules. Specifically, for what kinds of lesions is it appropriate to follow, and if followed, at what intervals? Therefore, we propose a set of guidelines, summarized in the Table, for the management of small pulmonary nodules detected on CT scans.

Note that the recommendations shown in the Table apply only to adult patients with nodules that are "incidental" in the sense that they are unrelated to known underlying disease. The following examples describe patients to whom the above guidelines would not apply.

Patients known to have or suspected of having malignant disease.—Patients with a cancer that may be a cause of lung metastases should be cared for according to the relevant protocol or specific clinical situation. Pertinent factors will include the site, cell type, and stage of the primary tumor and whether early detection of lung metastases will affect care. In this setting, frequent follow-up CT may be indicated.

Young patients.—Primary lung cancer is rare in persons under 35 years of age (<1% of all cases), and the risks from radiation exposure are greater than in the older population. Therefore, unless there is a known primary cancer, multiple follow-up CT studies for small incidentally detected nodules should be avoided in young patients. In such cases, a single low-dose follow-up CT scan in 6–12 months should be considered.

Patients with unexplained fever.—In certain clinical settings, such as a patient presenting with neutropenic fever, the

presence of a nodule may indicate active infection, and short-term imaging follow-up or intervention may be appropriate.

Previous CT scans, chest radiographs, and other pertinent imaging studies should be obtained for comparison whenever possible, as they may serve to demonstrate either stability or interval growth of the nodule in question.

A low-dose, thin-section, unenhanced technique should be used, with limited longitudinal coverage, when follow-up of a lung nodule is the only indication for the CT examination.

DISCUSSION

Not every focal opacity qualifies as a nodule. Unfortunately, the familiar lung nodule has eluded all efforts at precise definition. A committee of the Fleischner Society on CT nomenclature described the pathologic definition of a nodule as a "small, approximately spherical, circumscribed focus of abnormal tissue" and the radiologic definition as a "round opacity, at least moderately well marginated and no greater than 3 cm in maximum diameter" (47). Therefore, a linear or essentially two-dimensional opacity that does not have an approximately spherical component is not a nodule. In general, purely linear or sheetlike lung opacities are unlikely to represent neoplasms and do not require follow-up, even when the maximum dimension exceeds 8 mm (48).

Depending on their appearance and radiologic context, certain nodular opacities may be judged sufficiently typical of scarring that follow-up is not warranted.

Because at least 99% of all nodules 4 mm or smaller are benign and because such small opacities are extremely common on thin-section CT scans, we do not recommend follow-up CT in every such case; in selected cases with suspicious morphology or in high-risk subjects, a single follow-up scan in 12 months should be considered. We accept that this protocol could result in a few indolent cancers being missed, but we believe that the number of such instances would be extremely small relative to the reduction in the number of unnecessary studies. Given the high prevalence of small benign nodules, the requirement to follow every such case for a period of 2 years requires vast resources. The radiation burden for the affected population is also substantial, and this could be a cause of cancer in itself (10). Finally, there is no conclusive evidence, as yet, that serial CT studies with early intervention for detected cancers can reduce disease-specific mortality, even in high-risk patients (7). Therefore, we do not recommend follow-up CT for every small indeterminate nodule.

Management decisions should not be based on nodule size alone. While any calcification in a small nodule favors a benign cause, central, laminar, or dense diffuse patterns of calcification are reliable evidence of benignity (49). Fat content suggests a hamartoma or occasionally a lipoid granuloma or lipoma (50). Solid versus nonsolid appearance, spiculation, or other characteristics influence the likelihood of malignancy and probable growth rate in any given case (19,39,49,51,52). Longer follow-up intervals are appropriate for nonsolid (ground-glass opacity) and very small opacities (19,40). For instance, even if malignant, a nonsolid nodule that is smaller than 6 mm will probably not grow perceptibly in much less than 12 months (19,40). Also, as discussed earlier, it has been established that accurate measurement of growth in subcentimeter nodules is problematic (16).

Other features such as clustering of multiple nodules in a single location in the lung tend to favor an infectious process, although a dominant nodule with adjacent small satellite nodules can be seen in primary lung cancer (53,54). For a single nodule, upper lobe location increases the likelihood of malignancy, because primary lung cancers are more common in the upper lobes (55). On the other hand, small, irregular, benign subpleural opacities, presumably due to scarring, are extremely common in the apical areas in older patients, whereas triangular or ovoid circumscribed nodules 3–9 mm in diameter adjacent to pleural fissures commonly represent intrapulmonary lymph nodes (56). A history of cancer can greatly increase the likelihood of a nodule being malignant, depending on the nature and stage of the primary neoplasm (57).

The patient's age and the presence of comorbid conditions should influence management recommendations (58). For instance, an incidentally detected 5-mm indeterminate nodule in an 85-year-old patient with comorbid conditions is relatively unlikely to develop into a symptomatic lung cancer during the patient's lifetime and, therefore, does not necessarily require follow-up (5). However, noncalcified nodules larger than 8 mm diameter can bear a substantial risk of malignancy and should be managed accordingly (39). Depending on the circumstances, follow-up imaging studies or intervention may be appropriate. Conservative management is generally appropriate for nodules in very elderly patients or in those with major comorbid disease. Interval growth of any nodule suggests an active process, and further evaluation or intervention should be considered in such cases.

It is impossible to ignore medicolegal considerations when discussing management of pulmonary nodules. The current practice in the United States of recommending follow-up studies for all indeterminate opacities is partly related to perceived liability if a cancer should develop (59). When the medical community has preached the importance of early detection of cancer for so long, it may prove difficult to convince physicians and the public that follow-up CT of every nodule in every patient is unnecessary. Nonetheless, it is our hope that the guidelines presented here will support a practical and medically appropriate approach to the management of incidentally detected small pulmonary nodules.

The recommendations presented here are based on our current understanding of pulmonary nodules, and we expect that they will continue to evolve as more information becomes available.

References

1. Ost D, Fein AM, Feinsilver SH. The solitary pulmonary nodule. N Engl J Med 2003; 348:2535–2542.
2. Tan BB, Flaherty KR, Kazerooni EA, Iannettoni MD; American College of Chest Physicians. The solitary pulmonary nodule. Chest 2003;123(suppl 1):89S–96S.
3. Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules: application to small radiologically indeterminate nodules. Arch Intern Med 1997;157:849–855.
4. Midthun DE, Swensen SJ, Jett JR, Hartman TE. Evaluation of nodules detected by screening for lung cancer with low dose spiral computed tomography. Lung Cancer 2003;41(suppl 2):S40.
5. Henschke CI, Yankelevitz DF, Naidich DP, et al. CT screening for lung cancer: suspiciousness of nodules according to size on baseline scans. Radiology 2004;231(1):164–168.
6. Aberle DR, Gamsu G, Henschke CI, Naidich DP, Swensen SJ. A consensus statement of the Society of Thoracic Radiology: screening for lung cancer with helical computed tomography. J Thorac Imaging 2001;16(1):65–68.
7. Swensen SJ, Jett JR, Hartman T, et al. Screening for lung cancer with CT: Mayo Clinic experience. Radiology 2003;226(3): 756–761.

8. Henschke CI, Naidich DP, Yankelevitz DF, et al. Early Lung Cancer Action Project: initial findings on repeat screening. Cancer 2001;92:153–159.

9. Henschke CI, McCauley DI, Yankelevitz D, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999;354:99–105.

10. Brenner DJ. Radiation risks potentially associated with low-dose CT screening of adult smokers for lung cancer. Radiology 2004;231(2):440–444.

11. Mayo JR, Alrich J, Müller NL. Radiation exposure at chest CT: a statement of the Fleischner Society. Radiology 2003;228(1):15–21.

12. Imhof H, Schibany N, Ba-Ssalamah A, et al. Spiral CT and radiation dose. Eur J Radiol 2003;47(1):29–37.

13. Kalra MK, Maher MM, Toth TL, et al. Strategies for CT radiation dose optimization. Radiology 2004;230(3):619–628.

14. Benjamin MS, Drucker EA, McLoud T, Shepard JO. Small pulmonary nodules: detection at chest CT and outcome. Radiology 2003;226(2):489–493.

15. Revel MP, Lefort C, Bissery A, et al. Pulmonary nodules: preliminary experience with three-dimensional evaluation. Radiology 2004;231(2):459–466.

16. Revel MP, Bissery A, Bienvenu M, Aycard L, Lefort C, Frija G. Are two-dimensional CT measurements of small noncalcified pulmonary nodules reliable? Radiology 2004;231(2):453–458.

17. Yankelevitz DF, Gupta R, Zhao B, Henschke CI. Small pulmonary nodules: evaluation with repeat CT—preliminary experience. Radiology 1999;212:561–566.

18. Kostis W, Yankelevitz DF, Reeves AP, Fluture SC, Henschke CI. Small pulmonary nodules: reproducibility of three-dimensional volumetric measurement and estimation of time to follow-up CT. Radiology 2004;231(2):446–452.

19. Hasegawa M, Sone S, Takashima S, et al. Growth rate of small lung cancers detected on mass CT screening. Br J Radiol 2000;73:1252–1259.

20. Usuda K, Sato Y, Sagawa M, et al. Tumor doubling time and prognostic assessment of patients with primary lung cancer. Cancer 1994;74(8):2239–2244.

21. Winer-Muram HT, Jennings SG, Tarver RD, et al. Volumetric growth rate of stage I lung cancer prior to treatment: serial CT scanning. Radiology 2002;223(3):798–805.

22. Sone S, Li F, Yang ZG, 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.

23. Cancer statistics in Japan '99: index of tables—standardized cancer mortality ratio among daily smokers in Japan (cohort study 1966-1982). National Cancer Center Web site. http://www.ncc.go.jp/en/statistics/1999/tables.html. Updated December 1, 2004.

24. Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br Med J (Clin Res Ed) 1981;282(6259):183–185.

25. U.S. Department of Health and Human Services. The health consequences of smoking: a report of the surgeon general. Atlanta, Ga: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1982.

26. Guyatt GH, Newhouse MD. Are active and passive smoking harmful? determination of causation. Chest 1985;88(3):445–451.

27. Risch HA, Howe G, Jain M, Burch JD, Holowaty EJ, Miller AB. Are female smokers at higher risk for lung cancer than male smokers? a case-control analysis by histologic type. Am J Epidemiol 1993;138(5):281–293.

28. Blot WJ, McLaughlin JK. Are women more susceptible to lung cancer? J Natl Cancer Inst 2004;96(11):812–813.

29. Zang EA, Wynder EL. Differences in lung cancer risk between men and women: examination of the evidence. J Natl Cancer Inst 1996;88:183–192.

30. Bain C, Feskanich D, Speizer FE, et al. Lung cancer rates in men and women with comparable histories of smoking. J Natl Cancer Inst 2004;96:826–834.

31. Mayne ST, Buenconsejo J, Janerich D. Familial cancer history and lung cancer risk in United States nonsmoking men and women. Cancer Epidemiol Biomarkers Prev 1999;8:1065–1069.

32. Bailey-Wilson JE, Amos CI, Pinney SM, et al. A major lung cancer susceptibility locus maps to chromosome 6q2325. Am J Hum Genet 2004;75:460–474.

33. Lee PN. Relation between exposure to asbestos and smoking jointly and the risk of lung cancer. Occup Environ Med 2001;58:145–153.

34. Gottlieb LS, Husen LA. Lung cancer among Navajo uranium miners. Chest 1982;81:449–452.

35. Field RW, Steck DJ, Smith BJ, et al. Residential radon gas exposure and lung cancer: the Iowa Radon Lung Cancer Study. Am J Epidemiol 2000;151(11):1091–1102.

36. Swensen SJ. CT. Screening for lung cancer. AJR Am J Roentgenol 2002;179:833–836.

37. Pastorino U, Bellomi M, Landoni C, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. Lancet 2003;362:593–597.

38. Bach PB, Kattan M, Thornquist MD, et al. Variations in lung cancer risk among smokers. J Natl Cancer Inst 2003;95(6):470–478.

39. Henschke CI, Yankelevitz DF, Mirtcheva R, et al. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol 2002;178:1053–1057.

40. Aoki T, Nakata H, Watanabe H, et al. Evolution of peripheral lung adenocarcinomas: CT findings correlated with histology and tumor doubling time. AJR Am J Roentgenol 2000;174:763–768.

41. Li F, Sone S, Abe H, MacMahon H, Doi K. Comparison of thin section CT findings in malignant and benign nodules in CT screening for lung cancer. Radiology 2004;233(3):793–798.

42. Gadgeel SM, Ramalingam S, Cummings G, Kraut MJ, Wozniak AJ, Gaspar LE. Lung cancer in patients < 50 years of age: the experience of an academic multidisciplinary program. Chest 1999;115(5):1232–1236.

43. Swensen SJ, Viggiano RW, Midthun DE, et al. Lung nodule enhancement at CT: multicenter study. Radiology 2000;214:73–80.

44. Rohren EM, Turkington TG, Coleman RE. Clinical applications of PET in oncology. Radiology 2004;231(2):305–332.

45. Yamagami T, Iida S, Kato T, Tanaka O, Nishimura T. Combining fine-needle aspiration and core biopsy under CT fluoroscopy guidance: a better way to treat patients with lung nodules? AJR Am J Roentgenol 2003;180:811–815.

46. Suzuki K, Nagai K, Yoshida J, et al. Video-assisted thoracoscopic surgery for small indeterminate pulmonary nodules. Chest 1999;115:563–568.

47. Austin JH, Müller N, Friedman PJ, et al. Glossary of terms for CT of the lungs: recommendations of the nomenclature committee of the Fleischner Society. Radiology 1996;200:327–331.

48. Takashima S, Sone S, Li F, et al. Small solitary pulmonary nodules (≤1 cm) detected at population-based CT screening for lung cancer: reliable high-resolution CT features of benign lesions. AJR Am J Roentgenol 2003;180:955–964.

49. Erasmus JJ, Connolly JE, McAdams HP, Roggli VL. Solitary pulmonary nodules. I. Morphologic evaluation for differentiation of benign and malignant lesions. RadioGraphics 2000;20:43–58.

50. Gaerte SC, Meyer CA, Winer-Muram HT, Tarver RD, Conces DJ. Fat-containing lesions of the chest. RadioGraphics 2002;22(Spec Issue):S61–S78.

51. Wang JC, Sone S, Feng L, et al. Rapidly growing small peripheral lung cancers detected by screening CT: correlation between radiological appearance and pathological features. Br J Radiol 2000;73:930–937.

52. Takashima S, Sone S, Li F, Maruyama Y, Hasegawa M, Kadoya M. Indeterminate solitary pulmonary nodules revealed at populations-based CT screening of the lung: using first follow-up diagnostic CT to differentiate benign and malignant lesions. AJR Am J Roentgenol 2003;180:1255–1263.

53. Heitzman ER, Markarian B, Raasch BN, et al. Pathways of tumor spread through the lung: radiologic correlations with anatomy and pathology. Radiology 1982;144(1):3–14.

54. Yano M, Arai T, Inagaki K, Morita T, Nomura T, Ito H. Intrapulmonary satellite nodule of lung cancer as a T factor. Chest 1998;114:1305–1308.

55. Byers TE, Vena JE, Rzepka TF. Predilection of lung cancer for the upper lobes: an epidemiologic inquiry. J Natl Cancer Inst 1984;72:1271–1275.

56. Hyodo T, Kanazawa S, Dendo S, et al. Intrapulmonary lymph nodes: thin-section CT findings, pathological findings, and CT differential diagnosis from pulmonary metastatic nodules. Acta Med Okayama 2004;58(5):235–240.

57. Quint LE, Park CH, Iannettoni MD. Solitary pulmonary nodules in patients with extrapulmonary neoplasms. Radiology 2000;217:257–261.

58. Read WL, Tierney RM, Page NC, et al. Differential prognostic impact of comorbidity. J Clin Oncol 2004;22:3099–3103.

59. Berlin L. Malpractice issues in radiology: failure to diagnose lung cancer—anatomy of a malpractice trial. AJR Am J Roentgenol 2003;180:37–45.