

# Lung Cancer Screening with Low-Dose Chest CT: Current Issues

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Computed tomography offers many advantages over routine radiographs in screening for lung cancer, and it is clear that low-dose spiral CT screening can more frequently find considerably smaller lung cancers than previous detection tools. Recently, investigators have performed low-dose spiral CT scanning for screening of lung cancer, and have suggested that CT screening can depict lung cancers at smaller sizes and at earlier stages. With technological advances in spiral CT scanners, the detection rate of small noncalcified pulmonary nodules has markedly increased, with higher rates noted with thinner collimation of CT scanning. Unfortunately, the majority of these have proved to be benign, i.e. false positive results. If, even in part, CT features could be found to predict benign nodules without follow-up, the false-positive rate would be reduced, and consequently, the cost, emotional stress, radiation dose, morbidity and mortality associated with interventional procedures would also be reduced. There have been several studies trying to establish reliable CT features for benign lesions

in small pulmonary nodules and to determine their outcome. Although these efforts have not completely resolved the issue of false positive results, it is expected that lessons will be learnt on how to manage these small nodules through experience with screening in the near future. Because pulmonary nodules on CT are much more common in Korea than in western countries, the management algorithm for screening CT-detected nodules should be modified according to different circumstances, with consensus among related physicians and radiologists. In addition, to enhance patient care and avoid misunderstanding of inherent limitation of CT screening by the screening subjects, physicians, hospital managers as well as radiologists should provide proper information regarding CT screening to the screenees. (*Cancer Research and Treatment 2004;36:163-166*)

**Key Words:** Lung cancer, Low-Dose CT, Screening, Lung nodule, False-positive result

## INTRODUCTION

There are many reasons why lung cancer would be an appropriate disease for screening: lung cancer is a leading cause of cancer deaths worldwide; symptomatic lung cancer is generally lethal; early stage lung cancer can be managed curably; new diagnostic tools, such as spiral CT, can detect early lung cancer; and there is a defined high risk group, i.e., heavy smokers. So, lung cancer has been the target of numerous screening strategies. Over the past 10 years, low-dose spiral CT scanning for lung cancer has detected up to 85% of lung cancers in stage I, offering promise in increasing the cure rate, and ultimately decrease the mortality from this malignancy (1~7). Although large-scale studies, with longer follow-up periods, are required to show whether these promising results will translate into an improved lung cancer-related mortality in

the screened population, CT screening of the lungs to detect early carcinomas is now being performed at numerous radiology facilities worldwide, and the number of such examinations appears to be growing considerably.

With technological advances in spiral CT scanners and increasing use of CT for lung cancer screening, CT screening studies have raised several issues regarding false positive findings, patient's emotional stress, costs, unnecessary radiation exposure and interventional procedures, and lack of proper information to the subjects (6,8). In this review, how to interpret and manage the screening-detected lung nodules to decrease the false-positive rate, the recently recommended diagnostic work-up for positive results and the information that should be given to the subjects requiring screening are discussed.

## CURRENT ISSUES

### 1) False positive results

Previously reported rates of positive CT screening range from 11 to 69% (1~7), and the detection rate of small noncalcified pulmonary nodules has markedly increased as the image quality of multidetector CT scanners continuously

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improves due to thinner collimation. In fact, as Swensen assumed (6), it can easily be expected that almost all participants will have at least one positive CT examination result after several years of screening or follow-up CT scans. As a result of this high detection rate, the percentages of benign nodules among the positive results, i.e., the false positive rates, are 88 ~ 99% (1 ~ 7). Although there are varying inclusion criteria for positive results, the high false positive rate of screening-detected pulmonary nodules has become a major issue in CT screening for lung cancer. Despite the importance of how to manage these indeterminate pulmonary nodules during both screening and clinical practice, no consensus on a reliable strategy regarding management of these nodules has been reached.

The lessons how to manage small nodules will be learnt through experience with screening. In other words, the answers sought will only come from research on subjects actually undergoing screening (9). Even if only a part of screening- or clinically detected small pulmonary nodules could be predicted as benign without a follow-up CT scan, up until 2 years, the false positive rate would be reduced, and consequently, the cost, the patient's emotional stress and radiation exposure, as well as the morbidity and mortality associated with unnecessary interventional procedures, such as biopsy and surgery, would be reduced. There have been several efforts to characterize CT features and determine the outcome of small nodules detected on both lung cancer screening and from clinical practice (10 ~ 12). These reports have suggested that the CT features which were optimal for predicting benign nodules were the combination of a predominantly solid lesion and subpleural lesion or polygonal shape or high three-dimensional ratio (10), but these findings can also be seen in malignant nodules, and up until now, the only reliable finding for the characterization of the small benign nodules was the regression or resolution of lesions or 2-years stability (no growth) of the nodules on follow-up CT scans (11,12). In addition, there has been an increasing number of reports regarding intrapulmonary lymph nodes on CT scans (13 ~ 17). The previously reported prevalence of intrapulmonary lymph nodes in patients who had small (less than 12 mm) pulmonary nodules and underwent surgery was 18 ~ 46% (13,14). Therefore, there is a need to be aware of the intrapulmonary lymph nodes as a common cause of small pulmonary nodules. The typical radiological features of intrapulmonary lymph nodes include a subpleural or peripheral location, lower lobe predominancy (below the level of carina), a sharp border with ovoid and round shapes and a size less than 15 mm in diameter (13 ~ 18), as well as multiples. If the typical appearance of intrapulmonary lymph nodes on CT scan is noted, potentially those nodules can be excluded from other indeterminate nodules that need to be observed for at least 2 years or that require a biopsy at some point during the follow-up period.

Yankelevitz mentioned that if the smallest nodules are ignored, the frequency of false-positive findings is appreciably reduced, without creating false-negative results (19). He also maintained that the concept of a positive result must be confined to the findings that justify diagnostic workup. According to his opinion, the smallest nodules should not be viewed as positive test results. Furthermore, the nodules

requiring surgical removal should be appropriately selected. Therefore, a well-defined algorithm, which limits excessive diagnostic workups and unnecessary surgeries, is required. Henschke et al (20) recently reported the frequency of malignant nodules less than 5mm in diameter was 0 out of 378, and postulated that nodules smaller than 5mm do not justify immediate diagnostic workup. They recommended only annual repeat CT screening for those nodules.

In the future, the knowledge gained from the experience of large numbers of repeated screening and follow-up studies, and multidetector CT scanners with thinner collimation, would help in establishing reliable CT features of small benign nodules that was not previously possible, and as a consequence, the false positive rate would be markedly reduced.

## 2) Diagnostic work-up strategies

As mentioned above, screening CT is likely to identify a large number of small nodules, which may not represent malignant diseases, and a need to establish a uniform strategy for their management is required. Recently, Libby et al (21) presented a management algorithm for screening CT-detected pulmonary nodules after reviewing the experience of the Early Lung Cancer Action Project and the medical literature from 1993 to 2003;

Nodules <5 mm in diameter or nonsolid nodules 5 to 9 mm in diameter possess a very low risk of malignancy, so ELCAP recommends a repeat CT after 1 year. Part-solid or solid nodules 5 to 9 mm in size, and nonsolid nodules >10 mm in size, have an intermediate likelihood of malignancy; therefore, a repeat CT after 6 weeks may be useful to assess nodule growth or resolution (with or without antibiotics). If lung cancer is highly suspect, and the patient is considered to fit for thoracic surgery, a biopsy should be undertaken. If the nodule is judged to have an intermediate likelihood of being lung cancer, either PET or a period of radiographic observation, with a repeat CT after 6 to 12 weeks, should be suggested. For a new nodule, as assessed from the CT, an infectious etiology may be present, and empiric antibiotics may be justified. If resolution of the nodule occurs, no further evaluation is warranted; if growth occurs, a biopsy should then be performed. If no change occurs, depending on the other clinical factors, either a biopsy or follow-up CT may be reasonable. If a nodule fails to change over a 2-year period on CT, it is most likely benign; if it continues to grow despite benign biopsy findings, particularly if non-specifically benign, it must still be viewed with suspicion, and either sampled again for biopsy or resection.

With the rapid technical advances in CT, thinner collimation and volumetric analysis of a nodule is becoming possible, and the specific management recommendations are likely to change. The additional problem to overcome in managing nodules in Korea is the higher rate of positive results due to the higher prevalence of tuberculosis. Due to the high prevalence of tuberculosis, screening-detected pulmonary nodules are much more common in Korea than in western countries, and the management algorithm for these nodules should be modified

according to different circumstances to reduce the false-positive rate, which may reach 99% with modern multidetector CT techniques. Consensus on managing the algorithm of nodules among related physicians and radiologists should hopefully resolve this problem in the near future.

### 3) Proper information to screenees

Patients wanting chest CT screening performed for the detection of lung cancer usually expect that the screening will detect any early lung cancer potentially harbored, and that the lung cancer will be successfully cured, if discovered, in its early stage. If those expectations are not met, they may be very disappointed and even respond with a malpractice lawsuit. To avoid this extreme situation, as well as to enhance patient care, hospital managers, physicians and radiologists who decide to advertise or prepare written literature for CT screening of lung cancer for patients, should be extremely cautious of the content of such material (22). The Society of Thoracic Radiology commented that (8):

Screening has imposed obligation on the radiologist to warn the subject that a negative screen does not preclude the subsequent development of lung cancer, even between scans; ensure that the subject knows that some lung cancers may not be amenable to detection by CT screening; ensure that appropriate physicians are available to counsel and treat the patient with a positive result; ensure that patients understand the problem of the number of small lung nodules that are benign and the implications thereof.

This obligation could also be applied on those physicians participating in recommending CT screening for lung cancer to patients.

## SUMMARY

With the rapid technological advances in spiral CT scanners, the detection rate of small noncalcified pulmonary nodules has increased markedly, but the majority of these have proved to be false positive findings. It is, however, expected that in the near future lessons will be learnt, through screening experience, on how to manage these small nodules, and as a result the false-positive rate will be reduced. Because pulmonary nodules are much more common in Koreans than in Westerners and Europeans, the management algorithm for screening CT-detected nodules should be modified. Physicians, as well as radiologists, should provide proper information regarding CT screening to the screenees to enhance patient care and to avoid misunderstandings in relation to the inherent limitation of CT screening.

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