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Spiral CT for lung cancer screening: Is it ready for prime time?

ABSTRACT

Low-dose spiral computed tomography (CT) shows promise as a screening test for lung cancer, as it detects many more malignant pulmonary nodules than does standard plain radiography of the chest. Yet until more data are available we need to temper our enthusiasm. No studies have yet determined if using low-dose spiral CT as a screening test will lead to lower mortality rates. This paper reviews the issue of lung cancer screening and low-dose spiral CT.

KEY POINTS

Although screening with chest radiography and sputum cytology showed no significant effect on the lung cancer mortality rate in studies conducted in the 1970s, some experts question the validity of these data.

All screening tests have the inherent problems of lead-time bias (in which the test uncovers more cases of disease at an early stage but treatment does not affect the natural history of the disease) and overdiagnosis bias (in which the test uncovers many cases of disease that would never had led to a clinical problem).

False-positive results are common with low-dose spiral CT; the positive predictive value is less than 10%. All persons with positive results need to undergo follow-up scanning with high-resolution CT.

At present, no guidelines exist for using low-dose spiral CT as a screening test.

LOW-DOSE SPIRAL COMPUTED TOMOGRAPHY (CT) has shown encouraging preliminary results as a screening test for early detection of lung cancer.[1] If the benefit of this test can be verified and if questions about when and how it should be used can be resolved, spiral CT will fill an urgent need.

At present, screening for lung cancer is not recommended, even for persons at high risk,[2–4] because large-scale randomized trials performed in the 1970s failed to show a decrease in lung cancer mortality among persons screened with chest radiography and sputum cytology.[5]

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This issue has generated intense controversy, and many experts have rejected the idea that screening for lung cancer is futile.[6–8] Although everyone agrees that we need an effective strategy to reduce the morbidity and mortality of lung cancer, no major effort has been made to readdress this important issue.[9]

This article discusses:

- The need for a screening test for early detection of lung cancer
- Studies that used chest radiography and sputum cytology for screening
- Recent studies using low-dose spiral CT
- Current problems and limitations of low-dose spiral CT as a screening test
- Current status and the future prospects of lung cancer screening.

WHY LUNG CANCER IS A SUITABLE TARGET FOR SCREENING

Lung cancer is a good target for screening, and research into screening methods should be a top priority for several reasons.

Lung cancer is a common health problem

Lung cancer is a serious global health problem. The incidence of lung cancer has not declined despite an increasing public awareness of a direct cause-and-effect relation between smoking and lung cancer. In 1998, lung cancer was diagnosed in an estimated 172,000 people in the United States, and 160,000 people died of it.[10] It is the leading cause of cancer-related deaths in both men and women: more people die of lung cancer than of colorectal, breast, and prostate cancers combined.[11] Especially at risk are the nearly 49 million active smokers in this country and almost an equal number of ex-smokers. If early detection can lead to cure, an effective screening program could prevent a large number of premature deaths.

Lung cancer has a preclinical phase

The purpose of screening is to detect a disease during its preclinical phase. In lung cancer, radiological abnormalities almost always precede clinical symptoms, providing an opportunity for a screening test to detect localized tumors early.

Early diagnosis and treatment improves patient outcome

Early diagnosis improves outcome for patients with lung cancer. Overall, the 5-year survival rate for patients with lung cancer in the United States is only 13%; however, if the disease is discovered and treated surgically when it is still in stage I (confined to one lung without metastasis to lymph nodes or distant sites), the 5-year survival rate is 63% to 75%.[12–14] These data underscore the importance of detecting lung tumors early and removing them surgically.

WHY IS SCREENING FOR LUNG CANCER NOT RECOMMENDED NOW?

Even though the concept appears sound in theory, routine screening for lung cancer is not recommended because an optimal screening strategy has not been identified. An ideal screening test should be simple, noninvasive, inexpensive, and widely available. It should have high specificity. It should be backed by strong evidence that its use reduces disease-specific mortality. And it should be cost-effective. Unfortunately, the screening tests available until now—chest radiography and sputum cytology—do not appear to meet these criteria.

EARLY EXPERIENCE WITH LUNG CANCER SCREENING

Screening with chest radiography did not reduce lung cancer mortality

Although chest radiography is simple, inexpensive, and safe, no study has yet demonstrated that using it as a screening test reduces lung cancer mortality. Two studies, one from the Mayo Clinic[15] and one from Czechoslovakia,[16] compared regular screening with chest radiography against sporadic or no screening. In both studies, a greater proportion of lung cancers detected by radiographic screening were in the early stages and resectable, and the 5-year survival rate was higher among the persons with lung cancer that was detected by screening than among persons with lung cancer in the control groups. However, the lung cancer mortality rate was no lower in the screened groups than in the control groups.

Sputum cytology did not improve the results of lung cancer screening

Two other studies, one from Memorial Sloan-Kettering Cancer Center[17] and one from Johns Hopkins,[18] were designed to determine whether it might be more beneficial to perform sputum cytology along with radiographic screening vs yearly radiographic screening alone. It was not: in both studies, the combined approach detected lung cancer earlier than expected, but no difference in lung cancer mortality was found.

Only 15% of lung cancers detected without screening can be surgically removed

Why did screening fail to reduce lung cancer mortality?

The failure of radiographic screening to reduce lung cancer mortality has been attributed to two types of bias that are inherent in the screening process.[2,19]

Lead-time bias occurs when screening detects the disease early but does not affect the natural history of the disease. Because the patient and physician become aware of the disease earlier, survival appears to be prolonged but is not.

Over-diagnosis bias is the tendency of screening tests to detect extremely slow-growing tumors that may fulfill the histological criteria for a tumor, but are not likely to cause clinical symptoms or be responsible for death.

Both lead-time bias and over-diagnosis bias would lead to an apparent improvement in 5-year survival of lung cancer patients without actually reducing the lung cancer mortality.

Problems with early studies

Nearly every scientific advisory committee accepts the negative results of these early studies and advises against routine radiographic screening for lung cancer. However, several investigators seriously question the validity of the data on which this decision is based.

In both the Mayo and the Czechoslovakian studies, the incidence of lung cancer was higher in the screened group than in the control group, possibly owing to population heterogeneity, inaccuracies in diagnosis, and chance variations in the incidence of lung cancer between the groups.[20] Some cite the higher incidence of lung cancer in the screened groups as one of the reasons the studies failed to demonstrate a reduction in lung cancer mortality with screening.[21]

Lung cancer is the leading cancer-related cause of death in both men and women

Several other problems with the design of these studies have been noted. For instance, the Mayo study had less than 20% power to detect a 10% decrease in lung cancer mortality, and its follow-up period was insufficient.[22] The benefits of screening in the Mayo study were further diluted because only 75% of those in the screened group completed the 6-year program, while 50% of those in the control group followed the Mayo Clinic protocol and had annual screening chest radiography.[4]

The concept of over-diagnosis bias in relation to lung cancer has also raised considerable controversy.[23] Over-diagnosis bias is based on the assumption that at least some lung cancers have a slow, indolent, and benign course. But in fact, lung cancer typically has an aggressive course, and the morbidity and mortality rates are high. For instance, one study[24] showed that for patients with stage I lung cancers not treated surgically, the 5-year survival was only 14.3% if the cancer was detected by screening, and 3.7% if the cancer was detected by symptoms. Furthermore, indolent cancers such as prostate cancer are common incidental findings on autopsy; lung cancers are not.[25] Another argument is that even if some lung cancers run a more benign course than others, no one can predict the biological behavior of lung cancer in an individual patient.[26] Without this knowledge, the only practical way to reduce lung cancer mortality is to detect and remove every lung cancer early.

The controversy continues

Even though this controversy has been going on for nearly 3 decades, the fundamental questions surrounding this issue remain unanswered.[21] What is the alternative if chest radiography and sputum cytology are not useful for this purpose? Will a more sensitive test than plain chest radiography detect more lung cancers at an early stage and reduce lung cancer mortality?

Interest in this field has renewed, and preliminary studies with low-dose spiral CT are challenging the widely-accepted dictum against screening for lung cancer.[22]

ADVANTAGES OF LOW-DOSE SPIRAL CT

For diagnosing and staging lung cancer, CT is clearly superior to plain chest radiography. However, owing to its high cost, the time required for performing it, and concern about excessive radiation exposure with repeated testing, conventional CT of the chest is not considered suitable as a screening test for lung cancer. Fortunately, two recent advances in CT technology have largely offset these limitations.

- Low-dose CT—With low-dose CT the entire thorax is scanned with a lower radiation dose than used with conventional CT without any significant degradation of the image quality.[27–29]
- Spiral CT technology allows acquisition of imaging data from the entire thorax within 15 to 20 seconds. The imaging information is then reconstructed into axial sections. Spiral CT virtually eliminates the problem of motion artifacts because the entire scanning is typically

performed during a single breath-hold. Further, with conventional CT, a small lung nodule may fall between the CT slices and be missed. This is not likely to happen with spiral CT owing to its contiguous nature of scanning. Several investigators have reported that spiral CT is more sensitive than conventional CT in detecting pulmonary nodules.[30,31]

Low-dose spiral CT combines the two advances, thus setting the stage for a new era in lung cancer screening. It has many attractive qualities that make it a better screening test than conventional CT:

- It can detect some nodules as small as 3 to 5 mm (although it detects most nodules 7 mm or larger with a higher degree of accuracy (FIGURE 1).[32]
- It has a radiation exposure to the patient about one sixth the radiation exposure with conventional CT and only about 10 times more than the radiation exposure with plain chest radiography.[33,34]
- The scanning time is very short (15–20 seconds).
- It does not require contrast administration.

STUDIES OF LUNG CANCER SCREENING WITH LOW-DOSE SPIRAL CT

Japanese studies

Early studies from Japan showed positive results with the use of low-dose spiral CT screening for lung cancer.

Kaneko et al[35] performed low-dose spiral CT, plain chest radiography, and sputum cytology twice a year in 1,369 persons considered at high risk of lung cancer owing to current or prior tobacco use. A total of 3,457 low-dose spiral CT scans were performed over 18 months. Peripheral lung cancer was diagnosed in 15 patients either on the initial scan or on a subsequent one. Only 4 of these tumors were detectable on the simultaneous chest radiographs. Fourteen (93%) of 15 lung cancers detected by CT were stage I tumors; the mean diameter was 16 mm.

The investigators also compared the results of CT-based screening with their historical experience of screening more than 26,000 patients at high risk with chest radiography and sputum cytology over 18 years.

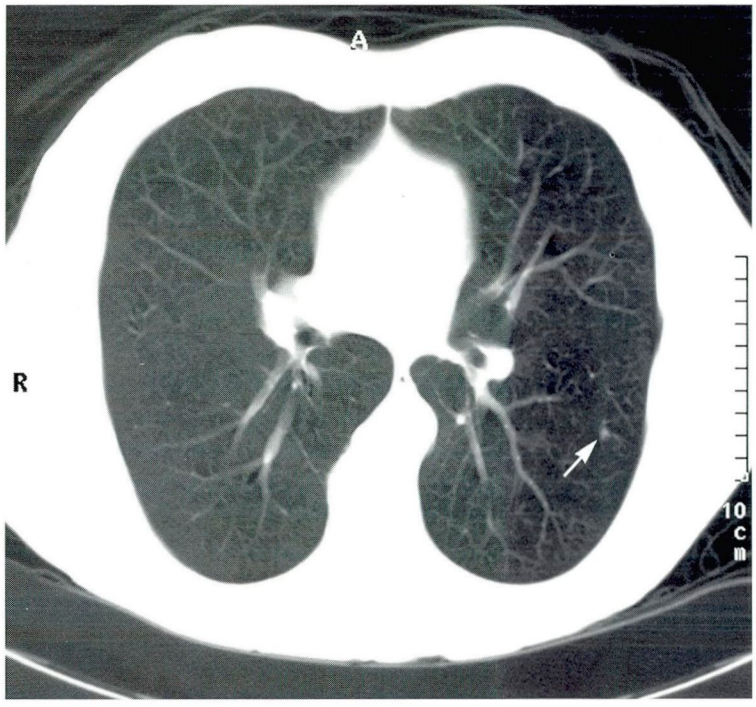

FIGURE 1. Low-dose spiral CT image showing a small nodule (arrow).

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During this time, only 53% of cancers were detected in stage I, and the tumors detected with conventional radiography had a mean diameter of 30 mm.

The scanning time is just 15 to 20 seconds

In another study, Sone et al[36] screened 3,967 volunteers between the ages of 40 and 74 years with both low-dose spiral CT (in a mobile CT unit) and miniature chest fluorophotography.[36] Nonsmokers outnumbered smokers by a ratio of 3:1. Lung cancer was detected in 19 patients on CT; the mean diameter of the tumors was 17 mm, and 16 of the 19 were in stage I. Miniature chest fluorophotography showed only 1 of 19 lung cancers seen on CT. Plain chest radiography performed before surgery missed tumors in 11 of 19 patients who had confirmed malignancy.

The Early Lung Cancer Action Project (ELCAP)

Henschke et al[37] recently reported initial results of the Early Lung Cancer Action Project (ELCAP), which also found promising results for screening with low-dose spiral CT.

In this study, low-dose spiral CT and plain chest radiography were performed in 1,000 volunteers at least 60 years old who had smoked for a median of 45 pack-years.

Whenever a noncalcified nodule was detected with low-dose spiral CT, the patient underwent high-resolution CT. If high-resolution CT did not show a benign pattern of calcification, further workup was recommended according to the size of the noncalcified nodule. Nodules 5 mm or smaller were followed with serial imaging with high-resolution CT. Biopsy was recommended for larger lesions.

The baseline screening revealed noncalcified nodules in 233 (23.3%) of the 1,000 participants compared with 68 (6.8%) by chest radiography. Lung tumors were detected in 27 participants (2.7%) by low-dose spiral CT and in 7 (0.7%) by chest radiography. Stage I disease was detected in 23 patients (2.3%) with CT and in only 4 patients (0.4%) with plain chest radiography. Overall, 26 of 27 CT-detected lung cancers were resectable.

Low-dose spiral CT detects lung cancer earlier than chest radiography

Only 15% of lung cancers detected without any special screening efforts can be surgically removed; the number increases to nearly 50% with screening chest radiography with or without sputum cytology.[15–18] In striking contrast, more than 90% of lung cancers detected with low-dose spiral CT in the ELCAP study were localized and were surgically resectable. Most were peripheral adenocarcinomas, which chest radiography frequently misses.

Spiral CT screening of all eligible persons would cost $12 billion per year

Although these results are encouraging, large-scale application of low-dose spiral CT to screen populations for lung cancer has many limitations that merit careful attention.

LIMITATIONS OF LOW-DOSE SPIRAL CT

False-positive results are very common

Many abnormalities initially suspicious for cancer on low-dose spiral CT prove benign after more definitive studies. For instance, in the study by Sone et al,[36] low-dose spiral CT showed suspicious findings in 219 (5.5%) of 3,967 persons screened, but only 19 proved to have lung tumors after subsequent studies. In the ELCAP study, CT showed suspicious findings in 233 (23.3%) of 1,000 participants, but only 27 proved to have tumors. These results suggest that the positive predictive value of low-dose spiral CT is less than 10% for detection of malignancy.[38]

Therefore, if low-dose spiral CT is used for screening, many patients will need additional imaging with high-resolution CT to characterize the lesion further. Depending on what the high-resolution CT discloses, a physician may elect to follow a "wait and watch" approach, send the patient for a biopsy, or, if the suspicion for malignancy is high, refer the patient for surgical removal of the lung nodule. If guidelines similar to those of the ELCAP study are followed, relatively few patients will need to undergo invasive procedures such as flexible bronchoscopy, video-assisted thoracoscopic surgery, and thoracotomy, and most of the patients who undergo this invasive workup will truly have a malignancy. The remaining patients, in whom immediate biopsy is not performed, will need a careful prospective observation with serial high-resolution chest CT.

This approach has several problems. High-resolution CT is expensive, and repeated imaging will expose patients to excessive radiation. Knowing that something is wrong on low-dose spiral CT will induce anxiety and fear of cancer among many healthy people, and unnecessary invasive procedures may be performed if the patient and the physician do not feel comfortable with the "wait and watch" approach.

Effect on lung cancer mortality is unknown

Population-based, randomized controlled trials provide the most compelling evidence for or against the usefulness of any screening test in reducing disease-specific mortality. To date, all the screening studies of low-dose spiral CT were based on a single-cohort, noncomparative design. The primary end point of these trials was to identify peripheral lung cancers—not lung cancer mortality. As a result, direct evidence does not yet exist on whether screening with low-dose spiral CT reduces lung cancer mortality.

Over-diagnosis of lung cancer is likely

On the contrary, there is concern that screening with low-dose spiral CT may lead to overdiagnosis of lung cancer.[39] For example, Sone et al[36] found lung cancer in 0.48% of non-

smokers, an incidence that was significantly higher than expected (the incidence among smokers was 0.52%). This has led to some speculation that many of the tumors detected by low-dose spiral CT may be clinically irrelevant and may never have surfaced if screening were not performed.[40]

Cost-effectiveness data are lacking

Before a screening test can be accepted as a general health care policy, it must undergo a thorough cost-effectiveness analysis. Although low-dose spiral CT is less costly than standard CT, if it were used to screen every eligible person the estimated cost would be more than $12 billion per year.[41] This is the cost for CT alone: the total cost of screening would be many times higher because many persons would require follow-up procedures such as high-resolution CT. Because the effect of screening with low-dose spiral CT on lung cancer mortality and morbidity has yet to be defined, a vigorous cost-effectiveness analysis cannot be performed at present.

Incidence screening results are not available

Owing to the lead-time bias, the rate of detection is expected to be high when persons at high risk are screened for the first time for a disease.[42] However, before a screening program can be implemented as a matter of health care policy, it has to show efficacy for both initial (prevalence screening) and future screening of the same persons (incidence screening). The ELCAP data show the efficacy of prevalence screening of persons at high risk. Information on the efficacy of incidence screening with low-dose spiral CT is lacking. The ELCAP and other ongoing studies are expected to provide this critical information in the future.

False-negative results are possible

Even though low-dose spiral CT appears to be quite sensitive in detecting early lung cancer, some lesions initially thought to be benign or insignificant on low-dose spiral CT later proved to be malignant.[32] This observation underscores the need to follow carefully every lesion detected on screening, regardless of how insignificant it looks.

UNRESOLVED ISSUES

Against a background of dismal lung cancer incidence and survival statistics, screening with low-dose spiral CT provides new hope of early detection and improved outcome—a welcome step in the right direction. Nevertheless, before it can be recommended for widespread screening, many fundamental issues need to be resolved.

Who should be screened?

Several basic questions need to be answered:

- Who should be screened?
- At what age should screening begin?
- When should screening end?

Most screening studies included patients older than 50 years, even though lung cancer is not uncommon in younger patients.[43] Because low-dose spiral CT has a low specificity for detecting lung cancer, it seems prudent to screen only people considered at highest risk of developing lung cancer, such as smokers and people with asbestos exposure.

Office spirometry might be used as an intermediate step in further choosing candidates for screening with low-dose spiral CT, because smokers with airflow obstruction have a higher lifetime risk of developing lung cancer than do smokers without airflow obstruction.[44,45] Spirometry may also identify persons in whom screening is no longer relevant because of the severity of airflow obstruction.

Office spirometry might help identify candidates for screening

The optimal screening interval needs to be defined

How often should low-dose spiral CT be performed if the initial study shows no abnormality? Subjects enrolled in ELCAP are undergoing repeat low-dose spiral CT annually. Although annual screening appears quite reasonable, a more precise answer is expected from future ELCAP data.

A uniform approach is needed for following lung nodules

A uniform approach is needed for the follow-up of nodules detected on low-dose spiral CT. Unless clear guidelines are developed, practice will vary widely. A defensive approach by physicians will generate unnecessary invasive tests. On the other hand, if resection of lung

cancer is delayed and the tumor becomes inoperable in the interim, it will deprive the patient of the chance of cure and will become a breeding ground for liability suits.

According to the ELCAP protocol, every suspicious lung nodule needs to be followed with high-resolution chest CT. To minimize unnecessary radiographic follow-up, the CT characteristics that distinguish benign from malignant nodules need to be identified more accurately.[46]

When a wait-and-watch approach is chosen, how soon should a follow-up high-resolution CT scan be performed after an initial one? In one study,[47] most malignant nodules larger than 5 mm showed growth on CT scans performed 1 month after the initial CT scan—a considerably shorter interval than the usual 3 months for repeat imaging for small and indeterminate pulmonary nodules. As suggested by Midthun et al,[48] a reasonable approach may be to repeat high-resolution CT in 6 months for nodules 3 mm or smaller, and in 3 months for nodules 4 to 7 mm.

Logistics need to be addressed

Several other logistic considerations need to be addressed before screening with low-dose spiral CT becomes a standard of care. Many radiology departments currently do not have either low-dose spiral CT or high-resolution CT. Considerable resources will be needed to upgrade the imaging capabilities of these departments, and their personnel will need technical training in how to perform and interpret low-dose spiral CT scans.

Helping patients quit smoking should be a top priority

FUTURE DIRECTIONS

Low-dose spiral CT has certainly spearheaded a new war against lung cancer. In addition to the advances in imaging techniques, work is progressing rapidly in looking for biomarkers of lung cancer in the sputum. Preliminary studies indicate that sputum immunocytology has a high potential to detect subclinical lung cancers.[49,50] Fluorescent bronchoscopy also appears promising, especially for detecting subclinical lung cancer in the central airways.[51]

Low-dose spiral CT is accurate in detecting peripheral lung cancers but tends to miss centrally located tumors. Sputum immunocytology is more likely to detect centrally located tumors. This raises an exciting possibility for the hybrid biomarker-CT approach to both prescreen persons for CT scanning and increase the robustness with which lung cancers of all cell types and locations can be detected.[52]

A number of ongoing studies are further addressing the value of low-dose spiral CT. In January 1999, the Mayo Clinic launched a lung cancer screening trial with support from the National Cancer Institute. This study has enrolled 1,500 persons 50 years of age or older, all of whom have a smoking history of at least 20 pack-years.[53] All subjects enrolled in this study will undergo baseline low-dose spiral CT followed by yearly sputum cytology and low-dose spiral CT. The aim is to determine the possibility of detecting 75% or more of lung cancers while still in stage I. Unfortunately, the study design will not provide information on the effect of screening on lung cancer mortality.

The recent positive findings with low-dose spiral CT have also led British investigators to plan a large multicenter randomized trial to study its role in screening smokers and former smokers for lung cancer.[54]

These and other ongoing studies will further increase our understanding about the exact role of low-dose spiral CT in lung cancer screening.

CURRENT SCREENING RECOMMENDATIONS

Recent studies of lung cancer screening with low-dose spiral CT have received extensive media coverage, and many well-informed patients are asking whether they should undergo chest CT in light of recent information. Unfortunately, even the scientific community seems to be leaning toward endorsing screening with low-dose spiral CT without adequate long-term follow-up or a thorough risk-benefit analysis.[55]

The practicing physician should realize that there are no current guidelines to support screening patients for lung cancer with low-dose spiral CT, and at present it can not be recommended for routine office practice.

At present, physicians need to keep a close watch on their patients and investigate for lung cancer on the basis of clinical suspicion. Moreover, helping patients to quit smoking should remain a top priority in clinical practice while waiting for additional information on this important health care issue.

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