Lung Cancer Screening

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Low-dose CT screening for lung cancer is a complex and controversial topic. This article reviews the history of lung cancer screening trials and addresses the principles and confounding biases associated with screening. Chest radiography was initially used for lung cancer screening in the 1970s. In the mid-1990s helical single-detector CT came into use, followed by helical multidetector CT, the current method of screening. Results from prevalence studies and a few single-arm incidence studies have raised concerns about overdiagnosis and the high rate of nodule detection. Follow-up studies and further investigation are needed. To this end, a randomized, controlled trial sponsored by the National Cancer Institute is underway to evaluate disease-specific mortality.

Introduction

Lung cancer is the most common cause of cancer-related death among men and women in the United States. More Americans die of lung cancer than of colorectal, breast, and prostate cancers combined, which are the second through fourth leading causes of cancer mortality. Despite tremendous efforts for improved methods of treatment, the overall 5-year survival rate is below 14% and has not changed significantly over the past several decades [1]. Non–small-cell lung cancer (NSCLC) accounts for approximately 75% of all lung cancers, and the majority of patients are diagnosed with symptoms that indicate a more advanced stage of NSCLC at diagnosis. The prognosis depends on the surgical stage at the time of diagnosis as measured by the TNM classification; patients with stage I disease may have 10-year survival rates of up to 70%. This has formed the rationale for early detection programs.

Screening

The goal of screening is to detect disease at a stage when it is not causing symptoms and when control or cure is possible. In addition to improving outcome, the screening test must also carry low risk, have acceptable levels of sensitivity and specificity, and be accessible and cost-effective. For cancer screening, disease-specific mortality (number of cancer deaths relative to number of individuals screened) is considered the ultimate test of screening effectiveness and the only test with no bias [2]. Survival (number of individuals alive following detection and treatment of disease relative to number of individuals diagnosed with the disease) has often been reported but is subject to biases including lead time, length, and overdiagnosis bias.

Lead time, length, and overdiagnosis bias

Lead time bias refers to the diagnosis of disease being made earlier in the screened group, resulting in a longer survival period but no delay in the time of death. Length bias refers to the tendency of screening to detect slow-growing disease. The probability of detecting disease is directly related to the growth rate of the tumor. Patients with aggressive tumors develop clinical symptoms rapidly and therefore have a shorter detectable preclinical period. The more slowly the lesion grows, the longer it is present without symptoms and the greater the likelihood of detection with screening. Thus, with indolent tumors, there is an apparent improvement in survival. Overdiagnosis refers to the detection of very slow-growing lesions that would have remained subclinical before the patient dies from other causes. An example of a "pseudodisease" of overdiagnosis is prostate cancer. Autopsy evidence of prostate cancer was shown in almost 30% of men aged over 50 years who died of unrelated causes [3]. Overdiagnosis can account for improvements in stage distribution, resectability, and survival with no change in disease-specific mortality.

Other concerns regarding the effectiveness of screening relate to the natural history of lung cancer [4•]. The basis for CT screening is its ability to depict smaller cancers, presumably of an earlier stage with potential for curative resection. However, even at 5 mm in size, a lung cancer has undergone approximately 20 doublings, yielding 10^8 cells. This is already late in the biologic history of the disease because death typically occurs with a tumor burden of 10^{12} cells [5]. Studies have shown that metastases can occur at the time of angiogenesis when lesions are approximately 1 to 2 mm in size [6]. Human tumors grown in nude mouse models can shed 3 to 6 million cells per gram of tissue every 24 hours, setting up the potential for metastatic deposits [7]. Questions have been raised about the correlation of tumor size with outcome. Patz *et al.* [8] found that

patients who had a 3-cm mass had the same survival rate as those with a 1-cm nodule. Heyneman *et al*. [9] found no relationship between stage at presentation and size of tumor, meaning that 1-cm and 2- to 3-cm lung cancers had similar stage distribution.

Chest radiography screening trials

In the 1970s, four major prospective, randomized, controlled trials by investigators from Johns Hopkins University [10], Memorial Sloan-Kettering Cancer Center [11], the Mayo Lung Project [12], and the Czechoslovakian Screening Study [13] were performed. These studies used chest radiography and cytologic examination of sputum at varying intervals to detect lung cancer in high-risk male smokers aged over 45 years. In total, 37,000 people were enrolled in these studies, which found more tumors in the screened group than in the control groups. The lesions were smaller and of an earlier stage of disease, with better resection rates and improved 5-year survival rates. However, overall mortality rate remained the same.

Mayo Lung Project

As the only trial with a true control group, the Mayo Lung Project study has been used most often for discussions about lung cancer screening. Analysis has focused on both the study design and interpretation of the results. This study showed an increased incidence of earlier-stage cancers (48% vs 32%), more resectable cancers (46% vs 32%), and improved 5-year survival rates in the screened groups compared with the control groups (33% vs 15%). However, lung cancer–specific mortality was not improved (3.2 vs 3 per 1000 persons screened). The disparity between these findings has been analyzed and reanalyzed with debate over the effect of lead time, length, and overdiagnosis bias. The Mayo Lung Project was designed to compare patients who were screened at 4-month intervals with those screened annually rather than the ideal comparison of screening with no screening. The study had less than 20% power to detect a 10% benefit in lung cancer mortality and a 55% power to detect a 20% benefit. The issue of contamination was raised when only 75% of the experimental arm completed the 6-year program and 50% of the control arm followed the advice of the Mayo Clinic and had annual screening. Ultimately, these early studies concluded that screening did not improve lung cancer specific mortality. Accordingly, the National Cancer Institute and the American Cancer Society have not recommended screening.

Helical CT

Diagnostic imaging of the chest has improved considerably since these early trials, which led to renewed interest in lung cancer screening. Amid the controversy surrounding the utility of chest radiography in detecting lung cancer, the helical CT emerged as a new screening tool. Helical CT allows the whole chest to be scanned in a single breath hold (12–15 seconds), which reduces motion artifact and allows the potential for mass screening. Current multidetector CT scanners afford significantly enhanced capability for detecting small nodules by allowing thinner slice images. Using low-dose techniques, the effective radiation dose is 0.65 millisieverts (mSv) compared with 5.8 mSv for conventional CT. The radiation dose for low-dose CT is 10 times that of chest radiography. Suggested screening helical CT protocols vary with the available imaging technology. For multidetector CT, parameters of 120 to 140 kVp and 40 to 100 milliampere-seconds with 2.5-mm slice thickness and 1.25-mm reconstruction intervals may be used.

CT screening trials

Screening trials using low-dose helical CT have been conducted in the United States and Japan. The two non-randomized studies from Japan used chest radiography, low-dose CT, and sputum cytology for screening at 6-month intervals over a 2-year period. Kaneko *et al*. [14] initiated their study at the National Cancer Center Hospital in Tokyo in 1993. Of 1369 participants aged over 50 years with a smoking history of more than 20 pack-years accounting for a total of 3457 screenings, 701 (20%) had a positive screening result. Of these, 15 (0.43%) lung cancers were detected on CT, whereas only four (0.12%) were demonstrated on chest radiography. Fourteen of these lesions were stage I (93%). Lesions detected on CT had an average diameter of 16 mm, compared with 30 mm for the patients screened with chest radiography. Results have been updated for 1180 participants given two or more incidence screenings at 6-month intervals for a total of 7891 scans [15]. Twenty-two (0.28%) lung cancers were detected with a total of 18 (82%) being stage IA. The 5-year survival rate was 64.9% for the incidence cases compared with 76.2% for the prevalence cases.

In the second Japanese trial, which started in 1996 in Nagano, Sone *et al*. [16] used a mobile CT unit to examine a low-risk population of volunteers including smokers and nonsmokers aged 40 to 74 years who were part of a national screening program using annual chest fluorophotography and sputum cytology. The study was comprised of 3967 subjects who received fluorophotography and low-dose helical CT, matched with control subjects who had fluorophotography alone. Sone *et al*. [17] reported that 5% (279 of 5483) had an abnormal result and 19 (0.48%) lung cancers were detected on CT, compared with 0.03% on chest radiography. CT missed one central lesion detected by sputum cytology. Sixteen (84%) of the lesions were stage I, and only three (16%) were stage IV. There was no difference in the rate of lung cancer detection in smokers compared with nonsmokers. A subsequent report on annual incidence screening showed that 3.7% (309 of 8303) had an abnormal result, and the rate of cancer detection was 0.41% (34 of 8303).

Missed lung cancers

The database from the Nagano trial generated two interesting reports on lung cancers missed at screening [18,19]. Of the 88 lung cancers diagnosed, 32 were missed on 39 of the CT scans, 23 were missed due to detection error with a mean size of 9.8 mm, and 16 were missed due to interpretation error with a mean size of 15.9 mm. Detection errors included subtle lesions appearing as ground glass opacities (91%), and lesions that were overlapped with, obscured by, or similar in appearance to normal structures such as blood vessels (83%). Interpretation errors were seen in patients who had underlying lung disease such as tuberculosis, emphysema, or fibrosis (87%). The second report revealed that 84% of missed cancers in that database were picked up using an automated lung nodule detection method with a false-positive rate of 1.0 per section. The computer detection method involved the use of gray-level thresholding techniques to identify three-dimensionally contiguous structures with the lungs as possible nodule candidates.

In the United States, the Early Lung Cancer Action Project (ELCAP) conducted by Henschke *et al*. [20•] was started in 1993 and enrolled 1000 individuals aged over 60 years with at least 10 pack-years of smoking history (median, 45 pack-years) who were deemed fit for thoracotomy with a life expectancy of at least 5 years. These patients then received chest radiographs and low-dose CT. Prevalence data from this single-arm trial confirmed that CT is more sensitive than chest radiography for the detection of lung cancer (2.7% vs 0.7%). Of the 27 lung cancers detected by CT, 23 (85%) were stage I. However, the number of advanced-stage cancers did not decrease when compared with the chest radiographic screening studies of the 1970s. This raises the question of whether the prevalence data represent a true "stage shift" allowing detection at an earlier stage or if they represent small, slow-growing tumors that may not affect overall disease-specific mortality. Because this was a single-arm study with no control group, only inferences can be made on whether CT will reduce lung cancer–specific mortality.

In Germany, the University of Munster reported results of a screening trial started in 1995 with 817 participants aged over 40 years with a smoking history of more than 20 pack-years. Twelve (1.3%) cases of lung cancer were detected, of which seven (58%) were stage I. Three lesions that required workup were found to be benign [21].

In 1999, the Mayo Clinic enrolled 1520 patients aged over 50 years with smoking histories of 20 or more pack-years [22•]. The patients had a prevalence CT followed by two annual incidence CT examinations. Unlike the previous CT screening trials that used single-slice helical CT, Swensen *et al*. [22•] were the first to use multidetector helical CT, which allows thinner slices. After 3 years of scanning, 2832 pulmonary nodules were identified in 1049 (69%) of the patients. The majority of these nodules were under 8 mm (95%). Forty cases of lung cancer were diagnosed: 26 at prevalence examinations and 10 at subsequent incidence examinations. The mean size of the NSCLCs detected at CT was 15.0 mm. Twenty-five of the 35 (60%) NSCLCs detected at CT were staged IA. The Mayo Clinic study identified 696 additional CT findings judged to be of clinical importance if they required further evaluation (*eg,* adrenal mass) or had substantive clinical implications (*eg,* aortic aneurysm).

Because helical CT screening can lead to detection of many small nodules that are indeterminate, there is great concern about its potential impact on medical resources. In the recent screening studies using helical CT, 23% of the ELCAP and 69% of the 1999 Mayo Clinic study participants had at least one nodule. In the Mayo Clinic study, depending on the size and characteristics of the lesion, the evaluation included serial follow-up CTs for nodules smaller than 8 mm, dynamic contrast-enhanced nodule densitometry or positron emission tomography for nodules of 8 to 20 mm, and biopsy for nodules larger than 20 mm. Nodules were considered benign if they contained a benign pattern of calcification, appearing diffuse, central, laminated, or chondroid. Nodules that remained stable or became smaller over a 2-year period of observation could also be considered benign. Nodules not meeting these criteria for benignity were considered indeterminate. The financial burden, potential complications from invasive procedures, and psychological impact of investigating these indeterminate lesions are not fully understood. The high rate of detection of noncalcified benign nodules is a cause for concern. The Mayo Clinic group estimated that approximately 99% of the nodules represented false-positive findings. Assuming the 9% to 13% incidence rate of indeterminate nodules in this study, almost all patients will have at least one false-positive screening examination after a few years.

These issues, along with the controversy over widespread unregulated use of CT screening for lung cancer and advertisements aimed at the general public, indicate that a randomized, controlled trial is needed to evaluate the disease-specific mortality benefit.

National Lung Screening Trial

The National Lung Screening Trial (NLST), funded by the National Cancer Institute and the American College of Radiology Imaging Network, is a multicenter randomized, controlled screening trial designed to detect a 20% or greater reduction in lung cancer–specific mortality. This study opened in September 2002 with a plan to enroll 50,000 participants aged from 55 to 75 years with a smoking history of 30 pack-years or more. The accrual period is 2 years at the 30 planned US sites. The study is comparing low-dose multidetector helical CT (2.5-mm slice thickness reconstructed at 1.25-mm intervals versus 5-mm slice thickness reconstructed at 3.75-mm intervals for the Mayo Clinic study) with chest radiography for screening. Patients are randomly assigned to receive either low-dose helical CT

or chest radiography at enrollment with the same screening test repeated 1 and 2 years later. Researchers will contact study participants to monitor their health on at least a yearly basis until 2009. Complementing the imaging aspect of screening is the collection of sputum, blood, and urine for future biomolecular markers of cancer at specified NLST screening centers. Issues regarding quality of life, smoking addiction, smoking cessation, and cost analysis will be studied.

Conclusions

Lung cancer screening with low-dose CT is a complex and controversial topic. CT is more sensitive than chest radiography for the detection of early lung cancer. It is unclear if this difference is due to a true stage shift with corresponding decrease in the number of advanced-stage cancers or if it is caused by overdiagnosis. The high rate of detection of small nodules and the ensuing follow-up studies and investigation carry financial burden and raise serious issues regarding quality of life, unnecessary radiation exposure, invasive procedures, and possible surgery with attendant morbidity and mortality. Randomized, controlled trials to address lung cancer mortality need to be performed before the true benefit of this test can be assessed.

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