CLINICAL PRACTICE

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Lung-Cancer Screening with Low-Dose Computed Tomography

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 60-year-old woman comes for follow-up regarding essential hypertension. She has no symptoms other than mild, long-standing dyspnea on exertion; she specifically reports that she has no cough or chest pain and that her weight has not changed. There is no personal history of cancer or family history of lung cancer. She reports smoking one pack of cigarettes per day since 16 years of age. On prior visits, she declined assistance with smoking cessation, citing her stressful life situation as the primary caretaker for her disabled husband. Should you advise lung-cancer screening with low-dose computed tomography (CT)?

THE CLINICAL PROBLEM

Lung cancer is the most common cause of death from cancer worldwide.[1] In the United States, it is the leading cause of death from cancer in both men and women, resulting in more deaths than breast, colorectal, and prostate cancers combined.[2] Despite advances in diagnosis, staging, and treatment, only 18% of patients with lung cancer are still alive 5 years after diagnosis.[2] Clinicians, scientists, and advocates have long sought a safe and effective screening test to identify lung cancer during its preclinical phase, when it is presumed to be more amenable to curative treatment.

Unfortunately, early trials of chest radiography and sputum cytology did not show that more versus less intensive screening reduced lung-cancer mortality.[3] The trial with the most controversial results compared the combination of radiographic and cytologic screenings performed every 3 months with the standard Mayo Clinic advice to undergo such screenings annually.[4] Enrollment was limited to men 45 years of age or older who had smoked at least one pack of cigarettes per day in the previous year. The group that underwent more frequent screening had increased rates of diagnosed stage I cancers and resectable cancers and better survival at 5 years, as compared with the group that underwent less frequent screening, but without a reduction in lung-cancer mortality.[5] Most observers attributed these seemingly paradoxical results to an overdiagnosis of indolent cancers in the group that underwent more frequent screening. Critics took issue with the absence of a true control group (i.e., a group that did not undergo any screening), as well as the relatively poor sensitivity of chest radiography and standard sputum cytology as tools for early detection.[6]

The disappointing results of these trials set the stage for uncontrolled studies of screening with CT in Japan, Europe, and the United States, which showed that CT was more sensitive than chest radiography for detecting both cancerous and noncancerous nodules.[7-11] Results from these studies were notable in two other ways. First, they showed the feasibility of techniques that used low doses of radiation,

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KEY CLINICAL POINTS

LUNG-CANCER SCREENING WITH LOW-DOSE COMPUTED TOMOGRAPHY (CT)

- The National Lung Screening Trial (NLST) showed that screening with low-dose CT reduced the risk of death from lung cancer by 20% among persons 55 to 74 years of age who had a smoking history of at least 30 pack-years and were current smokers or were former smokers who had quit within the previous 15 years.
- Risks of screening include frequent false positive findings that often require CT surveillance and less commonly lead to invasive biopsy or surgery that reveals benign findings.
- Most guidelines recommend that high-risk smokers and former smokers be offered screening with low-dose CT and engaged in a process of shared, informed decision making to weigh the pros and cons and make an individualized choice.
- There is concern that the favorable balance between the benefits and harms of screening observed in the idealized conditions of the NLST may be difficult to replicate when lung-cancer screening is introduced in diverse clinical practice settings.
- Current smokers should be advised that screening is not a substitute for smoking cessation. Patients with positive screening-test results are more likely than those with negative results to quit smoking, but the effect of participating in a screening program on the rate of smoking cessation is uncertain.

which reduced effective radiation doses by approximately 75 to 80%, as compared with techniques used to perform standard diagnostic CT of the chest, although the doses are still 10 to 15 times as high as those delivered by chest radiography.[12] Second, they showed that the potential harms of screening, including the use of unnecessary invasive procedures among patients with benign findings, could be minimized with the use of specific protocols for follow-up that relied heavily on noninvasive surveillance imaging.

More controversially, it was reported that the 5-year survival rate was much higher among patients with screening-detected lung cancer than among historical controls[13] — a finding that was vulnerable to bias, particularly from lead time (an apparent increase in survival attributable to the identification of disease before clinical manifestations developed) and overdiagnosis (the detection of cancers that would never have become symptomatic). Randomized, controlled trials were still needed to show reductions in lung-cancer–specific mortality in order for screening to be adopted in clinical practice; several trials were subsequently initiated in the United States and Europe.

STRATEGIES AND EVIDENCE

The National Lung Screening Trial (NLST), which included more than 50,000 persons enrolled at 33 U.S. centers, has thus far provided the strongest evidence regarding the potential benefits of lung-cancer screening. Participants were 55 to 74 years of age, with a smoking history of at least 30 pack-years (former smokers had to have quit within the previous 15 years)[14,15]; they were randomly assigned to three rounds of annual screening with low-dose CT or chest radiography. Radiography was used as an active control to facilitate recruitment and to enable comparison with the results of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, which ultimately showed that annual screening with chest radiography did not reduce lung-cancer mortality, as compared with no screening.[16]

The NLST showed a 20% reduction in lung-cancer mortality with low-dose CT versus chest radiography (247 vs. 309 deaths per 100,000 patient-years of follow-up).[17] In absolute terms, this translated to approximately 3 fewer deaths from lung cancer per 1000 high-risk persons who underwent low-dose CT screening (Table 1). To put this finding into context, the magnitude of benefit is at least as great as that reported for breast-cancer mortality with annual mammographic screening among women 50 to 59 years of age.[18,19] In addition, a 6.7% reduction in the relative risk of death from any cause was observed, although this benefit was explained almost entirely by fewer deaths from lung cancer.[20]

False positive findings were common with low-dose CT, but complications of invasive testing were not.[17] Across all three rounds of screening, 39% of the participants in the low-dose CT group had at least one positive result; more than 95% of these findings were falsely positive. Most patients with positive screening-test results required follow-up imaging, including 81% of the participants with positive results on baseline screening. After three rounds of screening, a minority of participants underwent invasive tissue sampling by means of needle biopsy (2%), bronchoscopy (4%), or surgery (4%). Relatively few of the surgeries (24%) were performed in patients with benign nodules, but most of the nonsurgical biopsies (73%) revealed benign findings and therefore were potentially avoidable. Among participants with a positive screening-test result in the low-dose CT group, 1% had at least one complication related to invasive testing, but only 20% of these complications occurred among participants who did not have lung cancer.

The reduction in lung-cancer mortality observed in the NLST has not yet been confirmed. Thus far, several smaller, randomized, controlled trials of low-dose CT screening performed in Europe have been inconclusive,[21-23] although only one of the trials (for which final results are not yet available) is adequately powered to detect a similar (25%) reduction in lung-cancer mortality.[24] False positive results have been common in most of the trials. A systematic review of eight randomized, controlled trials and 13 uncontrolled cohort studies of screening with low-dose CT showed that the average frequency of positive screening results was 20% per round of screening, although it ranged from 3 to 50% per round. Across studies, the rate of follow-up noninvasive imaging varied widely (1 to 45%), as did the rates of nonsurgical biopsy (1 to 4%) and surgical biopsy (1 to 6%); other than the NLST, no studies have reported on complications of invasive testing. In most of the studies, more than 90% of the positive results were false positive findings.[20]

Table 1. Potential Benefits and Harms of Three Rounds of Annual Screening with Low-Dose CT, as Compared with Chest Radiography or No Screening.*

Outcome	Difference
	no. of events/1000 persons screened
CT vs. chest radiography	
Death from lung cancer	3 to 4 fewer
Death from cause other than lung cancer	0 to 1 fewer
CT vs. no screening	
False positive result on low-dose CT	375 more
Invasive biopsy for benign nodule	41 more
Surgical procedure for benign nodule	10 more
Complication from invasive procedure for benign nodule	3 more
Radiation-induced cancer	Uncertain
Cessation of smoking	Uncertain

* Estimates are based on data from the National Lung Screening Trial.[1]

AREAS OF UNCERTAINTY

Several important questions about low-dose CT screening remain unanswered, and screening continues to be controversial. A key controversy is whether the NLST results are applicable to the Medicare population in the United States. In December 2013, the U.S. Preventive Services Task Force released a recommendation in favor of annual screening for adults 55 to 80 years of age with a 30-pack-year smoking history who either currently smoke or quit smoking within the past 15 years — a grade B recommendation representing "moderate certainty that [screening] is of moderate net benefit."[25] The task force based its recommendation to extend the upper age limit for screening on the results of mathematical modeling studies, which were calibrated to fit data from the NLST.[26] In so doing, they made an implicit judgment that the NLST results could be applied to the elderly population.

In April 2014, however, the Medicare Evidence Development and Coverage Advisory Committee voted that it had low confidence in the applicability of the NLST results,[27] citing concerns that only 25% of the participants were 65 years of age or older, that none of the participants were 75 years of age or older, and that a subgroup analysis did not show a significant benefit in participants 65 years of age or older (although the interaction between age and group assignment was not significant).[28] Additional post hoc subgroup analyses of NLST data, including assessments of the risks of complications and the relative frequency of true versus false positive results according to age, may further inform decision making. A final decision by the Centers for Medicare and Medicaid Services regarding whether such screening will be a covered health service is anticipated in late 2014 or early 2015.

Table 2. Guidelines for Lung-Cancer Screening with Low-Dose CT.

Organization	Year	Target Population*	Recommendation	Endorsement of Shared Decision Making	Additional Comments
American Academy of Family Physicians[46]	2013	Persons with a high risk of lung cancer on the basis of age and smoking history	Insufficient evidence to recommend screening	Yes	Screening cannot be recommended on the basis of a single study conducted in major medical centers
American Association for Thoracic Surgery[47]	2012			Not specified	Screening should be conducted in environments in which there are multidisciplinary teams for managing indeterminate and positive screening scans; desirable to create a program that supports smoking cessation
Tier 1		Persons 55–79 yr of age with ≥30-pack-yr smoking history	Recommendation on the basis of data from well-designed randomized, controlled trials		
Tier 2		Persons 50–79 yr of age with ≥20-pack-yr smoking history and another risk factor for lung cancer†	Recommendation on the basis of data from nonrandomized trials		
Tier 3		Lung-cancer survivors who have completed 4 yr of surveillance without recurrence	Consensus opinion		
American Cancer Society[48]	2013	Persons meeting the NLST criteria	Discussion about screening should be initiated	Yes	Recommends only if there is access to a high-volume, high-quality lung-cancer screening and treatment center
American College of Chest Physicians, American Society of Clinical Oncology, and American Thoracic Society[20]	2012	Persons meeting the NLST eligibility criteria	Grade 2B recommendation (i.e., conditional recommendation based on moderate-quality evidence) that screening should be offered	Yes	Suggest that screening be conducted in centers similar to those where NLST was conducted; screening is not a substitute for smoking cessation
American Lung Association[49]	2012	Persons meeting the NLST eligibility criteria	Screening with low-dose CT should be recommended	Choice to undergo screening must be an individual one; every patient should have the information required to make an informed decision	Patients should be referred to a facility that uses best practices for CT screening; smoking cessation is the best method of reducing lung-cancer risk among those who smoke

National Comprehensive Cancer Network[50]	2012			Patients should have a full understanding of risks and benefits	Multidisciplinary screening programs will be helpful; smokers should always be encouraged to quit smoking
Category 1		Persons meeting the NLST eligibility criteria	High-level evidence		
Category 2B		Persons ≥50 yr of age with ≥20-pack-yr smoking history and one additional risk factor for lung cancer‡	Lower-level evidence and consensus opinion		
U.S. Preventive Services Task Force[25]	2013	Persons meeting the NLST eligibility criteria, with upper limit for age extended to 80 yr	Grade B recommendation (moderate certainty of moderate net benefit)	Yes	Moderate net benefit depends on accuracy of image interpretation that is similar to the accuracy at NLST centers and resolution of most false positive results without invasive procedures; smoking cessation is the most important intervention to prevent lung cancer

* Eligibility criteria for the National Lung Screening Trial (NLST) were an age of 55 to 74 years, at least a 30-pack-year smoking history for current and former smokers, and cessation of smoking within the previous 15 years for former smokers.

† Examples of additional risk factors, as specified by the American Association for Thoracic Surgery, include chronic obstructive pulmonary disease (COPD), environmental or occupational exposure, prior cancer or radiation therapy, and genetic predisposition or family history.

‡ Examples of additional risk factors, as specified by the National Comprehensive Cancer Network, include radon exposure, occupational exposure, history of cancer, family history of lung cancer, COPD, and pulmonary fibrosis.

A related question is how to optimize the selection of candidates for screening. The potential benefits of screening are greatest in persons who are at the highest risk for death from lung cancer.[29] Indeed, 88% of the reduction in mortality in the NLST occurred among participants in the three highest quintiles of risk, and only 1% of the reduction occurred among participants in the lowest risk quintile, as estimated by a risk model that included age, sex, body-mass index, pack-years of smoking, presence or absence of emphysema, and status with respect to a family history of lung cancer.[30]

Although limiting screening to persons at highest risk represents the most efficient approach to screening, extending eligibility criteria to include those at lesser risk will inevitably prevent a greater number of lung-cancer deaths, albeit less efficiently. This trade-off represents a challenging problem for both policy-level and clinical decision making. As shown in a cost-effectiveness analysis that used NLST data, published in this issue of the *Journal*,[31] the cost-effectiveness of screening depends critically on how the target population is defined and on the underlying modeling assumptions, with a 95% confidence interval for the incremental cost-effectiveness ratio that ranged from $52,000 to $186,000 per quality-adjusted life-year gained in the primary analysis. In subgroup analyses, screening was most cost-effective in the following populations: persons 60 to 69 years of age, women, current smokers, and persons in the two highest quintiles of risk of death from lung cancer.

The potential harms of screening warrant additional consideration. Patients at high risk for procedure-related complications and those with limited life expectancy owing to chronic illness have less to gain from screening than those at low risk and those without chronic illness, respectively. However, mild chronic obstructive pulmonary disease (COPD) is an independent risk factor for lung cancer and is not a contraindication to lung-cancer screening or treatment. For persons with moderate-to-severe COPD, the trade-offs between benefits and harms are not well defined, because this group has been largely excluded from screening studies. Ultimately, the trade-offs will need to be weighed by patients and their physicians. To facilitate a personalized approach, models have been developed that estimate individualized risks of lung-cancer death[32-35] and predict complications of needle biopsy[36] and lung-

Table 3. Key Elements to Include in a Conversation about Screening for Lung Cancer with the Use of Low-Dose CT.

Annual lung-cancer screening of high-risk smokers and former smokers with the use of low-dose CT is at least as effective in preventing death from cancer as annual mammographic screening for breast cancer in women 50 to 59 years of age.
Among high-risk smokers and former smokers, screening with low-dose CT (along with subsequent evaluation and treatment) prevents one of five deaths from lung cancer.
Lung-cancer screening with low-dose CT is not a single test. It is a process that involves annual testing and follow-up of screening-detected abnormalities.
False positive test results occur in approximately one of five low-dose CT screening examinations. Each examination is approximately 20 times as likely to yield a false positive result as it is to reveal lung cancer.
Most false positive results will require follow-up with one or more subsequent CT scans, but a minority (5%) will require evaluation with invasive biopsy or surgery.
Screening for lung cancer with low-dose CT is not a substitute for smoking cessation. Stopping smoking is the most effective way to reduce the risk of death from lung cancer and has other important immediate and long-term cardiovascular and respiratory health benefits.

cancer surgery,[37] although further studies are needed to determine which models perform best.

There is also uncertainty about whether screening with low-dose CT can be performed safely and effectively in real-world practice settings, where resources and expertise are likely to be less available than those in the idealized trial settings of the NLST. Of greatest concern is the uncertainty about whether the relatively low risks of invasive testing for benign conditions and procedure-related complications observed in the NLST can be replicated in community-based practice. To address this concern, lung-cancer screening programs have been established in some academic centers and community hospitals, but the frequencies of invasive testing and complications in these settings have not been reported.[38,39] Some of these programs have developed standardized practices for the acquisition and interpretation of low-dose CT images, the notification of patients and providers about abnormalities detected by screening, and the evaluation of nodules and other abnormal findings. A potentially important but as yet unproven contribution to these efforts is the Lung CT Screening Reporting and Data System (Lung-RADS), a standardized system for interpreting and reporting the results of low-dose CT screening examinations that was developed by the American College of Radiology.[40] Given the complex logistics of arranging screening and follow-up, screening is best performed in the context of a well-developed program with standardized practices.

A key element of a comprehensive lung-cancer screening program is access to smoking-cessation services. Smoking cessation is the most effective way to reduce the risk of death from lung cancer, and it also has numerous other health benefits. Advocates contend that participation in a screening program represents a "teachable moment" during which counseling about smoking cessation might prove to be more effective than in other contexts. However, sparse data from randomized, controlled trials of low-dose CT screening have been inconsistent and are inconclusive thus far as an answer to the question of whether participation in a screening program improves rates of smoking cessation.[20,41] A possible unintended consequence of screening is that some current smokers with negative results on low-dose CT will be falsely reassured that they do not have lung cancer and will therefore continue to smoke. Several studies have shown that rates of smoking cessation are higher among persons with positive screening-test results than among those with negative results.[42-45]

GUIDELINES

In addition to the U.S. Preventive Services Task Force, many professional societies and advocacy groups have developed guidelines that endorse annual low-dose CT screening for high-risk smokers and former smokers (Table 2). Although eligibility criteria differ slightly across guidelines, most specify that screening should be performed in experienced centers and that candidates for screening should be engaged in a process of shared, informed decision making.[20,25,46-50] In contrast, the American Academy of Family Physicians concluded that the evidence was insufficient to make a recommendation for or against screening with low-dose CT.[46]

CONCLUSIONS AND RECOMMENDATIONS

The 60-year-old patient described in the vignette, a current smoker with a 44-pack-year smoking history, meets NLST and U.S. Preventive Services Task Force eligibility criteria for lung-cancer screening. According to the Memorial Sloan Ketter-

ing Cancer Center Lung Cancer Screening Decision Tool, her estimated risk of death from lung cancer over a period of 6 years in the absence of screening is 2.0%.[51] Assuming that the 20% reduction in lung-cancer mortality observed in the NLST is consistent across risk groups, her personal chance of benefiting from screening is slightly higher than the chance for the average NLST participant, with an estimated absolute risk reduction of 0.4%, or 4 fewer deaths per 1000 persons.

Hence, according to most of the current guidelines, this patient should be offered screening and engaged in a process of shared decision making in which the physician provides information about potential benefits and harms (Table 3) and the patient provides input about her values and preferences. Different persons are likely to value the trade-offs differently, and it is not unreasonable for an eligible person to decline screening. In this case, the physician should order spirometry to evaluate dyspnea on exertion and to rule out severe COPD, which, if present, would shift the balance in favor of not screening. Regardless of whether screening is performed, the patient should be advised that screening is not a substitute for smoking cessation, and treatment with behavioral support and pharmacotherapy should be offered to optimize her chance of successfully quitting smoking.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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