Computed Tomography Screening for Lung Cancer:
Where Are We Now?

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Low-dose computed tomography (LDCT) screening has been shown to result in detection of earlier-stage lung cancers, with a 20% reduction in cancer-related deaths. LDCT screening offers significant potential benefits to selected patients; however, many questions remain, including questions about the applicability of lung cancer screening in clinical practice.

Lung cancer remains the leading cause of cancer mortality worldwide, accounting for more deaths than colon cancer, breast cancer, and prostate cancer combined [1]; indeed, lung cancer is expected to result in more than 160,000 deaths in the United States this year alone [2]. Despite advances in clinical care and diagnostic imaging, most lung cancer patients present with advanced-stage disease, for which a cure remains elusive. The prognosis for patients with lung cancer is therefore generally poor, with an overall 5-year survival rate of approximately 16% [2]. However, early detection affords an opportunity to treat lung cancer at its earliest, most curable stage. Screening with low-dose computed tomography (LDCT) has recently been shown to result in the detection of earlier-stage lung cancers, as well as a significant reduction in cancer-specific mortality in high-risk patients.

LDCT Screening

The most informative study to have evaluated the effectiveness of imaging for lung cancer screening is the National Lung Screening Trial (NLST) [3]. Eligibility criteria for this randomized controlled trial are listed in Table 1. Patients were randomized to screening with either chest radiography or LDCT, and all patients received a total of 3 screening examinations: a baseline study followed by 2 annual screening examinations. A positive screen was defined as one that detected either a noncalcified pulmonary nodule measuring at least 4 mm in diameter or another finding possibly attributable to lung cancer. Among the 53,454 participants enrolled in this study, there were significantly fewer lung cancer deaths among those screened with LDCT than among those randomized to chest radiography (356 deaths versus 443 deaths), and there was a relative reduction in lung cancer–specific mortality of 20.3% over a median of 6.5 years of follow-up (P = .004) [3]. Of note, the NLST compares 2 screening modalities (LDCT and chest radiography) rather than comparing a cohort of patients who were screened with a second cohort who were not. Therefore the NLST may actually underestimate the benefit of computed tomography (CT) screening, and it is postulated that the reduction in mortality afforded by LDCT is likely greater than 20%.

TABLE 1.
National Lung Screening Trial (NLST) Patient Eligibility Criteria

Inclusion criteria
Age 55–74 years
≥ 30 pack-years smoking history
If former smoker, quit ≤ 15 years ago
Exclusion criteria
History of lung cancer
Treatment for or evidence of any other cancer in the past 5 years, except for nonmelanoma skin cancer or carcinoma in situ
Prior lung resection
Signs or symptoms that could be attributable to malignancy (eg, weight loss, hemoptysis)
Acute respiratory infection treated with antibiotics within 12 weeks prior to eligibility assessment
Chest computed tomography examination in the past 18 months

Prior to implementation of widespread lung cancer screening, the potential benefits of screening must be weighed against the potential risks, the most commonly cited of which include overdiagnosis, complications associated with the management of false-positive results, and radiation exposure.

Overdiagnosis and False-Positive Results

Overdiagnosis occurs when screening identifies histologically confirmed lung cancer that would not have resulted in a patient's death if left untreated. Potential harmful effects

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of overdiagnosis include the psychological stress that accompanies a diagnosis of cancer as well as the morbidity and mortality that may accompany unnecessary medical procedures. Overdiagnosis is inherent in any screening test; however, the extent of overdiagnosis with LDCT screening for lung cancer is currently unknown.

Another risk with all screening studies is the potential for both false-negative and false-positive results. The sensitivity of the screening test should be high enough to ensure that a cancer is not missed, while the specificity must be high enough to minimize the number of false-positive examinations. In the NLST, the sensitivity and specificity of LDCT screening were 93.8% and 73.4%, respectively [4]. Although 24.2% of LDCT screens were positive, the vast majority of these represented false-positive studies, because only 3.6% of patients with positive examinations actually had lung cancer [3].

With positive screening studies, additional testing is often required. Despite the high false-positive rate in the NLST, the majority of patients with a positive screening examination were managed noninvasively with follow-up imaging; only 11.4% of patients required invasive testing. Of those patients who underwent invasive testing, the rate of major complications was 0.06% for those without cancer and 11.2% for those with lung cancer. This suggests that, although LDCT screening has a higher rate of false-positive screens compared with other screening modalities, the number of invasive tests performed is low, complications from such procedures are rare, and the risks of additional testing are primarily incurred by patients who do have lung cancer [3].

Radiation Risks

Given the large number of people who would potentially be affected by widespread implementation of LDCT screening for lung cancer, it is important to minimize the amount of radiation exposure attributable to such screening. A standard diagnostic chest CT delivers approximately 8 millisieverts (mSv) of radiation [5]. LDCT can reduce the average effective dose to approximately 1.5 mSv, representing an 81% dose reduction; however, there may be considerable variation in the radiation dose delivered when LDCT is performed in clinical practice [3]. The level of radiation delivered can be reduced by reducing the tube current, increasing the pitch, or decreasing the tube voltage. Further dose reductions may be possible due to advances in CT technology and image reconstruction algorithms. By way of comparison, the radiation dose associated with LDCT screening for lung cancer is only slightly greater than that delivered during a standard 4-view mammogram.

Despite the use of a low-dose screening technique, the risk of radiation-induced malignancy is still a consideration. Unlike the tissue in solid organs, lung tissue becomes more susceptible to radiation-induced changes with increasing age. Furthermore, the risk of developing radiation-induced lung cancer may be increased in patients who smoke. To date, most of the data regarding radiation-induced malignancies comes from patients who received standard-dose imaging rather than LDCT. The mean latency period from radiation exposure to development of cancer is longer than 30 years for standard-dose screening examinations and is projected to be even longer for low-dose screening techniques. The average age of patients who underwent screening in the NLST was 62 years. Thus the risk of developing a radiation-induced cancer is extremely low when screening is performed in an appropriate population. Applying existing models to NLST data, estimates suggest that 1 cancer death per 2,500 patients screened may be attributable to radiation [6, 7]. Therefore, in the NLST population, the potential benefit of preventing lung cancer deaths was found to be greater than the potential radiation risk. However, modeling suggests that the risks associated with LDCT screening may outweigh the benefits in nonsmokers and in patients aged 50 years or younger [7].

Cost Effectiveness

Several factors influence the cost effectiveness of CT screening for lung cancer. The cost per quality-adjusted life-year (QALY) increases as the rate of overdiagnosis increases and as the prevalence of lung cancer decreases. The cost per QALY is likely to be highest during the first 2 years of screening due to costs associated with the evaluation of false-positive findings (eg, follow-up imaging to document 2-year stability of a low-suspicion nodule). Several studies have evaluated the cost effectiveness of lung cancer screening. A meta-analysis comparing the cost per life-year saved for various accepted screening modalities found that LDCT screening for lung cancer was as cost effective as colonoscopy screening for colon cancer and more cost effective than mammography screening for breast cancer [8].

The adoption of LDCT screening for lung cancer in the United States will depend largely on whether Medicare and private insurers are willing to underwrite the expense of implementing such a strategy. Estimates suggest that the total cost to screen the approximately 94 million Americans who fit the NLST high-risk criteria, at an average reimbursement rate of $300 [9], would approach $30 billion annually. However, the total cost of screening will likely be much higher, depending on negotiated reimbursement rates and the additional expenses incurred by the work-up of positive screening examinations. The cost of LDCT screening is currently not covered by Medicare and most private insurers. The Centers for Medicare & Medicaid Services will likely render a decision on CT lung cancer screening after careful review of the available peer-reviewed data, society recommendations, and cost-effectiveness analyses; private insurance providers will likely follow suit. The NLST cost-effectiveness data is expected to have a significant impact on these decisions.

Initial data from the NLST cost-effectiveness analysis was recently presented at a joint meeting of the National Cancer

Institute Board of Scientific Advisors and the National Cancer Advisory Board. The full analysis has not yet been published, but a news release dated June 24, 2013, from the American College of Radiology (ACR) stated that "CT lung cancer screening [is] appropriate when performed in the context of careful patient selection and follow-up, reducing lung cancer mortality by 20% . . . [and] is also cost effective" [10]. Another ACR press release published on the same day suggested that LDCT screening could be implemented on a large scale with acceptable population risks and costs [11].

Lung Cancer Screening Guidelines

Despite the promising results of the NLST and other studies that have evaluated LDCT lung screening, medical professional societies have been cautious in offering their endorsement of such screening, pending the final results of the NLST cost-effectiveness analysis that is currently under way. In the meantime, many professional societies have offered guidelines and recommendations based on the available data (see Table 2), including the American Cancer Society, the American College of Chest Physicians, the American Lung Association, the American Society of Clinical Oncology, the National Comprehensive Cancer Network (NCCN), and the US Preventive Services Task Force (USPSTF). The NCCN has given its highest recommendation (category 1) for LDCT screening for lung cancer, which is a stronger recommendation than the one given for screening mammography [12]. The USPSTF also recently endorsed LDCT screening for lung cancer, issuing a Grade B recommendation for high-risk patients similar to those included in the NLST; this recommendation is the same level as the USPSTF recommendation for screening mammography. The ACR is currently developing practice guidelines and appropriateness criteria for lung cancer screening to establish a national standard of care, which it plans to release in the spring of 2014. Until recommendations are formalized, the ACR refers patients and providers to the current NCCN guidelines.

Treatment Implications

One important criterion for a screening examination is the availability of an effective treatment that improves patient outcomes when it is provided in the preclinical phase (prior to the onset of symptoms) [13]. The efficacy of screening coupled with preclinical treatment (versus treatment once the patient becomes symptomatic) is difficult to definitively prove due to biases inherent in screening, which are beyond the scope of this discussion; however, with long-term follow-up, it may be possible to elucidate differences in survival between patients who were screened and those who were not [14, 15]. It is clear from outcomes data that early-stage lung cancers—those most often detected with LDCT screening—are more effectively treated than are advanced-stage cancers [2]. Early-stage lung cancer is most often treated with surgical resection (usually lobectomy) or with a combination of surgery and chemotherapy, whereas advanced disease is most often treated with chemotherapy (with or without radiation). Many surgeons have advocated video-assisted thoracoscopic (VATS) lobectomy, which is minimally invasive, as the new standard for lung resection. Compared with thoracotomy, the advantages of VATS lobectomy include shorter hospitalization, fewer overall complications, a higher rate of adjuvant chemotherapy completion, and improved long-term survival [16, 17].

Future Directions

Many questions remain and new questions arise as we seek to understand the implications of the NLST. Are the NLST results generalizable to other patient populations? At what age should screening begin, and for how many years should it continue? What is the most effective screening interval? Are there other criteria that should be considered to define a positive screen? Some of these questions may be answered by subanalysis of the NLST data or by ongoing European studies; other questions may require investigation with newly designed trials.

The NLST inclusion criteria are highly selective, and the trial does not provide evidence for or against screening in younger patients. Similarly, the results of the NLST should not be applied to individuals with a less extensive smoking history, including patients who have never smoked; however, individuals who have never smoked account for approximately 10% of all new lung cancer diagnoses [18]. In addition to age and personal smoking history, additional risk factors for lung cancer are recognized, including family history of lung cancer, personal history of malignancy, and carcinogen exposure other than tobacco. A recent study modeling LDCT screening results using inclusion criteria from the Prostate, Lung, Colon, and Ovarian Cancer (PLCO) trial, which included additional risk factors for lung cancer, found that the sensitivity of LDCT screening could increase from 71.1% to 83.0% ($P<.001$) without affecting specificity while detecting more lung cancers [19]. Current NCCN guidelines offer provisional recommendations for lung cancer screening in younger patients who have a less extensive or more remote smoking history and additional risk factors; these provisional recommendations are based on the findings of nonrandomized studies and on observational data [20-24].

Although the NLST was the first randomized trial to show a significant reduction in lung cancer mortality following CT screening, several other studies are ongoing. One of the largest is the Dutch-Belgian NELSON trial, which is expected to report final results in 2015. The NELSON study differs from the NLST in several ways. First, the NELSON trial is a true comparison of CT screening versus no screening, which should provide more definitive quantification both of lung cancer–specific mortality reduction in screened patients and of the risks associated with screening. Furthermore, the study is incorporating nodule volumetrics as one of the criteria for imaging follow-up, which may facilitate differentiation

TABLE 2.
Current Lung Cancer Screening Recommendations

Organization making the recommendations	Year	Recommendations
US Preventive Services Task Force (USPSTF)	2013	Screen with LDCT: age 55–79 years, ≥ 30 pack-years smoking history; if former smoker, quit within previous 15 years (Grade B)[a]
National Comprehensive Cancer Network (NCCN)	2012 (updated 2013)	Screen with LDCT per NLST eligibility criteria: age 55–74 years, ≥ 30 pack-years smoking history; if former smoker, quit within previous 15 years (Category 1)[b] Screen: age 50–74 years, ≥ 20 pack-years smoking history, and 1 additional risk factor other than secondhand smoke (Category 2B)[c]
American Association for Thoracic Surgery (AATS)	2012	Screen: age 55–79 years, ≥ 30 pack-years smoking history (Tier 1)[d] Screen: age ≥ 50 years, ≥ 20 pack-years smoking history, and ≥ 5% risk of developing lung cancer in 5 years (Tier 2)[e] Screen: Lung cancer survivors who have completed 4 years of recurrence-free surveillance and are still eligible for potential treatment (Tier 2)[e]
American Cancer Society	2012	Screen per NLST eligibility criteria. Screening linked to smoking cessation. Screening should be associated with expert multidisciplinary care. Shared decision making between patient and physician.
American College of Chest Physicians (ACCP)	2012	Screen per NLST eligibility criteria. Screening should be performed at centers that can provide expert multidisciplinary care, similar to that provided in the NLST (Grade 2B)[f].
American College of Radiology (ACR)	2012	Screening recommendations under development. Currently the ACR refers patients and providers to the NCCN guidelines.
American Lung Association	2012	Screen per NLST eligibility criteria. Do not screen with chest radiography. Screening linked to smoking cessation. Screening should be associated with expert multidisciplinary care. Advertising and promoting of screening should be ethical.
American Society of Clinical Oncology	2012	Screen per NLST eligibility criteria. Do not screen if patient has limited life expectancy.

Note. LDCT, low-dose computed tomography; NLST, National Lung Screening Trial.
[a]USPSTF Grade B: High certainty that the net benefit is moderate, or moderate certainty that the net benefit is moderate to substantial; recommend providing the service.
[b]NCCN Category 1: Based on high-level evidence, uniform NCCN consensus.
[c]NCCN Category 2A/B: Based on a lower level of evidence, uniform consensus that intervention is appropriate.
[d]AATS Tier 1: Patients determined to be at highest risk by Level 1 evidence (data from randomized prospective trials).
[e]AATS Tier 2: Patients determined to be at risk by Level 2 evidence (data from case control studies or nonrandomized trials) or Level 3 evidence (consensus opinion).
[f]ACCP Grade 2B: Weak recommendation based on moderate quality data.

between benign nodules and suspect nodules that require further evaluation. Preliminary data from the NELSON trial suggest a much lower false-positive rate with this strategy (7.9%); however, the factors contributing to this finding are not yet well understood; it is likely attributable, at least in part, to a lower prevalence of granulomatous disease in European populations [25]. The inclusion criteria for the NELSON trial also differ from those of the NLST. The NELSON study participants become eligible for screening at a younger age (50 years), and study participants include smokers with a shorter smoking history (the equivalent of approximately 15 or more pack-years) and former smokers with a shorter interval since quitting (10 years or less) [26]. The results from the NELSON study and other ongoing trials will be helpful in answering some of the questions raised by the NLST.

Summary

Results from the prospective, randomized NLST demonstrate that LDCT screening significantly reduces the rate of lung cancer deaths and is appropriate with careful patient selection and follow-up. Preliminary data from the NLST also suggest that LDCT screening is cost effective. Ongoing trials will aid in further refining screening guidelines. Although many questions remain, a growing quantity of data supports implementation of LDCT screening in routine clinical practice. Moving forward, it will be necessary to establish national, evidence-based screening and treatment guidelines to ensure that patients have access to care that is uniform in quality. To ensure that patients receive the benefits of screening and treatment that were demonstrated by the NLST, LDCT screening should ideally occur within a multidisciplinary program that includes experts in radiology, pulmonology, thoracic surgery, and oncology. NCMJ

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