

Screening for Lung Cancer



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KEYWORDS

• Lung cancer • Screening • Thoracic surgeons • Pulmonary nodules

KEY POINTS

- The goal of screening programs is to detect tumors in earlier, curable stages, consequently reducing disease-specific mortality.
- The issue of screening has great relevance to thoracic surgeons, who should play a leading role in the debate over screening and its consequences.
- The burden is on thoracic surgeons to work in a multidisciplinary setting to guide and treat these patients safely and responsibly, with low morbidities and mortalities of potential diagnostic or therapeutic interventions.

Lung cancer is a global health burden and is among the most common and deadliest of all malignancies worldwide. In the United States, lung cancer accounts for more than 25% of all cancer deaths, exceeding deaths from breast, colon, and prostate cancers combined.¹ More than 80% of individuals with lung cancer die of the disease, primarily because a large proportion of patients with lung cancer present with locally advanced or metastatic disease. Intuitively, early detection of resectable and potentially curable disease may reduce the overall death rate from lung cancer. Historically, screening for lung cancer was not recommended by most clinical societies and health care agencies in the United States. However, following the mortality benefit identified in the National Lung Screening Trial (NLST), published in 2011,² most US guidelines now recommend screening with low-dose computed tomography (LDCT) in at-risk populations.^{3–6} This shift in policy can be expected to significantly increase the number of patients found to have lung cancer, but also those found to have benign lung nodules. Much of the current debate has now turned toward identifying the most appropriate “at-risk” populations for screening, ensuring appropriate management of screen detected nodules, and defining the optimum duration of computed tomography (CT) screening.

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HISTORY OF LUNG CANCER SCREENING

Chest Radiograph Screening

The first lung cancer mass screening project was conducted by Brett in London from 1960 to 1964.⁷ Although not a randomized trial, 55,034 men were assigned to undergo either chest radiograph (CXR) every 6 months for 3 years (the screened group), or a single CXR at the beginning of the study, followed by a repeat CXR at the end of the 3-year period (the “unscreened” group). At the end of the 3-year period, more lung cancers were detected in the screened group compared with the “unscreened” group (132 vs 96 cases). In addition, resectability was enhanced in the screened group. Despite these findings, lung cancer–specific mortality was not different between the 2 groups.

In the 1970s, the National Cancer Institute funded 3 randomized trials for lung cancer screening using both CXR and sputum cytology at Johns Hopkins, Memorial Sloan-Kettering Cancer Center, and the Mayo Clinic.^{8–10} Again, more cancers were found in the screened groups of patients, and resectability rates were significantly higher in the screened group. Nonetheless, again there was no statistically significant difference in the lung cancer–specific mortality between the screened and “unscreened” populations in any of the trials.

Early Computed Tomography Screening Studies

In the 1990s, increased resolution and data-acquisition speeds of modern CT scanners rekindled interest in screening for lung cancer. Initial findings from Henschke and colleagues¹¹ of the Early Lung Cancer Action Project (ELCAP) showed that in a high-risk population, LDCT was superior to CXR in detection of lung nodules. Notably, 2.7% of those enrolled in the CT screening program had lung cancer, the great majority of which were stage I.¹² A subsequent report by the International-ELCAP (I-ELCAP) group addressed overall curability estimated through 10-year survival rates of patients found to have stage I lung cancer by CT screening.¹³ The investigators reported an estimated 88% 10-year survival rate, markedly higher than survival rates predicted by the current staging system or among those presenting as a result of symptoms. They inferred that because CT screening leads to early detection of lung cancer and because those lung cancers found as a result of CT screening are curable, that CT screening leads to a reduction in lung cancer mortality. Several other groups subsequently evaluated CT screening for lung cancer. A review by Black and colleagues¹⁴ published in 2007 identified 12 studies, including 2 randomized and 10 single-arm observational studies. Significant variability existed in the study populations and in the definition of a positive finding in each. The percentage of positive screenings ranged from 5.1% to 51%. From baseline screenings, 1.8% to 18% of positive findings led to a diagnosis of cancer. Most of the tumors were stage I (53%–100%), with a high resectability rate (>78%). Only one of the studies reported 5-year survival: 76% for patients with cancer detected at baseline screening and 65% for patients with cancer detected at annual repeat scanning.¹⁵

Screening for lung cancer with LDCT was not universally embraced, however. Bach and colleagues¹⁶ reported the findings from CT screening of 3246 high-risk patients from multiple institutions. The investigators reported a 3-fold increase in individuals diagnosed with lung cancer and a 10-fold increase in patients undergoing lung resection (compared with expected cases). They also found no evidence of a decline in the number of patients with advanced stages of disease or of deaths from lung cancer in the screened groups. The investigators concluded that CT screening may not meaningfully reduce the risk of dying from lung cancer and suggested that CT screening is

inherently prone to overdiagnosis, thus exposing patients to unnecessary surgery. The study generated controversy given that the follow-up was relatively short (3.9 years) and that at least 1 of the 3 studies did not require the exclusion of symptomatic individuals, possibly undermining the core concept of screening.

Modeling Approaches to Estimate Mortality Benefit

Given the inability of early randomized trials and prospective studies to prove a mortality benefit to screening, others have attempted to address the magnitude of lung cancer mortality reduction using modeling approaches. McMahon and colleagues^{17,18} from the Mayo Clinic used 1520 current or former smokers undergoing CT screening to model predicted cases of lung cancer and deaths, which were compared with a simulated unscreened control arm. The model ultimately simulated 500,000 cases per study arm based on 5 annual screening examinations, to generate precise estimates of mortality. At 6 year follow-up, the screening arm had an estimated 37% relative increase in lung cancer detection compared with the simulated control arm and a 28% relative reduction in cumulative lung cancer-specific mortality. Although the model included many assumptions, such as lung cancer incidence rates, adherence to the screening protocol, and treatment by established guidelines, the study made a compelling argument for a mortality benefit from CT screening.

Similarly, Foy and colleagues¹⁸ used a lung cancer mortality model developed within the Cancer Intervention and Surveillance Modeling Network (CISNET) to address the potential for mortality reduction by CT screening for lung cancer. The comparison matched members of a CT screening trial (New York-ELCAP) with age, sex, and tobacco exposure-matched control patients from the CARET (Beta-Carotene and Retinol Efficacy Trial), with well-established lung cancer incidence rates.¹⁹ The simulation was repeated 5000 times to compare expected lung cancer mortality between the 2 groups. With the caveat of the inherent assumptions made for the purposes of modeling, the study suggested a 45.6% relative reduction in lung cancer mortality in the group of patients screened with CT.

More recently, a modeling study was performed by the CISNET on behalf of the US Preventive Services Task Force (USPTF). Models were created using deidentified data from the NLST and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial.²⁰ The investigators judged a strategy of screening patients aged 55 to 80, with at least 30 pack-years, and no more than 15 years since quitting as the optimal scenario balancing benefits and harms. In this scenario, the estimated reduction in lung cancer mortality is between 8.6% and 23.5%. All of these studies, albeit models, suggested that LDCT screening protocols, logically followed by earlier treatment of lung cancer, do likely provide a mortality benefit.

The Gold Standard: the National Lung Screening Trial

Between 2002 and 2009, the NLST enrolled 53,456 individuals between the ages of 55 and 74.² All had a history of smoking of at least 30 pack-years and were either current smokers or former smokers who had quit within the past 15 years. Most individuals were male (59%) and younger than 65 years (73%). The trial compared low-dose CT screening (26,723) to CXR screening (27,733) using 3 annual screening rounds with 8 years of follow-up. In the CT screening arm, there were 354 deaths from lung cancer, compared with 442 in the CXR group, translating into a 20.3% reduction in lung cancer-related mortality. In addition, there was a 7% reduction in overall mortality in the CT arm of the trial. This absolute mortality reduction was unprecedented in the history of lung cancer screening and was greeted with much enthusiasm by advocates of CT screening. The NLST secondary analyses will continue to provide data over the

coming years. In addition, several European randomized trials^{21–27} are comparing lung cancer CT screening with no screening. It is expected that pooling the results of these trials and the NLST will further clarify the role for CT screening and better define screening protocols. It should be noted that both the DANTE (Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays)²² and the DLCST (Danish Lung Cancer Screening Trial)²⁵ trials failed to show a decrease in lung cancer mortality in the CT-screened patients; however, they were likely underpowered. The largest trial among these, the NELSON (Nederlands-Leuvens Longkanker Screenings Onderzoek) study, has not yet reported end results.

IMPORTANT STATISTICAL CONCEPTS

The efficacy of screening in reducing cancer-specific mortality may be confounded by lead-time, length, and overdiagnosis biases. Although the statistical arguments may be examined from many different vantage points and are sometimes difficult to interpret, they have been well described previously by Strauss.²⁸ In all screening trials, one must distinguish lead time from lead-time bias. The success of any screening program is dependent on a lead time in diagnosis and treatment; this in and of itself does not present a problem. Bias can arise when short-term survival rates are used to assess the value of screening in populations with and without lead time. Lead-time bias should not affect resectability, or more importantly, curability. In the subpopulations of patients with lung cancer in the older screening trials, there was an increased proportion of 5-year survivors in the screen-detected cases compared with those in the control arms in both the Mayo and the Czech studies.^{8,29} The survival curves never converged, suggesting that screening did increase the cure rate of patients with cancer. This mature data imply that lead-time bias does not explain differences in survival between those groups. The I-ELCAP investigators' effort to estimate 10-year survival rates, rather than shorter-term rates, was also an attempt to avoid any possible lead-time bias.¹³ The estimated cure rate occurs at the plateau phase of the survival curve, its asymptote, at which point the additional deaths that occur are from competing causes. Ongoing analysis of mature NLST data as well as data from other randomized trials will further help to clarify any potential effect of lead-time bias.

Length bias essentially refers to the tendency of screening to lead to the diagnosis of slower-growing cancers more frequently in the baseline round, because these tumors potentially may have been present for a considerable amount of time before the screening study. For tumors detected only on repeat rounds of screening, this is far less of a concern. A review of the Mayo data, however, demonstrates that survival rates were only slightly better in the prevalence cases when compared with incidence cases (40% vs 33%), those diagnosed at repeat screening.²⁸ In the I-ELCAP, no distinction was made in survival rates between the prevalence and incidence groups. In the CT screening arm of the NLST trial, 270 (48%) cancers were diagnosed on the incident CT, compared with 379 (62%) following repeat screening (NLST). Survival differences between the 2 groups were not reported, but will be important to evaluate in future reports.

Similar to the length-bias argument, the overdiagnosis hypothesis is based on the idea that screen-detected cancers may be indolent and perhaps even clinically insignificant. The lung cancer detection rates were higher in the screened groups in both the Mayo and the Czech studies. Despite this, mortality for the entire screened cohort in both studies was actually slightly higher. Similarly, in the CT-based study by Bach and colleagues,¹⁶ there was an increased rate of lung cancer detection, 144 cases versus 45 expected cases. Despite this increase in detection, there was no decrease

in the expected lung cancer mortality rate. The possibility of overdiagnosis has been used to explain these findings as well as the excellent projected 10-year survival in the I-ELCAP study. Several authorities suggest that many lung cancers detected by screening would not progress rapidly to the point of clinical detection and would therefore be unlikely to account for a meaningful share of deaths among screened individuals.

Perhaps the most challenging aspect of understanding the issue of overdiagnosis is defining the term itself. The phrase is often used synonymously with “pseudo-disease”; this implies that the disease would progress slowly and that the individual would die from competing illnesses long before the cancer becomes clinically significant. This definition may thus encompass patients with lung cancer who die of competing (or accidental) causes to be considered as examples of overdiagnosis regardless of tumor stage. The concept of overdiagnosis was first proposed based on data from the Mayo Lung Project. In that study, there was an excess of early-stage lung cancers in the screened group, yet no difference in mortality. Therefore, it was concluded that those excess predominantly early-stage cancers were overdiagnosed. However, when examined critically, they did not fit the profile of indolent cancers. They were on average 2 cm in diameter, not present on the baseline round, had a median growth rate of 101 days, and were nearly all invasive pathologically.⁸ Thus, in the screened arm, lung cancers were far more likely to be identified and cannot be thought of as indolent. The similar disease-specific survival rate between the groups may be explained by the high rate of competing causes of death in the screened group, where the number of cardiovascular deaths was nearly 4 times the rate of lung cancer deaths.

There are several other arguments against overdiagnosis. The first is based on the known epidemiologic evidence. For example, studies reported by Sobue and colleagues³⁰ and by Flehinger and colleagues³¹ have documented mortalities in excess of 80% for untreated screen-detected lung cancers. The high mortality of screen-detected small tumors argues against their presumed indolent or nonfatal nature. In fact, it seems that even the smallest lung cancers are almost always deadly. An analysis by Henschke and colleagues³² of the SEER (Surveillance, Epidemiology and End Results) database revealed an 87% 8-year fatality rate for untreated 6- to 15-mm primary non-small-cell lung cancer (NSCLC). A more recent review of the California Cancer Center registry by Raz and colleagues³³ examined long-term survival in untreated stage I NSCLC. Five-year overall survival was only 6%, with a median survival of 9 months.

More evidence against overdiagnosis may be found from autopsy studies. McFarlane and colleagues³⁴ reported that the rate of “surprise” lung cancer at autopsy was less than 1% and that many of these patients had in fact died of those cancers. Another study found a slightly higher (3.3%) rate of lung cancer at autopsy, but deemed none of the cancers to have been clinically insignificant, because lung cancer was thought to be the direct cause of death in more than half of the cases.³⁵ Further evidence against overdiagnosis may also be found in the I-ELCAP data. Henschke and colleagues³² reported that for the I-ELCAP screening trial, an expert panel of pulmonary pathologists confirmed that 95% of the patients with stage I cancer had invasive tumors that were morphologically indistinguishable from “garden variety” lung cancers. In addition, a subgroup of the I-ELCAP screen-detected cancers was analyzed for biomarkers using immunohistochemistry and fluorescence in situ hybridization.³⁶ The molecular alterations were found to be similar to those found in conventionally diagnosed cancers. Of note, all 8 I-ELCAP patients with untreated stage I cancer died within 5 years of screening.

Recently, Patz and colleagues³⁷ cited overdiagnosis as a potential reason for the mortality benefit in the NLST study. They used modeling estimates to determine that the probability is 18.5% (95% confidence interval [CI], 5.4%–30.6%) that any lung cancer detected by screening with LDCT was an overdiagnosed cancer. The investigators considered that when a bronchioloalveolar (noninvasive in new terminology) lung cancer was detected by LDCT there was a 78.9% (95% CI, 62.2%–93.5%) chance of overdiagnosis. In the NLST, there were 110 bronchioloalveolar cell carcinomas in the CT-screened arm, 95 of which were screen detected. In the CXR arm, there were only 35 bronchioloalveolar cell carcinomas, of which 13 were screen-detected (NLST). Given the lack of longitudinal studies to date, it is impossible to determine whether these were overdiagnosed indolent cancers or whether they would have progressed. The investigators concede that because their model was only based on 3 annual screens and an average of 7 years of follow-up, any estimate of overdiagnosis based on lifetime follow-up scenarios must be treated cautiously. Although the natural history of noninvasive lung carcinomas is not well understood, in general, the balance of both epidemiologic and pathologic evidence does not appear to make lung cancer a good candidate for high rates of overdiagnosis by screening.

CURRENT RECOMMENDATIONS

The American Association for Thoracic Surgery (AATS) established an interdisciplinary task to consider the findings from CT screening trials and provide recommendations applicable to daily clinical practice. Six unanimous recommendations (Box 1) were presented and accepted at the AATS 2012 annual meeting.⁴ The AATS guidelines recommend screening individuals aged 50 to 54 with a 20-pack history if additional risk factors are present. Recommendations also addressed the need for surveillance with annual LDCT in survivors of lung cancer, the need for patient self-risk assessment, and the need for multidisciplinary evaluation. Importantly, the AATS made no recommendation to stop screening after the 3-year time point used in the NLST, citing lack of scientific evidence for cessation of screening. The AATS also proposed that

Box 1
American Association for Thoracic Surgery Guidelines Task Force recommendations regarding low-dose computed tomography screening for lung cancer

1. Annual lung cancer screening with LDCT for smokers and former smokers between 55 and 79 years old with 30-pack-year history of smoking
2. Annual LDCT until the age of 79 in long-term lung cancer survivors to detect second primary lung cancers
3. Annual lung cancer screening with LDCT for smokers and former smokers between 55 and 79 years old with 20-pack-year history of smoking and additional comorbidities that infer increased risk of lung cancer greater than 5% over the following 5 years
4. Multidisciplinary approach to lung cancer screening, evaluation, and treatment
5. Development of a Web-based application for patient self-risk assessment
6. Continue AATS engagement with other specialties to develop and refine further guidelines

Adapted from Jaklitsch M, Jacobson F, Austin J, et al. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. J Thorac Cardiovasc Surg 2012; 144(1):33–8; with permission.

long-term cancer survivors should have an annual LDCT until the age of 79 to screen for second primary lung cancers.

The USPTF recommendations are similar to those of the AATS.³ They recommend annual screening for individuals aged 55 to 80 with a 30-pack-year smoking history, but suggest discontinuing screening when patients have not smoked for 15 years. The USPTF also addressed implementation of screening programs, smoking cessation counseling, shared decision-making, and standardization of follow-up of abnormal findings. The National Comprehensive Cancer Network (NCCN) has also recommended LDCT screening in selected individuals at risk for lung cancer.³⁸ High risk is defined as patients aged 55 to 74 years with at least a 30-pack-year smoking history without cessation greater than 15 years prior. They also recommended that persons aged 50 years or older undergo screening when they have at least a 20-pack-year smoking history and one additional risk factor. In addition to the AATS, USPTF, and NCCN, several other groups including the American College of Chest Physicians, the American Society of Clinical Oncology, the American Cancer Society, and the American Thoracic Society have all recommended screening for lung cancer with LDCT scan based on the results of the NLST.

Regardless of the method used to screen patients for lung cancer, controversy over the value and best paradigm of screening will likely continue to exist, much as it does for other cancers, including breast and prostate cancer. In 2009, the USPSTF released new recommendations for breast cancer screening, which were quite different from their 2002 recommendations.³⁹ The Task Force raised the recommended age to begin screening from 40 years to 50 years and recommended stopping screening at age 74. These recommendations generated significant national controversy. The USPSTF's interpretation of the screening data was subsequently refuted by some investigators, who continued to claim a benefit for screening in the 40- to 84-year age range.⁴⁰ Similarly, the value of screening for prostate cancer has also been called into question by the results of 2 disparate landmark studies.⁴¹ The European Randomized Study of Screening for Prostate Cancer reported a statistically significant cancer-specific mortality reduction of 20% favoring prostate-specific antigen-based screening.⁴² In contrast, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial showed no mortality reduction.⁴³ Undoubtedly, different structures of competing clinical trials, heterogenous "unscreened" populations, and evolving technological advances will also continue to make an absolute application of the data for lung cancer screening to clinical practice difficult.

RESECTION OF SCREEN-DETECTED LUNG CANCER

To date, lobectomy remains the standard of care for the management of NSCLC. However, the past decade has witnessed a resurgence of interest in sublobar resection for small, peripheral, early-stage lung cancers as well as for nonsolid nodules that are the radiologic manifestations of adenocarcinoma in situ and minimally invasive carcinoma. These lesions are currently detected with higher frequency owing to the more widespread use of CT scanning and the enhanced resolution of CT scanning devices. Their detection will likely continue to increase once CT screening programs are more widely implemented. The rationale for sublobar resection in such instances is supported by the results of several retrospective case series, mainly from Japan, showing that overall and disease-free survival are comparable to those achieved after lobar resection.^{27–30}

Recently, Altorki and colleagues³¹ reported the overall and cancer-specific survival for 347 patients with clinical stage IA NSCLCs manifesting as solid nodules in the I-ELCAP screening program. Ten-year survival was 85% for 53 patients treated by

sublobar resection and 86% for 294 patients treated by lobectomy. Cox survival analysis showed no significant difference between sublobar resection and lobectomy when adjusted for propensity scores or when using propensity quintiles. For those with cancers 20 mm or less in diameter, the 10-year rates were 88%, and Cox survival analysis showed no significant difference between sublobar resection and lobectomy using either approach. Despite these results, most lung cancers detected in the context of screening continue to be treated by lobar resection, which remains the standard of surgical care worldwide.

Currently, 2 randomized noninferiority trials, JCOG 0802 and CALGB 140503, are testing the hypothesis that lobar and sublobar resections are associated with comparable disease-free survival in patients with solid clinical stage IA NSCLC. The role of sublobar resection in nonsolid nodules is also being evaluated in a Japanese phase II trial (JCOG0804) in which patients with either nonsolid ground-glass nodules or part-solid nodules with a solid component of 25% or less were treated with wide wedge resection. Mature follow-up data from each of these trials on survival and recurrence are awaited.

In the meantime, sublobar resection is slowly emerging as a viable alternative to lobectomy, particularly in patients with nonsolid nodules that may represent indolent cancers, namely preinvasive or minimally invasive adenocarcinoma. The challenge in localizing such lesions intraoperatively may be significant, and the application of sublobar resection in such cases requires careful planning. An important aspect of such planning is the participation of an expert pulmonary pathologist who will be able to confirm on frozen section examination the diagnosis of cancer and the adequacy of the resection margins.

The role of sublobar resection in solid lesions is more controversial and should probably be limited to patients with limited cardiopulmonary reserve until the results of the randomized trials are available. However, when sublobar resection is attempted, the surgeon must ensure the absence of nodal metastases in the mediastinal and major hilar lymph nodes. The presence of nodal metastases should prompt conversion to lobectomy. Particular attention should also be directed to obtaining a satisfactory resection margin that is at least equivalent to the greatest diameter of the tumor and is confirmed to be free of disease on the frozen section examination. Such examinations can be challenging for pathologists, particularly for preinvasive and minimally invasive adenocarcinoma. In the absence of a qualified pathologist, an attempt should be made to obtain a wider margin around the tumor. Most thoracic surgeons emphasize the role of mediastinal nodal dissection or systematic mediastinal nodal sampling in the treatment of clinical stage IA NSCLC that manifests as a solid nodule. The merits of mediastinal nodal dissection in the case of nonsolid nodules are less clear because nodal metastases are rarely found in such instances.

Regardless of the extent of parenchymal resection and nodal dissection, minimally invasive approaches are strongly encouraged. Multiple studies have shown that video-assisted lobectomy and segmentectomy are oncologically equivalent to open thoracotomy approaches and are associated with significantly lower cardiopulmonary morbidity, less need for blood transfusion, and shorter length of hospital stay.^{32–34} In addition, data suggest that in the context of screening the use of minimal access surgery would be associated with improved cost-effectiveness.³⁵

SUMMARY

Lung cancer continues to be a deadly disease. The goal of screening programs is to detect tumors in earlier, curable stages, consequently reducing disease-specific

mortality. The issue of screening has great relevance to thoracic surgeons, who should play a leading role in the debate over screening and its consequences. Screening is especially important because screening protocols may generate a 10-fold increase in the number of patients presenting for surgical resection.¹⁶ The burden is on thoracic surgeons to work in a multidisciplinary setting to guide and treat these patients safely and responsibly, with low morbidities and mortalities of potential diagnostic or therapeutic interventions.

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