Reduced lung cancer mortality with low-dose computed tomographic screening

The National Lung Screening Trial Research Team of the National Cancer Research Institute has recently reported a large-scale trial showing that screening with low-dose computed tomography (CT) is associated with a significant reduction in lung cancer mortality compared with chest radiography in persons at high risk for lung cancer.[1,2]

What's new, what's important

More patients die from lung cancer than any other cancer. Tobacco remains the leading cause of this disease. The recent downward trend in lung cancer mortality is due to fewer people smoking, especially men. Tobacco cessation is still the most effective means of preventing lung cancer.

In addition to prevention, early detection plays a key role in improving cancer mortality. Classic examples of the benefits of such interventions are cancers of the cervix, colon, and breast. But lung cancer screening has remained elusive for many years. The recent NCI-sponsored study discussed here showed a 20% decline in lung cancer mortality in patients who underwent low-dose CT scanning once a year for 3 years.

We can argue about the pitfalls and downsides of this study forever. About one in five patients required follow-up procedures, and the cost/benefit ratio of CT screening for lung cancer is debatable. Unfortunately, that is true about any screening procedure, including mammography and colonoscopy.

As individual physicians or leaders in our respective institutions, we need to make sure we do what is right for our patients. In the accompanying commentary and sidebar ("How we screen"), you will see an example of how this can be approached.

— Jame Abraham, MD

From August 2002 through April 2004, 53,454 persons at high risk for lung cancer were enrolled at 33 US medical centers and randomized to three annual screenings with either low-dose CT (n = 26,722) or single-view posteroanterior chest radiography (n = 26,732). Data on lung cancer cases and deaths were collected through the end of December 2009. Eligible participants were aged between 55 and 74 years, had a history of smoking of at least 30 pack-years and, if former smokers, had quit within the past 15 years. Persons with a previous diagnosis of lung cancer, a chest CT within the preceding 18 months, hemoptysis, or unexplained weight loss of more than 15 lb in the preceding year were excluded from the study. Participants in the two groups were well matched for age at randomization, gender distribution (59% men in each group), and proportion of current smokers (48% in each group). The participants in the trial were younger, had a higher level of education, and were more likely to be former smokers than were respondents to a 2002–2004 US Census survey of tobacco use who matched the age and smoking history criteria of the trial.

As of the end of the data collection period, vital status was known for 97% of the CT group and 96% of the radiography group. The median duration of follow-up was 6.5 years, with a maximum duration of 7.4 years in each group. The rate of adherence to the screening protocol was 95% in the CT group and 93% in the radiography group across the three rounds of screening. In each of the three rounds, there were more positive screening results in the CT group (27%, 28%, and 17%, compared with 9%, 6%, and 5%); the lower rate of positive tests in the final screening in both groups reflected the fact that final screening tests showing suspicious abnormalities that were stable across all three screening tests were categorized as negative with minor abnormalities. Overall, at least one positive screening result occurred in 39.1% of the CT group and 16.0% of the radiography group. Clinically significant abnormalities other than those suspicious for lung cancer were identified in 7.5% of the CT group and 2.1% of the radiography group. Greater than 90% of positive tests in the first screening round led to diagnostic evaluation, with lower rates of follow up occurring in later rounds; diagnostic evaluations generally consisted of further imaging studies, with invasive procedures being infrequent. Across the three rounds of screening, 96.4% and 94.5% of positive results were false-positive in the CT and radiography groups, respectively.

A total of 1,060 lung cancers (645/100,000 person-years) were diagnosed in the CT group and 941 (572/100,000 person-years) were diagnosed in the radiography group, representing a significant rate ratio of 1.13 (95% confidence interval [CI], 1.03-1.23) favoring CT. In the CT group, 649 cancers were diagnosed after a positive screening test, 44 after a negative test, and 367 in participants who either missed screening or were diagnosed after the screening phase was over. In the radiography group, 279 cancers were diagnosed

Report prepared by Matt Stenger, MS.

Commun Oncol 2011;8:441–444

after a positive screening test, 137 after a negative screening test, and 525 in participants who either missed screening or were diagnosed after the screening phase. In both groups, stage IA and IB cancers were more frequently diagnosed after a positive screening test, compared with after a negative test or in the absence of screening. Fewer stage IV cancers were seen in the CT group than in the radiography group at the second and third screenings. CT screening identified a preponderance of adenocarcinomas, including bronchioloalveolar carcinomas (a designation that is no longer recommended, but that in the study referred to in situ, minimally invasive, or invasive adenocarcinoma in which neoplastic cell growth was restricted to preexisting alveolar structure). In both groups many adenocarcinomas and squamous cell carcinomas were detected at stage I or II, although the stage distribution was more favorable in the CT group. In general, small-cell lung cancers were not detected at early stages in either group. A total of 92.5% of stage IA or IB cancers in the CT group and 87.5% in the radiography group were treated with surgery alone or with surgery in combination with chemotherapy or radiotherapy or both.

A total of 356 deaths from lung cancer (247/100,000 person-years) occurred in the CT group, compared with 443 (309/100,000 person-years) in the radiography group, representing a relative reduction in the lung cancer death rate of 20% in the CT group (95% CI, 6.8%-26.7%; P = 0.004). When only persons who had at least one screening test were considered, the numbers of deaths from lung cancer were 346 in the CT group and 425 in the radiography group. The number needed to screen with low-dose CT to prevent 1 death from lung cancer was 320.

A significant 6.7% reduction in risk of death from any cause (P = 0.02) was observed in the CT group. Lung cancer accounted for 24.1% of all deaths in the study, but 60.3% of excess deaths in the radiography group were due to lung cancer. When deaths from lung cancer were excluded from the mortality analysis, the reduction in overall mortality in the CT group was reduced to 3.2% and was no longer statistically significant.

Rates of complications from diagnostic procedures following a positive screening test were 1.4% in the CT group and 1.6% in the radiography group. For the CT group and radiography group, 0.06% and 0.02% , respectively, of positive tests that did not result in a diagnosis of lung cancer and 11.2% and 8.2%, respectively, of those that did result in a diagnosis were associated with major complications following an invasive procedure. Sixteen participants in the CT group (including 10 with lung cancer) and 10 in the radiography group (all with lung cancer) died within 60 days after an invasive procedure. It is not known whether complications from the procedures caused the deaths; however, the low frequency of death within 60 days following the procedure suggests that death as a result of invasive diagnostic evaluation prompted by a positive screening test is a rare occurrence.

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Commentary

A new era for lung cancer detection

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Lung cancer is the second most common cancer and an all-too-common cause of cancer-related death in both men and women in the United States. Estimates for 2011 anticipate 221,130 new cases and 156,940 deaths from lung cancer.[1] In 2006 alone, the United States spent $10.3 billion on the clinical treatment and care of lung cancer patients.[1]

For more than 3 decades, international researchers have sought safe, effective, and minimally invasive methods for lung cancer screening. The goal has always been for early detection so that the disease can be identified at a potentially curable stage before the symptoms begin. At present, only 15% of lung cancers are found in the early stage and localized; most are well advanced at initial diagnosis. Early detection may also provide better therapeutic options, such as less invasive surgery, and the potential for

Manuscript submitted October 8, 2011; accepted October 9, 2011

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Disclosures: The authors have no relevant conflicts of interest to disclose.

better survival rates. In addition to emerging imaging modalities, such as low-dose spiral computed tomography (CT) and PET scanning, studies are underway to find biomarkers in blood and sputum to improve detection. Advanced bronchoscopic techniques, such as endobronchial ultrasound and navigational methods, also are extending the diagnostic reach of clinicians.

Early detection has been a key to mortality reduction for cervical, breast, and colon cancer, though previous trials for early detection of lung cancer have met with varying degrees of success. However, the recent National Lung Screening Trial (NLST) report confirmed improved survival for early lung cancer detection.[2,3] Investigators in the NLST, a large, randomized controlled large clinical trial involving more than 50,000 individuals who were at high risk for lung cancer, compared the effects of low-dose chest CT and chest radiographs and showed encouraging survival benefits. The results are consistent with those from the 1999 ELCAP (Early Lung Cancer Action Project) study,[4] which evaluated baseline and annual screening with low-dose chest CT and chest radiography in high-risk patients (n = 1,000). Malignant disease was detected by CT in 27 patients (2.7%; 95% confidence interval [CI], 1.8–3.8) and by chest radiography in 7 patients (0.7%; 95% CI, 0.3–1.3), with stage I malignant disease in 23 of the CT patients (2.3%; 95% CI, 1.5–3.3) and 4 of the chest radiography patients (0.4%; 95% CI, 0.1–0.9). Of the 27 CT-detected cancers, 26 were resectable.[3] Noncalcified nodules were detected in 233 patients (23%; 95% CI, 21–26) by low-dose chest CT at baseline, compared with 68 (7%; 95% CI, 5–9) by chest radiography. Biopsies were done on 28 of the 233 patients with noncalcified nodules. In addition, 27 of the 28 had noncalcified nodules and were followed without intervention. Although false-positive CT results are common, they can be managed with limited use of invasive diagnostic procedures. The role of experienced clinicians and radiologists was emphasized.

Another 2-year study for early lung cancer detection using chest CT and positron emission tomography (PET) in 1,035 heavy smokers, detected 22 cases of lung cancer, 11 at baseline and 11 in the second screening year.[5] Complete resection was achieved in 21 (95%) of the lung cancers, and 17 (77%) were pathological stage I. All of the cancers detected in the second screening year were stage I. The mean tumor size for the 22 cases at detection was 18 mm. There were no interval lung cancers in the 2.5 years of follow-up. This combined use of low-dose spiral CT and selective PET was also effective in detecting early lung cancer.[5] The investigators felt that lesions of up to 5 mm could be evaluated again at 12 months without major risks of progression.

In Europe, the Netherlands and Belgium launched the NELSON trial (the acronym for the Dutch title) in 2004,[6–9] a collaborative, randomized controlled trial of 16,000 people of whom half were screened with low-dose CT scans and half received no screening. In addition to looking for the impact of screening on mortality, the researchers are carefully tracking and evaluating the imaging abnormalities for type, shape, location, and growth rate. This is expected to provide valuable data for both medical imaging and molecular science researchers. The NELSON study researchers are using very low-dose scans with new computer-aided design software and are achieving unprecedented levels of 95% sensitivity and 99% specificity in the recognition of lung cancer.[6–9]

Although this large trial will not be concluded until 2015, two papers on preliminary NELSON findings were published in 2009[6–9] suggesting that lung cancer is being detected at stage I in 70% of cases, a finding that validates the ongoing ELCAP observational study that was started in 1992.

Although spiral CT scans can de-

How we screen

In response to the publication of the National Lung Screening Trial findings, which demonstrated reduction in lung cancer deaths with annual chest CT screening over 3 years, our institution has initiated a multidisciplinary pilot program for high-risk patients. The program offers a low-cost, self-pay, noncontrast low-dose helical chest CT scan in the first year, with careful follow-up monitoring, along with individual smoking cessation education that includes counseling and nicotine replacement medications. The program participant may also have two additional CT imaging studies in the following 2 years. Imaging is reviewed by the radiology service and the pulmonary medicine team. Abnormal imaging is evaluated applying published Fleischner criteria for lung nodules.[1] When clinically indicated, diagnostic and staging studies are chosen. These studies may include additional imaging, such as fusion chest CT and PET scanning; bronchoscopy with endobronchial ultrasound; and/or navigational guidance, transthoracic CT-guided biopsy, mediastinoscopy, video-assisted thoracoscopic lobectomy, and thoracotomy. Each new case is discussed during our weekly multidisciplinary lung cancer meetings, and the group agrees upon the treatment. We use established guidelines—protocols for lung cancer treatment as recommended by the National Cancer Institute and the National Comprehensive Cancer Network. For advanced, recurrent, or nonresponsive disease, we enroll eligible patients in clinical trials to further advance knowledge of lung cancer therapy.

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tect tumors in the earliest stages of disease, there is debate among the medical community if this earlier detection ultimately saves lives. Experts have raised concerns about overdiagnosis, or the detection of cancers that would not have caused symptoms before the patient died of other causes.[2,3] In addition, the invasive diagnostic procedures performed to evaluate imaging abnormalities have their own risks. False positives are common as scans may detect scar tissue or granulomas, raising false concerns for cancer. Many centers, including ours, have decided that for now, the benefits of early detection of lung cancer outweigh the anxiety and uncertainty created by false positives. We have begun a program for informed, voluntary annual chest CT for high-risk patients (see "How we screen"). We see the possibility of a national public policy decision to determine who will/may pay for early screening chest CT in these high-risk patients. The cost may be significant, so medical insurers are currently unlikely to have a keen interest in financing such testing. More clinical experience and additional research will certainly shed light on the science to inform this policy decision. Many centers, including several that participated in the NLST trial, have started offering low-cost, self-pay chest CT screening with counseling for smoking cessation. Experienced clinicians and radiologists will need to work together to detect true positives and minimize complications from false positive lesions.[10] Further understanding of the apparent benefit in nonmalignant disease outcomes from the NLST trial is also anticipated. We seem to be entering a long-awaited new era in lung cancer detection.

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