Lung Cancer Screening: Ready for Prime Time?

By Judy Peres

ews from the National Lung Screening Trial (NLST) in November made headlines worldwide: A screening program had succeeded in cutting deaths from the world’s most lethal cancer by 20%.

In this randomized, controlled trial, 54,000 current or former heavy smokers aged 55–74 years received either chest X-rays or low-dose helical computed tomography (CT) scans in an attempt to detect lung cancer early enough to reduce mortality. An estimated 222,520 cases of lung cancer will be diagnosed in the United States this year, and 157,399 people are expected to die of the disease—more than will die of breast, colon, and prostate cancer combined. The ramifications of a screening program that could make a dent in that number could hardly be overestimated.

“The finding is incredibly encouraging,” said Claudine Isaacs, M.D., principal investigator of the NLST at Georgetown Lombardi Comprehensive Cancer Center, which enrolled 1,800 patients in the trial. “It’s very impressive, especially given a malignancy for which our treatments are not all that effective.”

Several previous trials comparing chest X-rays to no screening failed to reduce deaths from lung cancer, although they greatly increased the number of small tumors detected. (The NLST confirmed that there is no benefit to screening with chest X-rays.) More recent studies, such as the Early Lung Cancer Action Project (ELCAP), have suggested a benefit to helical, or spiral, CT screening, which can detect much smaller tumors than can X-rays. But they were not controlled trials. This was the first prospective, randomized trial of the screening method.

To Be Widely Offered?

Some medical providers immediately began offering CT scans widely, even though the only individuals in whom CT screening had been shown to work were middle-aged or older people with a smoking history of at least 30 pack-years (the equivalent of one pack a day for 30 years).

Officials of the Bonnie J. Addario Lung Cancer Foundation (which sponsors a CT screening program at Sequoia Hospital in Redwood City, Calif.) issued a statement: “This definitive study demonstrated that annual CT scans in individuals at risk for lung cancer over the age of 50 reduced the risk of dying from this disease by 20%” (emphasis added).

Similarly, Westside Medical Imaging in Beverly Hills, Calif., proclaimed in a press release, “It is clear that in patients at risk, particularly those who have smoked for over 10 years, this is an indispensable part of your annual examination.” And Atlanta’s St. Joseph Hospital, on its website, invites anyone concerned about lung cancer risk to call or e-mail for a CT appointment.

The National Cancer Institute, which sponsored the NLST, advised the public not to extrapolate the results to other populations. “We’re not recommending CTs,” said Christine Berg, M.D., chief of NCI’s Early Detection Research Group and project officer for the lung screening study. “We’re saying the results only pertain to the group that was studied. The worried well, those exposed to secondhand smoke, the 50-year-old woman who smoked half a pack a day in college—we don’t want them to get the message that they should run out and get a CT.”

Some questioned whether the results should have been released at all, given that the study has yet to undergo peer review and the complete data have not been disclosed. “I don’t know why they’d roll this out without giving people like myself, or physicians who might be called on to do the test, the full story,” said H. Gilbert Welch, M.D., of Dartmouth, whose work has focused on overdiagnosis in cancer screening. “Why a press conference instead of a paper?”

Welch’s chief concern is that doctors and patients don’t have enough information to make informed choices. “This is a big benefit,” he said. “It may overwhelm
any harms. But people need to know: How many false positives? How many extra biopsies? How many extra surgeries?"

The data relating to those and other questions will be in the final report and several ancillary papers, which are expected to be published next spring, Berg said.

The official statement of the NLST’s Data and Safety Monitoring Board, which halted the trial, said 24% of the participants in the CT arm had positive scans that required follow-up, but less than 1% were eventually diagnosed with lung cancer. The complete statement is available at http://www.cancer.gov/images/DSMB-NLST.pdf.

Donald Berry, Ph.D., who like Welch has written extensively about overdiagnosis, had a similar worry. “The results are compelling, at least over this short period, that there’s a 20% reduction in lung cancer deaths,” said Berry, a statistician at the M.D. Anderson Cancer Center in Houston. “But the benefit has to be traded off against other things, and those other things aren’t at all clear at this point. We know there was a high false-positive rate: 95% of the abnormalities detected were not cancer. What happened to those patients? How many got biopsies? What were the sequelae? We don’t know yet.”

“If you count up the number of cancers they found in the CT group versus the X-ray group,” said Berry, “at the screen there’s 2.3 times as many. We know the X-ray screen is itself finding things you don’t want to find.” This is a big risk, he continued, not only for the patient—but also for our economy.

Extrapolating To Lower Risk
Everyone interviewed for this article expressed concern about the danger of extrapolating from the NLST. If providers start doing screening CTs on people at lower risk than the trial population, the harms could well outweigh any benefit.

“There are harms associated with CTs,” said Berg, “particularly in nonsmokers and females.” Both groups are likely to live much longer than heavy smokers, she explained, so they’re at risk of cancer developing from the radiation for a longer period. For women, chest CTs increase the risk of breast cancer as well as lung cancer. At the same time, the baseline risk of lung cancer in nonsmokers is so low that any benefit they might derive is small in absolute terms.

Assessing the NLST data will take months, or even years, for guideline-making groups such as the American Cancer Society and the U.S. Preventive Services Task Force to complete. But thoracic oncologist Martin Edelman, M.D., of the University of Maryland predicted that CT screening in current or former heavy smokers aged 55–74 years will shortly become part of routine medical practice.

Some, however, believe that may be premature. Leonard Berlin, M.D., professor of radiology at Rush Medical College in Chicago, noted that 796 deaths from lung cancer occurred during the NLST—442 in the X-ray arm and 354 in the CT arm—a difference of only 88 deaths in absolute terms.

“Yes, it’s 20%,” said Berlin, “but this is an unbelievably small sampling. It’s like calling the winner of an election when only 10% of the votes are in... The data, while promising, are quite incomplete.”

The data monitoring board decided to halt the trial when the mortality reduction in the CT arm crossed a predetermined threshold for efficacy. Any further data that might have accumulated would not have changed the statistically significant difference between the two arms, so the board felt that the study participants and the public needed to be notified.

Claudia Henschke, M.D., who heads the single-arm ELCAP trial, said the 20% mortality reduction was probably an underestimate. But other experts predicted that the 20% mortality reduction will probably erode over time because one can expect the radiation exposure from spiral CT scans to increase cancer incidence to some degree. Although the radiation dose of spiral CT is much smaller than that of regular CT, a team from Walter Reed Medical Center led by Michael Huppmann, M.D., estimated earlier this year that three to six cases of radiation-induced cancer would occur in every 100,000 individuals screened with low-dose chest CT over 15–20 years—an estimate that did not account for annual repeat or follow-up exams.

Nevertheless, the NLST had something rare in a cancer screening trial: a reduction in deaths not just from the target disease but also from all causes. “It’s almost unheard of for a screening trial to be able to tell you that,” said Welch. “You can’t do big enough studies in other diseases to reliably tell people that doing this screen will lower your risk of dying, period. But this population is so likely to die of the target cancer, it looks like we can say that.”

The 7% reduction in all-cause mortality should reassure even skeptics. According to Welch, it means the trial did not miss some serious harms associated with screening. “It’s always concerning, when you just measure disease-specific mortality, that you could be missing those extra heart attacks that occur after all the surgeries,” he said.

Another source of reassurance is that the NLST did not have a universal protocol for how to follow up positive CT results. All participants were treated by their own physicians (and at their own expense). Although this might be what Welch called “a recipe for a whole lot of lung biopsies and lung surgeries,” it also means that community practice will be more likely to reproduce the trial results.

Berg noted that, although the trialists could not mandate a particular strategy for working up suspicious findings, practice guidelines such as those of the Fleischner Society are widely available.

“There are ways to evaluate these nodules,” she said. “So if people in the community are having these scans, their radiologist can look to these guidelines to see the best practice for follow-up.”

Modeling Is Next
Ultimately, the data from the NLST will become grist for the mills of mathematical modelers. “We’ll be doing modeling to look at questions like the balance of risks and benefits to a woman who gets an annual CT and an annual mammogram,” said Berg. “We can’t answer all these questions from a randomized, controlled trial, but we can from modeling.”

CISNET (Cancer Intervention and Surveillance Modeling Network) teams will...
be among the first to look at the data. Several CISNET groups have engaged in a comparative modeling analysis that aims to predict the effect of CT screening on survival, mortality, and overdiagnosis. (One of them predicted a lung cancer mortality reduction of ~20%.) Until now, they have been simulating the Mayo Clinic CT screening trial, which did not have a control arm. Soon they will be able to simulate the NLST.

“We’re very much looking forward to working with NLST people to look at policy questions, using real data and combining other models and registry data,” said Pamela McMahon, Ph.D., of Harvard. “The big question is, what if you start screening nonsmokers?”

For policymakers and health care providers, cost-effectiveness will be an important consideration in establishing practice guidelines. In a preview of what they’re likely to find, McMahon’s group modeled CT screening of smokers last year and presented their findings in an abstract at the annual meeting of the Radiological Society of North America.

They found that annual CT screening of ever-smokers aged 50–74 years with at least 20 pack-years of cigarette exposure cost between $134,000 and $181,000 per quality-adjusted life year gained. They concluded that lung cancer screening with helical CT was not cost-effective relative to other U.S. cancer screening programs and was significantly more expensive than stand-alone smoking cessation programs.