Lung Cancer Screening Debate Continues Despite International CT Study Results

By Renee Twombly

Earlier this year, a lung cancer screening study received worldwide press when it found that computed tomography (CT) screening of patients at risk for lung cancer can lead to early detection. But the disputed report has not reduced the distance between two sparring groups of researchers.

The critical issue is whether CT screening can reduce lung cancer deaths: the ultimate test of any effective cancer screening. Can a screening clinical trial with no control arm prove a reduction in mortality? This study, the International Early Lung Cancer Action Program (I-ELCAP), had no control arm.

Investigators leading the I-ELCAP study argue that, despite their nonrandomized study design, there is no longer doubt that CT screening saves lives. In their October 26 New England Journal of Medicine report, the researchers estimated 10-year survival at 92% among patients whose stage 1 cancers were detected by CT and removed by surgery.

“We’ve shown that if we can detect early lung cancers earlier, they are highly curable and that it is cost effective,” said principal investigator Claudia Henschke, M.D., Ph.D., of New York Presbyterian Hospital–Weill Medical College of Cornell University. “For high-risk people, I think we should consider providing screening for them.”

However, researchers involved in the ongoing National Lung Screening Trial (NLST), a randomized, controlled trial comparing CT to chest x-ray screenings in 53,000 current and former smokers, said that knowing the I-ELCAP study’s “real” survival benefit is impossible because there was no control group and the researchers did not directly measure mortality (JNCI’s editor in chief is involved in the NLST). Unless there is a control group, they said, influences of well-known statistical biases and the lack of information about screening harms prevent using survival as a legitimate outcome in a screening trial.

“The use of survival as a surrogate endpoint for screening benefit is perilous because it is not related to mortality, and only a trial with a contemporaneous comparison arm can test for mortality differences,” said Denise Aberle, M.D., of the David Geffen School of Medicine at the University of California, Los Angeles, and a co–principal investigator of the NLST.

Using I-ELCAP to justify CT screening “is a rush to judgment,” she said.

Both sides suggest that patients might be harmed by following the other’s suggested course of screening. Henschke said her institution cannot now ethically enroll patients in a study of CT versus chest x-ray since CT is the better screening tool. Aberle said now that the public has been led to believe that CT is better, participation in NLST may suffer. Promoting CT screening now “is unethical because we do not know the benefits and we do not know the balance of risks versus benefits,” she said.

Robert Smith, Ph.D., director of cancer screening at the American Cancer Society (ACS), hopes that CT lung cancer screening works but understands that the definitive evidence is not yet there. (ACS has formally endorsed the NLST).

“It is hard to be on the fence in a way, but I have to be since establishing health policy related to screening requires not only strong evidence but consensus that the evidence is strong,” he said.

“I hope there is a benefit, but I am open to the fact that there may not be one or that it may be considerably smaller than estimated by the I-ELCAP study.”

Most Sensitive Screening Tool

The researchers all agree that CT can detect more lung cancers at an earlier stage than chest x-rays. Removing cancers as early as possible makes sense if all lung tumors are clinically significant and will eventually become lethal. Some researchers think that is the case since lung cancer survival is so low when diagnosed after symptoms occur. But the benefit of screening for early cancers is less clear, others argue, if most cancers detected by CT are so slow growing that they won’t cause harm, as is believed for many prostate cancers. Early detection would then not affect mortality.

The 20-year Mayo Lung Cancer Project gave the first evidence that some lung tumors are not harmful. More than 9,000 men at high risk of developing lung cancer were randomized to receive either chest x-rays and sputum tests three times a year for 6 years or their usual care. The results, published in 2000, showed that frequent x-rays caught more tumors and that the study arms had a large 5-year survival difference. But increased detection did not reduce mortality: The screening arm had more deaths. In a June 2006 JNCI paper, the Mayo authors examined 16 years of follow-up data that supported the overdiagnosis conclusion.

The possibility that all apparent lung cancer screening benefit is due to overdiagnosis has been overblown, Smith countered. All cancer screening has some overdiagnosis, “but the existing data do not allow us to draw any conclusions...
with confidence at this point. This is why we need results from the prospective trials.”

But the question of whether CT could detect tumors at an even earlier stage remained. In the late 1990s, Early Lung Cancer Action Program (ELCAP) investigators from Cornell scanned 1,000 high-risk people above age 60 with both a chest x-ray and low-dose CT. CT found more than three times as many suspicious nodules as x-rays. Researchers in 1999 reported in *The Lancet* that CT found malignant disease in 27 people, four times as many as were seen with x-ray. In this group, 23 had stage 1 disease, which Henschke said shows that CT was more sensitive at finding early tumors. Results published in *Cancer* in 2001 also confirmed that repeated annual CT screenings discovered 83% of lung cancers at the earliest stage.

**But Does It Save Lives?**

The ELCAP investigators then morphed into I (International)-ELCAP by extending the study to seven countries and 31,567 patients aged 40 or older, mostly smokers or former smokers. All patients underwent baseline screening between 1993 and 2005, and there were 27,456 annual screenings performed on some patients (the study does not break this figure down further). The scans found 484 lung cancers, 412 in their early stage. As of May 2006, 75 of the 484 participants diagnosed with lung cancer died of the disease, including two who died within 4 weeks of surgery and eight who did not seek treatment for early-stage disease.

Critics of the I-ELCAP study point out that the study included 3,299 study participants from Japan who never smoked, yet some of these people had tumors at initial screening. They say these tumors were probably indolent, possibly skewing survival statistics. And they say the 10-year predicted survival was based on only two patients—who could have been these outlying Japanese participants because the CT screening started earlier in Japan than in most of the participating centers.

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Generally, critics say there is little information in the NEJM study. Said Ned Patz, M.D., a professor of radiology at Duke University Medical Center, “There are no mortality statistics. There is no staging information, except for stage 1, and no pathological staging information. We don’t know how many patients were lost to follow-up or how many actually had annual screenings.” The NEJM study produced no evidence to show a benefit, he said. “What they are saying may be correct or it may not. We just don’t know.”

Others say that like other single-arm observational trials, this study probably suffers from inherent biases. Lead-time bias comes when you catch a cancer early but the patient lives no longer than he would have without screening. Length-time bias means that screening detects more slow-growing cancers than aggressive tumors, which often show up between screenings. Both skew survival numbers even when there is no change in the lung cancer death risk.

“No matter what you do, because of the nature of a screening test, you will always pick up more indolent cancers than aggressive cancers, so screening will always prolong survival, regardless of mortality benefit,” Aberle said. “The most aggressive cancers elude the screening test.”

Other researchers’ conclusions weren’t nearly as promising as those of the I-ELCAP study. After results of its chest x-ray study, the Mayo Clinic launched a second study of 1,520 people aged 50 or older, mostly smokers, and gave them five annual CT exams. The investigators discovered 68 lung cancers in 66 participants but found no difference in lung cancer mortality rates between their two study groups when compared by age and sex. The 2005 Radiology report concluded that CT screening does not reduce mortality and may do more net harm.

Because about 4,000 suspicious nodules were investigated in the I-ELCAP study, Mayo Clinic radiologist Stephen Swensen, M.D., said that a mass CT screening could end up killing more people than it saved.

“CT is amazingly powerful,” said Swensen, lead author of the Radiology report. “It can pick up lung cancers that are as small as a sesame seed, but it also sees a cartload of benign nodules, and a lot of people with those nodules end up getting surgical biopsies or surgery to remove lung lobes,” he said. And because as many as 4% of patients who undergo these surgeries die, “we just don’t know at this point whether we are doing more harm than good.”

Repeated CT radiation to the chest could also cause as much as a 5.5% increased risk of developing lung cancer, said David Brenner, Ph.D., D.Sc., a professor of radiation oncology at Columbia University. Sensitivity to radiation damage usually drops off with age, but “for reasons we don’t understand, radiation-induced lung cancer risks peak in middle age,” he said. Taken with what, because of smoking history, is already a high background risk, “you are taking cells that are already damaged and prompting them to become malignant cells.”

On the basis of these risks, Brenner reported in Radiology in 2004 that a mortality benefit of “considerably more than 5%” may be necessary to outweigh CT screening’s potential radiation risks.

Randomize Treatment?

To her critics, Henschke responds that all screening trials have biases—even randomized controlled screening trials, which she said are extremely difficult to conduct. The NLST trial screens for only 3 years: “Once you stop screening, the differences between the two arms go away,” Henschke said.

Henschke also dismissed criticism of the study’s lead-time bias, saying that it “comes in if you start comparing survival rates with only short-term follow up. But we had long-term follow up.” She also said that the 10-year survival estimate is based on a Kaplan–Meier survival curve, which “is used in every clinical trial you see for oncology.”

“I know it’s easy for the opposition to say, ‘Well, there’s more harm than good,’ but we’ve shown that if you carefully follow a regimen of screening that is updated, then there are not that many harms,” Henschke said. “We’ve developed a very careful regimen of screening because that minimizes the harm.”

She did not dismiss all randomized trials but said lung cancer screening does not need any. “I would have had no problem doing our screening test and then saying small, stage 1 lung cancers could be randomized into lobectomy versus limited resection,” she said. And for those who are concerned about overdiagnosis, patients could be randomized into immediate treatment versus later treatment, Henschke suggested.

David Burns, M.D., a tobacco control researcher at the University of California, San Diego, agreed that follow-up is a screening test’s most important measure. He said that the I-ELCAP investigators appropriately managed the tumors they found to prevent unnecessary procedures.

According to ACS’s Smith, some researchers have negatively reacted to I-ELCAP’s “very optimistic projections” because the team said it had the answer before the NLST trial is over.

“Lung cancer screening brings out strong opinions in people,” he added. “Some are very pessimistic about the idea of lung cancer screening and think it is unaffordable, while others think it works very, very well and is relatively cheap. We just don’t know who is right at this point, or if the true answer is somewhere between these two extremes. We’ll just have to wait.”