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Lung Cancer Deaths Reduced by CT Scanning, National Trial Halted

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November 4, 2010 — The huge randomized National Lung Screening Trial (NLST) in the United States has been stopped after 8-year results showed that screening heavy smokers with low-dose helical computed tomography (CT) significantly reduced deaths from lung cancer, compared with screening with chest x-rays.

"This is the first time that we have seen clear evidence of a significant reduction in lung cancer mortality with a screening test in a randomized controlled clinical trial," said Christine Berg, MD, NLST project officer for the Lung Screening Study at the National Cancer Institute (NCI), which funded the trial. Her comments appear in a press release from the NCI announcing the results.

This finding will "have implications for the screening and management of lung cancer for many years to come," Dr. Berg predicted.

Initial Reactions

"The fact that the NLST was stopped early so that the tremendous positive results could be made known speaks volumes to the ability of helical CT screening of high-risk individuals to save lives," according to a statement from the American College of Radiology (ACR). It also reports that the ACR looks forward to discussions about instigating a potential lung cancer screening program.

This is "a seminal moment" for the lung cancer community, the Lung Cancer Alliance declared in a press release. It also quoted James Mulshine, MD, from the Rush University Medical Center in Chicago, Illinois, as saying: "With this positive trial result, we have the opportunity to realize the greatest single reduction of cancer mortality in the history of the war on cancer."

Results Eagerly Anticipated

The NLST results have been eagerly anticipated. Previous studies on CT screening for lung cancer have yielded conflicting results. The major trial to date (the I-ECLAP trial headed by Claudia Henschke, MD, from the New York-Presbyterian/Weill Cornell Medical Center in New York City) suggested a mortality benefit, but it lacked a control group, and then became shrouded in controversy when it was revealed that the researchers received some funding from the tobacco industry.

Despite the controversy and criticism of that trial, proponents of CT screening called for national screening programs for lung cancer to be set up, and one group of researchers even questioned whether it was ethical for the NLST to continue in light of the benefits that had been seen. But a number of lung cancer experts, and the NLST, insisted in 2007 that the field wait for results from randomized trials.

The NLST provides the first results to come out of a randomized trial. "This large and well-designed study used rigorous scientific methods to test ways to prevent death from lung cancer by screening patients at especially high risk," said NCI director Harold Varmus, MD, in a statement.

Significant Reduction in Mortality

The trial began in 2002 and has involved more than 53,000 current and former heavy smokers 55 to 74 years of age. Individuals were randomized to undergo screening annually for 3 years with either CT or chest x-rays, and were then followed for another 5 years.

The results, which were reviewed by the trial's Data and Safety Monitoring Board on October 20, show a statistically significant difference in lung cancer mortality in the 2 groups, which led to the trial being halted. There were 354 lung cancer deaths among those who underwent CT screening and 442 among those who underwent chest x-ray (a 20% reduction).

"Lung cancer is the leading cause of cancer mortality in the United States and throughout the world, so a validated approach that can reduce lung cancer mortality by even 20% has the potential to spare very significant numbers of people from the ravages of this disease," Dr. Varmus explained.

"The results of this trial provide objective evidence of the benefits of low-dose helical CT screening in an older high-risk population, and suggest that if low-dose helical screening is implemented responsibly and individuals with abnormalities are judiciously followed, we have the potential to save thousands of lives," said Denise Aberle, MD, NLST national principal investigator.

"However, given the [strong] association between lung cancer and cigarette smoking, the trial investigators re-emphasize that the single best way to prevent lung cancer deaths is to never start smoking and, if already smoking, to quit permanently," she added.

Another finding from the study, which was not the primary end point, was a 7% reduction in all-cause mortality among people who were screened by CT, compared with those screened by chest x-ray. About 25% of all the deaths were due to lung cancer; the other deaths were related to causes such as cardiovascular disease, the NCI notes in its press release.

A fuller analysis of the results is being prepared for publication in a peer-reviewed journal in the next few months, according to the NCI.

Many Questions Remain

Approached for comment on the new finding, Michael Unger, MD, FACP, FCCP, who is director of the Pulmonary Cancer Detection and Prevention Program at Fox Chase Cancer Center in Philadelphia, Pennsylvania, pointed out that the actual data from the study have not yet been published. The results released so far "in essence" confirm the findings from the study by Dr. Henschke and colleagues, but many questions remain, he told Medscape Medical News.

"The most important is: Who is really at high risk?" he said. "Other questions include when and how long we should study the subjects." Then there is the issue of false positives, where the CT screen picks up lesions that are not lung cancer, he noted. Previous studies have reported high rates of false positives with CT screening for lung cancer, ranging from 25% to 70%.

"Basically, screening is not a test, it is a process involving correct diagnosis and most appropriate management," Dr. Unger said.

[This] marks a very big moment for the lung cancer field.

There are still questions that need to be answered, agreed Ella Kazerooni, MD, who was a site principal investigator for the NLST at the University of Michigan in Ann Arbor, and is also chair of the ACR Thoracic Imaging Committee. The trial started screening heavy smokers who were 55 years of age, and screened once a year for 3 years, she explained, "but we don't know if we could start screening at an earlier or later age, and if we could screen only every 3 or 5 years."

However, the fact that a reduction in mortality was shown "marks a very big moment for the lung cancer field," Dr. Kazeroni told Medscape Medical News. This is the first time that any test or screen for lung cancer has shown this, she emphasized.

These results now "open up the dialogue" about potential screening programs for lung cancer, and she anticipates that the new data will be scrutinized by professional organizations that draw up such recommendations, such as the American Cancer Society, the US Preventive Services Task Force, and the National Comprehensive Cancer Network. In addition, before any screening program can be instigated, its cost-effectiveness will need to be considered; the NLST will provide some of these data, she said.

Thus far, there has been no recommendation for lung cancer screening from any authority, but these new data might be a turning point.

"The early termination of the trial (on effectiveness grounds) does represent an important and positive development. Hopefully, authoritative agencies, such as the US Preventive Services Task Force, the American Cancer Society, and the American College of Chest Physicians, will now reconsider their nihilistic recommendations regarding screening for lung cancer," said Igor Karp, MD, MPH, PhD, assistant professor, Department of Social and Preventive Medicine, Université de Montréal, Quebec.

Dr. Karp was one of the researchers who, in 2007, questioned the ethics of continuing the NLST trial, arguing that the benefits of CT screening had already been shown.

"I, like many others, have been of the opinion that this trial was unnecessary, given the previously available evidence (notably from the I-ELCAP study) that low-dose [helical] CT-based screening serves to prevent death from lung cancer," he explained.

Dr. Karp said that he has "a somewhat mixed reaction" to the results that have been announced. "From the hypothesis-testing point of view, the NLST is not particularly interesting, [but] the question of the magnitude of the benefit is, indeed, very important," he told Medscape Medical News.

Benefit Might Be Underestimated

"However, it is unclear how informative this trial actually is in this regard, given its design and analysis (at least in its current form)," he noted, adding that he suspects that the magnitude of benefit might in fact be "much larger" than has been reported.

"One of the biggest issues here is that the reported 20% mortality reduction (which is, in fact, not really a mortality reduction, but just a proportional difference in empirical mortality rates) does not represent a meaningful parameter, so its interpretation presents a considerable challenge," he explained.

It certainly does not quantify the full potential benefit of the CT screening.

"What is clear, however, is that it certainly does not quantify the full potential benefit of the CT screening," he said, "because it is based on mixing relevant mortality experience during a relatively late subsegment of follow-up with irrelevant mortality experience during the early subsegment of follow-up (when no lung cancer deaths could have possibly been prevented by early intervention, so no survival advantage for the CT-screened arm could have been expected there a priori)."

Dr. Karp also pointed out that the results come from the "arbitrary regimen of 3 annual screenings, which by no means represents the optimal (or typical) regimen of screening."

In addition, there are no data yet on adherence to the protocol of screening; if this was low, the benefit of CT screening "would almost certainly be underestimated," he added.