Volume CT for Diagnosis of Nodules Found in Lung-Cancer Screening

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Lung cancer, the most lethal type of cancer, accounted for more than 159,000 deaths in 2009 in the United States alone,¹ and the annual number of new cases is expected to exceed 338,000 by 2030.² Smoking-cessation and other tobacco-control measures have succeeded in reducing the consumption of tobacco products — a considerable public health benefit.³ Nevertheless, 43 million Americans continue to smoke, and there are more than 43 million former smokers³ who have an elevated risk of lung cancer for the remainder of their lives.⁴

In the past few years, a number of trials involving lung-cancer screening with the use of computed tomography (CT) have been initiated to determine whether CT screening can substantially reduce mortality related to lung cancer; these trials are ongoing, and whether CT screening for lung cancer is beneficial is not yet known. In this issue of the Journal, van Klaveren et al. report results from one of these trials, a population-based, ongoing, randomized trial in the Netherlands and Belgium (Nederlands-Leuvens Longkanker Screenings Onderzoek [NELSON]).⁶ The article describes the approach to the diagnostic workup of nodules found on an initial CT screening. In the NELSON trial, the participants were randomly assigned to three rounds of spiral CT screening or no screening. The design of the study included detailed provisions for quality control of the imaging and a highly structured process for the workup of suspicious findings from the CT evaluation. The authors report the outcomes of diagnostic workups triggered by volumetric analysis of nodule growth.

Among the 7557 participants in the screening group, a noncalcified nodule between 50 mm³ and 500 mm³ in volume was discovered in 1451 subjects at the first screening; 518 of the nodules had a volume-doubling time of more than 400 days on a follow-up scan at 3 months. When participants who had nodules with this slow volume-doubling time were considered together with subjects whose scans were classified as negative at the first screening, and the combined group was followed for 2 years, 20 lung cancers were detected. Thus, a negative scan, which included the presence of nodules with a slow volume-doubling time, was associated with a point-estimate negative predictive value of 99.7%.

The use of volume growth as a criterion for malignancy was first proposed by Yankelevitz and colleagues,⁷ and the Dutch–Belgian group that conducted the current trial reports an independent application of this method⁶ using a defined process for image acquisition, quality control, and image interpretation. The current article is of interest because a validated methodology governing the way in which this kind of CT-screening workup is performed and reported does not exist.

The commercial software tool that was used in this study to determine the size and growth of nodules (the LungCare software package [Siemens Medical Solutions]) performed well. Fully automated volume determination was possible in the case of 94% of the new nodules and 98% of the preexisting nodules. With automated volume measurements, the opportunity for subjective errors is potentially reduced. From a developmental perspective, it is promising that a first-generation tool for the measurement of the volume of nodules can perform at the high level reported by van Klaveren et al. However, new scanners that provide imaging with higher resolution and that are capable of acquiring scans at a finer slice thickness (<1 mm) are already in routine clinical use. Therefore, ongoing development of tools for measuring nodule volume may be important to make optimal use of all the additional diagnostic information acquired by these new scanners. Addressing the need for systematic refinement of quantitative imaging is a major goal of the Quantitative Imaging Biomarkers Alliance sponsored by the Radiological Society of North America. This consortium of stakeholders from federal, academic, and commercial institutions is committed to the responsible integration of imaging biomarkers. The important issues inherent in this effort are described in detail on their Web site (www.rsna.org/Research/qiba_intro.cfm).

The article by van Klaveren et al. is important...
because it shows the diagnostic efficiency of a defined clinical management approach within the context of a randomized trial. The results suggest that the efficiency of the diagnostic workup for lung cancer can be improved by integrating the measurement of volume growth of lung nodules as an indicator of clinically significant lung cancer while limiting the need for additional costly or potentially harmful diagnostic procedures. This quantitative imaging application may represent an important advantage over the usual qualitative application of imaging tools in a cancer-screening context. However, this diagnostic-workup approach must be validated in the setting of routine clinical practice, to determine whether this approach can be applied with the same accuracy it had in the setting of a clinical trial. Independent confirmation of the successful integration of automated volumetric measurement into the CT-screening diagnostic workup is critical.

A problem raised by this analysis of screening management was the optimal interval for serial CT screening. In this trial, the intervals between follow-up screening tests varied. The number of interval cancers was approximately 5%, and the interval cancers were either stage III or stage IV cancers. Elucidating a process to optimize and customize the frequency of subsequent CT evaluations on the basis of the results of initial rounds of screening is an area of research that could improve the overall efficiency and yield of lung-cancer screening. An interesting question in this regard is whether adaptive Bayesian designs can be applied in a screening context, since this approach is currently being tested in a therapeutic setting. One could test whether adjusting the interval between screening evaluations on the basis of the biologic characteristics of the findings identified on the screening test improves the efficiency with which cases are identified. If so, this may allow the integration of functional information, such as imaging biomarkers, into an adaptive screening management process.

Dr. Mulshine reports receiving consulting fees from Savara Pharmaceutical, receiving grant support from the Optical Society of America–Kitware, and serving on the boards of the Prevent Cancer Foundation and the Lung Cancer Alliance, the International Advisory Board of the Roy Castle Lung Cancer Foundation, and the volume-CT committee of the Quantitative Imaging Biomarkers Alliance. He reports being listed as an inventor on 12 U.S. and international patents, some of which deal with molecular methods of lung-cancer diagnosis; over the past 2 years, he has received royalty payments from these patents. No other potential conflict of interest relevant to this article was reported.

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**Rise of the Machines — Left Ventricular Assist Devices as Permanent Therapy for Advanced Heart Failure**

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Traditionally, the only definitive therapy for patients who have advanced, medically refractory heart failure was replacement of the heart with another human heart. However, transplantation is an inadequate option in light of the large number of potential candidates, the lack of donors, and the coexisting conditions that make most potential candidates ineligible for transplantation. In this context, ventricular assist devices, or heart pumps, become an attractive option for patients who have advanced heart failure.

Rather than replacing the human heart completely, ventricular assist devices serve in a true “assistance” capacity by supplementing the car-