Nodule Size and Overdiagnosis in Lung Cancer CT Screening

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Radiologists recognized the diagnostic importance of lung nodule detection soon after the introduction of chest radiography (1). Chest x-rays were used for tuberculosis screening in asymptomatic populations, reaching a peak in the late 1950s (2). As the prevalence of tuberculosis declined, TB sanitarium closed and the screening programs were terminated. With the increase in smoking through World War II and thereafter, the prevalence of lung cancer grew to become a national public health concern. With the increased prevalence of lung cancer in the 1970s and 80s, screening was initially done with conventional chest x-rays. The Mayo Lung Project followed over 9000 male smokers over 45 years. After tracking smokers for 20 years, this large study indicated that screening for lung cancer with chest x-rays does not save lives (3,4).

The advent of body-computed tomography (CT), where the chest, abdomen and pelvis were evaluated using serial 1-cm slices, revolutionized radiology in the late 1970s (5). Subsequently, the introduction of spiral CT scanning and multirow detector CT (MDCT) scanners to clinical practice beginning in the late 1990s (6) stimulated interest in the potential of contiguous CT slices for lung cancer screening. MDCT has the unique ability among CT scanners to acquire volumetric datasets with subcentimeter resolution. The Early Lung Cancer Action Project (ELCAP) pioneered population studies with low-dose MDCT lung cancer screening in smokers with promising results (7). This study stimulated interest in the potential for CT-based lung cancer screening, despite controversy regarding its design (eg, randomization and controls). After the potential for lung cancer CT screening was demonstrated by ELCAP and others, the National Cancer Institute (NCI) decided to support the National Lung Screening Trial (NLST), the most expensive clinical trial to date. The NLST was a large, high-quality randomized trial, in which high-risk individuals were screened with MDCT (8). The NLST was successful and terminated early because of a substantial mortality benefit to the screened high-risk smoking population (9).

Oncologists have increasingly used imaging to stage and evaluate therapy in solid tumors as improvements were made in CT and other modalities (especially magnetic resonance imaging). Quantitative measurements of lesions and their changes were essential, so standardization began, first with World Health Organization (WHO) (10) measurement procedures and later with the Response Criteria for Imaging of Solid Tumors (RECIST) (11) and its successors. RECIST became important in NCI clinical trials, as its use was mandated by the National Cancer Institute’s Cancer Therapy Evaluation Program (CTEP) (12). The RECIST criteria were designed by an international group of experts that decided, among many specific requirements and criteria, that the threshold for measurable lesions would be 1 cm and that CT scans of solid tumors with slice thicknesses up to 1 cm would be acceptable. As a consequence, smaller nodules (eg, 5 mm and below), may not be detectable in the CT scans because volume averaging. There are many reasons for the selection of 1 cm slice thickness and lesion size criteria, including the fact that clinical trials are often opened in third world countries where CT scanners with 1 cm slice thickness limitation are used. Global harmonization of clinical trials is often essential for their successful completion, so the lowest common denominator in CT technology affects the protocol design, in this case the slice thickness.

The utilization of chest CT scanning has increased with improvements in imaging technology, resulting in its emergence as the preferred modality for management of many chest diseases. The high prevalence of incidentally detected lung nodules found on CT scans stimulated the development of standardized criteria for their management. Drawing upon the experience of ELCAP and others, the Fleischner Society published guidelines for pulmonary nodule management based on nodule size and risk (13). These criteria have been widely accepted and form the basis for standard practice today (14).

Of all the parameters that can be derived from images, lesion size is the simplest and most widely accepted. Despite potential advantages for lesion volume measurements, or other parameters such as surface area, shape, location, attenuation histogram, margin characteristics, contrast enhancement and others (15), lesion size remains the principal criterion for solid tumor or nodule evaluation. Lesion size is the basis for WHO and RECIST criteria (16). Lesion size was the basis for nodule evaluation in the NLST and other trials, so careful evaluation of the specific criteria used to determine nodule significance and need for follow-up is warranted.

In this issue of the Journal, Gierada et al. (17) examined the influence of lung nodule size on overdiagnosis (18) in the NLST study, stimulated by the New England Journal of Medicine paper (8) and other reports. The impact of lesion size criteria at the lower end of the scale (eg, <6 mm) on overdiagnosis is substantial. Based on their findings, the potential savings in resources used to follow up lung nodules in a screening population are large enough to justify consideration of a revision in criteria based on nodule size.

The future implications of the importance of nodule size should encourage others to determine the potential for automated measurements on nodules (19), where the discriminatory value of size can be augmented with other parameters to develop and validate lung nodule computer-aided diagnosis software systems that have the added benefit of reducing human observer variation on the low-dose lung CT scan test results (20).
References

Note
The author has no conflicts of interest to disclose.

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