

# Probability of lung cancer based on the size threshold and volume-doubling time for lung nodules detected in low-dose CT screening

Hyun Lee, Sang-Won Um

Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

*Correspondence to:* Sang-Won Um, MD, PhD. Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul, 135-710, Korea. Email: sangwonum@skku.edu.

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Lung cancer accounts for about 1.6 million deaths per year worldwide (1). Most patients are diagnosed with advanced disease, resulting in a very low 5-year survival rate. Screening with low-dose computed tomography (LDCT) has reduced the mortality from lung cancer by 20% (2). However, the main challenge with LDCT screening for lung cancer is the high prevalence of false-positive results and the relatively low incidence of lung cancer (3). The implementation of LDCT screening in public health requires validated guidelines to determine the optimum patient management strategies based on the characteristics of lung nodules. From this perspective, the size threshold is important because it determines which nodules need an immediate diagnostic work-up and those that do not need follow-up. Moreover, a validated protocol is needed to manage intermediate nodules because individuals with these nodules need subsequent follow-up, which has some risk of radiation exposure.

Currently, there are several recommendations for the size threshold of lung nodules when screening asymptomatic patients at high risk of developing lung cancers. The latest American College of Chest Physicians (ACCP) guidelines recommend that individuals with lung nodules less than 4 mm in size do not require additional CT follow-up. However, individuals with intermediate-sized nodules (4-8 mm) should undergo LDCT follow-up for 24 months at intervals of 3-12 months. Individuals with large nodules ( $\geq 8$  mm) require an immediate diagnostic approach using more invasive procedures (4). The National Comprehensive Cancer Network (NCCN)

guideline recommends annual LDCT for at least 2 years if the nodules are less than 6 mm in size. If the nodules are 6-8 mm in size, LDCT is recommended at 3 and 6 months, followed by annual LDCT for at least 2 years (5). A recent study by the Early Lung Cancer Action Project (ELCAP) suggested using a threshold of 7 or 8 mm instead of 5 mm to define positive nodules based on an analysis of data from the National Lung Screening Trial (NLST) (6). However, the size threshold of 8 mm or larger, recommended in the ACCP and NCCN guidelines, was based on the consensus statement of the Fleischner Society (7) and requires validation. Furthermore, increasing the size threshold that determines the need for CT follow-up is problematic in that it can decrease the sensitivity of detecting cancerous nodules; i.e., indeterminate nodules with cancerous changes.

The Dutch-Belgian lung cancer screening trial (the NELSON study) is the first randomized lung cancer screening trial based on nodule volume rather than nodule diameter (8). The ongoing NELSON study started in 2003. In 2009, the results of the first and second rounds of screening were published (8). The volumetry-based lung cancer screening strategy led to high negative predictive values (99.7% in first round, 99.9% in second round) and there were thought to be fewer false-positive results than in other lung cancer screening trials. Recently, a side-study analyzing 2 years' data from the NELSON study was published (9). This study calculated the probability of developing lung cancers within 2 years in individuals at high risk of lung cancers and stratified the risk by volume, volume-derived diameter, and volume-doubling time.

These results showed that individuals with small nodules [volume <100 mm<sup>3</sup> (0.6%) or diameter <5 mm (0.4%)] have a lung cancer risk that is not significantly different from those without nodules (0.4%). Individuals with intermediate nodules [a volume of 100-300 mm<sup>3</sup> (lung cancer probability, 2.4%) or diameter 5-10 mm (lung cancer probability, 1.3%)] should undergo assessment of the volume-doubling time. The volume-doubling time further stratified the probabilities: 0.8% for volume doubling times ≥600 days, 4.0% for volume-doubling times of 400-600 days, and 9.9% for volume-doubling times ≤400 days. Those with large nodules [≥300 mm<sup>3</sup> (lung cancer probability, 16.9%) or ≥10 mm (lung cancer probability, 15.2%)] should receive an immediate diagnostic work-up. In addition, they evaluated the sensitivity and specificity of the nodule threshold characteristics of this new stratification and compared them to the ACCP guidelines. The sensitivity of the volume-based protocol (90.5%) was comparable to the ACCP protocol (90.5%), with a higher specificity (94.9% *vs.* 87.2%), suggesting that lung nodule management based on nodule size and volume-doubling time performs better.

Although the results of this study provide some valuable information regarding the size threshold and volume-doubling time in lung cancer screening (9), some important factors need to be considered before they can be applied to clinical practice. First, volumetry-based lung cancer screening requires software that enables semi-automated nodule-volume measurement (LungCARE, Siemens, version Somaris/5 VB 10A-W), and this is not available at all lung cancer screening centers. The diameters in this article are estimates based on those assessed using semi-automated volumetry. Therefore, the data in this article cannot be applied to patients with specific sizes measured manually. Second, the LungCARE software is not able to calculate the volume of sub-solid nodules, and some inaccuracies might be involved. Finally, the size threshold and volume-doubling time suggested in this study should be validated in a large, reliable dataset.

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